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Informed Decision Making During Pregnancy: Risk Consideration in Clinical Practice and Research

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Abstract

This thesis addressed a cluster of issues related to risk and the pregnant woman's decision making in clinical practice and research. In terms of clinical practice, the minimal risk concept - a low risk standard codified in research ethics regulations - was applied to clinicians' information provision to the patient. As clinicians must discuss a variety of health risks, minimal risk standards may be useful as a threshold to demarcate risks that clinicians should discuss with the patient. Application of minimal risk standards to risk factors in pregnancy showed the usefulness and limitations of these standards. In terms of pregnant women's clinical research participation, analyses of national and international research ethics regulations suggested that regulations could potentially be overprotective. A grounded theory study revealed that pregnant women were protective of themselves and their fetus in considering clinical research participation. In determining whether a clinical research project involving pregnant women would be acceptable, obstetric healthcare providers emphasized the adherence to regulatory requirements while researchers in reproduction areas focused on scrutinizing the scientific quality and interpretation of prerequisite studies. These three populations shared safety concerns. While minimal risk standards may be useful in identifying risks to be discussed with the patient, determining permissible risk during pregnancy may be more complex, including consideration on the risk benefit ratio in the pregnant woman's context. This thesis has implications on risk communication in clinical practice and research, policies on clinical research with pregnant women, and education for healthcare providers, clinical investigators, and the general public.

Keywords

pregnant women, clinical research, research ethics guideline, minimal risk, risk benefit ratio, patient participation, informed consent, information provision

Co-Authorship Statement

I, Kyoko Wada, acknowledge that this thesis includes four integrated manuscripts that evolved as a result of collaborative endeavors. In the four manuscripts, the primary intellectual contributions were made by the first author in terms of the methodology, study design, ethics application, conducting literature review, collecting data, transcribing the interview record, coding and analyzing the data, and writing the manuscript. The contribution of the co-authors, Dr. Jeff Nisker, Dr. Marilyn Evans, Dr, Barbra deVrijer, and Dr. Barbara Hales was primarily providing guidance, supervision from their expertise, and intellectual and editorial support in writing the manuscripts.

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Chapter 1

1 Introduction

This thesis aimed to address a cluster of issues which revolve around the pregnant woman's informed decision making with a focus on health risk in clinical practice and research. Several research questions emerged from two different origins. One set of research questions derived from my involvement in two interdisciplinary team projects which investigated the risks of in utero exposure to environmental chemicals. The other set of research questions came from my experience as an ethicist to the research ethics board at a Canadian university, where I have noticed that pregnancy is virtually an automatic exclusion criterion in clinical studies reviewed at a full board level. These seemingly odd partners gradually began to converge and developed into the following four studies:

1. Implications of the concept of minimal risk in research on informed choice in clinical care
2. Implications of minimal risk standards in clinical research to information provision in prenatal and preconception care
3. Critical review of research ethics regulations on clinical research with pregnant women
4. A grounded theory study on the views of pregnant women, obstetric healthcare providers, and researchers in reproduction areas on clinical research with pregnant women.

In this opening chapter, the background and overall purpose pertaining to these four studies as well as an overview of the chapters will be introduced. In this thesis, "clinical research" is understood as "research that directly involves a particular person or group of people, or that uses materials from humans, such as their behavior or samples of their tissue" as per the United States (US) National Institute of Health (NIH) (National Institute of Health, 2012, Clinical Trials and Clinical Research, para. 1).

1.1 Background

1.1.1 Importance of maternal and fetal health and a paucity of evidence for prenatal and preconception care

A pregnant woman may need to make decisions about her health and her fetus's health in multiple layers, such as medical treatments, life style choices, management of health risks embedded in her daily life, or health research participation. What happens during pregnancy is critically important particularly for fetal health and pregnancy outcomes (Blackburn, 2013; Creasy, Resnik, & Iams, 2009; Sibai & Frangieh, 1995; Weissgerber & Wolfe, 2006) as well as a future person's lifelong health, such as susceptibility to allergic diseases and asthma (Prescott & Clifton, 2009), cardiovascular diseases (Barker, 2000; Godfrey & Barker, 2000; Langley-Evans & McMullen, 2010), or type 2 diabetes (Godfrey & Barker, 2000; Langley-Evans & McMullen, 2010; Woo & Patti, 2008).

Despite the importance of pregnancy health for women and their fetuses, prenatal and preconception care may not be as evidence based as clinical care for the general population due to the relative lack of clinical based research with pregnant women (Baylis & Kaposky, 2010; Charo, 1993; Kass, Taylor, & King, 1996; Lyerly et al., 2009b; Macklin, 2010; Mattison & Zajicek, 2006; McCullough, Coverdale, & Chervenak, 2005). Insufficient evidence for prenatal care is concerning in terms of the quality of prenatal care as, for example, clinicians may refrain from administering potentially desirable interventions that would routinely be administered to the non-pregnant patients for the fear - not evidence - of undesirable outcomes (Baylis, 2010; Lyerly et al., 2009a, 2009b). Thus despite the need to promote maternal and fetal health through evidence based practice, the paucity of research evidence with pregnant women is creating difficulties for clinicians' practice and potential for additional risks for pregnant women and their fetuses.

1.1.2 Informed decision making in clinical care and research

Informed decision making has often been discussed under the topic of "informed consent" which requires provision of pertinent information, a decision maker's capacity and his or her appreciation of the information, and voluntariness in giving consent (Grisso &

Appelbaum, 1998). Informed consent is recognized as an important opportunity for a person to protect him or herself by giving or not giving consent (Appelbaum, Berg, & Lidz, 2001; Grisso & Appelbaum, 1998) and is deemed indispensable prior to therapeutic or diagnostic procedures in clinical care (ABIM Foundation, ACP–ASIM Foundation, & European Federation of Internal Medicine, 2002; Appelbaum et al., 2001; Beauchamp, 2011; Faden, Beauchamp, & King, 1986) as well as in research participation (Appelbaum et al., 2001; Beauchamp, 2011; Faden et al., 1986; National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979).

With regards to information provision, risk is considered one of the important pieces of information to be communicated to the patient (Appelbaum et al., 2001). In clinical practice, however, despite much emphasis on risk in legal cases, there is no risk standard which specifies what level of risks should be disclosed to the patient (Rozovsky, 1990). On the other hand, in clinical research which appears more regulated than clinical practice (Beauchamp, 2011; R. J. Levine, 1988; Miller & Wertheimer, 2010; Rolleston, Lipsett, & Levine, 1979), the concept of minimal risk is employed as a risk threshold in terms of determining the level of ethics review or allowing alteration to the consent process (Kopelman, 2004; Reid & Krahn, 2007; Westra, Wit, Sukhai, & de Beaufort, 2011). Minimal risk as codified in research ethics regulations is not a threshold for risk disclosure (Kopelman, 2004) as information provision in clinical research is expected to be highly extensive (Council for International Organizations of Medical Sciences (CIOMS), 2002). Nevertheless, minimal risk is a notable risk concept that is lacking in current clinical practice.

1.1.3 Complexity of information for pregnant women's decision making about health

In prenatal and preconception care, provision of adequate information followed by discussion with the woman is vital for supporting her decision making about her and her fetus's health (Berghella, Buchanan, Pereira, & Baxter, 2010; Chandranipapongse & Koren, 2013; Hood, Parker, & Atrash, 2007). However, for pregnant women and women contemplating pregnancy, information to consider may be more complex compared with the non-pregnant populations due to the course of pregnancy (Blackburn, 2013; Creasy et

al., 2009; Sibai & Frangieh, 1995; Weissgerber & Wolfe, 2006), fetal development (Blackburn, 2013; Harding & Bocking, 2001; Mongelli & Gardosi, 2000; Rodeck & Whittle, 2009; Schoenwolf & Larsen, 2009; Wu, Bazer, Cudd, Meininger, & Spencer, 2004), and physiological differences of the pregnant body compared with non-pregnant bodies (Baylis, 2010; Broughton Pipkin, 2011; Goldkind, Sahin, & Gallauresi, 2010; Goodrum, Hankins, Jermain, & Chanaud, 2003; Hanretty, 2010).

Moreover, the paucity of research with pregnant women increases uncertainties in the information to be provided (Baylis, 2010; Charo, 1993; Kass et al., 1996; Lyerly et al., 2009b; Macklin, 2010; Mattison & Zajicek, 2006; McCullough et al., 2005). For example, safety based on the data from non-pregnant women in drug studies may not apply to pregnant women due to the differences in drug distribution, metabolism, and elimination (Baylis, 2010; Goldkind et al., 2010; Goodrum et al., 2003; Mattison & Zajicek, 2006). Further, as the woman and fetus are intertwined and influence each other (Blackburn, 2013), an ethically challenging task is the balancing of fetal risks and benefits against maternal risks and benefits (Levine et al., 2004; Strong, 2011). In cases where conflict of interest exists between the woman and fetus, the decision making will involve further complexities and dilemmas.

Given the critical nature of maternal and fetal health, understanding the pregnant woman's decision making about health is important. While receiving and understanding relevant pieces of information is central to the pregnant woman's decision making, complexities due to the course of pregnancy and fetal development make information more complicated compared with that for non-pregnant women. In addition, insufficient research with pregnant women compromises the information to be provided by clinicians. Also, clinicians may have challenges in addressing a variety of health risks to the woman and embyo/fetus within and outside clinical procedures without guidance as to what risk information should be provided to meaningfully support pregnant women and women planning pregnancy in their decision making regarding maternal and fetal health.

1.2 Purpose of this thesis

The purpose of this thesis is to address a cluster of issues related to the pregnant woman's informed decision making in the contexts of clinical practice and research with a focus on health risk. The goal is to construct a substantive model that illustrates decision making and risk consideration in prenatal and preconception care as well as in clinical research involving pregnant women.

1.3 Research questions

1. How do research ethics regulations stipulate the inclusion of pregnant women in clinical research?

2. What are the implications of the concept of minimal risk in research on informed decision making in clinical care?

3. What are the implications of the concept of minimal risk in research on clinicians' information provision, particularly risk disclosure to the patient in prenatal and preconception care?

4. How do pregnant women decide whether or not to participate in clinical research?

5. How do obstetric healthcare providers and researchers in reproduction areas determine whether a clinical research project with pregnant women would be acceptable?

1.4 Thesis overview

This thesis includes five independent articles: a scoping review, three conceptual studies, and an empirical study.

Chapter 2 reviewed risk concepts by two authors, Hansson and Lupton, as risk is an important player in both empirical and conceptual studies of this thesis. Hansson is a philosopher who has discussed the role of philosophy on risk studies, moral theories to address risk, and policies for risk management in public health. Lupton's work concerns epistemology of risk as well as sociocultural perspectives on risk in the context of

pregnancy. The discussions of these two authors inform the empirical research examining the views of pregnant women, obstetric healthcare providers, and researchers in reproduction areas on clinical research with pregnant women (Chapter 5) as well as conceptual studies exploring the minimal risk concept in clinical practice (Chapters 3 & 4).

Chapter 3 is an article entitled, "Implications of the concept of minimal risk in research on informed choice in clinical care" which was published in the *Journal of Medical Ethics*. This article argues that the minimal risk concept employed in national and international research ethics guidelines including the Tri-Council Policy Statement of Canada (TCPS2) (Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council Canada, & Social Sciences and Humanities Research Council of Canada, 2014) may assist clinicians in determining which risk in clinical procedures and everyday life should be discussed with the patient for him/her to make an informed decision about avoiding undesirable risks.

Chapter 4 is an article entitled "Implications of applying minimal risk standards in clinical research to information provision in prenatal and preconception care". This article applies the minimal risk concept explored in Chapter 3 to risk factors during pregnancy, such as smoking cigarettes and exposure to environmental chemicals. Employing five case studies, two types of minimal risk standards were applied to determine whether the risks of five substances are above or within minimal risk. This paper was accepted for publication in the *Journal of Obstetrics and Gynaecology of Canada*.

Chapter 5 analyzes how national and international research ethics regulations stipulate clinical research with pregnant women. Two international and four national research ethics regulations were reviewed. The regulations are compared in terms of the potential vulnerability and eligibility of pregnant women as research participants, conditions under which pregnant women may participate, and the requirement of paternal consent. This chapter is considered for publication in future.

Chapter 6 is a scoping review of empirical studies on the views of pregnant women, healthcare providers, and others on research with pregnant women. A thematic analysis was conducted regarding the findings of the reviewed studies. The themes identified are presented separately for pregnant women and those besides pregnant women, mostly healthcare providers. This manuscript is considered for future publication.

Chapter 7 discusses the background, methodology, and results of the empirical study investigating the views of pregnant women, obstetric healthcare providers, and researchers in reproduction areas on clinical research with pregnant women. Using constructivist grounded theory articulated by Charmaz, this study generated a model to explain the decision making processes of the above three populations regarding how they determine a clinical research project with pregnant women would be acceptable. Results are presented as a figure showing the relationship of categories identified through an iterative process of data collection and analysis. These categories and subcategories are presented with the supporting data.

The last Chapter 8 wraps up by summarizing the results and discussing the relationship of a family of studies included in this thesis and their implications as well as future research directions in related areas of study.

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Chapter 2

2 Risk concept by Hansson and Lupton

2.1 Introduction

This chapter reviews discussion of risk by two authors, Sven Ove Hansson and Deborah Lupton. Hansson is a philosopher who focuses on the ethical dimension of risk and public policies of risk management. Lupton, a sociologist and risk theorist, provides insight into epistemology of risk as well as sociocultural perspectives on risk in the context of pregnancy. These perspectives inform conceptual studies on the implication of the minimal risk concept in clinical practice (Chapters 3 & 4) and research ethic regulations in stipulating research with pregnant women (Chapter 5) as well as the grounded theory study (Chapter 7) as a "sensitizing concept" (p.259) (Charmaz, 2003) in providing guidance for seeking theoretical directions, building on previous works, and clarifying significance of the results (Charmaz, 2003, 2006).

2.2 Hansson, S.O.

2.2.1 Roles of philosophy in risk studies

Hansson (1993, 2011a, 2012a, 2012b) illustrates that modern risk studies began in the 1960s and 1970s with much focus on the risks of chemicals and nuclear power. While these studies occurred in a variety of disciplines such as statistics, epidemiology, economics, psychology, anthropology, and sociology, he argues that the involvement of values in risk issues was rather ignored even in the analysis of acceptable risk, and thus philosophers attempted to introduce the value dependent nature of risk into their early work. In the 1990s, philosophers became more engaged in risk studies, recognizing that philosophy had much to contribute to the (1) clarification of concepts, such as probability, safety, and precautionary principle, (2) identification of fallacies in risk analysis, and (3) value assumptions in risk analysis.

Hansson (2005) points out seven misconceptions about risk:

1. Risk has a single clearly defined meaning despite its use over 300 years and technical definitions that are different from the general use of this term.

2. The level of risk should be determined from the probability and seriousness of the outcomes.

3. Decision should be made by weighing risks and benefits.

4. Decisions should be made by experts.

5. Measures to reduce risk should be determined by the same standard regardless of the matter.

6. Risk assessment should be based on scientific facts.

7. Scientists can find serious risk if it exists.

With some overlap with the issues concerning the risk concept, Hansson (2004a) identifies logical and argumentative fallacies frequently found in the discussion of risk. The sheer size fallacy and the converse sheer size fallacy indicate that a new risk should or should not be accepted merely by comparison to the size of another risk which is already accepted. The fallacy of naturalness is criticized for justifying risks merely due to its naturalness. Several fallacies revolve around scientific evidence, such as (1) something is acceptable if no detectable risk and (2) no action is required if there is no scientific proof. Some fallacies concern expert knowledge, such as (1) scientists should decide on the risk policy, (2) expert consensus is inevitable, and (3) experts should be trusted when they disagree with the public. These criticisms on the risk concept and risk analysis illustrate the complexities to be considered in risk management. Particularly the over-simplified meanings of risk, taken-for-granted approach of weighing risks and benefits, blanket trust on science and/or experts in the determination of public policy, and the lack of oversight on undetectable risk suggest the confusion and pitfalls of risk discussions in the determination of permissible risk. These issues are further explored in his work on risk as it relates to ethics and public policy making.

2.2.2 Risk and ethics

Hansson (1999a, 2011a, 2012a) identifies eight philosophical perspectives on risk in relation to epistemology, decision theory, probability, science, technology, ethics, economics, and politics. Among these perspectives, I will focus on the ethical aspects of risk. Hansson (2007a) identifies three major approaches to risk studies to address ethical issues: (1) clarification of value dependence in risk assessment, (2) analysis of decision making concerning risk from ethical viewpoint, and (3) development of a moral theory to address risk.

2.2.2.1 Value dependence of risk

Hansson (2007a) holds that not only risk management but also risk assessment involves values. For example, he analyzes that non-controversial epistemic values related to science such as avoidance of errors can turn into controversial non-epistemic values through the emphasis on avoidance of type I error, i.e. minimizing false positive. He points out that strict adherence to avoiding type I error may impact on public health policies because such a value will result in *not* alarming any risk until potential health risk is demonstrated as statistically significant. According to Hansson (2007a), controversial non-epistemic values which may permeate into risk assessment include justifying risk through comparison with natural conditions, dismissing the possibility of harm if not detectable, and considering all risks as comparable and calculable in a mathematical manner. Hansson (2007b, 2010a) argues that it is necessary to discern what components – facts and values – are involved in the risk statement so that risk analysis will be meaningful at the individual and collective levels.

2.2.2.2 Decision making concerning risk

In regards to ethically sound decision making in risk management, Hansson (2007a) criticizes the standard risk analysis which relies heavily on risk defined as a product of probability and severity of adverse outcomes. He argues that such an approach does not address important ethical issues of agencies and interpersonal relationships. Hermansson and Hansson (2007) and Hansson (2007a) propose a three party model which identifies agencies in terms of those who (1) are exposed to risk, (2) make decisions regarding risk,

and (3) gain from the risks taken. These agencies may overlap. For example, those who are exposed to risk may also be the decision maker and beneficiary. Upon identification of these agencies in the risk context, he proposes to examine (1) the risks and benefits of the risk-exposed person, (2) fairness of risk benefit distribution across agencies, (3) the possibility of emancipating unfairness by redistribution, (4) the extent of the risk-exposed person's involvement in the decision, (5) the risk-exposed person's access to relevant information, (6) the possibility of the risk-exposed person's not being informed or included in the decision process, and (7) the decision maker's benefit from allowing risk exposure. This model illustrates a highly complex nature of risk assessment and acceptance.

In relation to weighing risks and benefits, Hansson (2004b) criticizes the basic principle which justifies risks if outweighed by benefits because it looks only at the net benefit and also does not consider the alternatives which could have greater benefits. Hansson (2004b) proposes that (1) all alternatives must be clearly identified and accurate in terms of benefits and probabilities and (2) convincing reasons exist to choose an alternative that maximizes expected benefits. He also refers to the collective and individualistic components comprising the net benefit as the analysis may likely differ depending on which component is prioritized. A potential compromise may be to combine both components and to justify risk if risk to the individual is reasonable against the collective benefits. In weighing risks and benefits, whether the emphasis is placed on the individual or society will impact differently on policy making. The choice may differ depending on the areas, such as economics or epidemiology. Hansson (2004b) claims that the choice is often based on conventions rather than deliberate analysis and that we need more discussions to determine an optimal principle for weighing risks and benefits to reach ethically acceptable decisions.

2.2.2.3 Moral theories to address risk issues

Consistent with his discussions of the risk benefit analysis, Hansson (1999a, 2001a, 2003a, 2007c, 2011a) maintains that none of the major moral theories can adequately appraise ethical aspects of risk issues, such as risk taking by self and exposing others to risk. He indicates two issues. First, moral theories address values that guide human

behaviors in idealistically deterministic situations while these theories have deferred decision making in nondeterministic situations to the decision theory that does not address ethical components. Hansson (2010b) claims that moral theories must be generalizable to be applied to nondeterministic situations as the decision theory which presumes idealized cause effect relationships - ignoring multiple conditions related to a particular effect - may not always be applicable to ethical issues. Second, Hansson (2007d) discusses if any theory among a spectrum of moral theories may be suitable for daily moral reasoning. He perceives that on one end of the spectrum is the individualistic camp such as deontology, modern economics, or medical ethics where risks and benefits are weighed largely within a person while on the other end is the collectivist camp such as utilitarianism where the weighing process is done at a collective level. He seeks a possibility of daily moral reasoning in a midpoint of these two extremes.

As another type of candidate for ethical thinking, Hansson (2007c) argues that we should employ everyday intuitions in addressing ethical issues in nondeterministic situations, particularly regarding imposition of risk on others. Specifically, he proposes a framework of hypothetical retrospection which is not a fully-fledged moral theory, but a systematic way of applying moral intuition to specific moral problems. According to hypothetical retrospection, a morally acceptable decision is made through the elimination of options that are less defensible based on the decision maker's values and currently available information. In contrast to major moral theories, hypothetical retrospection seeks compelling moral reasoning to justify exposing others to risk in each particular context. Hansson (2007c) suggests that reciprocity of exchanging risks and benefits for mutual convenience may be most defensible in the justification of exposing others to risk. Whether such reciprocity may be attainable may depend on each specific issue.

Hansson (1999a, 2001a, 2003a, 2007c, 2011a) rightly points out the value dependence of risk assessment, problems of the simplistic weighing of risks and benefits to justify risk, and the lack of relevant moral theories to address ethical issues concerning risk exposure. It may be critically important to clarify values embedded in risk assessment, identify agencies and exhaust alternatives in weighing risks and benefits, and develop a relevant

ethical theory to address risk issues. These perspectives are integrated in his work on risk and policy making.

2.2.3 Risk and public health policy

In relation to policy making concerning risk, Hansson (1999a, 2011a, 2012a) criticizes the (1) emphasis on the probabilistic approach to risk and (2) unpractical and arguably unethical aspects of scientific knowledge in supporting policies for public health.

2.2.3.1 Problems of the probabilistic approach to risk

Hansson (2007c) makes a distinction between risk and uncertainty by defining risk as "knowledge expressed in probability" and uncertainty as "knowledge that cannot be expressed in probability" (p.145). This plays an important role in his discussions, particularly in relation to public policy. Hansson (2002b, 2011b) discusses uncertainty - in contrast to probabilistic approaches – as well as strategies to manage uncertainty. He maintains that ironically, uncertainties grow as knowledge grows, both being products of scientific development. Hansson (1999a, 2011a, 2012a) analyzes that policy making may involve conflicts in considering risk. Pointing to an example of a nuclear power plant, he describes that some people may perceive risks very low while others may perceive risks very high. The former considers the very low probability of accidents while the latter fears catastrophic events and uncertainties.

Doorn and Hansson (2011) indicate that a probability is an estimate and that it involves a significant amount of uncertainty apart from the uncertainty that is not numerically captured. They maintain that the probabilistic approach alone does not address risk in its entirety. They introduce a safety factor approach which has been established in structural engineering to address risk (Doorn & Hansson, 2011). The safety factor approach considers uncertainties through considerations given to the likely sources of failure, such as unprecedented load, worse properties of the material than foreseen, failure mechanisms, and human error (Doorn & Hansson, 2011). They argue that the safety factor approach may complement the probabilistic approach to risk and that employing multiple approaches with some redundancy will improve the quality of safeguarding from harm (Doorn & Hansson, 2011).

2.2.3.2 Scientific knowledge and public health policy

In relation to the nature of scientific knowledge, Hansson (2005, 2007b) challenges the view that risk assessment should be based purely on scientifically validated evidence. He indicates that science has a strict standard which determines whether a piece of information should be included into the body of knowledge (Hansson, 2005, 2007b). He argues that depending on the context, it may be undesirable to go through this process of scrutinizing data particularly when it concerns risk (Hansson, 2005, 2007b). For example, when people want to know potential risks of a particular substance even if the harm is not scientifically demonstrated, another avenue may be required to incorporate scientific hypothesis into the body of knowledge or to discern such hypotheses that should inform practical decisions for policy making (Hansson, 2005, 2007b).

Regarding scientifically undetectable risk, Hansson (1999b) and Hansson and Rudén (2008) propose a risk neutral approach. For example, the neutral risk approach presumes the unknown toxicity of a chemical as the average toxicity of the tested chemicals with similar properties instead of labeling it as no risk. In terms of securing safety, they admit that labeling a substance of unknown risk as toxic may not be sufficient if the substance turns out to be highly toxic (Hansson, 1999b; Hansson & Rudén, 2008). However, they appear not to take the precautionary approach which they recognize as risk aversive and argue that the risk neutral approach is a significant step to address the problematic labeling of "no risk" for unknown risks, which seems prevalent in industries today (Hansson, 1999b; Hansson & Rudén, 2008).

Concerning particular populations which may have a higher sensitivity to harm, Hansson (1998, 2009) argues that application of the safety criteria for the average population to sensitive populations is ethically unjustifiable as the same criteria will not sufficiently protect the sensitive populations. He proposes either to protect the entire population with identical, stricter criteria or to provide population specific information as needed (Hansson, 1998, 2009). To determine the strategy, he indicates that we need to consider numerous factors, such as the degree of difference in susceptibility, costs of abatement, identifiability of sensitive populations, privacy protection, possibility of social exclusion, and previous or potential discrimination of these populations (Hansson, 1998, 2009). In

relation to the fetus, a strategy of removing women from a workplace in the event of pregnancy does not protect the fetus due to the higher susceptibility of the fetus when pregnancy is not yet confirmed (Hansson, 1998, 2009). This is an example that suggests a uniform standard for all populations may be preferable although other factors require consideration as well (Hansson, 1998, 2009).

In determining public policies, such as setting a limit to the level of chemicals for human protection, Hansson and colleagues (Doorn & Hansson, 2011; Hansson, 1998, 2001b, 2001c, 2002a, 2003b, 2008, 2012b; Rudén & Hansson, 2008; Schenk, Ruden, Hansson, & Gilek, 2008) indicate the need to recognize the complexity of the social decision making process. Hansson (2007e) argues that expert assessments should be presented in a way to reflect such complexities and that an interdisciplinary approach involving the decision theory, welfare economics, and moral theory may be desirable.

Hansson's criticism on depending solely on the probabilistic approach to risk may be endorsed as it does not encompass potential harm in its entirety. His arguments on the issues of undetectable risk and protection of particular populations such as pregnant women under a uniform standard may ignite further discussions on how risk should be understood, managed, and flagged to the public. These discussions may have implications in the pregnancy context on constructing rules for addressing risk.

2.3 Lupton, D.

2.3.1 Theorizing risk in social sciences

Lupton (1999a) illustrates different approaches to analyzing risk in social sciences and their epistemological positions. She classifies the approaches to those based on the (1) cognitive science perspective where risks are understood in terms of the probability and hazardous consequences and (2) sociocultural perspective which emphasizes the aspects left out from the cognitive science perspective. The cognitive science perspective which appears in technical and scientific arenas epistemologically takes a realist position. This perspective presumes that the risk pre-exists by itself and can be measured independently from social and cultural contexts. According to the cognitive science perspective, risks are to be identified and managed, and the expert knowledge tends to be trusted more than

lay responses which are perceived as more subjective and less accurate. By contrast, the sociocultural perspective understands risk in the social and cultural contexts where risks are being processed. Lupton (1999a) classifies the sociocultural perspective into three groups, epistemologically ranging from the weak to strong constructionist positions. On the weak constructionist side, risk is still perceived as an objective entity, yet cannot be totally independent from social and cultural dimensions. On the strong constructionist side, risk has no objective entity and is constructed through society, culture, and history. The weak constructionist position relates to critical structuralism while the strong constructionist position relates to post-structuralism and governmentality perspectives. Although Lupton (1999a) illustrates these different approaches to risk in a clearly distinguishable manner and suggests that typical research questions regarding risk differ across these approaches, she holds that these approaches are not only on a continuum but can also be combined in researching risk.

2.3.2 Pregnancy and the risk discourse

Lupton (1999a, 1999b, 1999c, 2012a, 2012b) draws on Foucault's notion of biopolitics (Foucault, 1978; Kelly, 2013) where self government and external government based on expert knowledge control a person's body. Such a notion also relates to neoliberalism as well as the negative aspects of individualism where people are deemed responsible for any undesirable outcomes. Lupton also draws on Beck's risk theory of reflexive modernization (Beck, 1992; Beck, Giddens, & Lash, 1994; Beck & Cronin, 2009) which interprets industrialized modern society as a risk society where people perceive risk as a daily issue at both the public and private levels. In such a society, people are responsible for making right decisions to address risks (Beck, 1992; Beck et al., 1994; Beck & Cronin, 2009).

In addition, Lupton (1999b, 2012a, 2012b) brings in feminist perspectives (Grosz, 1994; Kristeva, 1982; Shildrick, 1997) of the maternal body whose boundary is blurred due to the fetus in contrast to the male body which is self-contained. Lupton (2012b) holds that bodies need to be understood as a complex construct which is built through cultural, social, and biological processes. From such a social constructionist approach to embodiment, she identifies discourses, practices, and technologies revolving around risk

and the pregnant woman (including the fetus) which are significantly different from technical definitions of risk. Based on this approach, Lupton (1999b, 2012a, 2012b) indicates risk discourses that women cannot ignore. She analyzes the contemporary discourses and practices of the maternal and fetal bodies, and provides valuable insights into the pregnancy context where the woman is expected to take care of herself and the fetus (Lupton, 2012b).

In regard to the fetus, Lupton (2012b) argues that the fetus is considered much more valuable than the pregnant woman, which leads to huge attention on fetal risk and much neglect of the woman's subjectivity and needs. Technologies, such as ultrasound and laboratory tests which monitor pregnant women and fetuses have contributed to placing emphasis on women's responsibilities in nurturing the vulnerable fetus (Lupton, 2012b). Lupton (1999b, 2012a, 2012b) perceives that pregnancy is under the surveillance of the medical profession and pregnant women are deemed morally responsible for producing a "perfect baby" (1999b, p.69). She indicates that prenatal screening may emotionally influence pregnant women by motivating them to decrease the risk of any fetal abnormalities (Lupton, 1999b, 2012a, 2012b). Due to the expectations on pregnant women's behavior, they are under a huge amount of pressure to protect the fetus by avoiding fetal risk as much as possible although women are often portrayed as not completely capable of doing so (Lupton, 1999b, 2012a, 2012b).

In addition to the expectations on pregnant women to avoid risks to the fetus through self-regulation, Lupton (1999b, 2012a, 2012b) examines cultural discourses of the maternal body which is perceived as something ambivalent and chaotic. Drawing on feminist philosophers (Grosz, 1994; Kristeva, 1982; Shildrick, 1997) who indicate that the female body is seen as a deviation from the norm (male body) in a negative sense, Lupton (1999b, 2012a, 2012b) argues that the pregnant body is ontologically further disturbing than the non-pregnant body. The pregnant body is problematic as it contains the fetus within itself, which results in an ambiguous boundary between the self and others in contrast to an autonomous body which is clearly separated from other bodies. Thus the pregnant body poses risk to itself due to the ambiguity of not being self-

contained and poses risk to others as it is perceived as a grotesque anomaly in the cultural context (Lupton, 1999b, 2012a, 2012b).

Lupton's work is situated in a social constructionist paradigm and her analysis of pregnancy in the social and cultural contexts may speak much to the woman's experiences of pregnancy. It may also be noteworthy that her work on risk in the context of pregnancy is built on multiple perspectives from scholars who are within the interpretivist stripes although not strictly in the same epistemological paradigm.

2.4 Conclusions

Risk is a relatively new and evolving term with multiple meanings (Yoe, 2012) which must be understood in the context (Malmfors & Rosing, 2002). As a technical term across disciplines, the standard usage of risk refers to the expectation value of an undesirable event which is determined by the probability and severity of outcomes (Hansson, 2011a; Yoe, 2012). In contrast to such a technical description, disciplines such as anthropology, philosophy, and sociology have employed different approaches which consider social, cultural, and historical contexts in understanding and describing risk (Lupton, 1999a).

These perspectives on risk may bring structures and creativity in analyzing risk and perception of risk in relation to decision making during pregnancy. Philosophical perspectives by Hansson as well as sociological and feminist perspectives by Lupton provide valuable lenses to analyze attitudes and behaviors of healthcare providers and researchers in reproduction areas toward risk management as well as the needs and desires of pregnant women regarding risk disclosure and risk avoidance for their and their fetus's well being. The perspectives provided by Hansson and Lupton overlap in relation to their critique of the focus on the objective or technical definition of risk as both scholars discuss the dimensions of risk that are left out from the dominant technical definitions based on the probability and magnitude of harm. Hansson employs philosophical tools to clarify the risk concept and seeks ethically justifiable public policies regarding when and how risk should be flagged to the general public and how risk benefit should be distributed among the related agencies. Inspired by risk regulations and discussions on hazardous chemicals and the nuclear power plant, Hansson aims to

construct a model which can address risk acceptance in an ethically agreeable manner. On the other hand, Lupton theorizes risk in relation to epistemological positions which provide a theoretical framework to risk studies. She also analyzes the implications of the pregnant body as well as sociocultural perspectives on risk in the pregnancy context through the application of risk theories by Beck, Foucault, and several feminists. Her work convincingly illustrates the societal and cultural backgrounds of the woman's views, experiences, and behaviors during pregnancy.

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Chapter 3

3 Implications of the Concept of Minimal Risk in Research on Informed Choice in Clinical Practice*

3.1 Introduction

The concept of minimal risk in research as a "sorting threshold" (Kopelman, 2004, p.351) beneath which exception to informed consent and ethics review processes may occur has been codified for over 30 years in many national research regulations as well as by the Council for International Organizations of Medical Sciences (Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council Canada, & Social Sciences and Humanities Research Council of Canada, 2010; Council for International Organizations of Medical Sciences (CIOMS), 2002; Council of Europe, 2005; Department of Health and Human Services, 2009; Kopelman, 2004; Medical Research Council of South Africa, 2002; Wendler, 2005). In regards to informed consent in research, minimal risk constitutes one of the criteria for allowing modification to all or part of the consent process (Kopelman, 2004; Resnik, 2005) (45 CFR 46.116, 45 CFR 46.117; TCPS2, Articles 3.7; CIOMS Guidelines, Guideline 4). In clinical practice however, there is no concept comparable to minimal risk in research that would provide a low risk threshold for considering waiver of consent or alteration to the consent process. Conversely, acknowledgment of a minimal risk concept in clinical practice could insist that all risks above such a threshold require a formal consent process involving detailed discussion of risk. A minimal risk concept in clinical practice could go beyond discussion of risks of clinical therapies and procedures to include health risks in the patient's lifestyle such as unhealthy diet or environmental chemicals.

A clinician's failure to provide the patient with pertinent information has ethical and potentially legal implications (Appelbaum, Berg, & Lidz, 2001; Rozovsky, 1990). As clinicians are under considerable time constraints in their practice (Moayyeri, Soltani, Moosapour, & Raza, 2011), a minimal risk concept, such as that well described in clinical research could be helpful in terms of assuring appropriate information provision to the patient. Although clinical research and practice have different objectives (Beauchamp,

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2011; Levine, 1988), informed consent is an essential ethical requirement in clinical practice as well as in research (Appelbaum et al., 2001; Beauchamp, 2011). Historically, the Nuremberg Code (1947) articulated research ethics requirements. Over time, these requirements influenced clinical medicine (Manson & O'Neill, 2007). Legal proceedings in the 1950s and 1960s resulted in clinicians' acknowledging the significance of obtaining consent upon disclosure of relevant information, both in clinical practice and research (Beauchamp, 2011). Despite these common backgrounds, informed consent is highly regulated in clinical research compared with clinical practice (Beauchamp, 2011; Levine, 1988; Miller & Wertheimer, 2007). The differences of regulatory requirements between clinical research and clinical practice may evoke concern that patients may not be sufficiently protected compared with research participants (Beauchamp, 2011).

This paper explores the possibility of extending the minimal risk concept in research to information provision in clinical practice. First, we will discuss minimal risk in research regulations regarding informed consent. Second, as there is no minimal risk concept in clinical practice, we will discuss the existing elements and standards of information provision in clinical practice. Finally, we will explore how minimal risk in research may be applied to information provision and informed choice in clinical practice. Acknowledging the existence of a large amount of literature on risk, the risk concept used in this paper will primarily refer to the expectation value of an undesirable event, determined by the probability and severity of outcomes (Yoe, 2012). We will argue that extending the role of minimal risk in research as a low risk threshold to clinical practice may assist clinicians in understanding their obligation for information provision regarding risks in therapies, diagnostic procedures, and lifestyle choices.

3.2 Minimal risk in research

In research regulations regarding human participants such as the United States (US) Code of Federal Regulations (CFR) (45 CFR 46.102(i)) (Department of Health and Human Services, 2009) and the Tri-Council Policy Statement of Canada (TCPS2) (Chapter 2.B) (Canadian Institute of Health Research, Natural Sciences and Engineering Research Council of Canada, & Social Sciences and Humanities Research Council of Canada, 2014), risks may be considered below minimal risk when the likelihood and seriousness

of harm or discomfort are comparable to those of daily life. In research regulations such as the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Guidelines 4 & 9) (CIOMS, 2002) as well as in the US Code of Federal Regulations (CFR) (45 CFR 46.102(i)) (Department of Health and Human Services, 2009), risks are considered within minimal risk when the risks are not above the risks of routine clinical (physical and psychological) examinations. Similar concepts of minimal risk are employed across other national and international regulations with some differences (Kopelman, 2004) such as Guidelines on Ethics for Medical Research (Medical Research Council of South Africa, 2002) or Additional Protocol to the Convention on Human Rights and Biomedicine Concerning Biomedical Research (Council of Europe, 2005).

The risks of daily life or routine clinical examinations as thresholds embedded in the minimal risk in research standard has received much scrutiny, including commentators inquiring whose daily life or routine clinical examinations should be referenced and why risks in daily life or routine clinical examinations should serve the role as a low risk standard (Kopelman, 2004; Nelson, 2007; Wendler, 2005). Although these discussions largely focus on research with children in nontherapeutic situations and do not specifically discuss its relevance as a threshold in relation to informed consent (Freedman, Fuks, & Weijer, 1993; Nelson, 2007; Tauer, 2002; Wendler, 2005), they may provide insight into how a low risk standard could be determined.

Two interpretations of minimal risk are discussed widely in the literature (Kopelman, 2004; Nelson, 2007; Wendler, 2005). The absolute interpretation of minimal risk provides the same standard for everyone by referring to risks in daily life or routine clinical examination of an average healthy person (Kopelman, 2004; Nelson, 2007; Wendler, 2005). The relative interpretation of minimal risk leads to different standards across persons depending on what kind of risk that particular person lives with (Kopelman, 2004; Nelson, 2007; Wendler, 2005). The relative interpretation has been criticized as it may label high risk procedures as minimal risk procedures if the participant lives with high daily risk such as living in an unsafe neighborhood or routinely requiring a high risk clinical intervention (Kopelman, 2000; Kopelman, 2004;

Resnik, 2005). However, those who support the relative interpretation indicate that it can consider cultural and societal norms (Freedman et al., 1993) and that potential abuse may be addressed by research ethics committee (REC) members who have fiduciary duties to participants (Freedman et al., 1993), which is stipulated, for example, in the TCPS2 (Chapter 2-B). Nonetheless, leaving much to REC discretion may potentially lead to exploitation of participants (Kopelman, 2000; Resnik, 2005) particularly when REC members are influenced by the value of research or the prestige of the investigators (Tauer, 2002).

Next, it is a normative choice to determine that risks in daily life or routine clinical examinations are relevant to serve the roles of minimal risk (Freedman et al., 1993; Kopelman, 2004). The daily life standard has been criticized for involving higher risks compared with the routine clinical examination standard (Kopelman, 2004; Nelson, 2007; Wendler, 2005). Daily life involves a variety of harms, ranging from very trivial to highly serious with various possibilities (Kopelman, 2004; Nelson, 2007; Resnik, 2005; Wendler, 2005). By contrast, routine clinical examinations for healthy persons may involve very low physical risks (Kopelman, 2004; Nelson, 2007; Wendler, 2005) although these examinations may involve potentially high psychosocial risk due to personal information collected prior to such examinations if not kept confidential (Kopelman, 2000; Levine, 1988).

Comparing minimal risk standards across research regulations, Kopelman (2004) concludes that the absolute interpretation of the routine clinical examination standard is more justifiable than others as it sufficiently excludes high risks. She articulates that some concern regarding potentially serious psychosocial harm due to inappropriate disclosure of private information may be extremely low due to clinicians' compliance with fiduciary duties (Kopelman, 2004). Kopelman (2004) also proposes that the routine clinical examination standard should rather be understood as risks involved in these examinations per se and not information collected alongside these examinations. Similarly, Resnik (2005) proposes to employ only the routine clinical examination standard. He argues that rather than flexibility, the clarity of the standard and consistency in its application should take priority to secure fairness or justice. On the other hand,

Freedman et al. (1993) argue that the daily life standard is morally justifiable as (1) research risks are substitutive due to people's exposure to daily risks while not participating in research and (2) daily risks are socially acceptable. The first point is criticized as daily risks are usually associated with some purpose or benefits whereas research does not guarantee any benefit to the participant (Wendler, 2005). Indeed the total benefit gained from the same time frame may likely decrease particularly in research without potential therapeutic benefits to participants. The second point is also criticized as what is socially acceptable may not necessarily be clear (Kopelman, 2004) and daily risks are not always socially acceptable but simply unavoidable (Wendler, 2005). Perhaps, a socially acceptable standard is what may be justifiable.

3.3 Informed consent and minimal risk in research

Informed consent, independent ethics review, and special protection to vulnerable populations are among the basic requirements in conducting ethically sound research (Emanuel, Wendler, & Grady, 2008). Among these requirements, informed consent enables a person to protect oneself through the opportunity to receive information and to give or not give consent (Appelbaum et al., 2001; National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979). Although a person has a basic right not to be researched upon without informed consent (Capron, 2008), alteration to the informed consent process in minimal risk research can occur if other criteria are satisfied, such as REC approval, very low likelihood of a particular adverse consequence, and impracticality of obtaining consent (45 CFR 46.116(c); TCPS2, Article 3.7; CIOMS, Commentary on Guideline 4). Further regarding information provision, research regulations stipulate extensive risk disclosure, i.e. reasonably foreseeable risk (TPCS2, Article 3.2, 45CFR46.116(a,2), CIOMS Guideline 5(9)), discomfort (45CFR46.116(a,2), CIOMS Guideline 5(9)), and inconvenience (CIOMS Guideline 5(9)). However, there are debates over the extensiveness of information provision depending on the research procedures and context, which largely revolve around information that is meaningful for the participant's decision making (Drazen, Solomon, & Greene, 2013; Faden, Beauchamp, & Kass, 2014; Macklin & Shepherd, 2013; Truog, Morris, Robinson, & Randolph, 1999; Wendler, 2013).

3.4 Informed consent in clinical practice

Informed consent is an essential part of standard of care in clinical practice (ABIM Foundation. American Board of Internal Medicine, ACP-ASIM Foundation. American College of Physicians-American Society of Internal Medicine, & European Federation of Internal Medicine, 2002). Unlike clinical research, there has been little focus in clinical practice on below what risk level a potential complication of a therapeutic or diagnostic procedure need not be discussed with a patient. However, circumstances seem to exist which allow clinicians to proceed with certain clinical procedures with implicit consent, suggesting conditions for not requiring formal consent or risk disclosure may exist (American Hospital Association, 2006; Appelbaum et al., 2001; Canadian Medical Association, 2004; General Medical Council (United Kingdom), 2008; Manson & O'Neill, 2007; Oliveira, Nesbitt, & Murphy, 2006; Pozgar & Santucci, 2012; White, Rosoff, & LeBlang, 2007; World Medical Association, 2009).

3.4.1 Elements of information provision in clinical practice

As part of information provision regarding clinical therapies and procedures, the elements of disclosure must take into consideration: (1) the patient's diagnosis, (2) the nature of the procedure, (3) alternatives, (4) risks and benefits of the proposed procedure and the alternatives, and (5) prognosis with and without the therapy or procedure (American College of Physicians, 2011; Appelbaum et al., 2001; British Medical Association, 2009; Rozovsky, 1990; White et al., 2007; World Medical Association, 2009). These elements of disclosure commonly appear in professional guidelines for clinicians (American College of Physicians, 2011; British Medical Association, 2009; World Medical Association, 2009) as part of the information which need be communicated to the patient in considering diagnostic or therapeutic procedures.

The law has given much emphasis on the risk component of disclosure and this has considerably influenced clinical practice (Appelbaum et al., 2001). According to court cases, risks that (1) are so obvious, (2) are known to the patient, (3) are very unlikely, or (4) could not be known to the clinician at the time of disclosure can be exempt from disclosure (Rozovsky, 1990). Nevertheless, legal obligations differ across jurisdictions

(Appelbaum et al., 2001) and no clear legal rule exists to specify the level or types of risks that need not be disclosed (Rozovsky, 1990). The criteria developed from the court cases seem to refer to the familiarity of the risk to the patient and the clinical community rather than to the risk level. For a clinician's liability protection, Appelbaum et al. (2001) recommend that clinicians should disclose risks that are (1) relatively minor but likely to occur and (2) extremely unlikely but very serious - even if not deemed an obligation - as there is no guarantee that all agents involved will agree on what risk qualifies for non-disclosure. Their recommendation includes consideration to the frequency and seriousness of risk (Appelbaum et al., 2001), which may be similar to how minimal risk in research is framed but obviously less concrete.

3.4.2 Standards of information provision in clinical practice

Standards of disclosure have evolved largely through legal proceedings determining whether clinician's disclosure was adequate (Appelbaum et al., 2001; Jackson, 2010). Mainly, three standards of disclosure are recognized: the professional, reasonable patient (person), and subjective standards (Appelbaum et al., 2001; Jackson, 2010; Pozgar & Santucci, 2012; Rozovsky, 1990). Relevance of disclosure is determined by what a typical agent in each category would perceive as sufficient disclosure (Appelbaum et al., 2001; Jackson, 2010). The influence of legal cases shifted focus from the traditional professional standard to the reasonable patient standard (Beauchamp, 2011; White et al., 2007). The President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research (1982) indicates that the reasonable patient standard can identify a relevant amount of information to support the patient's decision-making and protect clinicians from the patient's retrospection.

The subjective standard arises from the intention of information provision in professional practice guidelines to be bi-directional and multi-purpose (American College of Physicians, 2011; American Medical Association, 2006; World Medical Association, 2009), with the appreciation that interactive flows of information are required for the clinician's understanding of the patient's values and concerns which are required for a good clinical relationship and meaningful informed choice (Bowman, Spicer, & Iqbal, 2012). Although the subjective standard appears ethically preferable to the reasonable

patient standard as what is considered “reasonable” may differ across persons (Appelbaum et al., 2001; Rozovsky, 1990; White et al., 2007), full reliance on the subjective standard may not be feasible both legally and ethically as it may be too demanding for clinicians and be open to the patient’s retrospection in court (Appelbaum et al., 2001).

3.4.3 Explicit versus implicit consent in clinical practice

Consent can be implied by persons’ action, inaction, words, and silence under particular contexts where they can reasonably be expected to know what they are consenting to (Appelbaum et al., 2001; Pozgar & Santucci, 2012). The concept of “general consent” is a practical device to authorize “routine” procedures which all patients commonly go through upon being seen at healthcare institutions without specific consent (Pozgar & Santucci, 2012). A general consent form is usually signed when the person registers as a patient (American Hospital Association, 2006; Pozgar & Santucci, 2012). The concept of “general consent” assumes the patient’s familiarity with the practice or procedure and its context allows implied consent for that practice or procedure (Appelbaum et al., 2001; Pozgar & Santucci, 2012).

Explicit and specific consent is deemed necessary for invasive procedures and intrusive uses of information and tissues to reduce ambiguities regarding the procedures for which consent was obtained (Manson & O'Neill, 2007). Some documents by healthcare institutions refer to paradigmatic examples to describe when explicit consent is required (American Hospital Association, 2006; Oliveira et al., 2006). For example, a patient brochure by the American Hospital Association (2006) states that a separate consent besides general consent may be required for procedures such as surgery or experimental treatment. The Mayo Clinic Medical Manual (Oliveira et al., 2006) indicates that procedures which are more invasive than a simple intravenous line require explicit consent. By contrast, the World Medical Association (World Medical Association, 2009) provides a simple rule, stipulating that procedures involving risk or more than mild discomfort require informed consent. (General Medical Council (United Kingdom), 2008) states that written consent is preferred when complex information or significant risk is involved, investigational components are included, or the consequence of the

procedure may affect the patient's social or personal life. As described in these documents, risks or potentially serious outcomes of the procedure call for explicit consent (American Hospital Association, 2006; General Medical Council (United Kingdom), 2008; Oliveira et al., 2006; World Medical Association, 2009). However, rules such as more than mild discomfort or significant risk may be rather abstract. Also, good examples could be misleading without a specific rule since examples cannot be exhaustive. Significantly, the Canadian Medical Association (2004) states that procedures for others' benefit require explicit consent, which may share some aspects with the research context where participants are not guaranteed to receive direct benefits.

3.5 Application of minimal risk in research to clinical contexts

Although concepts of information provision and consent in the research context are not always analogous with the clinical context, there are important learnings from the large literature on minimal risk in research that may be useful to clinical practice well beyond the circumstances in which implied consent is widely used (Appelbaum et al., 2001; Manson & O'Neill, 2007; Oliveira et al., 2006; Pozgar & Santucci, 2012; American Hospital Association, 2006; Canadian Medical Association, 2004; General Medical Council (United Kingdom), 2008; World Medical Association, 2009). In this section we explore how the concept of minimal risk in research may be applied to clinical practice, particularly regarding guiding clinicians as to what information should be discussed with the patient, not only regarding particular therapeutics and procedures but health promotion.

Current criteria regarding information provision to the patient generally do not refer to a specific low risk standard. A clinical minimal risk concept comparable to minimal risk in research may assist clinicians in determining the low health risks that need be discussed and those that do not. A clinical minimal risk concept may be particularly important for family physicians who need to address a wide range of health risk factors beyond clinical procedures and therapies. For example, in prescribing acetylsalicylic acid, which side effects in adult men in addition to gastrointestinal problems should a clinician disclose to the patient? In women who are pregnant or planning pregnancy, must a clinician discuss

potential but not yet proven risk of household products such as flame retardants and plasticizers? A clinical minimal risk concept may enhance the patient's informed choice regarding numerous health risks above a minimal risk standard and also save clinician time and resources by providing guidance as to what low risk factors need to be discussed.

In terms of information regarding clinical procedures, the elements of disclosure and the reasonable patient standard may be suitable particularly for procedures which are deemed the standard of care as recommended in professional practice guidelines or resulting from legal cases. For less common clinical procedures, the subjective standard of disclosure may also be used as it enables clinicians to identify necessary information through communication with the patient as well as the patient's medical and social backgrounds. However, considering the time constraints of clinicians' practice (Moayyeri et al., 2011), implementing a clinical minimal risk concept could further facilitate the process of determining risks to be discussed and those that require discussion only if raised by the patient. A clinical minimal risk concept may complement currently employed criteria regarding clinicians' risk disclosure in identifying whether a particular risk should be discussed for the patient's informed decision making.

A clinical minimal risk concept may also have a role in evaluating a variety of risks in the patient's everyday life such as unhealthy diet, substance use, or exposure to environmental chemicals, some of which remain uncertain in terms of their potential harm or are not necessarily addressed by clinical guidelines. Needless to say, it is ideal if all risk factors are evaluated at the level of professional bodies, regulatory agencies, or society in general. Nonetheless, regulatory responses may not necessarily be timely enough for all potential health risks that are emergent while patients may be anxious about numerous risk factors through the media. Regarding some of these risks, it could be in the patient's best interest to be informed about them particularly if they potentially have significant consequences on health, i.e. clearly above minimal risk, and if they are avoidable although uncertainties and the lack of regulatory recommendations should be communicated. Concerning these miscellaneous health risks, a clinical minimal risk concept may be used together with the existing criteria to guide clinicians.

Applying the discussions of absolute versus relative interpretation of minimal risk in research (Freedman et al., 1993; Kopelman, 2000; Kopelman, 2004; Nelson, 2007; Resnik, 2005; Tauer, 2002; Wendler, 2005), the relative interpretation of minimal risk may be problematic if a patient lives with high daily risk due to factors such as environment, occupation, recreation activities, or health status as it suggests that higher risks in clinical care are minimal risks and thus need not be disclosed. For example, if a person with a serious illness requires a high risk procedure on a regular basis, the relative interpretation may determine that a different procedure involving a similar level of risk can be performed without disclosing specific risks of the procedure. Likewise, people with a high risk occupation may not be informed about some risk factors which are communicated to most people. Thus the absolute interpretation which sets common criteria for everyone may work better as the relative interpretation identifies any risks in a particular person's everyday life as minimal risk for that person, which results in their not being informed about those risks or equally high risks.

Regarding moral justification of the daily life standard, the argument that risks are substitutive (Freedman et al., 1993) may suit better with clinical procedures as they usually have benefits to the patient as do activities in daily life. Limiting the scope of discussion to a simplified risk benefit calculation, the relative interpretation of the daily life standard may be morally justifiable in determining what amounts to minimal risk in clinical care. Nevertheless, the risk substitution justification may result in different standards across persons depending on each person's daily life, which is not desirable for guiding clinicians' information provision about particular low risks. Also, the elusiveness of the daily life standard (Kopelman, 2004; Nelson, 2007; Resnik, 2005; Wendler, 2005) should be cautioned against when applied to clinical practice. Moreover, justification based on the claim that daily risks are socially acceptable (Freedman et al., 1993) may fail to appropriately identify risks that should be discussed with the patient. We contend that the absolute interpretation of the daily life standard is a better model for information provision in clinical care, with some modification required to improve clarity and to ensure exclusion of high risks. An example model may be risks in a healthy adult's daily life at home in a safe neighborhood.

Moral justification of the routine clinical examination standard based on its adequate exclusion of high risk (Kopelman, 2004) and fairness due to less ambiguities in risk assessment (Resnik, 2005) pertains to the clinical context. In fact, the routine clinical examination standard, particularly its absolute interpretation overlaps with some of the criteria in current clinical practice as routine clinical examinations for healthy persons usually fall under procedures that do not require risk disclosure or explicit consent. Considering the similarities between the routine clinical examination standard and extant clinical criteria for information provision, the routine clinical examination standard appears justifiable in the clinical context for the reasons indicated in the research context. This standard may be useful as it succinctly clarifies a component of existing criteria for clinicians' risk disclosure.

3.6 Conclusions

Minimal risk in research as a threshold which constitutes a condition for allowing modification to the informed consent process may be extended to help clinicians determine a low risk threshold below which discussion of a particular risk is not required with patients and above which discussion should occur. The absolute interpretation of the daily life standard used in minimal risk in research may be useful with modification in clinical practice. The absolute interpretation of the routine clinical examination standard clarifies a component of extant clinical criteria for risk disclosure. Professional organizations should consider integrating the concept of minimal risk in developing guidelines for facilitating clinicians' information provision to promote the patient's informed choice.

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Chapter 4

4 Implications of applying minimal risk standards in clinical research to information provision in prenatal and preconception care*

4.1 Introduction

Clinicians have the obligation to provide patients with the information to make informed choices regarding medications, procedures and tests (Appelbaum, Berg, & Lidz, 2001; Faden, Beauchamp, & King, 1986; Freedman, 1975; Manson & O'Neill, 2007; Research, 1979), as well as health promotion and harm avoidance (Amiel et al., 1991; McWilliam, 1993). Failure to provide a patient with relevant health information has ethical implications and possibly legal ramifications (Appelbaum et al., 2001; Rozovsky, 1990). However, limitations on the allotted time of clinicians with each patient (Moayyeri, Soltani, Moosapour, & Raza, 2011; Payne, 2003) make it difficult for them to discuss preventative strategies regarding health harms of lower certainty.

For pregnant women and women contemplating pregnancy, provision of relevant information may be more complex because of the increased uncertainties due to the relative lack of health related research with pregnant women (Baylis, 2010; Charo, 1993; Kass, Taylor, & King, 1996; Lyerly et al., 2009; Macklin, 2010; Mattison & Zajicek, 2006; McCullough, Coverdale, & Chervenak, 2005). Some elements such as X-ray to the abdomen that may be low health risk for non-pregnant women may not be low risk for pregnant women (Blackburn, 2013; Creasy, Resnik, & Iams, 2009; Sibai & Frangieh, 1995; Weissgerber & Wolfe, 2006) or the embryo/fetus (Blackburn, 2013; Harding & Bocking, 2001; Mongelli & Gardosi, 2000; Rodeck & Whittle, 2009; Schoenwolf & Larsen, 2009; Wu, Bazer, Cudd, Meininger, & Spencer, 2004). Thus, although promotion of embryonic/fetal "health" through preconception and early pregnancy counseling is an important part of clinical care (Berghella, Buchanan, Pereira, & Baxter, 2010; Chandranipapongse & Koren, 2013; Hood, Parker, & Atrash, 2007; Johnson et al., 2006), the complexity of risk for pregnant women and fetuses and the lack of sufficient research

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make it difficult for clinicians to determine what risks should be discussed.

In clinical research, there is an important threshold concept termed “minimal risk” which constitutes a condition for allowing waiver or modifications to the informed consent process and may have implications on information provision (Kopelman, 2004; Reid & Krahn, 2007; Westra, Wit, Sukhai, & de Beaufort, 2011). We (KW, JN) have recently proposed that the concept of minimal risk in research could be extended to clinical practice; risks which fall below the minimal risk standard would not need to be discussed by clinicians with their patients, while risks above this threshold would need to be discussed (Wada & Nisker, 2015). This clinical minimal risk concept may assist clinicians in determining which low risks need to be discussed with women who are pregnant or planning a pregnancy.

In this study, we will first consider the minimal risk standards in three research ethics regulations: The Council for International Organizations of Medical Sciences (CIOMS) Guidelines (Guideline 4) (CIOMS, 2002) discuss minimal risk as risks involved in a routine physical or psychological examination for which formal consent is usually not required. The United States (US) Code of Federal Regulations (CFR) (45 CFR 46.102(i)) (Department of Health and Human Services, 2009) employs both daily life and a routine clinical examination to describe minimal risk. Canada’s Tri-Council Policy Statement (TCPS2) (Chapter 2-B) (Canadian Institute of Health Research, Natural Sciences and Engineering Research Council of Canada, & Social Sciences and Humanities Research Council of Canada, 2014) discusses minimal risk as risks involved in the research participant’s daily life.

The minimal risk standards differ slightly across regulations in determining minimal risk for pregnant women and fetuses. The minimal risk standard in the CIOMS Guidelines (CIOMS, 2002) may refer to risks in routine clinical examinations for a healthy pregnant woman and healthy fetus, such as ultrasound. Regarding the CFR (Department of Health and Human Services, 2009) which is open to multiple interpretations (Kopelman, 2004; Reid & Krahn, 2007; Wada & Nisker, 2015), Strong (2011) suggested that minimal risk for the pregnant woman should be interpreted as risks common in a healthy adult’s daily

life or routine clinical examination and that minimal risk for the fetus should be interpreted as fetal risks associated with a healthy pregnant woman's daily life or risks in a routine examination of a healthy fetus. Therefore, Strong's interpretation of the routine clinical examination standard (Strong, 2011) in the CFR (Department of Health and Human Services, 2009) is very similar to that in the CIOMS Guidelines (CIOMS, 2002). The minimal risk standard of the TCPS2 is based on risks in a particular person's daily life (Canadian Institute of Health Research et al., 2014), and thus any risk in a particular pregnant woman's daily life will be deemed within minimal risk for that woman. For example, a set of risks resulting from cigarette smoking in pregnancy will be considered above minimal risk for a non-smoking pregnant woman whereas the same set of risks could be considered minimal risk for a pregnant woman who smokes on a daily basis. On the other hand, we feel that Strong's interpretation of the daily life standard (Strong, 2011) in the CFR (Department of Health and Human Services, 2009) based on a healthy adult's daily life and fetal risks associated with a healthy pregnant woman's daily life sets a common standard for all pregnant women and fetuses. As we (KW, JN) have discussed elsewhere (Wada & Nisker, 2015), a common standard for everyone may be more appropriate as a threshold for determining what risk need to be discussed with the patient. In the following case studies, we applied the minimal risk standard of the CIOMS Guidelines based on routine clinical examinations (CIOMS, 2002) and Strong's recommended interpretation of the daily life standard (Strong, 2011) in the CFR (Department of Health and Human Services, 2009).

The purpose of this study is to explore the potential of minimal risk standards in research to the clinical care of pregnant women and women considering pregnancy by applying such standards in research to information provision in prenatal and preconception care. Using case studies, we present three well established risks: cigarette smoking, excess alcohol consumption, and folic acid deficiency, and two less established risks not discussed in routine practice, exposures to phthalate plasticizers (found in cosmetics and food packaging (Meeker, Sathyanarayana, & Swan, 2009; Sharma, Ashley, Hodgson, & Nisker, 2014)) and brominated flame retardants (BFRs) (found in household dust, drapes, upholstery, and carpets) (Eljarrat & Barceló, 2011).

4.2 Case Studies*

4.2.1 Case Study I: Cigarette smoking and pregnancy

In human studies, maternal cigarette smoking is associated with a higher rate of fetal growth restriction (McCowan et al., 2009; Naeye, 1981), spontaneous abortion (Ness et al., 1999; Nielsen et al., 2006), preterm birth (McCowan et al., 2009), and sudden infant death syndrome (Mitchell et al., 1993; Shah, Sullivan, & Carter, 2006) (Table 1). The US National Vital Statistics Report (2003) showed a higher infant mortality rate among the infants of women who smoked during pregnancy compared to the infants of non-smoking women (Mathews & MacDorman, 2006). A review of 83 human studies and 18 animal studies suggested that maternal cigarette smoking was also associated with an increased risk of obesity in offspring (Behl et al., 2013). In terms of a dose response relationship, a Danish study which selected 343 women who experienced spontaneous abortion and 1578 women who gave birth from a cohort of 11,088 women showed 20% increase in the risk of spontaneous abortion per five cigarettes smoked (Nielsen et al., 2006). Also, a study of 1,362,169 infants identified in the Swedish Medical Birth Registry (1983-1996) showed a dose response relationship between maternal smoking and small head circumference for gestational age (smaller than two standard deviations) to be significant ($P<10^{-6}$) (Källén, 2000).

Animal studies (Table 1) demonstrate that maternal exposure to cigarette smoke ingredients causes a significant increase in fetal mortality (Farkas, Hussein, Ariano, Sitar, & Hasan, 2006), carboxyhemoglobin (Farkas et al., 2006)**,** hematocrit (Farkas et al., 2006), and lower birth weight (Farkas et al., 2006). Both active and second hand smoking appears to influence fetal weight and crown-rump length, particularly when the exposure occurs at early stages of pregnancy (Esposito, Horn, Greene, & Pisano, 2008).

Applying the routine clinical examination standard of the CIOMS Guidelines (CIOMS, 2002), maternal cigarette smoking is above minimal risk for the fetus as smoking increases the incidence of fetal death (Mitchell et al., 1993; Ness et al., 1999; Nielsen et al., 2006), infant death (Mathews & MacDorman, 2006; Mitchell et al., 1993; Shah et al., 2006), and cognitive (Batty, Der, & Deary, 2006) and behavioral (Linnet et al., 2003;

*All the tables are at the end of this article (pp.64-73)

Shea & Steiner, 2008) problems as well as nicotine dependency (Buka, Shenassa, & Niaura, 2003; Porath & Fried, 2005) in an offspring's later life (Table 1). Using Strong's interpretation of the daily life standard (Strong, 2011), maternal cigarette smoking is also above minimal risk for the fetus as the risks to the pregnant smoker's fetus is higher than the risks to the fetus of a healthy pregnant woman who does not smoke in her daily life. Given the risks of cigarette smoking to the pregnancy, a discussion of avoiding cigarette smoking with pregnant women and women planning pregnancy is imperative. Further, the existence of professional practice guidelines (Society of Obstetricians and Gynaecologists of Canada, 2011) obligates clinicians to discuss cessation of cigarette smoking or the provision of clinical care would fall below the standard of care.

4.2.2 Case Study II: Alcohol consumption and pregnancy

In humans, excess alcohol consumption during pregnancy is associated with Fetal Alcohol Spectrum Disorder (FASD), which may include prenatal (Patra et al., 2011; Strathon, Howe, & Battaglia, 1996) and postnatal growth restriction (Strathon et al., 1996), facial anomalies (Martínez-Frías, Bermejo, Rodríguez-Pinilla, & Frías, 2004), and neurocognitive developmental problems (Korkman, Kettunen, & Autti-Rämö, 2003; Strathon et al., 1996; Streissguth, 2007). Table 2 presents studies reporting the influences of in utero alcohol exposure on pregnancy complications (Marbury et al., 1983; Patra et al., 2011), fetal growth (Patra et al., 2011), spontaneous abortion (Andersen, Andersen, Olsen, Grønbæk, & Strandberg-Larsen, 2012; Windham, Von Behren, Fenster, Schaefer, & Swan, 1997) and infant mortality (Strandberg-Larsen, Grønboek, Andersen, Andersen, & Olsen, 2009). A case control study investigating 4705 cases and 4329 controls showed a higher incidence of anomalies in the offspring of heavy drinkers (Martínez-Frías et al., 2004) (Table 2). A "safe" amount of alcohol consumption during pregnancy has not been determined (Frost, Gist, & Adriano, 2011; Mengel, Searight, & Cook, 2006). A prospective cohort study of 5628 women who consumed alcohol to various degrees, including binge drinking episodes during the first 15 weeks of gestation, showed no association between alcohol consumption and small for gestational age, reduced birth weight, preeclampsia, or spontaneous preterm birth (McCarthy et al., 2013). A systematic

review of 46 clinical studies did not reveal clear evidence of adverse outcomes for low to moderate alcohol consumption in pregnancy (Henderson, Gray, & Brocklehurst, 2007).

In animal studies (Table 2), the brain weight of rats exposed to alcohol during the period equivalent to the third trimester in humans was lower compared with controls, and was inversely correlated with blood alcohol concentration (r=-0.91) (Bonthius, Goodlett, & West, 1988). Craniofacial anomalies occurred in chick embryos exposed to alcohol at various stages of cranial neural crest cells development and differed depending on the gestational age of exposure (Cartwright & Smith, 1995).

Applying the routine clinical examination standard of the CIOMS Guidelines (CIOMS, 2002), animal studies (Bonthius et al., 1988; Cartwright & Smith, 1995) and a number of human studies indicate that alcohol consumption during pregnancy affects fetal health (Andersen et al., 2012; Marbury et al., 1983; Patra et al., 2011; Windham et al., 1997) and the later life of offspring (Martínez-Frías et al., 2004; Strandberg-Larsen et al., 2009) (Table 2), and is thus above the minimal risk threshold. However, as studies of low to moderate alcohol consumption may not show clear evidence of harm in humans (Henderson et al., 2007) and anomalies in animals (Martínez-Frías et al., 2004; McCarthy et al., 2013), low to moderate alcohol consumption may be considered below minimal risk according to the CIOMS Guidelines (CIOMS, 2002). Applying Strong's interpretation of the daily life standard (Strong, 2011), maternal alcohol consumption is also above minimal risk for the fetus, particularly if the alcohol consumption is "heavy" since a heavy drinker cannot be deemed to be a healthy pregnant woman. Whether low to moderate alcohol consumption is recognized as part of healthy pregnant women's daily life could be controversial, particularly due to the inconclusive evidence of harm. Nevertheless, despite the lack of conclusive evidence of adverse outcomes for low to moderate consumption of alcohol during pregnancy (Henderson et al., 2007), professional guidelines recommend that clinicians discuss alcohol consumption with pregnant women throughout the course of pregnancy in the belief that there is no clear safe limit (Carson et al., 2010). Heavy alcohol consumption during pregnancy is above the minimal risk threshold and failure to discuss alcohol intake during pregnancy is below the standard of clinical care.

4.2.3 Case Study III: Folic acid insufficiency and pregnancy

In human studies, folic acid insufficiency is associated with neural tube defects (NTDs) (Goh & Koren, 2008), including anencephaly, spina bifida, encephalocele, and meningocele, as well as oral clefts (Goh & Koren, 2008) and congenital heart defects (Goh & Koren, 2008) among other malformations (Goh & Koren, 2008). Maternal folic acid supplementation reduces the occurrence of NTDs (Smithells et al., 1980, 1981; N. Wald & Sneddon, 1991) (Table 3). The fortification of grains with folic acid since 1998 has decreased the incidence of NTDs by at least 26% in the US and 50% in Canada (Mills & Signore, 2004). However, depending solely on food intake may not be reliable as storing and cooking can reduce folic acid in food (Talaulikar & Arulkumaran, 2011). Supplementation, in addition to food fortification, reduces the risk of NTDs in a dose dependent manner (0.4 mg/day-36%, 1 mg/day-57%, 5 mg/day-85%) (N. J. Wald, Law, Morris, & Wald, 2001). However, there are debates regarding the optimal dosage and fortification. Excessive supplementation may cause health problems, including an increased incidence of cancer (Choi, Yates, Veysey, Heo, & Lucock, 2014; MacQuarrie, 2014) whereas a study showed that supplementation with 5 mg/day during pregnancy was not associated with an increase in cancer or cardiovascular risk (Taylor et al., 2015). Health Canada (Health Canada, 2009b) and the Public Health Agency of Canada (Public Health Agency of Canada, n.d.) recommend a daily dose of 0.4 mg whereas the Society of Obstetricians and Gynaecologists of Canada (Wilson et al., 2015) recommends 0.4mg for low risk pregnancies, 0.4 to 1 mg for moderate risk pregnancies, and 0.4 to 4 mg for high risk pregnancies, depending on the stage of pregnancy; supplementation is also recommended prior to conception.

While the mechanisms underlying the benefit of folic acid supplementation have been analyzed in animal studies, they are still not well understood (Beaudin et al., 2012; Lee, Lee, Oh, & Chang, 2010) (Table 3). A comparison of folic acid supplementation with non-supplementation in rats suggested that folic acid played a key role in the maintenance of myelin in the central nervous system (Lee et al., 2010). A study conducted with a mouse model with a higher incidence of NTDs indicated that

exencephaly occurred under folic acid deficiency alone and not in combination with choline deficiency (Beaudin et al., 2012).

As insufficiency of folic acid is associated with an increased occurrence of NTDs (Goh & Koren, 2008) and folic acid supplementation studies demonstrate a lower occurrence rate of NTDs (Smithells et al., 1980, 1981; Wald & Sneddon, 1991) (Table 3), application of the routine clinical examination standard of the CIOMS Guidelines (CIOMS, 2002) or Strong's interpretation of the daily life standard (Strong, 2011) suggest that insufficient folic acid intake is above minimal risk in pregnancy and thus clinicians should inform women about the risks of folic acid insufficiency as part of clinical care.

In Canada, not discussing the risk of folic acid insufficiency in prenatal care or with women planning pregnancy falls below the standard of clinical care, particularly as there are recommendations from Health Canada (Health Canada, 2009b) and the Public Health Agency of Canada (Public Health Agency of Canada, n.d.) as well as a professional practice guideline (Wilson et al., 2015) on folic acid supplementation. Folic acid insufficiency is above minimal risk and must be discussed with pregnant women and women planning pregnancy.

4.2.4 Case Study IV: Phthalates and pregnancy

Phthalate plasticizers are widely used in food containers and personal care products, such as lotions and cosmetics (Meeker et al., 2009), and have received wide media attention as household chemicals dangerous to women's health (Canadian Broadcasting Company, 2011; Martin, 2010). In a Canadian empirical study in 2014, Sharma and coauthors (Sharma et al., 2014) reported that pregnant women are concerned about risks of phthalate plasticizer exposure during pregnancy and want to know more about them, particularly from their physicians. Some of the phthalates, such as di(2-ethylhexyl) phthalate (DEHP) and dibutyl phthalate (DBP), are regulated by the Canadian government not to exceed 1000 mg/kg in vinyl used for products that are intended for care of children under four years old and for play or learning by children under 14 (Government of Canada, 2010). However, no regulatory requirements exist for pregnant women or fetuses.

In human studies, occupational exposure in the production of phthalate plasticizers has been associated with a higher rate of female infertility and miscarriage (Aldyreva, Klimova, Iziumova, & Timofeevskaia, 1975; Latini, Scoditti, Verrotti, De Felice, & Massaro, 2008). Prenatal phthalate exposure may influence neurological and behavioral development, particularly in girls (Engel et al., 2009; Whyatt et al., 2012). A review of five studies from Asia, Europe, and the US suggests that childhood exposure to phthalate plasticizers may increase asthma and eczema (Braun, Sathyanarayana, & Hauser, 2013). Maternal phthalate exposure (Table 4) has been associated with changes in the male reproductive system, such as decreased anogenital distance, cryptorchidism, and hypospadias (Swan, 2008). Phthalate concentrations in cord blood may correlate with shorter gestational age at birth (Latini et al., 2003). A relationship between phthalate exposure and endometriosis has also been reported (Cobellis et al., 2003).

Animal studies indicate that maternal phthalate exposure affects development of the male reproductive system, with outcomes such as cryptorchidism (Fisher, Macpherson, Marchetti, & Sharpe, 2003), small testis (Fisher et al., 2003), and reduced anogenital distance (H. M. Scott et al., 2008) (Table 4). In utero exposure to phthalates reduces the mRNA expression of steroidogenic genes involved in testosterone synthesis (Parks et al., 2000) and the expression of insulin-like hormone 3 (Insl-3), with effects on the descent of the testis (V. S. Wilson et al., 2004).

The risk of exposure to phthalates (Table 4) may be above the minimal risk threshold set by the routine clinical examination standard (CIOMS, 2002). However, the evidence in both human and animal studies may not be sufficient to determine whether maternal phthalate exposure is above minimal risk based on the routine clinical examination standards. Using Strong's interpretation of the daily life standard in pregnancy (Strong, 2011), exposure to phthalates is likely to be part of a healthy (or any) pregnant woman's daily life, and thus phthalates fall below the minimal risk threshold.

4.2.5 Case Study V: Brominated flame retardants (BFRs) and pregnancy

BFRs are extensively used in carpets, draperies, upholstery, children's pajamas, computers, TVs, and other household items to reduce the speed of fire propagation (Aleksa, Carnevale, Goodyer, & Koren, 2012; Eljarrat & Barceló, 2011; Lorber, 2008; Vorkamp, Thomsen, Frederiksen, Pedersen, & Knudsen, 2011). BFRs are persistent, bio-accumulative, and have become widespread in the environment (Staskal Wikoff & Birnbaum, 2011). The commercial formulations of several congeners of polybrominated diphenyl ether (PBDE) BFRs were prohibited by the European Union in 2004 as well as in California and Hawaii in 2006 (Environment Canada, 2013). In Canada, PBDE BFRs were identified as "toxic substances" under the Canada Environment Protection Act (1999) in 2006, followed by the prohibition of manufacturing PBDE BFRs and using, selling, or importing several PBDE congeners in 2008 (Environment Canada, 2013). The Health Canada website (accessed October 5, 2015) lists human breast milk among the sources for PBDE exposure although it indicates that the PBDE level in Canadian food does not cause health risk (Health Canada, 2009a). Recently, BFRs have gained significant media attention for their potential harm on human health (Canadian Broadcasting Company, 2012; Gross, 2013).

In humans (Table 5), accidental prenatal exposure to large quantities of the polybrominated biphenyl (PBB) BFRs was associated with high maternal serum concentrations of PBBs and an increase in the incidence of genitourinary conditions, such as cryptorchidism in male offspring (Small et al., 2009; Small, Murray, Terrell, & Marcus, 2011), and spontaneous abortion (Small et al., 2009, 2011). An association between the PBDE BFR concentrations in breast milk with cryptorchidism has also been reported (Main et al., 2007; Main, Skakkebaek, Virtanen, & Toppari, 2010). As the PBDE concentrations in umbilical cord serum are higher than in maternal serum, it is likely that fetal exposure to PBDEs is higher than maternal exposure (Chen et al., 2013).

Animal studies (Table 5) indicate adverse outcomes of exposure to BFRs, such as endocrine disruption (Ding et al., 2007; Fowles, Fairbrother, Baecher-Steppan, & Kerkvliet, 1994; Jagnytsch, Opitz, Lutz, & Kloas, 2006; Kitamura et al., 2005), including

effects on thyroxine production (Kim et al., 2009; Kuriyama, Talsness, Grote, & Chahoud, 2005) and sex steroid levels (Kim et al., 2009), as well as hepatotoxicity (Germer et al., 2006; Ronisz, Farmen Finne, Karlsson, & Förlin, 2004; Szymańska, Piotrowski, & Frydrych, 2000) and neurotoxicity (Branchi, Alleva, & Costa, 2002; Timme-Laragy, Levin, & Di Giulio, 2006). Also, an influence of BFR exposure on the fertility of male offspring is suggested by the decrease in sperm counts and the relative weights of the testes and epididymides (Kuriyama et al., 2005).

Although human studies and animal studies suggest potential fetal risks of BFR exposures (Table 5), we question whether the research to date is sufficient to suggest that exposure to BFRs is above the minimal risk based on the routine clinical examination standard by the CIOMS Guidelines (CIOMS, 2002). Thus, physicians may not be required to discuss the risks of BFR exposure with pregnant women and women contemplating pregnancy. Further, according to Strong's interpretation of the daily life standard (Strong, 2011), the ubiquity of BFRs in the environment (Staskal Wikoff & Birnbaum, 2011) means a healthy (or indeed any) pregnant woman is likely be exposed to BFRs on a daily basis and thus BFRs are below the minimal risk threshold.

4.3 Discussion

The routine clinical examination standard for minimal risk in the CIOMS Guidelines (CIOMS, 2002) places maternal cigarette smoking, excess alcohol consumption, and folic acid insufficiency above the minimal risk threshold. It is more difficult to determine whether phthalates or BFRs are above minimal risk on the basis of the evidence available from human and animal studies. Using Strong's interpretation (Strong, 2011) of the daily life standard in the CFR (Department of Health and Human Services, 2009), maternal cigarette smoking, excess alcohol consumption, and folic acid insufficiency are above the minimal risk threshold, whereas phthalates and BFRs could be below the minimal risk standard due to their presence in any healthy pregnant women's daily life. A minimal risk standard based on the risks in routine clinical examinations of a healthy adult and healthy fetus (CIOMS, 2002; Strong, 2011) and a minimal risk standard based on risks in a healthy adult's daily life (Strong, 2011) or fetal risk associated with a healthy pregnant woman's daily life (Strong, 2011) could be useful in assisting clinicians in determining

what risks should be discussed in preconception or prenatal care. However, it appears that minimal risk standards based on daily life may have limitations under certain circumstances in clinical care. Strong's recommended interpretation (Strong, 2011) of the daily life standard in the CFR (Department of Health and Human Services, 2009) determines any ubiquitous (and unavoidable) risks in everyone's daily life as minimal risk regardless of its potential harm. Also, a minimal risk standard based on a particular person's daily life, as in the Canadian TCPS2 (Canadian Institute of Health Research et al., 2014), points to different minimal risk standards depending on the person's daily risks. Although the daily life standard may work as a threshold concept in the research context, it may not function for determining risks to be discussed with a patient in clinical care depending on the ubiquity of risk or the daily risks of each person.

A minimal risk standard could be advantageous in addressing emerging risk factors that have not yet been addressed by professional bodies or regulatory authorities (Wada & Nisker, 2015). Risk factors not addressed at the regulatory level are likely those with a low level of risk, remaining uncertain in human and animal research. However these uncertain risks may be worrisome to pregnant women and women contemplating pregnancy because of media (Canadian Broadcasting Company, 2011; Martin, 2010; Wenner Moyer, 2011) and internet sources as in the case with phthalates (Sharma et al., 2014) . When a woman's concerns regarding potentially harmful products are brought to her clinician, discussion should occur regardless of the risk level. However, clinicians may not be comfortable discussing a wide array of potential health risk factors outside clinical procedures in the absence of national or international professional practice guidelines, or continuing professional development programmes which are evidence informed (Bradley, 2002; Sathyanarayana, Focareta, Dailey, & Buchanan, 2012; Thorley, Turner, Hussey, & Agius, 2009). A minimal risk standard may provide some guidance for clinicians (Wada & Nisker, 2015) when asked by patients for information by comparing these risks to risks in routine clinical examinations for a healthy pregnant women and fetus or fetal risks associated with a healthy pregnant woman's daily life. Standard sources which pregnant women frequently access outside of their clinicians' offices, such as the MotherRisk website (Motherisk, 2015), could also use the minimal risk standard in considering whether information on gestational exposure of a particular

chemical should be included in their website where references for occupational and environmental exposures are listed.

One might also consider if particular risks are avoidable as a factor as to whether clinicians should discuss the risk with their patients; it may seem more important to discuss risks that are avoidable rather than those that are not. If exposure to common chemicals can be reduced substantially by individual choice, such as for phthalates by avoiding cosmetics and plastic containers for food or water, phthalate avoidance may be worthy of discussion as pregnant women would likely make efforts to reduce their exposure, as they do for alcohol and cigarettes. If so, informing pregnant women about potential harm and methods to reduce exposure to such chemicals could be deemed appropriate care although insufficient evidence exists as to whether phthalates are above the minimal risk threshold and whether exposure reduction leads to harm reduction.

Concerning BFRs, avoidance is more difficult due to their wide spread existence (Darnerud, 2003) and their bio-accumulation (Frederiksen, Vorkamp, Thomsen, & Knudsen, 2009). Pregnant women and women contemplating pregnancy are exposed to BFRs through food, air, and dust in the home, workplace and outdoors (Frederiksen et al., 2009). BFRs are inhaled (Jones-Otazo et al., 2005) or absorbed through dermal contact with dust (Lorber, 2008), with dermal absorption from house dust constituting a large portion of exposure (Lorber, 2008). Another concern is the long half-life of BFRs (Geyer et al., 2004). In contrast to phthalates, such as di(2-ethylhexyl)phthalate (DEHP) which has a short urinary elimination half-life of approximately 12 hours (Schmid & Schlatter, 1985), BFRS are persistent in humans, with estimated half-lives of, for example, 64 days for hexabromocyclododecane (HBCDD) and 1214 days for hexabromodiphenyl ether (BDE-154) (Geyer et al., 2004). Given their propensity to bio-accumulate, it may be difficult to reduce exposure once women consider becoming pregnant. Another factor that cannot be underestimated is the personal cost of risk avoidance. Buying furniture, drapes, carpets, and mattresses containing less toxic flame retardants may be more burdensome than replacing plastic containers with glass containers or avoiding personal care products containing phthalates. Thus, reducing BFR exposure may be challenging for women who are financially less secure. In the absence of regulatory restrictions, the

feasibility of reducing exposure to potentially harmful chemicals depends on the cost and effectiveness of behavioral changes at an individual level.

Delays in the development of governmental or professional regulatory policies that may have a major impact on information provision in clinical practice could be due to the uncertainty of evidence for the effects of phthalates and BFRs in human studies rather than the ubiquitous nature of these chemicals. However, media portrayals of the effects of both phthalates and BFRs claim certainty in harms of exposure (Canadian Broadcasting Company, 2011, 2012; Gross, 2013; Martin, 2010; Wenner Moyer, 2011), which may be worrisome to many pregnant women and women contemplating pregnancy. Some of them may want to discuss the seemingly certain risks of phthalates and BFRs with their clinicians.

Scott (2012) has argued that buying one's way around potentially harmful chemicals is an option available only to the wealthy and thus regulatory changes should be taken rather than depending on the individual efforts of pregnant women. Health policies that depend on an individual's behavioural changes increase inequality among socioeconomic groups (Lorenc, Petticrew, Welch, & Tugwell, 2013). Further, poverty is an important social determinant of embryo health (Mykitiuk & Nisker, 2010), which may have implications on discussions of the risks associated with exposure to BFRs and phthalates.

In 2013, the Royal College of Obstetricians and Gynaecologists in the United Kingdom issued a Scientific Impact Paper, "Chemical exposures during pregnancy: Dealing with potential, but unproven, risks to child health" (Bellingham & Sharpe, 2013). This paper addressed maternal exposure to environmental chemicals and provided advice for clinicians in communicating with pregnant women to reduce the exposure to environmental chemicals in general through their life styles, such as choosing fresh food rather than processed food, reducing the use of plastic containers and personal care products, and minimizing exposure to newly produced fabrics and cars during pregnancy. Walsh (2013) criticized this document from the viewpoints of toxicology and public health in that following these recommendations to reduce exposures can be costly to women.

In 2013, a Committee Opinion by the American College of Obstetricians and Gynecologists (ACOG) entitled, “Exposure to toxic environmental agents” (American College of Obstetricians and Gynecologists, 2013) pointed out the limitation of individual efforts in avoiding environmental chemicals and emphasized the importance of policy level interventions. Commenting on the ACOG opinion, Rubenstein (2013) indicated the challenges of implementing stricter regulations for environmental chemicals due to the disagreement on the quality and sufficiency of evidence across stakeholders, including the issue of who owes the burden of proof (Rubenstein, 2013). However, in 2015 the International Federation of Gynecology and Obstetrics called for policy level interventions to prevent exposure to environmental chemicals (Di Renzo et al., 2015).

Regarding BFRs, Hansson (2008) claimed that the scientific issue of clarifying the adverse outcomes of BFRs and whether human exposure to BFRs should be avoided were two separate questions, although the former informs the latter. Hansson (2008) proposed that a certain amount of data – not necessarily satisfying the criteria of scientific knowledge – should guide policy making if the seriousness of the outcome is socially acknowledged. Nonetheless, it remains controversial as to which uncertain risks should be addressed by regulatory agencies and professional bodies, and why disclosure of uncertain risk should become part of the standard of care.

4.4 Conclusion

The minimal risk concept in research regulations as applied to clinical practice may be useful to help clinicians and their professional organizations determine what risks need be discussed in preconception and prenatal care. When applying the minimal risk standards in research to prenatal and preconception care, we have found that cigarette smoking, excess alcohol intake, and folic acid insufficiency are above the minimal risk threshold for information provision and clinical discussion, whereas BFRs and phthalates may currently fall below such a threshold due to insufficient evidence of harm reduction. However, media and internet sources make it difficult for clinical discussions to be avoided.

Table 1 Human and animal studies regarding cigarette smoking in pregnancy

Adverse outcomes	Smoker	Non-Smoker	Significance	Reference
Human studies				
Spontaneous abortion	OR 1.8		95% CI=1.3,2.6 (compared with non-smokers)	Ness et al 1999
	OR 1.20		95% CI=1.04, 1,39 (20% increase in risk for additional 5 cigarettes/day)	Nielsen et al 2006
Sudden infant death syndrome (SIDS)	OR 4.09		95% CI=3.28, 5.21	Mitchel et al 1993
Infant mortality	1.1%	0.66%	71% higher	Mathews et al 2006
Preterm birth	10%	4%	p=0.006	McCowan et al 2009
IUGR	17%	10%	p=0.03	
Birth weight	2898 g	3341g (stopped smoking)	p<0.01	Naeye 1981
Head circumference	33.8 cm	34.4 cm (stopped smoking)	p<0.001	Naeye 1981
Behavioral disorders & cognitive impairment			increased	Batty et al 2006, Buka et al 2003, Linnet et al 2003, Porath & Fried 2005, Shea & Steiner 2008

Animal studies		
Higher maternal & fetal mortality		Farkas 2006
Higher carboxyhemoglobin & hematocrit	p<0.001	
Lower birth weight	p<0.001	
Lower fetal weight	p=0.04	
Lower crown-rump length	p<0.05	Esposito 2008
	p<0.05	

OR: Odds ratio
GDS: gestational days

Table 2 Human and animal studies of excess alcohol consumption

Adverse outcomes	Alcohol consumption	Significance	Reference
Human studies			
Placental abruption	>14 drinks/wk	OR=2.8; 95% CI:1.1-7.8	Marbury et al 1983
Spontaneous abortion (1^{st} trimester)	>3 drinks/wk	OR=2.3; 95% CI: 1.1-4.5	Windham et al 1997
	≥4 drinks/wk	OR=2.82; 95% CI: 2.27-3.49	Andersen et al 2012
Preterm birth	>18g/day		Patra et al 2011 (meta-analysis)
Low birth weight	>10g/day		
Infant mortality (among term birth)	≥4 drinks/wk (adjusted hazard ratio=2.71)	95% CI: 35-5.45	Strandberg-Larsen et al 2009
	3 binge episodes (adjusted hazard ratio=1.97)	CI: 1.10–3.54	
CNS problems	Heavy drinking (>92g/day)	p<0.00001	Martinez-Frias 2004
Eye anomalies		p=0.00009	
Microcephaly		p=0.004	
Facial anomaly		p=0.000000	

Oral clefts		p=0.036	
Congenital heart defects		p=0.002	
Animal studies			
Lower brain weight (mg)	Ethanol 6.6g/kg/day (rat) Control 7612.3+-8.4mg		Bonthius 1998
	2.5% ethanol 7485.0+-11.1	Not significant	
	7.5% ethanol 6146.2+-7.8	p<0.01	
	15% ethanol 5333.5+-11.5	p<0.01	
Effects on neural crest cell development (craniofacial anomalies)	Ethanol 0.43mmol/egg at different stages: Gastrulation stage: 65% Neurulation stage: 61%	p<0.05 (against control and treatment at later stages)	Cartwright 1995

OR: Odds ratio

Table 3 Incidence of neural tube defects and folic acid (FA) supplementation

Adverse outcomes	FA Suppl	No FA Suppl	Significance	Reference
Human studies				
Neural tube defects	0.6% Multivitamin including FA 0.36mg	5%	p<0.01	Smithells et al 1980
Neural tube defects	0.7% Multivitamin including FA 0.36mg	4.7%	p<0.0003	Smithells et al 1981
Neural tube defects	1.0% FA 4mg	3.5%	Trial stopped earlier than planned. FA: 72% protective effect (RR 0.28, 95% CI 0.12-0.71) Other vitamins: no effect (RR 0.80, 95% CI 0.32-1.72	Wald & Sneddon, Medical Research Council (UK) 1991 4 arm study: -Multivitamin and FA 4mg -FA4mg -Multivitamin -no suppl
Animal Studies				
Cerebrocortical expression of MBP	Rat with FA 8 mg/kg diet (2weeks before mating till the end of	Rat without FA supplementation -No increase on Day 20 of pregnancy	p<0.05	Lee 2010

	lactation) -87% higher on Day 20 of pregnancy compared with before pregnancy	compared with before pregnancy		
Exencephaly	-No NTDs in embryos of dams on choline deficiency diet (n=100) or control diet (n=152)	-Observed only in 18 (33%) of Shmt1-null embryos of mouse dams on FA deficiency diet	p=0.004	Beaudin 2012

FA: Folic acid
RR: relative risk
CI: confidence interval
MBP: myelin basic protein
Shmt1: one of the three enzymes in the folic acid metabolic pathway

Table 4 Human and animal studies of phthalate exposures

Adverse outcomes	Phthalate levels or treatment	Significance	Reference
Human studies			
Decreased anogenital distance	Analysis based on 5 metabolites (urine) converted to a scoring system	p<0.00001	Swan et al 2008
Incomplete testicular descent	Coefficient of $\log_{10}$ of MEHP(maternal urine): -1.258	p=0.048	Swan et al 2008
Premature birth	Cord blood: MEHP 0.52mcg/ml	p=0.033	Latini et al 2003
Neurological (orientation) score low in female offspring (neonate)	Linear decline with increase in high molecular weight phthalates in maternal urine	p=0.02	Engel et al 2009
Mental development score low in female offspring (3 yo)	Correlates to increase in $\log_e$ mono-n-butylphthalate	Estimated adjusted beta-coefficient -2.67 (95% CI:-4.70,-0.65)	Whyatt et al 2012
Animal studies			
Cryptorchidism	DBP 500mg/kg/day (GD 13-21)	p<0.001	Fisher et al 2003
Small testes	DBP 500mg/kg/day (GD 13-21)	p<0.001	Fisher et al 2003
Reduced anogenital distance	DBP 500m/kg/day (GD 15.5-57.5)	p<0.001	Scott et al 2008

Testicular testosterone low	DBP 500mg/kg/day (GD 13-21)	$p<0.05$	Fisher et al 2003
Plasma testosterone low	DBP 500mg/kg/day (GD 13-21)	$p<0.01$	Fisher et al 2003
Testis weight correlated with anogenital distance	DBP 500m/kg/day (GD 15.5-57.5)	$p<0.001$	Scott et al 2008

DEHP: di-(2-ethylhexyl)phthalate (most commonly used plasticizer)
MEHP: mono-(2-ethyl-hexyl)phthalate (metabolite of DEHP)
DBP: dibutyl phthalate
GD: gestational day

Table 5 Human and animal studies of exposure to brominated flame retardants (BFRs)

Adverse outcomes	BFR levels or treatment	Significance	Reference
Human studies			
Polybrominated biphenyls			
GU conditions in male offspring (33/464) 3 fold increase in hernia & hydrocele	Maternal serum >5ppb vs <1ppb	p=0.04	Small et al 2009
higher spontaneous abortion rate with higher serum PBB	<1ppb vs 1-3.16ppb	OR=2.75; p=0.04	Small et al 2011
	<1ppb vs >3.17ppb	OR=4.08; p=0.04	
Polybrominated diphenyl ethers			
Breast milk PBDE higher in infants with cryptorchidism	4.16 vs 3.16ng/g fat	p<0.007	Main et al 2007
PBDE higher in cord serum than maternal serum (higher exposure to fetus suspected)	OH-PBDE 49.76 vs 32.84 ng/g fat	p=0.0011	Chen et al 2013
	PBDE: 45.51 vs 32.07ng/g fat	p=0.0028	
Animal studies			
Sperm & spermatid count↓ Testis & epididymidis/BW↓ Serum LH → Serum testosterone →	PBDE 300mcg/kg (GD 6)	p<0.05	Kuriyama et al 2005
Thyroid weight ↑	BDE	p<0.05	Kim et al

Adrenal weight ↓	320mg/kg/day	2009
	(GD 6-18)	
Estradiol (female) ↓	BDE 5mg/kg/day	
Testosterone →	(GD 6-18)	

BW: body weight
GU: genitourinary
LH: lutenizing hormone
OH-: hydroxylated
OR: odds ratio
PBB: polybrominated biphenyl
PBDE: polybrominated diphenyl ether
GD: gestational day

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Chapter 5

5 Critical Review of Research Ethics Regulations on Clinical Research with Pregnant Women

5.1 Introduction

Research ethics guidelines and regulations play pivotal roles in guiding investigators, health related industries, legal advisors, and research ethics committees (Allesee & Gallagher, 2011). Not only do these guidelines stipulate ethical conduct of research but may also address liability concern of investigators and industries (Allesee & Gallagher, 2011; Charo, 1993; Lyerly, Little, & Faden, 2008a). Among these guidelines, the United States (US) Code of Federal Regulations (CFR) (Department of Health and Human Services, 2009) has been discussed in relation to the underrepresentation of pregnant women in clinical research (Baylis & Kaposky, 2010; Lyerly, Little, & Faden, 2008b; Uhl, Miller, & Kennedy, 2004). Some authors criticize that the CFR has an exclusionary framework in addressing pregnancy and argue for an inclusionary framework where investigators are required to justify the exclusion of pregnant women rather than their inclusion (Baylis & Kaposky, 2010; Lyerly, Little et al., 2008b). By contrast, others point to the transition of the US policies from the exclusion to inclusion of women in the 1990s (Goodrum, Hankins, Jermain, & Chanaud, 2003) and emphasize that the CFR does not mandate automatic exclusion of pregnant women (Allesee & Gallagher, 2011; Uhl et al., 2004). These opposing views on the CFR have not been completely resolved. Moreover, other national and international regulations regarding this issue have been little discussed.

This chapter examines four national and two international research ethics regulations on clinical research with pregnant women (Table 6): the US Code of Federal Regulations (CFR) (Department of Health and Human Services, 2009), Tri-Council Policy Statement of Canada (TCPS2) (Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council Canada, & Social Sciences and Humanities Research Council of Canada, 2014), National Statement of Ethical Conduct in Human Research of Australia (Australian Regulation) (National Health and Medical Research Council, Australian Research Council, & Australian Vice-Chancellor's Committee, 2007 (updated

2014)), Guidelines on Ethics for Medical Research of South Africa (South African Guideline) (Medical Research Council of South Africa, 2002), Additional Protocol to the Convention on Human Rights and Biomedicine concerning Biomedical Research of the Council of Europe (European Guideline) (Council of Europe, 2005), and International Ethical Guidelines for Biomedical Research Involving Human Subjects (CIOMS Guideline) (Council for International Organizations of Medical Sciences (CIOMS), 2002). This chapter analyzes how these guidelines stipulate pregnant women's eligibility as research participants and conditions under which they may be included in research. Some of these national and international research ethics guidelines involve factors that could lead to overprotection of pregnant women and fetuses.

Table 6 National and international ethics regulations on human research

National regulations	United States	United States Code of Federal Regulations (CFR)
	Canada	Tri-Council Policy Statement of Canada (2nd ed) (TCPS2)
	Australia	National Statement of Ethical Conduct in Human Research of Australia
	South Africa	Guidelines on Ethics for Medical Research of South Africa
International regulations	CIOMS*	International Ethical Guidelines for Biomedical Research Involving Human Subjects
	Council of Europe	Additional Protocol to the Convention on Human Rights and Biomedicine concerning Biomedical Research of the Council of Europe

*CIOMS: Council for International Organizations of Medical Science

5.2 Vulnerability and eligibility of pregnant women as research participants

Some of these regulations noted in 5.1 depict pregnant women as vulnerable (Table 7). The CFR of the US employs a population-based approach to vulnerability which identifies pregnant women together with fetuses and neonates as a vulnerable population (45CFR46 Subpart B) alongside prisoners (45CFR46 Subpart C) and children (45CFR46 Subpart D). These populations are addressed separately from the general population

(45CFR46 Subpart A) in the framework of the CFR. Other examples of vulnerable persons described as "vulnerable to coercion or undue influence" in the CFR are "mentally disabled persons, or economically or educationally disadvantaged persons" (45CFR46.111(a)(3), (b)). The CFR states that vulnerable populations qualify for special attention of the research ethics committee (45CFR46.111(a)(3)) and that research involving vulnerable populations must include additional safeguards to protect them (45CFR46.111(b)). The Australian Regulation (Section 4) also includes pregnant women among special populations, such as children, people in dependent relationships, or persons with cognitive impairment, i.e. those who require specific ethical considerations although the term "vulnerable" is not used. The Australian Regulation stipulates that research with pregnant women requires full board ethics review regardless of the nature of research (5.1.6), careful ethics review on a case by case basis (4.1.3), and women's access to counseling for decision making when necessary (4.1.4). The European Guideline has a slightly different tone, identifying pregnant women as persons in a "special situation" (Article 18). Although this guideline does not explicitly endorse pregnant women's eligibility as participants, they are clearly distinguished from persons who lack capacity to provide consent (Article 15).

Other regulations and guidelines do not necessarily identify pregnant women as a vulnerable population and thus are more inclusive in considering pregnant women's eligibility as research participants. In the CIOMS Guideline, pregnant women are presumed eligible to participate in research as long as they are well informed about risks and benefits to themselves, their fetus, future children, and fertility (Guideline 17). Pregnant women are not included in the list of vulnerable groups (Guideline 13) but are considered potentially vulnerable only under coercive pressure in cultures and communities where fetuses are more valued than women (Commentary on Guideline 17). The CIOMS Guideline also states that childbearing potential should not be an exclusion criterion although contraceptives should be used if harm to pregnancy is known (Guideline 16). Similarly, the South African Guideline clarifies that pregnant women are competent in decision making except for limited occasions (5.3.1.1.3) and their exclusion from research requires justification based on scientific evidence of fetal risk (7.1.3.1). The Canadian TCPS2 also stipulates that women should not be automatically excluded

from research at any stages of reproduction (Article 4.3). While employing the notion of vulnerability based on the lack of decisional capacity and voluntariness as in the CFR, the TCPS2 articulates vulnerability in a more flexible manner: “Individuals or groups may experience vulnerability to different degrees and at different times, depending on their circumstances” (Glossary, p.197). In contrast to the population-based approach in the CFR, the TCPS2 employs a context-based approach where vulnerability is determined by whether potential participants are capable of fully protecting themselves in a given research context. Furthermore, the TCPS2 mandates that vulnerability itself should not determine whether the person should or should not be included in research (Article 4.7). That is, anyone could be vulnerable depending on the research context and further, those determined vulnerable should not be excluded or included, simply due to their vulnerability.

5.1 Conditions under which pregnant women may participate

5.1.1 Precedence of non-pregnant women studies

As shown in Table 7, the CFR requires non-pregnant women studies to provide risk benefit data for research with pregnant women (45CFR46.204(a)). Other five regulations do not refer to non-pregnant human studies as a prerequisite.

5.1.2 Precedence of pregnant animal studies

Table 7 shows that the CFR requires pregnant animal studies to provide risk benefit data for research with pregnant women (45CFR46.204(a)). Similarly, the CIOMS Guideline requires prior pregnant animal studies with a focus on teratogenicity and mutagenicity (Guideline 17). Other four regulations do not refer to pregnant animal studies as a prerequisite.

Table 7 Comparison of regulations regarding research with pregnant women

	US CFR	Canadian TCPS2	Australian Regulation	South African Guideline	European Guideline	CIOMS Guideline
Pregnant women as research participants	Vulnerable population	Eligible as participants Should not be excluded at any stages of reproduction	Specific ethical consideration required Full board ethics review required even if low risk; careful review on a case by case basis Access to counseling	Special group Usually competent Exclusion requires justification (scientific evidence of fetal risk)	Special situation *Incompetent persons addressed separately	Eligible as participants Vulnerable depending on culture/community Contraceptive required if risk to pregnancy known
Risk benefit consideration for including pregnant women	Risks to fetus justified by benefit to fetus or woman Fetal risk within minimal risk in nontherapeutic research Belmont Report : fair participant selection	Balancing of risk and benefits Consideration extended to risk/benefits of excluding pregnant women Vulnerability do not directly indicate exclusion	Fetal research acceptable if fetal health promoted Minimize & monitor fetal pain/distress; suspend/stop if desirable Fetal risk not acceptable in nontherapeutic research involving drug/procedure	Attention required to woman and fetus in nontherapeutic research	Nontherapeutic research acceptable only when: -Indirect benefit -Not feasible without enrolling pregnant women -within minimal risk or minimal burden	Research must meet the needs of woman and fetus as participants and in general Fair participant selection
Prior pregnant animal studies	Required	-	-	-	-	Required with focus on teratogenicity and mutagenicity
Prior non-pregnant woman studies	Required	-	-	-	-	-
Paternal involvement	Paternal consent required in research with fetal benefit	Woman decides	Other stakeholders may be involved upon the woman's wish	Paternal consent always required	-	Paternal opinion desirable in research with fetal benefit

5.1.3 Risks and benefits to the woman and fetus

The six regulations share general rules that risk must be (1) minimized and (2) justified by direct benefit to the participants or by indirect benefit of producing generalizable knowledge (45CFR46.111(a); TCPS2, Application of Article 1.1; Australian Regulation, Chapter 2.1; South African Guideline 7.2.1; European Guideline, Article 6; CIOMS Guideline 8). Beyond these general rules, however, these regulations take slightly different approaches in addressing risks and benefits in research involving pregnant women (Table 7).

The CFR revolves around fetal risk. In therapeutic research (research with potential therapeutic benefits to participants), fetal risk must be justified by potential direct benefit to the participating woman or fetus. In nontherapeutic research (research without any prospect of direct therapeutic benefits to participants), fetal risk must be within minimal risk, i.e. risks equivalent to risks involved in daily life or routine clinical examinations (45CFR46.204(b)). However, a limit to or justification of maternal risk is not referred to at all. Thus it is unclear how maternal risk may be justified and whether maternal risk in nontherapeutic research must be within minimal risk. Similarly, the Australian Regulation has a focus on the fetus. Fetal research is acceptable if it promotes fetal health (4.1.7) and if certain conditions, such as minimizing fetal pain and distress, are met (4.1.8). The Australian Regulation does not allow nontherapeutic research with pregnant women if it involves drugs and procedures entailing fetal risk (4.1.10), which is stricter than the CFR which allows minimal risk.

The South African Guideline (7.1.3.1) and European Guideline (Article 18) express equal attention to the woman and fetus although the descriptions are limited to nontherapeutic research. The South African Guideline simply draws attention to the well being of the woman and fetus while the European Guideline states that nontherapeutic research is acceptable only when it involves no more than minimal risk or minimal burden (discomfort) and cannot be conducted without pregnant women (Article 18). The

European Guideline is similar to the CFR in terms of the risk limit in nontherapeutic research. Nevertheless, the risk limit in the European Guideline clearly applies to both the woman and fetus.

The CIOMS Guideline addresses risk benefit consideration mainly from the needs (benefit) of the woman and fetus and not from the risks involved. Pregnant women's participation is restricted to research with direct benefit to the woman or fetus, or indirect benefit of generalizable knowledge for future pregnant women and fetuses (Guideline 17). Although knowledge must contribute to future pregnant women, it is not clear whether permissible research is restricted to obstetric research. Considering some pregnant women with general medical conditions, such as hypertension, diabetes, or depression, the CIOMS Guideline may not necessarily be restricting pregnant women's participation to obstetric research. In terms of risk, the general rule - risk justified by direct or indirect benefit - presumably applies although the risk benefit distribution between the woman and fetus is not specifically clarified.

The TCPS2 captures risks and benefits in a broader sense compared with the other regulations. In addition to the risks and benefits of including pregnant women, researchers and research ethics committees must consider "the foreseeable risks and potential benefits of excluding pregnant or breastfeeding women" (Application of Article 4.3, p.49). In some regulations (CIOMS Guideline 12; Australian Regulation 1.4), the potential outcomes of excluding pregnant women might be addressed through the requirement of fair participant selection. In the US context, fair participant selection is articulated in the Belmont Report (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979) as a justice issue (C.3). The South African Guideline includes the Belmont Report (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979) in its appendix as an important reference. Nevertheless, the TCPS2 may be unique in pointing to risks and benefits of excluding pregnant women in weighing risks and benefits of the research study.

5.1.4 Paternal consent

Three regulations (45CFR46.204; South African Guideline 5.3.1.1.3; CIOMS Guideline 17) require the involvement of the fetus's father in the decision for the pregnant woman to participate in research (Table 7). The South African Guideline requires paternal consent for all research with pregnant women (5.3.1.1.3). The CFR requires paternal consent when research has potential direct benefit only to the fetus (45CFR46.204(e)) whereas maternal consent suffices when research has potential direct benefit to the woman or no direct benefit to the woman or fetus (45CFR46.204(d)). The CIOMS Guideline states that "it is desirable in research directed at the health of the fetus to obtain the father's opinion also, when possible." (Commentary on Guideline 17, p.74). The wording ("desirable", "opinion", or "when possible") suggests less importance compared with paternal consent being required as in the CFR or South African Guideline.

The Australian Regulation states that other stakeholders may be included in the woman's decision making upon her request (4.1.5). The TCPS2 does not refer to other stakeholders, stating that the pregnant woman's consent authorizes all types of research affecting the fetus and fetal tissue, and that the woman's "autonomy and physical integrity" must be respected (Application of Article 12.9, p.179).

5.2 Discussion

5.2.1 Eligibility of pregnant women as research participants

The CFR, Australian Regulation, and European Guideline do not clarify pregnant women's eligibility to participate in research. Particularly, the CFR and Australian Regulation identify pregnant women as vulnerable or always in need of special protection. While the Australian, South African, and European Guidelines do not use the term vulnerable, these regulations also deem pregnant women differently from the general population. The notion of vulnerability in the CFR, CIOMS Guideline, and TCPS2 is in line with the Belmont Report (B.1; C.3) (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979) where vulnerable persons are those who lack decisional capacity or voluntariness, and thus unable to fully protect their best interests.

Nevertheless, the term “vulnerability” may not be a well delineated concept as it could be based on numerous grounds, such as the person's decisional capacity, serious illnesses, level of education, or economic disadvantage (Hurst, 2008; Iltis, 2009; C. Levine et al., 2004; Ruof, 2004). Regarding the CFR, some authors question why pregnant women are classified as a vulnerable population (Blehar et al., 2013; Coleman, 2009; Rothenberg, Hayunga, Rudick, & Pinn, 1996). Particularly, the population-based approach to vulnerability of the CFR (45CFR46 Subpart B) has been much criticized (Blehar et al., 2013; Mastroianni, Faden, & Federman, 1994; Rothenberg et al., 1996; Schonfeld, 2013). The Australian Regulation also appears to employ the population-based approach as it depicts pregnant women as a population that always requires a higher level of ethics review (5.1.6). Determination of a particular group of persons as vulnerable may stereotype them rather than meaningfully protect them (Coleman, 2009; C. Levine et al., 2004). The population-based approach applied to pregnant women could imply that their research participation is rather exceptional and that their inclusion requires justification, which could restrict their inclusion in research (Baylis, 2010; Lyerly, Little et al., 2008b). By contrast, the context-based approach described as in the TCPS2 (Application of Article 4.7) where a person is deemed vulnerable depending on the research context may better illustrate the participant’s vulnerability because a person may be vulnerable under a particular context but not in another. Although there seems no empirical evidence, the population-based approach could undermine pregnant women’s eligibility as research participants.

Another critical issue related to the notion of vulnerability is the appropriateness of excluding those who are identified vulnerable from research. Historically, some groups of people, such as prisoners, cognitively impaired, or economically disadvantaged were prone to exploitation by being included in research (Beecher, 1966). On the other hand, the blanket exclusion of so called vulnerable populations from research to protect them resulted in depriving them of the opportunity to receive direct benefits of research participation as well as indirect benefits of scientific knowledge applicable to the population to which they belonged (Meltzer & Childress, 2008; Zion, Gillam, & Loff, 2000). The lessons learnt from the irrelevant inclusion and exclusion illustrate the shortcomings of directly associating vulnerability with the eligibility criteria. This issue

could be addressed by clarifying that a person's vulnerability and eligibility as a research participant are two separate issues as in the TCPS2.

Further, focusing on the vulnerability of research participants, Coleman (2009) criticizes the understanding of vulnerability as the inability to protect one's own interest and argues that it may be more meaningful to clarify what specifically makes particular persons vulnerable in the research context and protect them for that particular aspect. Coleman's (2009) view takes the context-based approach a step further and provides a supportive framework for enhancing research with those who are prone to be labeled vulnerable. As some authors indicate, pregnant women may not be vulnerable but they simply require scientific or medical attention that is different from the general population (Blehar et al., 2013; Lyerly, Little et al., 2008b). Research with pregnant women may be more feasible through addressing specific concerns regarding the woman (and fetus) as research participants rather than erring on the side of excluding them all together to avoid any kind of undesirable outcomes. To date, various study designs, ranging from observational to interventional, have been proposed to address pregnancy related concerns (Charo, 1993; Goodrum et al., 2003; Howard, Tassinari, Feibus, & Mathis, 2011; Macklin, 2010), including randomized controlled trials in a modified manner (Baylis, 2010; Goldkind, Sahin, & Gallauresi, 2010). Seeking suitable study designs with relevant safety measures may be one of the critical strategies in addressing issues inherent in including pregnant women in clinical research.

5.2.2 Risk benefit distribution among the woman, fetus, and society

A favorable risk benefit ratio is one of the most important ethical requirements for conducting human research (Emanuel, Wendler, & Grady, 2008). A general rule of minimizing risks (45CFR46.111(a)(1); TCPS2, Application of Article 1.1; Australian Regulation, Chapter 2; South African Guideline 7.2.1; European Guideline, Article 6; CIOMS Guideline 8) appears unambiguous and uncontroversial in any contexts. By contrast, balancing risks and benefits is a complicated process without any standardized approach, which may be much left to the discretion of research ethics committees (Kopelman, 2000; Levine, 1988). In research with pregnant women, risks and benefits

may be further complicated by the two agents - the woman and her fetus - with potential conflict of interests.

Research ethics regulations tend to place emphasis on fetal well being rather than maternal well being. Some regulations exclusively (1) address fetal risk (45CFR46.204; Australian Regulation 4.1.7), (2) set a limit to fetal risk in nontherapeutic research (45CFR46.204; Australian Regulation 4.1.10), (3) draw attention to fetal risks such as teratogenicity in conducting pregnant animal studies (CIOMS Guideline 17), and (4) refer to fetal risk as a justification for excluding pregnant women (South African Guideline 7.1.3.1).

Strong (2011) holds that more protection to the fetus is justifiable as the fetus lack decisional capacity for self-protection. Indeed the fetus's inability to protect oneself should not be ignored. Also, attention to teratogenicity and mutagenicity in pregnant animal studies (CIOMS Guidelines 17) is relevant particularly for drug and device studies where much concern is anticipated from striking cases such as thalidomide (Lancaster, 2011; Smithells & Newman, 1992) and diethylstilbestrol (Titus-Ernstoff et al., 2001). Nevertheless, physiological complexities of the pregnant body may also require attention (Baylis, 2010; Broughton Pipkin, 2011; Goldkind et al., 2010; Goodrum et al., 2003). Excessive emphasis on one agent may potentially restrict the research needs of the other. Much attention to fetal risk as expressed in several aspects of these regulations may not necessarily optimize risk benefit distribution in research with pregnant women. Moreover, as the fetus is physically dependent on the woman and the woman may at times be affected by adverse events to the fetus (Blackburn, 2013), it might not be reasonable to place emphasis on either of the two agents in considering risks and benefits. While much remains to be discussed, the imbalance of attention between the fetus and woman needs to be rectified as it may overlook maternal risk as well as restrict research with potential benefit to the participating woman as well as future pregnant women.

Risk benefit consideration extended to the repercussions of excluding pregnant women (TCPS2, Application of Article 4.3) may highlight clinical issues such as little research evidence for prenatal care as problematized by several authors (Lyerly et al., 2009;

Macklin, 2010; Mattison & Zajicek, 2006). For example, in considering whether or not to include pregnant participants in a hypertension drug study, potential outcomes of excluding them are the disadvantages of no potential direct benefit to the participating pregnant woman and suboptimal hypertension treatments for future pregnant women as well as the advantages of not exposing pregnant women and fetuses to risks in research. The foreseeable disadvantage for future pregnant women due to the lack of data for their healthcare could shift the risk benefit calculation more favorably towards the inclusion of pregnant women depending on the significance of the health issue at stake. Nevertheless, this approach may be employed with caution. A major concern of this approach is that it adds complexities to the risk benefit assessment since so many factors of a different nature are balanced against one another. Basically, balancing risks to participants and knowledge for future generations is more complex than balancing risks and benefits within an individual (Levine, 1988). Moreover, it is potentially problematic to justify risks to an individual by collective societal benefits (Levine, 1988). Incorporating the disadvantages for future generations due to the lack of knowledge in the risk benefit consideration could be further complicated and controversial. The basic rule tells that the participant's well being should be given the top priority regardless of any other benefits (Declaration of Helsinki, 8) (World Medical Association, 2013). Given the absence of agreed on procedural steps for balancing risks and benefits in pregnant or non-pregnant populations (Levine, 1988), specific guidance on extending the risk benefit consideration to the repercussions of excluding pregnant women could be highly complex and challenging.

At a practical level, we may have to fall back to the research ethics committees for each case as stipulated in the Australian Regulation (4.1.3). Nevertheless, it should not be left virtually open to the discretion to the research ethics committee members as they could be influenced by the value of research or excellence of investigators in a particular research community (Tauer, 2002) as well as a variety of safety and liability concerns (Allesee & Gallagher, 2011; Hall, 1995). Much remains to be discussed to specifically address risks and benefits to the woman, fetus, and society.

5.2.3 Paternal involvement in the consent process

Paternal consent adds an extra layer to the consent process and thus this requirement must be justified by good reasons. As adults are deemed capable of giving or not giving consent unless otherwise demonstrated, the main purpose of paternal consent (45CFR46.204(e); South African Guideline 5.3.2.2.3) or opinion (CIOMS, Commentary on Guideline 17) may be aimed at protecting the fetus's best interest. Instead of requiring paternal consent for all research (South African Guideline 5.3.2.2.3), it may be preferable to specify the types of research that require paternal consent depending on the needs to protect the fetus.

In some regulations, paternal involvement is required in research with benefit only to the fetus while the woman's consent suffices for research without any benefit to the fetus (45CFR46.204(d); CIOMS Guideline 17). This is somewhat difficult to understand as the fetal risk benefit ratio is more favorable in research with fetal benefit than research without fetal benefit. Alternatively, it could be understood that paternal consent should not interfere with the woman's decision to participate in any research with potential benefit to the woman regardless of fetal risk. Nevertheless, the requirement of paternal consent or opinion is not completely clear in terms of its effectiveness if aimed at fetal protection. For the fetus's best interest, paternal consent could be better framed around fetal risk although paternal involvement in the decision for the pregnant woman to participate may be debatable regardless of the fetal risk benefit ratio.

5.3 Conclusion

This critical review examined four national and two international ethics regulations regarding pregnant women's eligibility as research participants and conditions for their inclusion. National and international research ethics regulations involve factors that could overprotect pregnant women and fetuses, and potentially restrict important research with pregnant women. Rather than identifying pregnant women as a vulnerable group of persons, endorsing pregnant women's eligibility as research participants may function positively toward their inclusion in research. An excessive focus on fetal risk may not necessarily optimize risk benefit distribution among the woman, fetus, and society.

Paternal consent requires clear justification to be stipulated in regulations. Much discussion is required to codify acceptable risks to the woman and fetus as well as strategies for balancing risks and benefits among the woman, fetus, and society.

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Chapter 6

6 Scoping review: Views of pregnant women and other stakeholders on clinical research with pregnant women

6.1 Introduction

Pregnant women are often excluded from clinical research (Shields & Lyerly, 2013), particularly interventional studies investigating non-obstetric conditions (Domínguez, Ramos, Torrents, García, & Carné, 2012). Fair participant selection requires relevant inclusion as well as relevant exclusion of particular populations (Emanuel, Wendler, & Grady, 2008). A lack of research with particular populations results in depriving them from potential direct benefits of therapeutic research and indirect benefits of the most updated science applicable to the population represented in research (Meltzer & Childress, 2008; Zion, Gillam, & Loff, 2000). With regards to indirect benefits, critics have problematized insufficient research-based evidence to support safe and optimal prenatal care for the woman and her fetus (Baylis, 2010; Charo, 1993; Chervenak & McCullough, 2003; Kass, Taylor, & King, 1996; Lyerly, Little, & Faden, 2008a; Macklin, 2010; Mastroianni, Faden, & Federman, 1994; Mattison & Zajicek, 2006; McCullough, Coverdale, & Chervenak, 2005; Minkoff, Moreno, & Powderly, 1992).

Stakeholders in health care and research with pregnant women, such as pregnant women, healthcare providers, researchers in the related fields, pharmaceutical companies, research ethics committee (REC) members, women, and the general public may be reluctant to include pregnant women in clinical research for a variety of reasons, for example, teratogenicity fears and liability concerns (Allesee & Gallagher, 2011). Suggestions to address stakeholders' concerns include: (1) guidance to researchers, drug companies, legal advisors, and REC members (Allesee & Gallagher, 2011; Brandon, Shivakumar, Lee, Inrig, & Sadler, 2009; Lyerly et al., 2008a; Lyerly, Little, & Faden, 2008b), (2) optimal resource allocation to cover the additional cost for research with pregnant women (Allesee & Gallagher, 2011), and (3) strategies to address liability concerns (Allesee & Gallagher, 2011; Charo, 1993; Fullerton & Sadler, 2004; Lyerly et al., 2008a; Lyerly, Little et al., 2008b; Schonfeld, Brown, Amoura, & Gordon, 2010).

Also, obtaining informed consent could be complicated due to the involvement of the fetus who cannot give consent (Helmreich, Hundley, Norman, Ighedosa, & Chow, 2007). In addition, women face societal and familial expectations that focus on fetal safety and well being over pregnant women's rights and needs as an autonomous person (Lupton, 2012). Enrollment of pregnant women in clinical research is influenced by the perceptions of the stakeholders (Allesee & Gallagher, 2011; Brandon et al., 2009; Lyerly et al., 2008a; Lyerly, Little et al., 2008b).

This chapter is a scoping review aimed at summarizing the research findings and identifying the gap in literature (Arksey & O'Malley, 2005) regarding empirical studies on pregnant women's and other stakeholders' views on clinical research with pregnant women. To date, empirical studies have captured the pregnant or postpartum woman's and others' views on research with pregnant women in various settings, ranging from real to hypothetical research to be considered by the participants as well as with different methodologies. This review is guided by the thematic analysis approach of Dixon-Woods, Agarwal, Jones, Young, & Sutton (2005). As thematic analysis ranges in various focuses (Dixon-Woods et al., 2005), this review was data driven rather than theory driven, more descriptive than interpretive, and considered both frequency and explanatory potential of the themes. The main goal of this review is to illustrate the breadth of previous findings and to identify gaps in empirical studies examining the women's and others' views on clinical research with pregnant women. In this review, clinical research refers to "research that directly involves a particular person or group of people, or that uses materials from humans, such as their behavior or samples of their tissue" as clarified by the United States (US) National Institute of Health (NIH) (National Institute of Health, 2012).

6.2 Methods

The following steps proposed by Arksey and O'Malley (2005) were taken to systematically retrieve relevant studies for conducting a scoping review:

1. The research question for this review was formulated: What is known from the literature about the views of pregnant women and other stakeholders on conducting clinical research with pregnant women?

2. To answer this question, a systematic literature search was conducted using electronic databases (PubMed, EMBASE, CINAHL, Scopus, and Dissertation & Theses) for identifying potentially relevant original papers. Key words, such as "pregnant women" OR "expectant mother", "clinical research" OR "trial", "patient selection" OR "participation", "attitude" OR "motivation" were employed. Specific search terms for identifying relevant papers in each database are presented in Table 8.

3. Eligible studies were empirical studies which examined pregnant women's and others' views on pregnant women's participation in clinical research, published in peer reviewed journals from January 1980 to March 2015 (preliminary search retrieved no paper before 1990) in any language. No restriction was applied in terms of the study design. Exclusion criteria were studies which investigated: (1) views on participating in non-clinical research such as participating in a discussion group, (2) particular issues of a subpopulation of pregnant women such as adolescents or substance abusers, and (3) challenges specific to a particular profession (such as midwives) in conducting research.

4. Selected papers were charted to include the following information: the author(s), year of publication, study location, study populations, purposes of the study, methodology, outcome measures, and main findings.

5. Studies selected through the above process were summarized based on the charted information and the original paper as needed. This review did not intend any quality assessment of the retrieved papers. The studies being diverse in their settings and methodologies, this review does not aim at synthesizing the study results but rather identifies themes from the findings of the reviewed studies to illustrate what is known regarding the views on clinical research with pregnant women. To illustrate the breadth of findings in studies with a variety of study designs and settings, thematic analysis was data driven and the themes were determined by both the frequency of

similar findings and potential in explaining the pregnant women's and others' views on clinical research with pregnant women.

Table 8 Search terms for the database

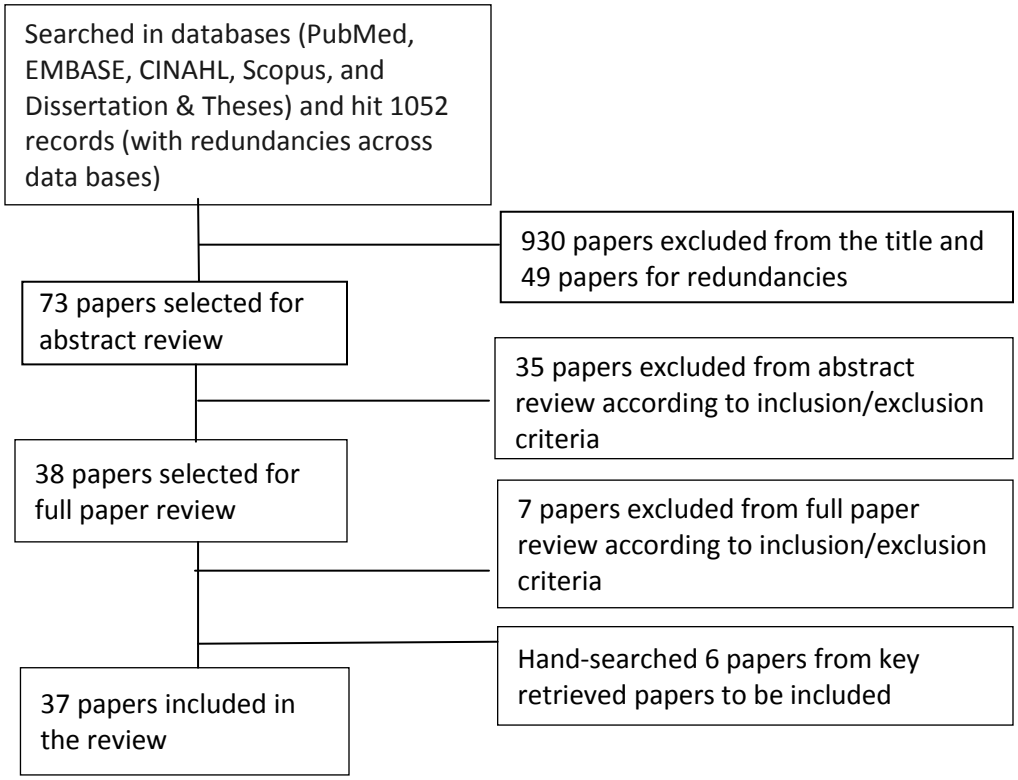
Database	Search Terms
PubMed	pregnancy/pregnant women trial/research patient selection/participation/recruit pregnant women/psychology/refusal/motivation attitude of health professionals
EMBASE	Pregnancy/attitude to pregnancy clinical research/clinical trial patient participation maternal behavior health professional attitude/physician attitude
Scopus	pregnancy/pregnant women clinical trial/research research participation/participant recruitment/patient selection attitude/view/perception/motivation/decline/reason (With "Limit" to 'medicine', 'nursing', 'psychology', 'pharmacology, toxicology, pharmaceutics', 'health professions'
CINAHL	expectant mother clinical trials/randomized control trials research subjects/participation attitude of health professional
Dissertation & Theses	pregnancy/pregnant women trial/research patient selection/participation

6.3 Results

6.3.1 Literature search results

The initial database search revealed 1052 papers including overlaps across databases and searches (Figure 1). From each manuscript title, 73 papers were identified for abstract review. Retrieved papers were written in English or French although search was conducted without any language restriction. From careful application of the inclusion and exclusion criteria developed in the course of preliminary literature search, 38 papers were selected for full paper review. Further application of inclusion and exclusion criteria resulted in 31 papers. Hand-searching from the references of key retrieved papers that discussed the results as they relate to previous studies on pregnant women's views identified six relevant papers. In total, 37 papers were included for review and thematic analysis (Figure 1).

Figure 1 Literature search process



6.3.2 Overview of the studies included in this review

Table 9 shows the countries where the studies were conducted. The vast majority of studies were conducted in Western countries, particularly in the United States (US) and United Kingdom (UK) where two thirds of the studies were undertaken. Only two studies were conducted outside Western countries, one in Asia and the other in Africa. The number of studies conducted in the years 2000 to 2009 increased to 21 from 5 in the years 1990 to 1999 and the increasing trend continued in the next six years (2010-2015). (Table 10).

Table 9 Countries where research was undertaken

Country	Number of studies
United States	15
United Kingdom	9
Australia	4
Canada	2
Finland	2
Netherland	2
New Zealand	1
Pakistan	1
Cote D'Azure	1
Total	37

Table 10 Published year and type of analysis

Year	Quantitative analysis only	Qualitative analysis included	Total
1990-1999	3	2	5
2000-2009	13	8	21
2010-2015	4	7	11
Total	20	17	37

The methodology and settings differ considerably across studies. In terms of the methodology, 20 studies were quantitative studies, 13 studies were qualitative, and four studies employed mixed methods (Table 11).

Table 11 Participants and methodologies

Participants	**Methodology**		
	Quantitative (Survey/Questionnaire)	Qualitative (In-depth interview)	Mixed Method
Pregnant or Postpartum Women	Daly2003 Daniels2006 Dorantes2000 East1996 East1997 East2006 Gatny2012 Hendrix2009 Hutton1990 Joseph2008 Lamvu2005 McLeod2004 Nechuta2009 Nechuta 2012 Promislow2004 Rohra2009 Smyth2009 Turner2008 vanDelft2013	Baker2005 Coulibaly-Traore2003 Founds2007 Halkoaho2010 Kenyon2006 Lyerly2012 Mohanna1999 Rengerink2015 Smyth2012	Ferguson2000 Lavender2009R odger2003
Healthcare Providers	Haas2010 Turner2008	Founds2007 Halkoaho2012 Mudd2008 Penn1990	Ngui2014
Drug Industry Related		Shields2012	
Community Members			Ngui2014

Approximately two thirds of the studies were in the "real setting" (the participants were recruited to an actual research project) whereas one third of them were in the hypothetical (specific research study or research in general) setting (Table 12). The research considered by the participant were classified as drug studies (n=10), vaccine studies (n=3), clinical procedures not involving pharmaceutical agents (n=13), and epidemiological studies including genetic and other specimen collection (n=12) (Table 10). Besides epidemiological studies, the majority of studies conducted in the real setting investigated the participant's views on research in the perinatal period (the period from

the onset of labor to restoration of normal uterus after the delivery (Last, 2007)), particularly during intrapartum. Except for one study on pregnant women's views on participating in a H_1N_1 vaccine study (Lyerly, Namey, Gray, Swamy, & Faden, 2012), all studies investigated the views on participation in either obstetric research or research that could be undertaken only with pregnant women.

Table 12 Types of research considered by the participant

			Real (retrospective) research		Hypothetical research
Procedures and risks			Labor/Perinatal	Non-perinatal	
Main procedure considered	Potential additional risk	Drug	Dorantes2000 Ferguson2000 Kenyon2006 Mohanna1999 Rengerink2015 Smyth2009 Smyth2012	Hutton1990	Rodger2003 Shields2012
		Vaccine		Coulibaly-Traore 2003 Daly2003 Lyerly2012	
		Other Clinical Procedures or Not Specified	East1996 East1997 East2006 Founds2007 Hendrix2009 McLeod2004 Rengerink2015	Baker2005 (multiple, not specified)	Haas2010 Lavender2009 Penn1990 Turner2008
	No risk	Follow up/ Specimen Collection	Joseph2008 Lamvu2005 Promislow2004 Rohra2009 Daniels2006 vanDelft2013 Halkoaho2010 Halkoaho2012		Gatny2011 Mudd2008 Nechuta2009 Nechuta2012 Ngui2014

Most studies in the review concern the views of pregnant women and a few studies examine the views of healthcare providers and other stakeholders (Table 11). The majority of these studies revolved around pregnant women's reasons for or against participation, some primarily focused on recruitment issues. The themes identified for

pregnant women's views concern risks, benefits, recruitment processes, and miscellaneous limitations to participate in research during pregnancy (Table 13) while themes that illustrated others' views (Table 14) were mostly focused on barriers and concerns about conducting research with pregnant women in their institutions. In the following sections, themes identified from pregnant women's views, and then those identified from healthcare providers' and others' views will be presented.

6.3.3 Themes identified from pregnant women's views

A total of 31 studies examined the views of pregnant women. The themes were as follows: altruism (benefits to others), benefits to herself and fetus, risks to herself and fetus, weighing risks and benefits, methodological concerns, recruitment processes, and physical, psychosocial, and relational limitations.

6.3.3.1 Altruism (Benefits to others)

Many studies reported that women take part in research to help create knowledge, to contribute to science, or to help future pregnant women (Baker, Lavender, & Tincello, 2005; Daniels et al., 2006; Dorantes, Tait, & Naughton, 2000; East & Colditz, 1996; Founds, 2007; Gatny & Axinn, 2012; Hutton, Wilkinson, & Neale, 1990; Joseph, Neidich, Ober, & Ross, 2008; Kenyon, Dixon-Woods, Jackson, Windridge, & Pitchforth, 2006; Lamvu et al., 2005; McLeod, Barrett, Hewson, & Hannah, 2004; Mohanna & Tunna, 1999; Promislow et al., 2004; Rengerink, Logtenberg, Hooft, Bossuyt, & Mol, 2015; Rodger et al., 2003; Smyth, Duley, Jacoby, & Elbourne, 2009). Contribution to medicine was the primary reason for 43% of 669 participants to be in a prospective study investigating causes of spontaneous abortion (Promislow et al., 2004). One study surveying pregnant women about hypothetical research involving either interview, specimen collection, or collection of pregnancy outcome information showed that participants whose motivations included altruism and self-learning were more motivated compared with participants with other motivations (Gatny & Axinn, 2012). Analyzing racial differences in the motivations of pregnant women who participated in a study investigating risk factors for spontaneous abortion and preterm birth, Lamvu et al. (2005)

indicated that altruism was expressed more by white women compared with other ethnic groups.

Despite many studies reporting altruism as a motivating factor for research participation, Gatny and Axinn (2012) pointed out that altruism may not be the main reason for pregnant women to participate and that pregnant women might mention altruism due to the positive connotation of altruism in society across cultures. The results of several studies support such a claim. For example, pregnant women in a qualitative study examining their views on participating in a multicentre randomized controlled trial (RCT) involving antibiotics for preterm labor expressed that they would want to help others only if there was no risk to themselves and their fetus (Kenyon et al., 2006). Also, studies with pregnant women which indicated altruism as a motivator for participating in clinical research were mostly epidemiological studies without any physical risks nor potential direct benefit to the participating woman (Daniels et al., 2006; Gatny & Axinn, 2012; Joseph et al., 2008; Lamvu et al., 2005; Promislow et al., 2004). Moreover, some of these epidemiological studies included potential benefits of medical attention such as extra ultrasounds (Daniels et al., 2006; Lamvu et al., 2005; Promislow et al., 2004). Although altruism is one of the frequently expressed motivations for pregnant women to participate in research there are other overriding factors.

Several studies indicated conflicting factors for pregnant women to consider when deciding whether or not to participate in clinical research (Baker et al., 2005; Kenyon et al., 2006; Mohanna & Tunna, 1999). For example, investigating the views of women who declined to participate in a study on the effectiveness of nifedipine to prevent preterm labor, Mohanna and Tunna (1999) identified women's feelings of conflict between the duties to society by contributing to knowledge and her responsibilities to the fetus by acting in its best interest. It is noteworthy that in this study, many women who declined drug trial participation felt positive to be interviewed because they felt they were given an alternate opportunity to help others (Mohanna & Tunna, 1999). Similarly, Baker et al. (2005) pointed out that even the women who never declined to participate in any research to which they were recruited were in a dilemma, such as considering altruism versus self-protection and enhanced care versus inferior care. Pregnant women may want to help

others; however, not expose themselves and their fetuses to risk or inferior healthcare. These researchers indicated that all participants expressed concern about the fetus and were only willing to participate in non-invasive research (Baker et al., 2005). Such attitudes also support pregnant women's wish to help others if no risks to the woman or fetus are foreseen. As illustrated in these studies, a pregnant woman's wish to help others or society may be modified by other factors which will be discussed later under the themes of benefits and risks.

6.3.3.2 Benefits to herself and fetus

The literature indicated that pregnant women's perceived benefits of research participation to themselves or their fetus vary. Perceived benefits noted in the literature included potential therapeutic benefits such as receiving a drug or vaccine (Coulibaly-Traoré, Msellati, Vidal, Welffens Ekra, & Dabis, 2003; Kenyon et al., 2006; Lyerly et al., 2012; Rengerink et al., 2015; Smyth et al., 2009; Smyth, Jacoby, & Elbourne, 2012), receiving additional medical attention such as an extra ultrasound, other medical examinations, or increased access to healthcare (Coulibaly-Traoré et al., 2003; Daniels et al., 2006; Gatny & Axinn, 2012; Lamvu et al., 2005; Promislow et al., 2004), having additional learning opportunities about pregnancy and health (Daniels et al., 2006; Founds, 2007; Gatny & Axinn, 2012; Lamvu et al., 2005; Promislow et al., 2004), and monetary compensation (Daniels et al., 2006; Gatny & Axinn, 2012).

Perceived direct benefits of research participation may be combined with other motivators as well. For example, conducting semi-structured interviews with 40 women who participated in a RCT testing prophylactic use of anticonvulsants for pre-eclampsia in the perinatal period, Smyth et al. (2012) reported that self-benefits, benefits to the fetus, and altruism were the three major factors that motivated pregnant women to participate. The findings of this study suggested that direct benefits to the woman and her fetus may be the key factor as the majority of pregnant women were prone to believe that research would bring direct benefits to themselves and only five out of 40 women mentioned altruism as the exclusive reason to participate (Smyth et al., 2012). Rodger et al. (2003) reported that women were motivated more by direct benefit compared with altruism in a hypothetical RCT involving low molecular heparin for treating thrombophilia. In this

study, 68% of the women showed appreciation for fetal benefits while 27% for their own interests, implying the pregnant woman's priority towards the fetus (Rodger et al., 2003). As mentioned previously under the theme of altruism, direct benefits to the participating woman and her fetus could be the primary motivating factor to participate (Kenyon et al., 2006).

Increased medical attention related to clinical research participation may be another form of perceived benefit. Although observational research does not have therapeutic benefits of having health conditions being treated, it may have benefits of being followed by qualified healthcare professionals, such as having extra medical tests (Gatny & Axinn, 2012; Lamvu et al., 2005) or ultrasound (Promislow et al., 2004). Access to healthcare itself may also motivate pregnant women to participate in research as shown in a placebo RCT of preventing mother-child HIV transmission in Africa (Coulibaly-Traoré et al., 2003). Access to healthcare was perceived as a huge benefit, particularly if the woman had limited access to healthcare due to a scarcity of resources in the community. In addition to receiving healthcare, learning about pregnancy or health related issues in the course of participation was also reported as beneficial by women (Daniels et al., 2006; Founds, 2007; Gatny & Axinn, 2012; Lamvu et al., 2005). Concern about their own pregnancies could also motivate women to seek more medical attention or information (Lamvu et al., 2005; Promislow et al., 2004). A comparison across ethnic groups in terms of motivations to participate in research suggested that African Americans were more likely to participate if research could promote pregnancy health through learning about health (Lamvu et al., 2005).

Finally, monetary compensation for participation in research was considered a motivating factor by some pregnant women (Daniels et al., 2006; Gatny & Axinn, 2012). In a cohort study involving specimen collection (vaginal swab, saliva, and blood), 27% of the participants indicated monetary compensation as among the important factors they considered when deciding to participate (Daniels et al., 2006). However, studies using hypothetical settings showed contrasting results. One study investigating pregnant women's attitudes toward participating in epidemiological research in the perinatal period showed women's willingness to participate even without monetary compensation

(Nechuta et al., 2009). Another study examining pregnant women's attitudes toward biological specimen collection during pregnancy suggested that the importance of monetary compensation for women was complex, depending on factors such as the woman's education level, marital status, race, and parity (Nechuta et al., 2012).

6.3.3.3 Risks to herself and fetus

Pregnant women's perception of research risk plays positive and negative roles in their decision making process regarding whether or not to participate in clinical research. Women were more motivated to participate if they perceived no or low risks (Baker et al., 2005; Dorantes et al., 2000; Lyerly et al., 2012; Smyth et al., 2009) whereas they were more reluctant to participate if they perceived unacceptable risks to themselves or their fetuses (Baker et al., 2005; Dorantes et al., 2000; Hendrix et al., 2009; Hutton et al., 1990; Mohanna & Tunna, 1999; Rengerink et al., 2015; Rodger et al., 2003). In considering participation in obstetric anesthesia research, nearly 80% of study consenters perceived low risk to the fetus while over 40 % of decliners expressed concern about fetal safety (Dorantes et al., 2000). As indicated in this obstetric anesthesia study, women may be particularly concerned about fetal risk in research (Dorantes et al., 2000). Baker et al. (2005) conducted a qualitative study with 17 postpartum women who had participated in multiple studies, both observational and interventional, during pregnancy. Five women who declined at least one study participated in an individual interview and 12 women who did not decline any study participation joined one of the four focus groups. Baker et al. (2005) indicated that all participants including those who never declined research participation during pregnancy expressed concern about the fetus and were pleased if research procedures were non-invasive. In a hypothetical study involving heparin administration, the researchers reported that pregnant participants were particularly concerned about fetal risk, concluding that having a favorable risk benefit ratio to the fetus is the dominant factor for women to participate (Rodger et al., 2003).

Also, risk communication with pregnant women may affect the recruitment as indicated in a study examining the decliners of research involving nifedipine to prevent preterm labor (Mohanna & Tunna, 1999). The researchers of this study pointed out that providing a letter of information without any active involvement of the research staff to discuss

risks would discourage participation. They also indicated the difficulty of explaining the balance between the risks for taking the drug and risks for not taking the drug (Mohanna & Tunna, 1999).

Adding to the challenges in communication, pregnant women's understanding of the information and perception of risk may further influence their decision. As mentioned regarding the obstetric anesthesia research (Dorantes et al., 2000), the same study was perceived differently between the consenters and decliners in terms of safety (nearly 80% of consenters perceived low risk while over 40 % of decliners perceived unacceptable risk). Further, there seems to be a perception that interventions such as drugs or vaccines are to be avoided during pregnancy (Daly, Toth, & Giebink, 2003; Hutton et al., 1990; Rodger et al., 2003). Investigating pregnant women's willingness to participate in a pneumococcal conjugae vaccine study, 46% of decliners indicated concerns about vaccination during pregnancy (Daly et al., 2003). Similarly, more than 30% of the decliners of a low dose heparin study indicated that drugs should not be used during pregnancy or that pregnant women should not be invited for drug studies (Hutton et al., 1990).

6.3.3.4 Weighing risks and benefits

Although fetal risk seems to be critically important, pregnant women weigh the benefits and risks in each research context (Kenyon et al., 2006; Lyerly et al., 2012; Rodger et al., 2003) as well as using common sense (Kenyon et al., 2006) for their decision making. In a H1N1 vaccine study, pregnant women thought the benefit of early access to the new vaccine outweighed the risk of the new vaccine itself (Lyerly et al., 2012). In a hypothetical placebo RCT of heparin injection, women accepted potential risks to themselves if the benefit to their fetuses and the course of pregnancy could be promising (Rodger et al., 2003) . As shown in these three studies, pregnant women weighed risks against direct benefit to themselves or their fetuses in considering participation in clinical research.

Table 13 Themes identified from pregnant women's views

Themes	Subthemes	
Altruism (Benefits to others)	**Helping society and future pregnant women** (Baker 2005, Daniels 2006, East 1996, Dorantes 2000, Founds 2007, Gatny 2012, Halkoaho 2010, Hutton 1990, Joseph 2008, Kenyon 2006, Lamvu 2005, McLeod 2004, Mohanna 1999, Promislow 2004, Rengerink 2015, Rodger 2003, Smyth 2009)	
Benefits to herself and fetus	**Benefits to fetus/woman** (Coulibaly-Toraore 2003, Kenyon 2006, Lyerly 2012, Rengerink 2015, Rodger 2003, Smyth 2009,2012) **Medical attention** (Coulibaly-Toraore 2003, Daniels 2006, Gatny 2012, Lamvu 2005, Promislow 2004) **Learning about pregnancy** (Daniels 2006, Founds 2007, Gatny 2012, Lamvu 2005, Promislow 2004) **Compensation** (Daniels 2006, Gatny 2012, Nechuta 2009, 2012)	
Risks to herself and fetus	**Acceptable risk** (Baker 2005, Dorantes 2000, Lyerly 2012, Smyth 2009)	**Unacceptable risk** (Baker 2005, Dorantes 2000, Hendrix 2009, Hutton 1990, Mohanna 1999, Rengerink 2015, Rodger 2003) **Drug/vaccine be avoided during pregnancy** (Daly 2003, Hutton 1990, Rodger 2003)
Weighing risks and benefits	**Weighing risks and benefits** (Kenyon 2006, Lyerly 2012, Rodger2003)	**Conflicting duties to society and fetus** (Baker 2005, Mohanna 1999)
Methodology	**Acceptable methodology** (Daly 2003)	**Unacceptable methodology** (Baker 2005, East 2006, Founds 2007, Hendrix 2009, Lyerly 2012, Lavender 2009, Mohanna 1999, Rengerink 2015, Rodger 2003, Smyth 2009,Turner 2008)
Recruitment processes	**Good recruitment processes** (Founds 2007, Halkoaho 2010) **Trust in professionals** (Joseph 2008, Kenyon 2006, Halkoaho2010, Rengerink 2015, Smyth 2012) **Sufficient information** (Dorantes 2000, East 1996, East 2006, Dorantes 2000, Halkoaho 2010, Hutton 1990, Rengerink 2015, Rodger 2003) **Sufficient time** (Rengerink 2015)	**Problems in recruitment processes** (Baker 2005, Kenyon 2006, Mohanna 1999, Smyth 2009, Smyth 2012, vanDelft 2013) **Timing of recruitment & information** (Baker 2005, East 2006, Ferguson 2000, Halkoaho 2010, Rengerink 2015) **Insufficient information and/or understanding** (Coulibaly-Toraore 2003, Ferguson 2000, Joseph 2008, Kenyon 2006, Smyth 2012) **Wanting individually tailored approach** (Baker 2005, Mohanna 1999, Smyth2012)
Physical, psychological, social, & relational factors	**Family support** (Rengerink 2015) **Feeling positive** (Rengerink 2015)	**Labor pain** (Dorantes 2000, Founds 2007) **Needle** (Daly 2003, Rodger 2003, Rohra 2003) **Fear of unknown** (Dorantes 2000, Hutton 1990; Rengerink 2015)) **Feelings of uncertainty** (Rengerink 2015) **Feeling vulnerable** (Baker 2005, Smyth 2009) **Lack of privacy** (Dorantes 2000) **Confidentiality concern** (Halkoaho 2010) **First child** (Lavender 2009) **Family objection/consult** (Daly2003, Dorantes2000, McLeod 2004, Rengerink 2015, Rohra 2003)

6.3.3.5 Methodological concerns

Randomization was discussed in several studies (Hendrix et al., 2009; Lavender & Kingdon, 2009; Rengerink et al., 2015; Turner et al., 2008). Pregnant women did not agree to be randomized to either hospital birth or home birth although they were willing to be enrolled in a cohort study comparing the outcomes depending on the place of birth (Hendrix et al., 2009). Regarding a hypothetical RCT looking at vaginal birth versus elective cesarean section, 73% of pregnant women expressed dislike for not having their choice of the mode of delivery and 27% considered the study unethical (Turner et al., 2008). In another study asking postpartum women about whether they would have participated in research comparing the mode of delivery, the majority said they would not have participated in such a study and questioned the benefit of the trial (Lavender & Kingdon, 2009). In this study, postpartum women valued vaginal birth as natural and would have felt being cheated if not given the choice (Lavender & Kingdon, 2009). Also, pregnant women were discouraged to participate if they perceived differences in the risk benefit ratio depending on the assigned procedure (Baker et al., 2005). That is, if they felt that one research procedure might be inferior to the other, they would not participate for the fear that they might have to receive an inferior treatment.

In addition to randomization, blinding which made the participant unaware of the treatment being performed was identified as a negative factor by pregnant women (Rengerink et al., 2015; Smyth et al., 2009). Similarly, pregnant women felt against the use of a placebo in drug related research (Mohanna & Tunna, 1999; Rengerink et al., 2015; Rodger et al., 2003). On the other hand, pregnant women appreciated the H1N1 vaccine study as it did not involve any placebo, and thus all participating women would receive the vaccine (Lyerly et al., 2012). Pregnant women preferred to be in the intervention group such as using pulse oximetry for monitoring the fetus during labor (East, Chan, Brennecke, King, & Colditz, 2006) or taking particular posture to correct breech presentation (Founds, 2007). In terms of methodological issues, pregnant women were reluctant about participating in research that involved randomization, blinding of procedures, and use of a placebo or non-intervention group.

6.3.3.6 Recruitment processes

In the recruitment process, healthcare providers' encouragement positively influenced women with breech presentation (after 32 weeks) to participate in a RCT comparing 15 minutes knee-chest posture for seven days and no intervention (Founds, 2007). Also, pregnant women recruited for giving their placenta for a placenta perfusion study felt positive about participation when they felt healthcare professionals were ethical and committed to the research project (Halkoaho et al., 2010). Indeed, trust in healthcare professionals is an essential factor for enhancing pregnant women's participation in both interventional and observational research (Halkoaho et al., 2010; Joseph et al., 2008; Kenyon et al., 2006; Rengerink et al., 2015; Smyth et al., 2012). Another enhancing factor was pregnant woman's perception that she received sufficient information about the research (Dorantes et al., 2000; East & Colditz, 1996; East et al., 2006; Halkoaho et al., 2010; Hutton et al., 1990; Rengerink et al., 2015; Rodger et al., 2003). Related to information provision, a concerning issue was pregnant women's understanding of risk and other relevant information about research. Inaccuracies in the woman's understanding may ironically enhance participation, such as an assumption of safety of antibiotic administration during preterm labor (Kenyon et al., 2006), no side effects for magnesium sulfate for preeclampsia (Smyth et al., 2009), and direct benefits to the participant in a study collecting maternal blood, cord blood, and child DNA (Joseph et al., 2008), as well as a poor understanding of the placebo (Coulibaly-Traoré et al., 2003).

On the other hand, pregnant women did not want to participate in research when the timing of recruitment and information provision was not optimal for them, such as during labor (Baker et al., 2005; East et al., 2006; Ferguson, 2000; Halkoaho et al., 2010; Rengerink et al., 2015). Comparing pregnant women who participated in research on a pain controlling drug during labor (n=26) and men and women who participated in several other non-obstetric studies (n=78), the satisfaction about information provision and their understanding were lower in the study with pregnant women (Ferguson, 2000). Also, a study on the views of pregnant women with preeclampsia who participated in a study involving prophylactic use of anticonvulsants uncovered differences in the desired type and style of information (Smyth et al., 2009; Smyth et al., 2012). Some pregnant

women wanted the research team to be more sensitive to the fact that they were pregnant (Baker et al., 2005) and that they must understand the information under a stressful situation (Kenyon et al., 2006). A qualitative study with women who participated or declined participation in one of the eight clinical trials during pregnancy or postpartum revealed that both consenters and decliners felt the need for sufficient time to consider participation as being approached for research participation was unexpected (Rengerink et al., 2015). Also, the preferred manner of initially being approached for research testing nifedipine in preterm labor differed across women (Mohanna & Tunna, 1999). A study in the context of preterm labor revealed that women valued social and emotional interactions with the person who approached them for recruitment (Kenyon et al., 2006). Such interactions included accommodating the woman's needs and preferences in when or how they want the research to be explained (Kenyon et al., 2006). Considering differences across pregnant women's needs, some authors recommend a more individualized approach to the consent process (Baker et al., 2005; Mohanna & Tunna, 1999; Smyth et al., 2012).

6.3.3.7 Physical, psychosocial, and relational limitations

Various factors apart from the research itself appeared as limitations for pregnant women to participate. For example, labor pain discouraged women from considering participation in research aimed at finding the minimum local analgesic concentration of local anesthetics (Dorantes et al., 2000) or in a study examining an intervention for breech presentation (Founds, 2007). As a mixture of physical and psychological limitations, some women indicated fear of needles (Daly et al., 2003; Rodger et al., 2003; Rohra et al., 2009) or inexplicable fear that inhibited them from participating in research (Dorantes et al., 2000; Hutton et al., 1990).

When researchers were also healthcare providers, some women experienced the feeling of vulnerability (Baker et al., 2005; Smyth et al., 2009). Smyth et al. (2009) reported women's perception of being pressured to participate or that healthcare providers were more committed to research rather than to clinical care. In another study, however, some women felt powerless when recruited by clinician investigators while others felt it easier to decline due to the good clinical relationship developed in the course of pregnancy

(Baker et al., 2005). Family objection was reported in several studies (Daly et al., 2003; Dorantes et al., 2000; McLeod et al., 2004; Rengerink et al., 2015) including one study from Pakistan (Rohra et al., 2009). On the other hand, another study on the pregnant woman's decision making in a RCT involving a drug and a placebo indicated that family opinions had little influence compared with the weight given to the physician's opinion (Smyth et al., 2012). Although inconclusive, previous studies may suggest both healthcare providers and family members having some influence on the pregnant women's decision making about research participation. There has been no study that demonstrated cultural influences in terms of family objection.

Finally, pregnant women were concerned about the lack of privacy when participating in a study during labor (Dorantes et al., 2000) as well as inadvertent disclosure of personal information when providing placenta for research purposes (Halkoaho et al., 2010). A study of primigravid women's views on a hypothetical RCT comparing planned vaginal birth and planned cesarean section revealed that 59 out of 64 women did not want to participate (Lavender & Kingdon, 2009). One of the main reasons was that they wanted to be perfect with the first child (Lavender & Kingdon, 2009). This may suggest that some women may hesitate being involved in anything experimental particularly with their first child.

6.3.4 Themes identified from professionals' and other stakeholders' views

Eight studies investigated the views of stakeholders other than pregnant women (Table 14). Six studies researched obstetric healthcare providers (Founds, 2007; Haas, Wunder, Wolf, & Denne, 2010; Halkoaho, Kirsi Vähäkangas, Häggman-Laitila, & Pietilä, 2012; Mudd et al., 2008; Penn & Steer, 1990; Turner et al., 2008) while one study examined African American healthcare providers whose practice was not restricted to obstetric care as well as community members regarding inclusion of pregnant women and children in genetic research (Ngui, Warner, & Roberts, 2014). Another study investigated pharmaceutical industry related persons, including persons in regulatory agencies (Shields, 2012). Within the small number of studies, the themes identified are barriers and concerns, and being a professional.

Table 14 Themes identified from healthcare providers' and others' views

Themes	Subthemes
Barriers & concerns	**Methodology** (Penn 1990, Turner 2008) **Potential deviation from standard of care** (Penn 1990) **Risk** (Shields 2012) **Medico-legal liability** (Penn 1990, Shields 2012) **Privacy** (Mudd 2008, Ngui 2013) **Staffing level** (Penn 1990) **Time constraint** (Founds 2007, Mudd 2008, Penn 1990) **Lack of understanding** (Ngui 2013)
Being a professional	**Seeking evidence based alternatives** (Founds 2007) **Discrepancy as a personal & professional matter** (Haas 2010)

6.3.4.1 Barriers and concerns

Obstetric healthcare providers perceived various barriers in the clinical setting of their affiliated institutions in conducting clinical research with pregnant women. Considering a RCT comparing two delivery methods of preterm breech, 11 out of 36 hospitals could not reach a consensus among the obstetric consultants as they perceived the barriers due to the insufficient staffing level of the antenatal clinic for obtaining informed consent and the low availability of skilled professionals for delivery of preterm breech (Penn & Steer, 1990). Related to the staffing level, several studies indicated that obstetric healthcare providers felt challenged to dedicate their time for research (Founds, 2007; Mudd et al., 2008; Penn & Steer, 1990). The issue of time constraint pertained to obstetric healthcare providers (Penn & Steer, 1990) and other staff in the delivery room or prenatal clinic including those engaged in clerical work (Mudd et al., 2008). In addition, midwives (Halkoaho et al., 2012) as well as other hospital staff (Mudd et al., 2008) feared that the patient flow might be disrupted by research activities. Persons related to pharmaceutical

industries indicated a psychological barrier due to historical tragedies such as the repercussion of thalidomide (Shields, 2012).

Regarding methodological issues, researchers associated with pharmaceutical companies anticipated more work in achieving scientific validity or more complexity in study designs and analyses when including pregnant women in research (Shields, 2012). Deviation from the standard of care was a concern among obstetric consultants who were asked about the relevance of a RCT comparing vaginal delivery versus caesarean section for preterm breech (Penn & Steer, 1990). Considering standard of care for preterm breech, some obstetric consultants determined that this RCT was not methodologically sound (Penn & Steer, 1990).

Other concerns acknowledged by some healthcare providers and others in pharmaceutical industries or related agencies included potential harm to the research participant (Shields, 2012) as well as liability issues (Penn & Steer, 1990). Apart from physical or psychological risks, protection of privacy was also a concern for research involving specimen and data collection (Mudd et al., 2008; Ngui et al., 2014). A study examining the views of African American healthcare providers and community members on genetic research revealed insufficient understanding of genetics, differences between research and clinical care, and privacy issues not only among community members but also among healthcare providers despite their favorable attitude toward genetic research (Ngui et al., 2014).

6.3.4.2 Being a professional

Being a professional consists of two subthemes: seeking evidence based alternatives and discrepancy as professional and personal matters. First, Founds (2007) identified seeking evidence based alternatives to current care as a motivation for healthcare providers to consider being involved as investigators in research of postural management for breech presentation. Although healthcare providers found it difficult to integrate research into their busy practice, they were motivated if they could see a clear benefit of improving future clinical care (Founds, 2007). Second, an online anonymous survey investigating obstetric healthcare providers' attitudes on research with pregnant women revealed some

discrepancy in the professional's endorsement of research depending on whether it was considered for the patients (83.2%) or for themselves and their families (66.4%) ($p<0.001$) (Haas et al., 2010). This finding suggests that professionals might enroll patients in a study in which they would not enroll their family or themselves.

6.4 Knowledge gaps and implications for future research

To date, the vast majority of the studies investigated pregnant women's motivations to participate in obstetric research primarily during the perinatal period and in epidemiological research involving health data or specimen collection. This may be understandable as pregnant women's participation particularly in non-obstetric, interventional research is reported to be rare (Domínguez et al., 2012). Although challenging, more research is required regarding the views of pregnant women and other stakeholders on interventional or non-obstetric research to clarify pregnant women's experiences of participation and the difficulties involved in conducting such research.

There is a paucity of research on other stakeholders' views compared to pregnant women's views. Regarding the participants, although pregnant women are key stakeholders as they authorize the research to happen to themselves, it may be necessary to further investigate the views of other stakeholders, such as healthcare providers, researchers, family members, REC members, community members, health industries, and regulatory bodies. Pregnant women's consent to participate is not the only condition that must be satisfied for a research study to be undertaken. A research project must be planned by researchers and approved by the REC. Obstetric healthcare providers are key players in the recruitment of pregnant women for research purposes. Also, health industries may not sponsor a study if they perceive significant barriers. Thus the views of those who relate to the conduct of research with pregnant women must be investigated to address their concerns or seek better strategies for research to happen.

Also, most studies were conducted in Western countries, with US and UK studies comprising two thirds of the total number of studies. A lack of a global perspective due to little research conducted in Asian and African countries must be addressed. Some previous studies have shown that pregnant women and other stakeholders' attitudes

toward research with pregnant women may differ across ethnicities (Lamvu et al., 2005; Nechuta et al., 2012; van Delft et al., 2013). It cannot be assumed that what applies to Western countries would apply to other countries with different social, cultural, or historical backgrounds.

The methodology of nearly two thirds of the reviewed studies was quantitative, using surveys or structured interviews to describe the trends or views of participants on research involving pregnant women. Qualitative approaches are suitable for examining people's experiences with a particular phenomenon, understanding what lies behind the issues that are little known, providing fresh insights into known issues, and giving details which may not be possible with quantitative approaches (Strauss & Corbin, 1990). Pregnant women's experience of research participation as well as women's and other stakeholders' attitudes toward research with pregnant women and the processes by which they determine the acceptability of such research are complex. More qualitative research is needed for exploring the pregnant woman's decision making process about research participation or their meanings of research participation. For other key stakeholders who have been little researched, qualitative research may be useful for capturing important factors in their decision making process about whether a particular research project may include pregnant women.

Limitations mentioned by authors of the reviewed studies also provide suggestions for future research. Regarding quantitative studies, a few researchers indicated a lack of standardized instruments for examining the participant's understanding about research and attitudes toward research with pregnant women (Haas et al., 2010; Joseph et al., 2008). Developing a standardized tool for evaluating the participant's views on research with pregnant women may enable comparison and integration of the results across studies. Such a tool may help developing guidance for planning research with pregnant women and their recruitment.

The themes identified from the findings of previous studies examining pregnant women's reasons to participate or not in clinical research were as follows: benefit to others, self benefits, risks to the woman and fetus, weighing risks and benefits, methodological

concerns, recruitment process, and physical, psychosocial and relational limitations. These studies identified various facilitators and barriers for pregnant women's participation in research in terms of their attitudes toward research, their understanding about the study, their experience in the recruitment process, and miscellaneous limitations for participation. While these studies show few conflicting results regarding factors that may influence women's decision making, an identified gap was the lack of clarity regarding how these factors are prioritized or integrated in the pregnant woman's decision making process.

The themes identified from the views of healthcare providers, persons related to pharmaceutical industries, and community members on pregnant women's research participation were as follows: barriers and concerns, and being a professional. However, literature search for this review revealed only eight relevant papers. The findings largely revolved around healthcare providers' concerns and perceived barriers for conducting research in a particular institution. However, how healthcare providers perceive the needs and importance of research with pregnant women has not been well documented. In addition, the themes identified from the analysis of previous studies on healthcare providers were not necessarily pregnancy specific but rather applicable to any clinical research. It seems important to further investigate how healthcare providers recognize pregnancy specific factors in considering research with the pregnant population.

6.5 Conclusions and limitations

This scoping review mapped the current state of literature on pregnant women's and other stakeholders' views on clinical research with pregnant women. The key findings include the characteristics of empirical studies to date in terms of the methodology, place where research was conducted, participants, types of research with pregnant women considered by the participants, and themes identified from the views and attitudes of pregnant women and other stakeholders on clinical research with pregnant women.

There were more quantitative studies compared with qualitative studies, a paucity of research with healthcare providers, persons related to pharmaceutical industries, and community members, more studies examining views on pregnant women's involvement

in obstetric research compared with non-obstetric research and on pregnant women's involvement in non-interventional research compared with interventional research, and a scarcity of studies in Asian and African countries. The themes identified from the results of pregnant women's views describe women's reasons for and against research participation. The themes identified from the results of other stakeholders' views mostly describe these stakeholders' concerns regarding research with pregnant women. A gap in the pregnant women's views on clinical research with pregnant women was the insufficiency of the data to understand how pregnant women integrate various positive and negative factors in deciding whether or not to participate in research. Also, little is known about how other stakeholders recognize the importance of research with pregnant women and pregnancy specific concerns that may discourage them from enhancing research with pregnant women, both of which are important for the stakeholders to determine whether a particular research project may include pregnant women.

A limitation of this review is the low number of studies with stakeholders besides pregnant women to date. Other limitations came from various research settings and conditions across the reviewed studies, such as investigating the participant's views on the actual research versus hypothetical research (Daly et al., 2003; Lavender & Kingdon, 2009) or the views of decliners versus consenters (Kenyon et al., 2006; Lyerly et al., 2012). Thus it was difficult to compare and synthesize the results across studies.

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Chapter 7

7 Views of pregnant women, obstetric healthcare providers, and researchers in reproduction areas on clinical research with pregnant women: A grounded theory study

This chapter describes a grounded theory study which explores decision making about clinical research with pregnant women from the perspectives of pregnant women, obstetric healthcare providers, and researchers in reproduction areas. This chapter begins with the background of this study. Then the purpose, research questions, methodology, and results will be presented followed by discussions, limitations, and implications of the findings.

7.1 Background

7.1.1 Underrepresentation of pregnant women in clinical research

There has been a reported lack of clinical research with pregnant women. In the United States (US), 95 % of 368 phase IV clinical trials registered from October 2011 to January 2012 excluded pregnant women although drugs used in these trials were not contraindicated during pregnancy according to the Food and Drug Agency (FDA) pregnancy category (Shields & Lyerly, 2013). Also in the US (2000-2009), the majority of non-observational clinical research with pregnant women were pregnancy related, 53% being maternal or fetal preventive studies and 47% being therapeutic studies among which 59% researched on-going obstetric conditions (Domínguez, Ramos, Torrents, García, & Carné, 2012). These data suggest that pregnant women are rarely included in clinical research, particularly interventional studies investigating non-obstetric conditions.

7.1.2 Historical background

Clinical research conducted with vulnerable populations, such as prisoners, children with cognitive impairments, and disadvantaged minorities generated serious concern as these populations were taken advantage of their vulnerable position to serve as research

participants often without being disclosed about the purpose of the study and the risks involved (Emanuel, Wendler, & Grady, 2008). Considering human abuse in research during World War II, the Nuremburg Code (1947) (CIRP Library, 1996) and the Declaration of Helsinki (1964) (World Medical Association, 2013) have established ethical guidelines for research involving humans. Among the important stipulations are: (1) voluntary informed consent cannot be compromised, (2) vulnerable populations must be protected, (3) risks to the participant must be proportionate to the importance of the study, and (4) the participant's well being is to be given the top priority. In 1966, Beecher (1966) published a landmark paper on 22 examples of ethically questionable research published in reputable academic journals, where he identified two major problems: (1) participants were not informed about the research purpose and risks involved and (2) researchers lacked a sense of responsibility to protect the welfare of participants.

The historical background of human abuse in research has led the regulations and guidelines to focus on the protection of participants, particularly vulnerable populations who were conveniently used without informed consent (Emanuel et al., 2008). The US Code of Federal Regulations (Department of Health and Human Services, 2009) has been influential in the discussions of research ethics across jurisdictions. The Belmont Report (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979) has set out a basic set of rules regarding ethical conduct of biomedical and behavioral research involving humans. These principles are respect for persons, beneficence, and justice. In relation to participant selection, the Belmont Report states that justice requires fair distribution of research risks and benefits among people. In addition, it defines vulnerable populations as persons with diminished autonomy, and states that they must be provided with additional protection. Such a protectionist trend was prominent across policies and guidelines (Emanuel et al., 2008).

In the 1990s, however, the protectionist approach shifted toward an inclusionary approach based on the recognition that fair participant selection requires relevant inclusion as well as exclusion of particular populations (Emanuel et al., 2008; Meltzer & Childress, 2008). The difficulty of enrolling vulnerable populations resulted in further disadvantages of these populations as they could not receive (1) direct benefits from

participation in some therapeutic research and (2) indirect benefits from the most updated outcomes of science as a member of the population represented in research (Meltzer & Childress, 2008; Zion, Gillam, & Loff, 2000). In contrast to the exclusionary guidelines by the Food and Drug Administration (FDA) regarding premenopausal women, the NIH implemented policies stipulating that women and minorities be included in research unless compelling reasons exist to exclude them (Charo, 1993; Goodrum, Hankins, Jermain, & Chanaud, 2003). Specifically with regard to gender, females were often excluded from clinical research under the fear that the hormonal cycle may skew the results and analyses for both male and female require higher costs (Baird, 1999; Mastroianni, Faden, & Federman, 1994). Although research with non-pregnant women has dramatically increased in the US over the years, pregnant women still remain underrepresented in clinical research despite the Institute of Medicine Report (1994) which recommended that pregnant women should be deemed eligible as research participants (Lyerly, Little, & Faden, 2008b). The issues with pregnant women may pertain to postnatal breastfeeding women and women with childbearing potential as these women are similar to pregnant women in terms of the possibility of affecting the offspring (Begg, 2008).

Current regulations address pregnant women's research participation in various ways across jurisdictions. For example, the US Code of Federal Regulations (CFR) (Department of Health and Human Services, 2009) still classifies pregnant women and fetuses among vulnerable populations that require additional protection (45 CFR 46 Subpart B, 2009) although policies have shifted much to rectify the issues caused by the exclusion of pregnant women. In contrast, the Tri-Council Policy Statement of Canada, 2nd edition (TCPS2) (Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council Canada, & Social Sciences and Humanities Research Council of Canada, 2014) does not classify pregnant women as a vulnerable population. The TCPS2 clearly stipulates that childbearing potential, pregnancy, or breastfeeding should not be automatic exclusion criteria for research participation (Article 4.3). Nevertheless, the TCPS2 holds that the enrollment of these women should be determined through the balancing of risks and benefits to the woman and her fetus or infant as well as the disadvantage of excluding them (Article 4.3), which may be open to a considerable

range of interpretations. In the Council for International Organizations and Medical Sciences (CIOMS) Guidelines (CIOMS, 2002), pregnant women are not mentioned in the list of populations identified as vulnerable (Guidelines 13, 14, 15). Nonetheless, research must be based on the health needs of pregnant women (Guideline 17), which can be restrictive toward including pregnant women. Although the policies on pregnant women's research participation are clearly moving from the exclusionary to inclusionary framework, their underrepresentation in clinical research has not been resolved.

7.1.3 Clinical and ethical problems of excluding pregnant women from research

Underrepresentation of pregnant women in clinical research has caused serious problems as many authors have indicated (Baylis, 2010; Charo, 1993; Chervenak & McCullough, 2003; Kass, Taylor, & King, 1996; Lyerly, Little, & Faden, 2008a; Macklin, 2010; Mastroianni et al., 1994; Mattison & Zajicek, 2006; McCullough, Coverdale, & Chervenak, 2005; Minkoff, Moreno, & Powderly, 1992). Pregnant women constitute a subpopulation whose drug distribution, metabolism, and elimination differ from non-pregnant women due to the physiological properties related to pregnancy (Baylis, 2010; Goldkind, Sahin, & Gallauresi, 2010; Goodrum et al., 2003; Mattison & Zajicek, 2006). Moreover, the limited types of studies conducted with pregnant women entail bias with regard to pharmaceutical safety (Koren & Nickel, 2010). The central concern is the lack of evidence to guide effective and safe clinical practice and decision making, which affects both the woman and her fetus (Baylis, 2010; Charo, 1993; Kass et al., 1996; Macklin, 2010; Mattison & Zajicek, 2006; McCullough et al., 2005). Furthermore, without research data to determine a therapeutic dose, clinicians may administer inadequate dose to pregnant women and enhance drug resistance, which compromises procedures such as antiviral treatments (Goldkind et al., 2010).

While pregnant women are often excluded particularly from drug studies (Shields & Lyerly, 2013), they may require medications for various reasons (Lyerly et al., 2008a; Lyerly, Little, & Faden, 2008c). They may already be on medication for pre-existing health conditions before becoming pregnant or may develop conditions that require additional medication during pregnancy (Lyerly et al., 2008a; Lyerly, Little, & Faden,

2008c). Pregnant women may have a variety of diseases such as hypertension, diabetes, psychiatric illness, cancer, and autoimmune diseases, none of which should be left untreated (Lyerly et al., 2008a; Lyerly, Little, & Faden, 2008b). Based on the database of the Health Maintenance Research Network Center for Education and Research on Therapeutics in the US, a retrospective study revealed that 64% of the pregnant women who gave birth to their child from 1996 to 2000 received a prescription medication (excluding vitamins and mineral supplements) during 270 days prior to delivery (Andrade et al., 2004). The use of prescription drug during pregnancy has increased over time in the US according to the Slone Epidemiology Center Birth Defects Study (1976-2008) and the National Birth Defects Prevention Study (1997-2003) which together interviewed more than 30,000 women about drug use during pregnancy (Mitchell et al, 2011). This US study indicated that prescription drug use increased by 60% from 1976, culminating with approximately 50% of women using at least one prescription drug in 2008 (Mitchell et al, 2011). Also, medication during pregnancy may also include over-the-counter drugs and herbal products, which may cause interactions with one another (Mattison & Zajicek, 2006). Lyerly et al. (2008a) claim that in the US, two-thirds of pregnant women take four to five medications, and that in some developing countries, drug treatment for malaria is an issue. A population-based cohort study based on the Medical Birth Registry of Norway and the Norwegian Prescription Database (2004-2006) showed that approximately 30% of pregnant women were using drugs among which 57% were prescribed drugs (Engeland et al, 2008). A French study which examined original prescription forms of 1000 women who gave birth in 1996 revealed that 99% of the women were prescribed at least one drug during pregnancy and that 79% of the women were prescribed drugs without any safety information based on human or animal studies (Lacroix, Damase-Michel, Lapeyre-Mestre, & Montastruc, 2000). Although the figures indicating medication use during pregnancy differ across countries as well as across studies, they point to pregnant women's need for medication for various purposes.

From an ethical viewpoint, disproportionate representation of pregnant women in research is problematic as it results in depriving them of indirect and direct benefits of research (Baylis & Kaposky, 2010; Mastroianni et al., 1994; Minkoff et al., 1992). The indirect benefit is to receive safe and effective treatment based on research evidence as a

population and the direct benefit is to participate in therapeutic research particularly when the participation is the only avenue to treatment (Baylis & Kaposky, 2010; Mastroianni et al., 1994; Minkoff et al., 1992). Hall (1995) criticizes that automatic exclusion of pregnant women from clinical trials is clearly unethical and illegal. She points out that the US Code of Federal Regulations does not demand automatic exclusion and that such exclusion is based on a false justification to protect the (1) fetus from harm, (2) researchers from liability, and (3) scientific integrity of the study as pregnant women are physiologically different from the general population.

In relation to women with childbearing potential, Beran (2006) criticizes the mandate for women to withdraw from research in the event of a pregnancy. Recognizing that a significant influence on the fetus is likely to have occurred by the time pregnancy is confirmed and thus automatic withdrawal from the study may not be in the best interest for the woman and fetus, Beran (2006) argues that the participant's autonomy to choose whether to remain in the study or to withdraw should be respected. From a slightly different perspective, Macklin (2010) criticizes the mandate to withdraw upon becoming pregnant and argues that women should be monitored throughout the pregnancy as harm to the fetus can occur at any gestational stage. Beran (2006) and Macklin (2010) argue for securing maternal and fetal well being as well as the woman's autonomy. Regarding the mandate for women to use contraceptives during research participation, Schonfeld and Gordon (2005) stress that (1) excessive restrictions on the contraceptive method has much focus on the fetus and (2) some contraceptives such as oral hormonal medication may be too invasive. They argue that these mandates on women with childbearing potential are against the principle of autonomy and respect for persons.

As discussed, due to the historical background of human exploitation in research, regulations and guidelines initially focused on protecting research participants, particularly vulnerable populations, such as children, prisoners, individuals with mental illness, or those institutionalized for disabilities by excluding them from research (Emanuel et al., 2008). Ironically, however, excluding particular populations from research resulted in further disadvantages for these populations (Emanuel et al., 2008; Meltzer & Childress, 2008) as they were deprived from potential direct benefit from

research participation and research evidence to support their clinical care (Emanuel et al., 2008; Meltzer & Childress, 2008). Pregnant women have been considered one of those vulnerable populations (Lyerly, Little, & Faden, 2008b) demonstrated in the statistics of clinical research with pregnant women in recent years (Shields & Lyerly, 2013) as indicated in the beginning of this chapter. Particularly, pregnant women are excluded from non-observational research investigating non-obstetric conditions (Domínguez, Ramos, Torrents, García, & Carné, 2012).

Considering clinical and ethical problems resulting from insufficient clinical research with pregnant women, it is important to explore the stakeholders' views on clinical research involving pregnant women. To date, the views of pregnant women have been studied mostly in terms of their reasons to participate or not to participate in research (Chapter 6). Compared with pregnant women, other stakeholders have been little researched, mostly limited to healthcare providers (Chapter 6). These studies overall revealed healthcare providers' concerns about research with pregnant women or perceived barrier in conducting such research (Chapter 6).

7.2 Purpose

The goal of this grounded theory study is to generate a substantive theory to explain the decision making processes involved in considering pregnant women's participation in clinical research. The purpose of this study is to understand the processes used by pregnant women, obstetric healthcare providers (physicians from various specialties who see pregnant women in their practice, obstetric nurses, midwives), and researchers in the areas related to reproduction to determine under what conditions clinical research with pregnant women may be considered acceptable.

7.3 Research questions

1. How do pregnant women feel about conducting clinical research with pregnant women?

2. How do pregnant women decide whether or not to participate in a particular clinical research project?

3. How do obstetric healthcare providers and researchers in the reproduction field feel about clinical research with pregnant women?

4. How do obstetric healthcare providers and researchers in the reproduction field determine whether a particular clinical research project with pregnant women is acceptable?

In this study, clinical research refers to the definition by the United States National Institute of Health (NIH) (National Institute of Health, 2012) as follows: "research that directly involves a particular person or group of people, or that uses materials from humans, such as their behavior or samples of their tissue" (Clinical Trials and Clinical Research, para. 1). This widely acknowledged definition encompasses biomedical and behavioral research involving humans, which may suit this study as it uses both types of research examples in exploring the participant's views.

7.4 Methodology

7.4.1 Constructivist grounded theory

7.4.1.1 Grounded theory

This study employed constructivist grounded theory articulated by Charmaz (2003; 2006). Grounded theory is an approach originally developed by Glaser and Strauss (1967) to systematically analyze qualitative data through identification of themes and categories emerging from the data toward developing an explanatory theory beyond a simple description (Corbin & Strauss, 2008). Grounded theory is deemed suitable for researching social or psychological processes that have been little studied or not studied in enough breadth or depth (Birks & Mills, 2011; Charmaz, 2003; Holloway & Todres, 2003; Milliken, 2010; Urquhart, 2013; Sandelowski & Barroso, 2003; Stern, 1980). Social or psychological processes may be understood as human responses in “all aspects of the natural, dynamic nature of life” (Birks & Mills, 2011, p.18) such as “action or emotional response to the given context” (Corbin & Strauss, 2008, p.229).

7.4.1.2 Philosophical positioning

Grounded theory ranges in several schools based on the differences in the understanding of knowledge creation (Charmaz, 2003; Mills, Bonner, & Francis, 2006). Traditional grounded theory by Glaser and Strauss took an objectivist position which endorses positivistic understanding of reality comparable to that in natural science, i.e. assuming reality in an external world to be discovered and observed (Charmaz, 2003; Lincoln & Guba, 2003). Due to such a position, the objectivist grounded theory aims at developing a verifiable theory which can provide explanation as well as prediction (Charmaz, 2003). Later, Strauss and Corbin shifted from the traditional grounded theory to a less positivistic version of the grounded theory (Charmaz, 2003). The way they explicate their version of grounded theory reflects both postpositivism as well as constructivism (Charmaz, 2003; Mills et al., 2006). Strauss and Corbin may be more in the positivist or objectivist positioning (Charmaz, 2003) although they have not explicitly clarified their ontological positioning (Mills et al., 2006).

In contrast to positivism, constructivism is ontologically situated in a relativist position, assuming multiple realities (Guba & Lincoln, 1994; Lincoln & Guba, 2003; Ponterotto, 2005). Epistemologically, constructivism takes a subjectivist position, understanding that research findings are co-created by the researcher and participants through their dialectical transaction (Charmaz, 2003; Ponterotto, 2005). Methodologically, constructivism belongs to the interpretivist tradition (Guba & Lincoln, 1994; Lincoln & Guba, 2003; Ponterotto, 2005). Thus in constructivist grounded theory, data are constructed by participants from their experiences and the researcher aims to interpret the participants' meanings of their experiences (Charmaz, 2003; Charmaz, 2006). The research findings or the developed theory may be transferable to similar issues and fields but not expected to provide prediction since causality is incomplete and the findings are deemed not generalizable (Charmaz, 2003).

7.4.1.3 Why constructivist grounded theory was chosen

Constructivist grounded theory was used to undertake this study for several reasons. First, the literature review (Chapter 6) indicated that there is limited in-depth knowledge about

the views of pregnant women and particularly other stakeholders on clinical research with pregnant women. Regarding pregnant women's views on clinical research, previous empirical studies have primarily focused on their motivation to participate or issues related to recruitment strategies. Little is known about how pregnant women feel about clinical research or how they prioritize various factors when considering research participation. Also, most studies, quantitative or qualitative, explored pregnant women's views on participation in research related to obstetric conditions or research that can be conducted only with the pregnant population. Regarding healthcare providers and researchers in reproduction areas, research has been sporadic. Minimal investigation has been conducted on their views on conducting clinical research with pregnant women. How they determine a research project with pregnant women may be acceptable has hardly been explored.

Second, the research questions which focused on the psychological processes of the participant suited constructivist grounded theory (Birks & Mills, 2011; Charmaz, 2003; Holloway & Todres, 2003; Milliken, 2010; Urquhart, 2013). Making a decision to participate in clinical research may be a complex process for a pregnant woman, considering information which may likely be more complicated compared with non-pregnant women and potentially involving her partner, other family members as well as healthcare providers (Helmreich, Hundley, Norman, Ighedosa, & Chow, 2007). Similarly, regarding healthcare providers and researchers in the areas of reproduction, constructivist grounded theory may be appropriate for understanding their perception of clinical research with pregnant women and the processes they use to determine acceptable study designs, procedures, inclusion criteria such as gestational stage or health status, safety measures, various research contexts including the societal and scientific backgrounds of the study considered.

Third, the recognition that findings are a co-creation of the participants and researcher made sense to me. In the process of drafting a research proposal including research questions and interview guides, recruiting participants, collecting and analyzing the data, I was involved as a principal investigator, facilitator, listener, and interpreter. These roles could not be ignored in creating knowledge through a research project. Also, the topic

touched my experiences of pregnancy, being a patient, and being an obstetric healthcare provider and clinical researcher, all of which may have influenced the course of research, particularly in the data collection and analysis. I might further say that my interest in the topic itself influenced the findings. I perceived the exclusion of pregnant women from clinical research as an issue that needed to be addressed. The final product of my research investigating the views of pregnant women, obstetric healthcare providers, and researchers in reproduction areas would inevitably involve my interpretation of their views.

7.4.2 Methods

Methods must be congruent with grounded theory as a methodology (Sandelowski & Barroso, 2003). Due to the nature of inquiry, the research process in constructivist grounded theory is flexible, emergent, and open to various possibilities (Charmaz, 2003; Charmaz, 2006). Data collection and analysis were conducted simultaneously and in an iterative way (spirally between data collection and analysis) to identify categories, and to analyze the relationships between the categories toward theory development (Charmaz, 2006).

7.4.2.1 Sampling

Initially, purposive sampling was conducted to recruit the following participant groups.

1. Pregnant women: age18 or older

2. Obstetric healthcare providers from various professions (physicians, nurses, and midwives) and across physician specialties as long as their current practice involved pregnant patients

3. Researchers (basic science) in reproduction areas

There was no exclusion in terms of the gestational stage and the level of pregnancy or other health risk for the pregnant women as long as their conditions were stable enough to participate in the interview. As the interviews were conducted in English, inclusion criteria included English speaking for all three groups. Also, the participants were limited

to those who gave informed consent to participate and to have the interview audio-recorded.

In contrast to quantitative research, it is difficult to establish a strict rule that determines a definite sample size that would produce an adequate amount of usable data in qualitative research as many factors are involved (Morse, 2000). These factors include the scope of the study, nature of the topic, quality of data, study design, and use of shadowed data (Morse, 2000). In this study, the estimated sample size for pregnant women was ten to 20 and that for healthcare providers and researchers was eight to 15. The difference between women and other two groups were based on the recognition that these professionals would be more homogeneous compared with pregnant women in their experience and thinking process due to their common professional backgrounds, particularly education and daily work in relation to the nature of the topic of this research.

In seeking possibilities of building and saturating categories identified from data analysis, theoretical sampling was conducted for each group to elaborate on the categories until theoretical saturation was reached, i.e. no more new categories would emerge and thus theoretical directions would be exhausted (Charmaz, 2006). In total, 12 pregnant women, 10 obstetric healthcare providers and 9 researchers in reproduction areas were recruited to reach theoretical saturation. Theoretical saturation and theoretical sampling will be discussed further under the data analysis. Participants were from London areas, Hamilton, and Montreal.

7.4.2.2 Recruitment

To recruit pregnant women, posters (Appendix A) and flyers were placed at the following locations in London, Ontario: waiting rooms of the obstetric outpatient clinic at Victoria Hospital, offices of midwives, and offices of family physicians. Women who saw the posters or flyers and were interested in participation were expected to call a toll-free contact phone number. Interested potential participants left their first name and a call back number for more information in the answering machine of the contact phone. Then the researcher checked the message and called back to set up an interview. The name and contact information of participants were deleted after the completion of the interview.

However, throughout the recruitment period which lasted for seven months, all pregnant women were recruited in person either through (1) an obstetrician or staff in the outpatient clinic or ward at Victoria Hospital in London, Ontario, (2) the researcher in the waiting room of an outpatient clinic in Victoria Hospital, or (3) the researcher at the Baby Expo in London, Ontario. In addition, one pregnant woman who was recruited was already known to the researcher. Most of the pregnant participants were recruited through Victoria Hospital.

Obstetric healthcare providers (physicians of various specialties whose practice involves pregnant women, obstetric nurses, and midwives) and researchers in reproduction fields were recruited mainly through the researcher and members on the research team in person or by email, using their email addresses publicly available from the website of the affiliated institutions. In addition, flyers (Appendix B, C) were given to potential participants in person by the researcher at relevant professional meetings in London and Montreal. A few healthcare providers and researchers were already known to the members of the research team while others were searched from relevant websites of academic and healthcare institutions.

7.4.2.3 Data collection

Data was collected from May, 2014 to November, 2014. Semi-structured, in-depth one-on-one interviews were conducted, audio-recorded, and transcribed verbatim. For pregnant women, the interviews took place at an available private room in the outpatient clinic of Victoria Hospital or over the telephone. For healthcare providers and researchers in reproduction areas, the interview took place at their private office or over the telephone. The interviews lasted approximately 30-40 minutes. The interview was closed when the researcher felt that enough data were collected. There was no participant who expressed their wish to end the interview before the researcher indicated.

The interviews were conducted using an interview guide which was identical across the three groups except for slight changes to suit their roles in clinical research with pregnant women (Appendix D). The questions were open-ended to loosely guide discussion and elicit rich data (Charmaz, 2006). The questions were modified and refined throughout the

course of research. Typically, interviews began by inviting the participants to share their initial views with a broad open-ended question, such as "How do you feel about research with pregnant women?" Questions remained open and flexible while focusing in on specific topics, such as, "What would be the important factors for you to decide whether or not to participate in research during pregnancy?" Paraphrasing, probing, and reflection were used throughout the interviews to help the participant articulate their feelings, thoughts, and give meaning to their responses. When the researcher felt necessary, prompts were used to facilitate the conversation as well as to elicit more in-depth descriptions from participants. For example, in considering fetal outcomes as an important factor, prompts, such as "How do you feel about your baby?" or "Could you describe more about safety?" were used. Non-verbal behaviors and observations made during the interviews as well as other contextual factors, such as having a family visit or being transferred to another room with higher surveillance, which can potentially be important for data analysis were recorded as field notes. These observations with pregnant women include emotional moments in talking about particular events such as previous miscarriage, trust in her healthcare provider, or hesitation in describing her thoughts about events in previous pregnancies. After each interview, I reflected on the overall conversation that took place and wrote down issues that stood out to me. I also wrote down anything that was common with other participants or anything in stark contrast with other participants.

Demographic data were collected from each participant at the end of the interview. However, at times, I asked pregnant women her gestational stage at the beginning as it was a piece of information not too personal and also functioned as an ice breaker. Demographic data for pregnant women included the participant's age, level of education first pregnancy or not, gestational stage, pregnancy complications, medical conditions, and any events in family members' or friends' pregnancy that could have affected the participant's feelings or attitudes about pregnancy. Demographic data for obstetric healthcare providers and medical researchers included the number of years of professional practice or research, the area(s) of practice and/or research, and the percentage of work related to pregnant women or reproductive health.

7.4.2.4 Data analysis

The transcript of each interview was initially read while listening to the audio-recording to ensure accuracy. The transcript was then analyzed in two phases: initial coding and focused coding (Charmaz, 2006). Coding is a process of defining what the data is about and seeking conceptual abstraction of the data (Bryant & Charmaz, 2007; Charmaz, 2006). Constant comparative methods and iterative processes were used in data analysis, comparing data with data, data with categories, and a participant from another participant (Charmaz, 2006). QSR N-Vivo 10 (QSR International 2013) was used to manage the data obtained from the three groups of participants. Data analysis was conducted separately for each group (pregnant women, obstetric healthcare providers, researchers in reproduction areas) as each of these groups take different roles in the context of clinical research with pregnant women. That is, pregnant women are potential participants, healthcare providers are potential investigators of clinical research involving pregnant women or recruiters for such research, and researchers in reproduction areas are primarily basic scientists who provide knowledge for enabling clinical research with pregnant women.

During initial coding, the data were fractured into small blocks and the codes stayed close to the data to remain open to various theoretical possibilities (Charmaz, 2006). At this stage, all codes were in gerund forms, such as "avoiding any risk", to preserve actions (Charmaz, 2006). The initial coding was conducted basically line-by-line. Initial coding enabled me to refrain from imposing preconceptions and delve into the data with a fresh pair of eyes (Charmaz, 2006). Before initial coding, I reviewed the field notes to refresh my memory of the interview.

Focused coding reassembled the fractured data to explain larger or multiple segments of data through identifying significant or frequent codes (Charmaz, 2006). Focused coding was more selective and directed toward theory development and thus I made decisions regarding how to categorize the data through identifying codes that were more analytical than others (Charmaz, 2003; Charmaz, 2006). Focused codes were developed by constant comparison of the data and were refined in further comparative processes. The categories which explain the data emerged from the focused codes (Charmaz, 2003). The entire

coding process was emergent, iterative, including going back to the data even at later stages when exploring the relationship between categories and identifying the most significant category. Examples of subcategories, codes, and data under a category in the course of research are shown in Appendices E, F, and G. To be in line with Charmaz's terminology (Charmaz, 2006), instead of using "themes" and "subthemes" which are often used in presenting the results of qualitative research, I used "categories" and "subcategories" to describe the model that emerged from data analysis.

In keeping with constructivist grounded theory, theoretical sampling was used to saturate the categories, i.e. reach theoretical saturation where new data would not add any new properties to the categories and any possibility of developing new categories (Charmaz, 2006). Theoretical sampling was also emergent. As the interview progressed, I hypothesized theoretical possibilities to explain the data, apply hypotheses or tentative ideas to explain the data, and explore the most relevant explanatory theory (Charmaz, 2006). As I accumulated more data, I examined the data by testing hypotheses emerging from the observed data, which is called abduction or abductive inference (Charmaz, 2006). For example, a hypothesis I tested in the course of researching obstetric healthcare providers was to explain their decision making process by "acting for the patient's best interest" as the main overarching process. As I applied this hypothesis to subsequent data, however, I recognized that this process could not encompass other categories, such as "respecting the woman's decision". I tried to be cautious about closing categories or leaving redundant categories without exhausting analytical possibilities (Charmaz, 2006). Given the skepticism over verification of theoretical saturation, I tried to stay open to any analytic possibilities in the field (Charmaz, 2006). The iterative process of seeking theoretical saturation enabled further conceptualization of the categories which should be "concrete, specific and analytic terms" (Charmaz, 2006, p.115).

Memo writing is considered important in grounded theory for analyzing the data from an early stage of research and throughout (Charmaz, 2006). Early memos help focusing on uncovering processes in the data while advanced memos categorize the data and tracks how categories emerge and develop throughout the research process (Charmaz, 2006).

Particularly, advanced memos have important roles in identifying incomplete categories and gaps in data analysis (Charmaz, 2006).

All research activities leading to important decisions were rigorously documented as memos throughout the research process to provide an audit trail and to permit a critical appraisal of the findings and decisions made at various stages of research. For example, I reflected on the participant's feeling and attitude toward clinical research with pregnant women. Participation in the interview was indeed voluntary and thus the data came from participants who were likely to be interested in the topic of clinical research with pregnant women. It turned out that participant after participant expressed positive attitudes, stating that research with pregnant women was important. Particularly in terms of pregnant women, the fact that I interviewed only those who consented to participate in this research could have brought a bias into the data and might have to be considered in data analysis.

In the beginning, memos helped to clarify what I saw in the data. Gradually, memos shifted to categorizing the data and became more analytical. In analyzing a new transcript, I explored categories in multiple ways that might explain the participant's feelings and decision making processes regarding clinical research with pregnant women. I used comparison across the data of the same participant and across participants to explore theoretical directions. In memo-writing, I clarified each category to reduce ambiguity and to be consistent in its use throughout the data across the three groups. In addition, I focused on important concepts such as risk, safety, or benefit to examine the categories and to refine them. Also, in the course of analysis, I identified negative cases that could not be subsumed into the developed categories. I explored potential explanations of these cases. An example of a negative case was the woman's attitude toward consulting others in their decision making. Almost all women wanted to consult their partner or attending physicians in deciding whether or not to participate in clinical research. One woman claimed she would decide by herself, feeling that she would be in the best position to think about her child's best interest. This may be explained by her background that she had two previous pregnancies with complications. She could have felt herself more experienced than others. Also, she was not totally rejecting others' opinions but

expressing that her opinion would likely be the best. Another example was a healthcare provider who did not perceive that research with pregnant women was difficult except for timely recruitment. A possible explanation for this view is that this healthcare provider was conducting research in the perinatal period where the fetal development would no longer be affected compared with other, particularly early stages where teratogenicity could be a huge issue.

In managing a huge amount of data with the three groups of participants in this study, memo writing was pivotal for staying organized while being open to various theoretical directions. Through memo writing, I was able not only to deepen my ideas but also to work on some pieces of data as much as possible at a certain point of research and come back to them later to explore further with more data and ideas across the three groups. For example, concepts such as risk and safety were revisited many times as it appeared across participants in all groups. Early memos discuss the difficulty of obtaining clear views on an acceptable level of risk in research. Gradually, terms such as "safety", "no risk", and "uncertainty" emerged in the memos to be discussed. I tried to clarify each term in the context where it was used by the participant and also compared the meaning across participants as well as among and across groups. I particularly focused on a participant who articulated risk, safety, and uncertainty. Through these analyses, I concluded that risk cannot be discussed alone but must always be discussed together with unknown risks and benefits.

Finally, the core category which appeared as most important in terms of explaining the decision making processes was identified through an iterative process of data collection and analysis. Strategies for identifying the core category included theoretical sorting of memos, diagramming, and integrating memos, which are all closely related (Charmaz, 2006). Sorting analytical memos served to create theoretical links across categories and to integrate categories through comparison at a conceptual level. In sorting and integrating memos, diagramming was helpful for the visual presentation of how categories may relate to one another (Charmaz, 2006). Alongside memo writing, I drew diagrams illustrating the relationship of emergent categories. Going back to the raw data, these diagrams (earlier examples of diagrams in Appendix H) were revised numerous

times along with incorporating new data. Through major and minor revisions to the categories and diagrams illustrating the relationship among these categories, I tried to build a strong explanatory theory to answer the research questions. The core (most important) category and relationship between the categories illustrated how each group of participants - pregnant women, obstetric healthcare providers, and researchers in reproduction areas - would make decisions about the acceptability of clinical research involving pregnant women.

7.4.2.5 Reflexivity

Reflexivity plays an important role in qualitative research (Finlay, 2002). Reflexivity may be defined as “thoughtful, conscious self-awareness” which is essential for a qualitative researcher (Finlay, 2002, p.533). The term “reflexivity” is used in several different ways and also interchangeably with terms such as reflection, critical reflection, and reflectivity (D'Cruz, Gillingham, & Melendez, 2007). Reflection and reflexivity are on a continuum (Sandywell, 1996) and are sometimes used interchangeably (Finlay, 2002). Reflexivity weighs more on interrogating the interpretations of the world whereas reflection has more neutral attitudes to understand the world (Sandywell, 1996). Reflexivity involves "a more immediate, continuing, dynamic, and subjective self-awareness” (Finlay, 2002, p.533) whereas reflection simply concerns thinking about something (Finlay, 2002). In qualitative research, exercising reflexivity contributes to strengthening integrity and trustworthiness of the data collection, analysis, and overall findings (Finlay, 2002). Reflexivity is required throughout the research process to elaborate on the researcher’s assumptions and preconceptions (Charmaz, 2006; Finlay, 2002). Using reflexivity in conducting research may enable examining the influence of the researcher’s own position and views, evaluating the research process, and offering an audit trail of methodologically important decisions to others (Finlay, 2002).

In undertaking this study, reflexivity was required to examine numerous aspects of conducting research, such as my preconception about the topic, professional and personal backgrounds, and experiences during the interview. My motivation and background for conducting this study may have influenced the course of research. I started this research hoping to find a possibility of enhancing clinical research with pregnant women through

uncovering the stakeholder's views on research with pregnant women. I was motivated to explore this topic mainly due to my clinical backgrounds as well as my interest in research ethics, particularly protection of participants and fairness in participant selection. Recognizing the importance of prenatal care for the woman and fetus, I was also interested in improving prenatal care as a woman who had an overall healthy pregnancy but was always concerned about a possibility of events requiring healthcare procedures contraindicated during pregnancy, such as X-rays or exposure to potential teratogens. These factors have inevitably influenced the way I planned the study, conducted the interviews, analyzed the data, and wrote up the paper. Throughout the course of research, I wrote reflective memos on how my values and assumptions might have influenced the data collection and analysis processes. For example, to uncover my values and assumptions, I wrote memos after each interview to examine my positive and negative feelings towards the participant's comments and their description of their attitudes and behaviors in relation to pregnancy.

7.4.3 Literature review for grounded theory studies

Charmaz (2006) recognizes that the timing of literature search has been debatable in conducting a grounded theory study as some authors suggest that the researcher should avoid forcing any preconception on the data analysis and theory development. Indeed, grounded theory concerns discovering theories grounded in data and some qualitative studies do not explicitly employ any theories; however, no qualitative study begins purely from observation and data collection (Creswell, 2014). In general, theories with explanatory properties may be tested as a hypothesis or may support developing research questions (Creswell, 2014). Literature review that is relevant for theorizing may be recommended (Sandelowski & Barroso, 2003). Charmaz (2006) points out that the importance may be placed on connecting the work to previous works through meaningful comparison. Literature review should clarify the researcher’s ideas, invite readers to theoretical discussions, and articulate specific contribution of the study to the extant body of knowledge (Charmaz, 2006). Grounded theory as a methodology can be used with "sensitizing concepts" (Charmaz, 2003, p.259) which can provide starting points for analyzing the data. Specifically, sensitizing concepts or theoretical perspectives may be

used for the researcher to elaborate on theoretical directions, to acknowledge previous works, and to illustrate the significance of the constructed theory by locating it amid these previous works (Charmaz, 2006). Sensitizing concepts are "points of departure" (Charmaz, 2006, p.171) to prepare an interview guide and examine data. At the same time, the researcher should not be limited by these concepts and theories and remain open to what may emerge from the empirical data (Charmaz, 2006).

In this study, I systematically reviewed previous empirical work on the topic of pregnant women's and others' views on research with pregnant women. I conducted a scoping review of 36 studies (Chapter 6). Also, as risk appeared to be an important concept in my research, I chose two authors, Lupton and Hansson, as theoretical perspectives to deepen my understanding of risk (Chapter 2). Deborah Lupton, a sociologist, theorizes risk in general (Lupton, 1999a) and discusses risk in the context of pregnancy (Lupton, 1999b; Lupton, 2012a; Lupton, 2012b). Sven Ove Hansson is a prolific philosopher, addressing how philosophy can speak to safety issues in science and technology (Hansson, 2002; Hansson, 2004; Hansson & Rudén, 2006; Hansson, 2007; Hansson, 2011; Hansson, 2012a; Hansson, 2012b; Hansson, 2012c).

7.4.4 Quality criteria of constructivist grounded theory

Qualitative research is assessed by a set of quality criteria which differs from quantitative research (Sandelowski & Barroso, 2003). Some of these criteria are common across qualitative methodologies whereas others are specific to a particular methodology (Sandelowski & Barroso, 2003). The study must be suitable for using grounded theory, and methods employed for data collection and analysis must be congruent with grounded theory, such as simultaneous data collection and analysis, theoretical sampling, well developed categories emerging from the data, clarity in the relationships between the findings that build a theory, and consideration given to negative cases (Sandelowski & Barroso, 2003). Further, Charmaz (2003) indicates methods commonly used for constructivist grounded theory: memo writing for data analysis, two step coding process, constant comparison across participants, time, and incidents as well as between data and categories and between categories.

Specifically for constructivist grounded theory, Charmaz (2006) discusses quality criteria, i.e. credibility, originality, resonance, and usefulness. To achieve credibility, the data must be adequate to support the theory. Particularly, systematic comparisons, the appropriateness of the categories in encompassing the width of observations, and a strong reasoning in the analysis are required. When published, the readers should be able to assess the researcher's argument based on the data presented in the paper. Originality refers to the freshness of the categories as well as the social and theoretical significance of the work in terms of its contribution to the extant body of knowledge. Resonance concerns whether the categories well explain the participants' experiences and thus the developed theory appears relevant from the participant's viewpoint. Usefulness is about the transferability of the analysis and categories to the actual world. Usefulness is also about the contribution of the work in directing further research and making an impact on society (Charmaz, 2006). Credibility and originality may be understood as the basic components supporting resonance and usefulness (Charmaz, 2006).

As discussed earlier (7.4.1.3) regarding the reasons for choosing grounded theory, the research questions of this study well suited grounded theory. The research questions concerned the participant's decision making process – how they determined whether a clinical research with pregnant women would be acceptable. Also, pregnant women's views on participating in research during pregnancy have not been researched enough particularly in terms of how pregnant women prioritize various factors in their decision to participate or not. Moreover, a limited number of studies investigated the views of healthcare providers on clinical research with pregnant women. Researchers engaged in basic science studies in reproduction areas have not been studied at all despite the significance of their work which provides data to support clinical research with pregnant women.

The methods employed were consistent with grounded theory as a methodology. I conducted simultaneous data collection and analysis and developed categories emerging from the data through an iterative process. Memo writing was conducted throughout the data analysis and writing stages. Throughout the research process, from planning, data collection and analysis, and writing, I wrote reflective memos to clarify my feelings and

thoughts in the course of research. The relationships between the categories were clarified and the main category which is overarching to other categories was identified through diagramming categories, going back to subcategories of each category to confirm its fit in the diagram, and going back to the data when I felt any doubt about the explanatory power of each category or subcategory. I have given consideration to negative cases in developing categories (7.4.2.4). The data were analyzed and categories were constructed in an iterative manner as described throughout the course of research so that the categories and relationships between the categories have a strong connection with the data, encompassing the depth and width of the participant's views and experience.

In terms of originality, I constructed categories that would bring new perspectives on the participant's decision making process about what kind of research would be acceptable for including pregnant women. This was more challenging for pregnant women compared with other two groups as pregnant women have been more studied on the related topics, particularly their reasons for and against research participation. For pregnant women, I focused more on refining current knowledge by aiming to clarify their priority factors in the decision making process and the thoughts behind these factors. Particularly, I tried to focus on why they might accept risk, which has not been discussed much. In terms of obstetric healthcare providers, as a limited number of previous studies had much focus on their concerns and perceived barriers in relation to conducting clinical research with pregnant women, I probed more into how they perceive the importance and needs of such research to shift the focus on their perceived benefit which has been little studied. For researchers in reproduction areas who have not been studied to date, the findings have brought new and original perspectives to the field.

For resonance, I tried to adequately capture the process by which the participants determined whether a particular clinical research study would be acceptable. I paraphrased or summarized the participant's important remarks during the interview to make sure I understood what they wanted to describe. I also asked participants to clarify their descriptions during the interview whenever I felt ambiguities or wanted them to further describe a topic. For example, to understand more about the pregnant woman's attitude of being protective to the fetus, I asked "Why do you feel that way?" or "How do

you feel about your baby?" For some of the issues that I noticed a lack of clarity after the interview was completed, I tried to elicit response from subsequent participants through modifying the interview guide and prompts.

Finally, regarding usefulness, the results may be applicable to explaining inherent difficulties in including pregnant women in clinical research, supporting healthcare providers' and researchers' communication with pregnant women considering research participation, and developing education programs for healthcare providers and trainees as well as the research community in terms of conducting clinical research with pregnant women. Further, the results may have implications on healthcare providers' communication with the pregnant patient in clinical care and the need for education of the general public about the importance of pregnancy health. Also, the results point to the need for more research with other stakeholders such as research ethics committee members or persons in health industries as well as conceptual discussions on justification of risk in research where two agents (woman and fetus) are involved. These implications and future research directions will be discussed later (7.8 & 8.4).

7.4.5 Ethical considerations

Ethics approval was obtained from the Health Sciences Research Ethics Board (HSREB) of Western University (Western REB#105122) (Appendix I) and Clinical Research Impact Committee and Lawson Administration of the Lawson Health Research Institute (Lawson Approval #R-14-164) (Appendix J). These approvals demonstrate that ethical requirements stipulated in the Tri-Council Policy Statement of Canada (2nd edition) (TCPS2) (Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council Canada, & Social Sciences and Humanities Research Council of Canada, 2014) were satisfied. In the following sections, I will discuss basic ethical requirements in the informed consent process and confidentiality as well as the use of reflexivity in qualitative research as it relates to ethical considerations (Guillemin & Gillam, 2004)

7.4.5.1 Informed consent process

Informed consent was obtained from all participants prior to the interview. The letter of information (LOI) (Appendix K) described the purpose of research and what was involved in participation. The LOI clarified that participation was voluntary and that withdrawal from research was possible without any penalty, and that participants did not have to answer any questions that they would not want to. A master list to link the participant's name and an identifier code was made in case the participant wanted to withdraw all or part of the data after the interview. Participants read the LOI or the LOI was read to the participants who were interviewed over the telephone (Appendix L). Written consent was obtained from the participants who were interviewed face to face, and oral consent was obtained and documented for the participants who were interviewed over the telephone (Appendix M).

7.4.5.2 Confidentiality and anonymity

Protecting the participant's privacy was considered throughout the research process. Specifically in this study, the following procedures were taken to maintain confidentiality to the highest degree possible:

- Personal names and contact information (telephone number) were encrypted and deleted when the interview was completed.

- Audio-recordings were deleted after being transcribed.

- Transcripts (electronic) of the interview and demographic data (electronic) were given identifier codes instead of personal names. These data were kept in a password protected computer. Access to the data was limited to the research team members as per specified in the document submitted to the REB at Western University.

- The master list to link the participant and the data (transcript of the interview and demographic data) was kept in a locked cabinet in my supervisor's office at Victoria Hospital, London, Ontario. The master list will be shredded after the publication of results.

- Consent forms were kept in a locked cabinet separately from the master list in the supervisor's office at Victorial Hospital, London, Ontario and will be kept for five years after publication of research results.

- Transcripts of the interview will be kept in a password protected computer in the supervisor'soffice at Victoria Hospital, London, Ontario for five years after the publication of results.

Protection of privacy may be challenging in qualitative research as the data may, even without any direct personal identifiers such as names or telephone numbers, potentially identify the participant due to the in-depth nature of inquiry (TCPS2, Article 10.4). In regards to the dissemination of results, a leading journal, *Qualitative Health Research*, recommends that demographic data should be presented only as a group data and not for each individual to minimize the violation of confidentiality (Morse, 2007). As indirect personal identifiers may also re-identify a person through their combinations (TCPS2, Chapter 5, p.56), it may be preferable not to link a set of demographic data to each individual participant, particularly if the topic involves very personal and sensitive issues. For this reason, all demographic data for the three groups are shown in an aggregate format. In citing the data from the interview transcripts, I provided some pieces of information about the participant only when they were relevant and necessary for the interpretation of the data and subsequent discussions.

7.4.5.3 Reflexivity and ethical considerations

While moving from one interview to another, transcribing the audio-recording after each interview, and analyzing the transcripts, I began to feel that ethical considerations could be broad and somewhat unpredictable. Although I had assumed no particular risk for the participants, there could be potential emotional stress for pregnant women. For example, I realized that I could be triggering women’s emotional stress by asking about adverse events in previous pregnancies as part of demographic data.

Guillemin and Gillam (2004) maintain that reflexivity which is widely acknowledged as an essential process in qualitative research may be applied for addressing ethical issues as

well. Reflexivity may be applied to address ethical issues which are not necessarily codified in research ethics regulations or deliberations in the ethics review process (Guillemin & Gillam, 2004). This is not to say that research ethics regulations or ethics reviews are meaningless for qualitative research or that they are completely alien to the use of reflexivity (Guillemin & Gillam, 2004). Rather, reflexivity completes and extends what is stipulated in research ethics regulations, such as respect for persons, beneficence, and protection of privacy (Guillemin & Gillam, 2004).

Indeed, reflexivity is understood as “thoughtful, conscious self-awareness” (Finlay, 2002, p.533) with a focus on self interrogation (Sandywell, 1996). Particularly in interacting with participants, exercising reflexivity may raise sensitivity to subtle and potential ethical issues that could be critical for securing the participant's well being. For example, a pregnant woman (inpatient) who had agreed to participate had to move to another room for a higher level of monitoring on the day an interview was scheduled. Both the woman and the nurse at her bedside said that an interview would not be a problem. Nonetheless, I slightly hesitated as I sensed her unhappy mood. As she was confirming her consent, I eventually conducted the interview as cancelling or postponing the interview could be overly protective. However, I later reflected on this event and felt inconclusive regarding what I should have done. I still do not know what could have been the best solution in this case. What I learned, however, was that I should have been more prepared as these sudden changes in the pregnant woman's conditions could always happen

7.5 Results

The findings will be presented in the following order: pregnant women, obstetric healthcare providers, and researchers in reproduction areas. Categories and subcategories identified for each group will be described in detail with supporting data. An explanatory theory of the participant’s decision making process regarding whether a particular clinical research project with pregnant women would be acceptable is presented for each group in Figures 2, 3, and 4.

7.5.1 Pregnant women

7.5.1.1 Demographic characteristics

Table 15 shows the demographic characteristics of pregnant women in this study.

Table 15 Demographic characteristics of participants

Characteristics		Number of participants
Age (years)	20-29 30-39 40-49	5 6 1
Gestational age (weeks)	13-28 29-40	3 9
Education	College University Graduate School	6 2 4
Number of previous births (parity)	0 1 2	8 3 1
High-risk pregnancy		5
Pregnancy complications (current)	Placenta previa Hyperemesis Shortened cervix Preterm rupture Twin None	2 2 1 1 1 5
Health issues (on medication)*	Depression Anxiety Hyperemesis None	1 1 2 9
Events in previous pregnancies**	Miscarriage Still birth Preterm Hydatidiform mole None	3 1 1 1 3
Events in relatives' or friends' pregnancy that may have influenced their view on pregnancy		0

*One woman had 2 issues **One women had 3 events

A total of 12 pregnant women were interviewed. The pregnant women's average age was 30.6 years, ranging from 22 to 41 years. The average gestational age was 29.8 weeks, with a range of between 16 and 37 weeks. All participants were well educated, having college to graduate level education. The pregnancies of five women were considered high-risk. These five women were hospitalized at the time of the interview. Seven women had at least one previous pregnancy, among which four had experienced pregnancy complications, such as miscarriage. None of the participants recalled any events, such as severe nausea or abortion, in their family members' or friends' pregnancies that could have influenced their perception of pregnancy or child birth.

7.5.1.2 Pregnant women's decision making process

In exploring the pregnant woman's decision making process regarding whether or not to participate in clinical research, six categories were identified: protecting myself and my fetus, gathering information, wanting to see benefits, focusing on safety, considering my values and beliefs, and deciding with others (Figure 2). Table 16 shows subcategories under each of these categories. Protecting myself and my fetus was the most important category as it directly relates to the other categories which together described their decision making process regarding research participation. The findings suggest that a pregnant woman's decision making begins by gathering information about what the research is about and how research participation will impact her and her fetus' well being. The pregnant woman wanted to see the benefit of the research to herself and her fetus as well as for future pregnant women, and ensure safety to herself and her fetus. Pregnant women also felt that their decision to participate in research would be influenced by personal values and beliefs about procedures involved in research participation, such as taking a vaccine or providing their placenta after delivery. They were inclined to involve others, such as their partner or family physician in making their decisions.

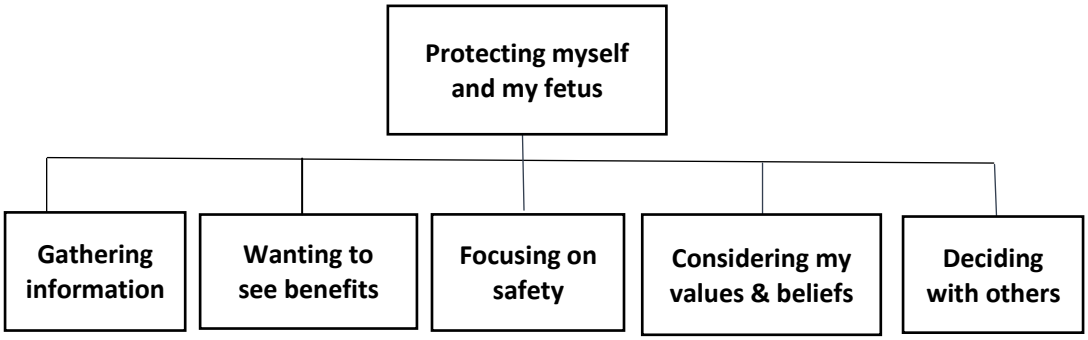

Figure 2 Pregnant women's decision making process

Table 16 Subcategories under each category in Figure 2

Category	Subcategory
Protecting myself and my fetus	• Feeling responsible for my health and my fetus's health • Avoiding risk to the fetus
Gathering information	• Wanting relevant information from researchers • Self-seeking for more information
Wanting to see benefits	• Wanting to help future pregnant women and fetuses • Wanting benefits to myself and my fetus
Focusing on safety	• Avoiding anything untested • Not going beyond clinical needs • Taking risk only if necessary
Considering my values and beliefs	
Deciding with others	• consulting my family • consulting my doctor

7.5.1.2.1 Protecting myself and my fetus

This main category describes pregnant women's desire to protect herself and her fetus from harm. Subcategories are as follows: feeling responsible for my health and my fetus's health, and avoiding risks to the fetus.

Feeling responsible for my health and my fetus's health

Most participants expressed changes in their attitudes and behaviors toward being healthy after becoming pregnant. Many felt responsible for the well being of themselves and their future child. All pregnant women expressed that they refrained from doing anything that could compromise the course of the pregnancy. PW10 described her change in way she exercised: "*I don't do weight lifting any more. So I just go and walk on the treadmill.*" PW07, who was experiencing her first pregnancy, described dealing with headaches after becoming pregnant:

> *Apparently, you can take Tylenol if you have a headache during pregnancy, but I stopped. Instead of taking Tylenol, I buy peppermint essential oils and rub on your temples, so you don't have to physically take anything. So, no. I've totally been trying to do, um, maybe I'm an oxymoron because I am trying to do everything for the baby except for my exercise* (PW07).

PW07 also mentioned giving up hair dye for the benefit of her fetus. PW09 who had experienced a stillbirth commented on her change in attitude toward pregnancy, the fetus, and life in general:

> *Oh, my attitude completely changed afterward. Towards more than just like medicine and health, but towards everything. I'm always afraid to do anything now. Before, I kind of, I was kind of open to do a lot back in those days. ... I figure you are partially responsible for your health for how healthy your child is unless there's other problems* (PW09).

PW04 described why she felt responsible for the fetus: "*I suppose it's the love you already feel when you are pregnant even before the baby's born. The love you have for the baby. I think it's maternal.*"

Avoiding risks to the fetus

Women commented they would tolerate minor temporary symptoms to themselves, but they did not want to cause any risk to the fetus by participating in research. PW07 stated:

> *Say, they said you might get nauseous or something or diarrhea. You can live with diarrhea. But what if they said you could lose your baby or your baby can have a third eye. Well, all of a sudden, it doesn't, it doesn't matter how much they pay me. It doesn't matter* (PW07).

PW07 stated that she could tolerate minor symptoms as she "*never got morning sickness" and "had no symptoms of like being pregnant*". By contrast, PW11 who had been suffering from nausea and headaches throughout her pregnancy did not want to add any more discomfort, even if minor, expressed: *If I wasn't so sick, then those side effects wouldn't bother me, I don't think."*

Regarding the fetus, however, all the women felt that any increase in fetal risk due to research participation was unacceptable. PW03 described her sense of the fetus's vulnerability and the need to be cautious:

> *You are dealing with a very fragile baby that's not 100% developed, right? So there's a lot of factors that can affect it. Um, and just, like they can stress out really quick, like harsh chemicals or stuff like that. I think I would be a little bit more leery or more cautious of doing anything along those lines* (PW03).

Her views were echoed by other women. Women were very protective of the fetus as PW02 stated: "*I know it's something precious and I know it's, uh, delicate. And I know there's little tiny things that can compromise pregnancy."*

7.5.1.2.2 Gathering information

This category describes pregnant women's need for information to make sure that the research will be useful for future pregnant women and cause no harm herself or her fetus. Subcategories are as follows: wanting relevant information from researchers and self-seeking for more information.

Wanting relevant information from researchers

All pregnant women would seek for information before deciding whether or not to participate in clinical research. As PW06 stated: "*I just want to know the information behind it before I decide to participate.*" PW03 wanted the "*details in common language because I would never understand the doctor language*." All pregnant women wanted to know the purpose and processes involved in the research study. Others commented on the value of conducting the research. PW04 indicated determining "*whether the research was a good thing to be researching or useful thing*" would be critical. In examining the research process, PW02 wanted to ask questions about any harm the research could have on her pregnancy: "*Can it compromise pregnancy? Is it going to hurt?*" In addition to wanting to know the risks associated with the research, PW01 referred to self benefits: "*I would ask about the potential risks for the baby and mother, and potential benefits*." PW07 questioned how the research would fit her particular context: "*Why do I want to do it?*"

More than half of the participants wanted clarification of how their personal information would be handled. PW06 felt comfortable providing health related information but wanted to make sure personal information about herself and her baby would not be public: "*As long as my, like my health information, my baby's information wasn't released. Yeah, I don't like that. Other than that, if it was just data, then it's ok."* PW07 did not want any of her personal identifiers to be collected:

> *As long as they aren't collecting your own personal information like your social insurance number, where do you live, all those kind of, like personal things. Just like a survey, follow through, no identity* (PW07).

Also, PW07 commented on the significance of knowing the sponsor of the research or who will most benefit from research: "*Is it for the medical society or is it for, like the government, secret service, like society, um, who's the research for, like who's collecting it, who's behind it?"* She wanted to know that the research project was "*medically examined*", without "*a bias on money*", and not "*just benefiting the drug company*".

Self-seeking for more information

More than half of the women wanted to seek information beyond what would be given by the researcher. PW12 considered seeking more information if the provided information was felt insufficient:

> *So if he [researcher] has background information or information sheet that I can go through and make a decision of my own, then it really depends on what I read and if I want to know the possibilities of anything happening or any doubtful things, then I would want more information before going forward to it* (PW12).

Regarding a hypothetical vaccine study, PW04 said that she "*would do a lot of research*" on her own in addition to reading the letter of information provided by the researcher. In searching further information, PW04 was skeptical about the internet information as "*it must be hard to go back and find out what's right and what's not*". Some women stated they would consult others, mostly their attending physicians, for more information. For example, PW03 said she would "*talk to the doctor".*

7.5.1.2.3 Wanting to see benefits

This category indicates pregnant women's desire to participate in research which has benefits to society or future pregnant women as well as potential benefits to themselves and the fetus. Subcategories are as follows: wanting to help future pregnant women and wanting benefits to myself and my fetus.

Wanting to help future pregnant women

All participants responded positively when asked about how they felt about research with pregnant women. Most described research as important, particularly in terms of understanding more about pregnancy complications and related health issues. PW02 stated: "*I think it's really important, essential, like, to understand like any complications or psychological follow up of pregnant women or any side of pregnancy."*

Most women expressed that research would not guarantee direct benefits to the participants. As PW03 stated: "*when you research, you don't necessarily know it's going*

to be good or bad". Nevertheless, women felt positive about contributing to knowledge that might improve health of future pregnant women. PW05 said:

> *I personally just like that idea that I would be, um, one to help out and benefit, um, not necessarily I'm benefiting from it, but you know, other people are benefiting from if I'm allowing them to do research* (PW05).

Several women with complications during their current or previous pregnancy expressed their wish to help others in similar situations. PW04 related the wish to help others after her experience of miscarriage: "*So it's because of my experience that makes me, yeah, wanting to help somebody by participating. Other people might have the same thing."*

Wanting benefits to myself and my fetus

All women felt more positive about research if it was beneficial to the participating woman or fetus. Some women clarified that self benefit was most important as PW03 stated: "*I would want to have the purpose or benefit for me."* Similarly, PW01, who was on medication for hyperemesis wanted therapeutic benefits under the assumption that the active drug would be beneficial in treating her condition:

> *For my condition, as long as it shows in active drug that it benefits me and correlated benefit to my baby, by all means sure, include my data. But if I'm in a control group, uh, I'd rather not* (PW01).

PW10 described research as being beneficial at the societal level as well as at the personal level of having additional medical attention or receiving further data about herself:

> *Research is meant to help people, and so, me included. I can help. But it's not only to help other people. Medically, it's good to know what's going on. ... for example, if they take my blood for research about one of the medication I'm taking, I would want to know what the results were* (PW10).

PW06 described research participation as beneficial as it could provide her with learning opportunities: "*I guess if I get, um, you get some more, kind of knowledge out of it for*

yourself, then it's kind of good." PW06 gave examples such as discovering "*what's happening*" in the course of pregnancy and learning about "*nutrition or anything like that*" which could benefit herself and her fetus.

7.5.1.2.4 Focusing on safety

This category describes the women's emphasis on securing safety for herself and her fetus so that they will not be harmed in any way. All pregnant women expressed concern about safety when considering research participation. Subcategories are as follows: avoiding anything untested, not going beyond clinical needs, and taking risk only if necessary.

Avoiding anything untested

All participants felt uncomfortable with taking part in research that was testing something for the first time. PW11 "*felt a little nervous*" about research involving anything "*without certified or something, some kind of assurance*". Regarding participation in a hypothetical research involving a new vaccine, PW01 exclaimed: "*Oh, so new vaccines. That, then I would probably hesitate. Yeah, I probably would not consent."* Similarly, PW12 commented: "*I would avoid that. I don't want to be the first guinea pig. I would rather have it try with somebody else."* In considering participation in a hypothetical study involving a new drug, PW06 said: "*I don't know. Probably somebody else, sorry, but I don't like kind of, I don't like trying things that's not safe for sure*."

In the context of testing a new substance, PW07 wanted to identify any associated risks: "*I'll have to see what the risks are. But yeah, it could be ok if you are able to figure out that they've seen it's safe enough for humans to be tested."* Although women commented research was "*a good thing*" (PW05) or at least felt "*fifty-fifty for it*" (PW09), they endorsed research "*as long as it's done in a safe way because nobody wants to risk their health or their child's health*" (PW05).

Not going beyond clinical needs

Some women considered research participation acceptable only if the procedures involved were necessary for their clinical conditions. PW11 was taking a prescription

drug for hyperemesis although she wanted to refrain from taking any drug during pregnancy. She explained:

> *So it was really, if I don't take it and I'm sick. Like everyday, I'm in hospital. So that was my only choice. So you end up hospitalized or I take this pill that's been safe for pregnancy* (PW11).

Similarly, PW02 commented: "*I wouldn't go further than like what needs to be done just for my pregnancy."* PW01 who was willing to go through a magnetic resonance imaging (MRI) for medical indications was "*quite hesitant*" to do so solely for research purposes:

> *If I had a condition where something has to be checked on the MRI for me or for fetus, that's ok. But for purely investigative research, I would question. I wouldn't sign up for that* (PW01).

Regarding an additional ultrasound outside clinical routine for a research purpose, PW06 who expressed being comfortable undergoing ultrasound for clinical purposes responded: "*For research purposes? No*".

Taking risks only if necessary

The pregnant women commented on taking risk only if they had important health issues that needed to be addressed. PW10 explained how she would consider taking risks through using an example of a pregnant woman diagnosed with cancer. She stated how she might examine such a situation:

> *I would have to ask, like if it's a tumor, can it grow in a few months or can you wait nine months? Because if it's something that is slow … deliver the baby and then do the MRI or whatever* (PW10).

PW08 considered taking risks *"if there was no choice"* due to her or her fetus's health conditions. PW03 explained participating in an interventional study if any intervention was necessary for her or her fetus:

Like if I had a really serious problem or my baby had a serious problem and there was something, like so the research can benefit or help the situation get better, I might be inclined to do it. Um, but if it was unnecessary, I would be more wary of being involved in research. If it involved like medicines or chemical, um, it just like myself personally, and I try and avoid to take any medicines unless there is a serious issue (PW03).

7.5.1.2.5 Considering my values and beliefs

This category indicates that pregnant women considered their own values and beliefs in making a decision to participate in research. Most pregnant women referred to their values and beliefs about health, health management, pregnancy, or body in considering research participation.

Pregnant women's responses varied regarding hypothetical research collecting specimens, such as the placenta after delivery or blood left over from clinical use. While the majority was comfortable with giving specimens that could be taken without any invasive procedures, several women felt uncomfortable for reasons difficult to explain. For example, when asked about the reasons for not wanting to provide her blood sample for research, PW09 simply stated: "*No, it's just the personal thing, yeah*". PW10 who was comfortable with providing specimens such as blood or placenta for research purposes anticipated objections from other women based on their personal values and beliefs about placenta or blood: "*Yeah, so, uh, to me, I won't see any problems. But it comes to personal values or beliefs."* PW11 described further, showing understanding to others who might feel uncomfortable participating in a study collecting placenta: "*Now, in some cultures, I know they keep placenta, but I'm not, me per se. ... Depending on culture, religion or other things, some people may not be comfortable."*

When asked about participation in drug research, PW03 described her basic attitude about the use of medications for dealing with health problems during pregnancy: "*I'm not the one to run to a doctor or go grab prescriptions or pills, that kind of stuff. I try to deal with it naturally."* Regarding a hypothetical flu vaccine study, PW02 described her health management strategy: "*Maybe it's my way of living. You know, I try to live as healthy as I*

can. I don't get flu in winter. And people around me who get vaccinated, and they are sick all winter, usually." These women explained their reasons to decline participation based on their beliefs about taking drugs or vaccines.

7.5.1.2.6 Deciding with others

This category describes women's decision making in terms of their relationships with family members, friends, and healthcare providers. Subcategories are as follows: consulting my family and consulting my doctor

Consulting my family

In deciding whether or not to participate in research during pregnancy, the majority of women said they would consult others, such as their partner, other family members, friends who experienced pregnancy, and physicians. The majority of participants stated that they would consult their partner. PW08 said that she would consult her partner because "*the baby is ours*". In terms of participating in interventional research where the fetus could be affected, PW07 stated: "*I have to make sure he's on board for sure*". Regarding her family members' thoughts about participating in research during pregnancy, PW06 said: "*I kind of take their opinions pretty good*".

PW11 said she could decide by herself, saying "*I'm pretty comfortable about how I feel and I know my body*." Nevertheless, she described her trust in her family:

> *I think my family is very supportive, my entire family including my fiancé's side and as long as the baby comes out ok, obviously healthy is what people want. But if it comes out with some kind of problem or issue, um, it would be doubtless still we are family, so that I don't think they would look at it and worry at all* (PW11).

Consulting my doctor

A few pregnant women expressed much trust in their physician and valued their professional opinion about research participation. Regarding whether or not to participate in a hypothetical flu vaccine research, PW12 said:

> *Um, honestly, I don't know much about that because I haven't really looked into any of that. Yeah, I haven't got any background on that yet. I have to look into it. But yeah, in the line of, if my doctor says it's ok, then I'm ok with it* (PW12).

While PW12 seemed to *"work quite a lot on the internet*", she was comfortable with following professional advice rather than deciding by herself based on whatever information she could gather. Similarly, PW05 stated about research involving a new vaccine: "*I'll consult the physicians about their thoughts about it. Again, um, then it's a possibility that I can participate*." Although PW05 added "*as long as it's not putting me or baby at risk*", she left a small possibility of participation in a new vaccine study if her physician endorsed it.

7.5.2 Obstetric healthcare providers

7.5.2.1 Demographic characteristics

A total of ten obstetric healthcare providers were interviewed. The participants consisted of eight medical doctors, one midwife, and one obstetric nurse. The specialties of the medical doctors were obstetrics and gynecology, family practice, endocrinology, nephrology, neurology, orthopedics, anesthesia, and psychiatry. All of the participants had the experience of conducting clinical research and two physicians had the experience of conducting research with pregnant women. They had an average of 12.6 years of professional practice with a range of between 4 and 27 years. The proportion of their work with pregnant women was in average 31.1%, ranging from one to 100%.

7.5.2.2 Obstetric healthcare providers' decision making process

Four categories were identified to describe the obstetric healthcare provider's decision making process about whether a research study with pregnant women would be acceptable: satisfying regulatory requirements, weighing risks and benefits, giving priority to safety, and respecting the woman's decision. Figure 3 illustrates the relationships of these categories in describing their decision making process. Table 17 shows subcategories under each category. Satisfying regulatory requirements was

identified as most important as it appeared to be a key concept in explaining how health providers determine if clinical research with pregnant women would be acceptable. Obstetric healthcare providers often referred to research ethics regulations as well as other guidance from regulatory authorities and professional bodies in describing their decision making processes. The other three categories were perceived as among the important factors addressed in these regulatory requirements. To confirm a favorable risk benefit ratio of research, obstetric healthcare providers weighed risks and benefits (indirect benefit to support future clinical care and direct benefit to the participating woman and fetus) of the research considered. At the same time, healthcare providers had much emphasis on safety for the participating woman and fetus, erring on the side of securing safety in weighing the risks and benefits. Also, healthcare providers expressed that the pregnant woman's decision to participate constitute an important condition for the research to occur.

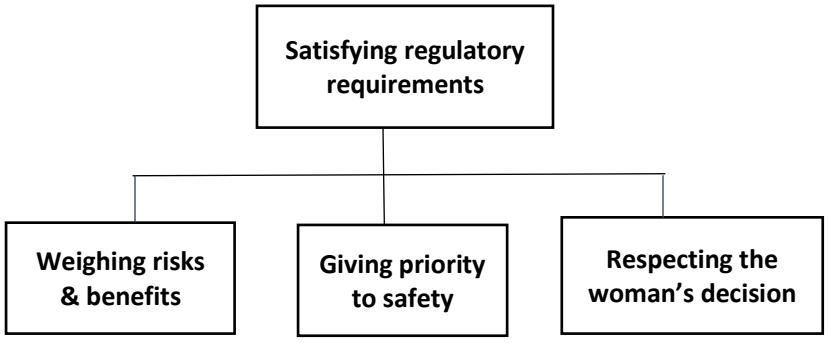

Figure 3 Obstetric healthcare providers' decision making process

7.5.2.2.1 Satisfying regulatory requirements

This category explains the obstetric healthcare providers' overarching attitude of adhering to the regulatory requirements for conducting research with pregnant women. Subcategories are as follows: seeing common requirements across populations and seeing pregnancy specific requirements.

Table 17 Subcategories under each category in Figure 3

Categories	Subcategories
Satisfying regulatory requirements	• Seeing common requirements across populations • Seeing pregnancy specific requirements
Weighing risks and benefits	• Contributing to evidence based practice • Assuming pregnant women want benefits of research • Considering pregnant women's openness to risk
Giving priority to safety	• Safety for the participating woman and fetus • Unknown risks
Respecting the woman's decision	• Providing pertinent information • Supporting the woman to make her decision • Respecting personal values and beliefs

Seeing common requirements across populations

All healthcare providers recognized that requirements for conducting research involving pregnant women had much in common with those for the general population. HP06 stated: "*The standard for research development is the same for all populations.*" HP05 commented: *"I'm comfortable with it as long as it's REB [research ethics board] approved.*" HP10 described: "*I've already been trained in the era where strict regulations were in place for clinical trials*"; and thus if the research is "*brought through the right channels, and ethics and everything and informed consent obtained and properly approved*" and "*properly conducted*", it would be acceptable.

Requirements on risks, benefits, and privacy were discussed by many healthcare providers. HP04 referred to some rules applicable to all populations such as "*the risk is the least it can be to achieve whatever you are trying to achieve in your study"* and *"individuals are not identifiable".* HP10 indicated that an important requirement would be benefits to society, adding that whether research is acceptable depends on *"what question you are asking and why the question is being asked*".

Seeing pregnancy specific requirements

All healthcare providers recognized additional requirements for clinical research with pregnant women compared with the general population. Prior to conducting research involving pregnant women, "*clinical non-pregnant human research*" (HP06) and "*some different types of pregnant animal research"* (HP06) must have occurred to ensure its safety for participants and a prospect of benefit for future pregnant women. HP05 felt comfortable with the completion of these prerequisite studies, assuming that regulatory authorities would flag foreseeable risks and problems upon completion of these prerequisites:

> *As long as there's been no alarms because I'm sure there would be, um, Health Canada, as long as Health Canada has given a green light, yeah, go ahead and test it with pregnant women* (HP05).

7.5.2.2.2 Weighing risks and benefits

In evaluating a research study for pregnant women, all participants considered weighing risks to the woman and her fetus against benefits to future prenatal care (indirect benefit) and potential health benefits to the participating woman and/or fetus (direct benefit). This category consists of the following subcategories: contributing to evidence based practice, assuming pregnant women want benefits of research, and considering pregnant women's openness to risk.

Contributing to evidence based practice

Obstetric healthcare providers expressed that research with pregnant women must contribute to answering important scientific and clinical questions that would improve prenatal care. HP04 commented on the importance of generating knowledge to answer these questions, which might motivate the stakeholders:

> *I think that the benefit of research that it's going to help or improve care. Or, um, improve their health or baby is the key to motivating both healthcare provider to*

> *participate in research, you know, but also, um, for the woman to want to participate* (HP04).

HP04 gave an example of research that she would support:

> *What I am interested in myself is looking at smoking cessation because a lot of women do stop smoking, for example in pregnancy, and then they recommence after the baby or later in pregnancy. So, you know, looking at why they restart would be a good sort of topic to look at* (HP04).

Several obstetric healthcare providers expressed dissatisfaction with current standards of prenatal care and the paucity of updated evidence. HP02 criticized that standards of care for pregnant women might be irrelevant to the current pregnant woman as "*sometimes research is just so old*" despite the changes in "*women's life*" and "*how we practice medicine*". HP02 expressed the need for research to update standards of care with research based evidence. For example, HP02 pointed out a potentially problematic use of antibiotics to prevent a very low possibility (1-2%) of a serious fetal infection in women tested positive for Group B streptococcus:

> *I think we need a better way, more research to help us have a better way of dealing with it. ... But the fact that we don't know, we are just administering, and it's large doses, not a little bit, right? So that's a lot and it's crossing placenta* (HP02).

HP02 proposed that research might determine a way to identify a very small portion of women at risk for a serious fetal infection as the current standard of care would result in administering a massive dose of antibiotics without any benefit and with potential harm to 98 to 99% of the women and their fetuses.

HP07 questioned the practice of stopping medication required for medical conditions once the patient became pregnant or even when the patient expressed her wish to become pregnant:

> *How many patients do we take off medication because we are worried about pregnancy? And then they have a bad event, we never say it's because of stopping the medication* (HP07).

HP07 criticized the excessive focus on the potential harm of continuing the medication during pregnancy and little attention paid to the potential harm of stopping the medication. HP07 argued that the "*harm*" of not conducting research or not having reliable data must also be considered in the discussion of clinical research with pregnant women:

> *So you have a patient with lupus, or you have a patient with rheumatoid arthritis, or you have a patient with a kidney disease. And you are not using medication that can help them because of the potential risk, and that may cause harm to the mother. So I think it would be useful to have better data for pregnant patients so that we can treat them effectively* (HP07).

Assuming pregnant women want benefits of research

Many of the obstetric healthcare providers commented that the pregnant woman would be motivated by both direct benefits to herself and/or her fetus as well as indirect benefits of knowledge for future pregnant women:

> *I think if they can see benefit to themselves, if they can see benefits to the future people's baby, their experience is going to help someone else, I mean we all like that generally, you know, pregnant women particularly if there is a value* (HP04).

On the other hand, HP01 suggested that pregnant women would be more motivated to participate in research if they could see "*how the situation is going to help me"* rather than by the value of the research for future patients. HP01 stated: "*So if benefits outweigh the risks, if they see that, they may consider. I mean my sense is that if more of direct benefit to that person."*

Considering pregnant women's openness to risk

All obstetric healthcare providers discussed that the pregnant woman's openness to risk or permissible risks associated with research would differ depending on her existing health issues. HP09 provided an example of a hypertensive pregnant woman considering participation in a hypertension drug study which might involve some risk but might benefit in controlling the woman's blood pressure. HP09 described the relationship between the woman's openness to research risk and her current control of blood pressure:

> *Well, if her blood pressure is not controlled, it's something good to explore other options. If it is well controlled, side effects well tolerated, then there's no real reason to change it. ... If it's unstable, that's a different ball game* (HP09).

Similarly, HP03 stated that a pregnant woman might go for an interventional study even with a low prospect of benefit if she had a critical health problem that could potentially benefit from research participation:

> *So I think you can recruit women to say we are actually not sure, um, whether this therapy might be beneficial, um, in the context of a situation where it's already posing risk to the mother and baby. I think that would be, that would be acceptable* (HP03).

7.5.2.2.3 Giving priority to safety

Although a basic strategy in evaluating a research project was weighing its risks and benefits, obstetric healthcare providers wanted to err on the side of avoiding or minimizing risk to ensure maternal and fetal safety. The subcategories are as follows: safety for the participating woman and fetus and unknown risks.

Safety for the participating woman and fetus

Obstetric healthcare providers were concerned about increased risks associated with research participation and wanted to assure safety to the participating pregnant woman. HP02 described pregnant women's concerns: "*They are going to want to know that what's being put into their body is safe for them and safe for the baby they are growing"*. All healthcare providers assumed that pregnant women would not accept any risk, particularly fetal risk. HP05 commented: "*Risk to the fetus? No. No risk to the fetus*".

Similarly, HP03 described: "*I just don't think moms like to take risks for babies*". HP03 anticipated that "*entering into a potential harm situation"* would not only cause difficulty in recruiting pregnant women but also in obtaining ethics approval.

HP08 also assuming pregnant women's wish to avoid any risk articulated conditions for addressing barriers for conducting a drug study:

> *If you know, if you got the knowledge of the pharmacology and the pharmacokinetics of the drug, then you can reassure your pregnant woman that there's no harm. Then that would be acceptable* (HP08).

Unknown risks

Several obstetric healthcare providers expressed concerns about unknown risks associated with research. HP07 pointed out the limitation of pregnant animal studies for identifying risks, saying: "*I don't think thalidomide did anything with animals. And in humans, it caused all sorts of deformity*." HP01 described potential long term consequences that may take time - even a generation - to be clarified in terms of the causal relationship:

> *Imagine some of the chemicals we give to the patient, it could have a lot of long term consequences for the child, which we will know about, but probably won't know about for that particular individual, um, because by the time that child grows up and whatever, I may be retired* (HP01).

In discussing unknown risks, HP06 described "*safety*" and "*unsafety*" based on known and unknown risks:

> *Safety should cover the risks we know and risks we don't know. And when there's too much risks of unknown, too much that we don't know, that increases unsafety, the lack of safety (HP06).*

HP06 suggested a way of considering unknown risks in the process of weighing risks and benefits by introducing a concept of "*safety*" or "*unsafety*". According to HP06, a limited

amount of information about the procedures involved in research increases unknown risks and thus decreases safety.

7.5.2.2.4 Respecting the woman's decision

This category describes the obstetric healthcare provider's recognition that research with pregnant women requires endorsement of pregnant women, which is considered as the requirement of informed consent in regulations. This category consists of following subcategories: providing pertinent information, supporting the woman to make her decision, and respecting personal values and beliefs.

Providing pertinent information

All healthcare providers considered it important to provide potential participants with sufficient information, particularly on risks and benefits. As HP08 said: "*Just with any clinical trial, risks and benefits of the study have to be explained."* Besides risks and benefits, HP01 emphasized that research should not be misunderstood as clinical care: "*I would be very upfront with them and tell them that, look, this is a study I've been asked to recruit for and available for you*". Further, in comparing research and clinical care, HP06 highlighted that "*going above and beyond what is necessary according to the standard of care is not necessarily better."* HP02 expressed her wish to be as unbiased as possible in providing information: "*It's my job to try and provide them with unbiased information."* Similarly, HP06 described: "*I have an obligation to present the options even if I personally do not fully agree with some of the options."*

Supporting the woman to make her decision

HP06 described consent as a process where the participant must take an active role in understanding the information for decision making: "*I always advise patients who are considering participation in research, to see this as a process, not a one time decision, to take time to read and reread and question*." HP05, who was conducting clinical research with pregnant women, explained the advantage of taking time for the consent process:

> *I think I mean I have to because they need to make an informed decision and I need to make sure I feel comfortable enrolling them in the study. So I do supply the information but I want the decision to be theirs* (HP05).

In either clinical care or research, obstetric healthcare providers wanted to support the woman but leave the decision to her. HP02 stated: "*I don't always agree with what they do. But it's not, it's not, uh, my job to agree with them*."

In gaining pregnant women's understanding about the value of research for improving clinical care, HP03 commented: "*I think you could try to do a lot of patient education around it*". HP01 stated that explaining the relevance of a particular research project in the patient's context may enhance the patient's understanding about its significance:

> *If I tell them why this might fit in, what we are trying to find out about disorder and how their participation will really help with this, and this is my assessment of the risk benefits and how it would help them. I think it makes a difference to the recruitment itself when you actually connect it to whether and how they may play a part in a larger progress of scientific evidence* (HP01).

Respecting personal values and beliefs

From their everyday practice, most obstetric healthcare providers acknowledged the differences across patients in their decision making process. Using an example from clinical practice, HP06 indicated the patient's cultural backgrounds and personal values which could influence the decision making about treatment options:

> *To treat the mother can put the fetus at a significant risk. ... Sometimes the answer was "save the mother, we don't focus on the fetus" and in another case, it was "we cannot put the fetus at any risk"* (HP06).

Obstetric healthcare providers commented on the diversities in pregnant women's situations. Based on her clinical encounters, HP02 described various contexts of pregnancy which might change the meaning or value of pregnancy, fetus, or family:

> *We get teens and we get much older women, and we get single women, right? Um, wanted pregnancies, unwanted pregnancies, and that makes people feel different. We had a couple of surrogates that had been in care. So the baby they are carrying isn't even theirs* (HP02).

7.5.3 Researchers in reproduction areas

7.5.3.1 Demographic characteristics

A total of nine researchers in reproduction areas were interviewed. The participants' areas of research were reproductive and developmental toxicology, reproductive endocrinology, development of oocyte, spermatogenesis, impact of environmental pollutant on male fertility, mechanisms controlling preimplantation, placental function, developmental origin of health and disease, and social determinants of child health. They had an average of 23.8 years of conducting research in reproduction related areas with a range of between five to 35 years. The proportion of their current research related to reproduction was in average 86.1%, ranging from 15 to 100%.

7.5.3.2 Researchers' decision making process

Five categories were identified regarding how researchers in reproduction areas determined whether or not a research study involving pregnant women would be acceptable: examining research with pregnant women, weighing risks and benefits, considering complex nature of risk, connected with women, clinicians and society, and respecting the woman's decision (Figure 4). Subcategories under each category are presented in Table 18. Examining research with pregnant women was considered the most important category as it described the researcher's consistent attitude pertaining to the other categories describing their decision making process. Weighing risks and benefits was a basic strategy for researchers to make certain the benefits outweighed risks. At the same time, researchers felt the need to consider the complex nature of risk and the challenges in ensuring safety for the participating woman and her fetus from a scientific viewpoint as well as from a person's perception of risk. The researchers also felt the need

to be connected with women, healthcare providers, and society to formulate meaningful research questions and to receive feedback on the research project. Researchers wanted to respect the pregnant woman's decision to participate or not regardless of their endorsement of research.

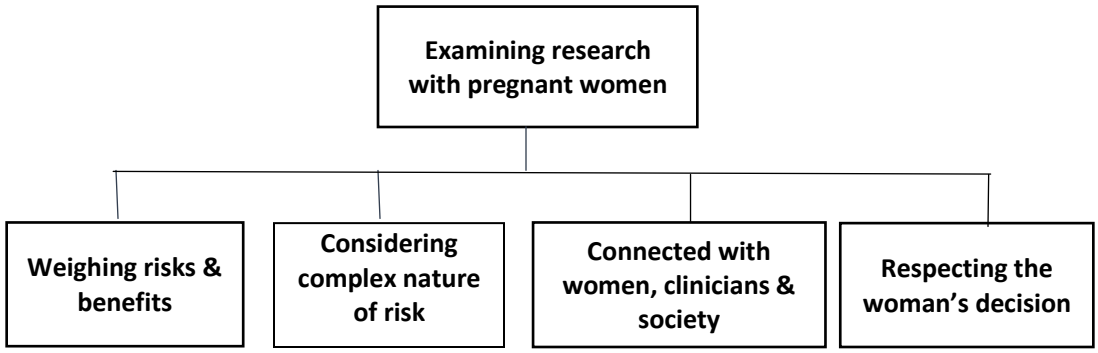

Figure 4 Decision making process of researchers in reproduction areas

Table 18 Subcategories under each category in Figure 4

Category	Subcategory
Examining research with pregnant women	• Drawing a line between the general and pregnant populations • Carefully applying pregnant animal models to pregnant women
Weighing risks and benefits	• Endorsing research with clear benefits • Considering pregnant women's openness to risk • Considering problems of excluding pregnant women
Considering complex nature of risk	• Nothing is black and white • Unknown risks • Wanting pregnant women to feel safe
Connected with women, clinicians and society	• Identifying research questions • Review by professional and lay communities
Respecting the woman's decision	• Providing pertinent information • Assuming women's understanding insufficient • Respecting personal values and beliefs

7.5.3.2.1 Examining research with pregnant women

This category describes the researcher's attitude of wanting to be careful in planning clinical research with pregnant women. Subcategories are: drawing a line between the general and pregnant populations and carefully applying pregnant animal models to pregnant women.

Drawing a line between the general and pregnant populations

Recognizing the importance of what happens during pregnancy, researchers in reproduction areas were cautious about undertaking research with pregnant women even when evidence revealed it safe for the non-pregnant humans. Regarding an example of a drug study, R02 insisted that all possible steps must be exhausted before conducting research with pregnant women:

> *If we reach the point that we tested this drug in human population and in pregnant animal models, and we think we've got anything we could possibly have got to that point, and now we ask the question, "Can this drug help pregnant women in regulating blood pressure?" Then I think at that point, we have no choice but to ask pregnant women to participate and I would be fine with tha*t (R02).

R02 commented the influence of the fetus, which constitutes a major difference between the pregnant and non-pregnant populations: "*I am only comfortable, in pregnant women to be in a study that is clearly proven that it will not harm the fetus*."

R07 reflected on a hesitation in testing a new vaccine with pregnant women compared with testing it with the non-pregnant population:

> *It's funny. I, uh, although I'm less worried about the general population with the new vaccines, I, um, you have to try them out. But with pregnant women, I do draw a line. So a new vaccine, I'll be willing to take it as an adult. But as a pregnant mom, I don't think so. I know it's interesting* (R07).

R05 referred to the immaturity of the fetus as "*vulnerability*" to explain why we might be very careful with the fetus:

> *The baby certainly doesn't have a full immune system, doesn't have a full set of cards to deal with any adverse issues, like bad vaccines. So if the vaccine misbehaves in an adult, we have an ability to treat it, deal with it longer, you know, we're more sustainable. But the fetus already has, um, vulnerability to begin with. ... If something is going to happen from the vaccine, the adult can deal with it better than the baby* (R05).

Carefully applying pregnant animal models to pregnant women

Researchers wanted to be careful in applying the results of pregnant animal studies to pregnant woman studies. R08 commented: "*You can't translate directly from an animal study to a human study and say that a dose that has been shown to be safe in an animal study can be safe in a human study"*. Similarly, R06 discussed the challenges of interpreting the results of pregnant animal studies into pregnant women as "*we don't know, usually, how much it applies to pregnant women"* and thus *"you really have to be very careful in what you say and how you say it"* because "*there are always implications that you don't expect"*. R06 presented an example of retinoic acid which was mistakenly believed safe for humans due to insufficient analysis and interpretations of the animal models:

> *Based on some of the animal experiments, they thought that this analogue of retinoic acid was less teratogenic. And it was mice and rats. And they thought that the dosage human patients were getting were very low. So they thought there would be no malformation. But they were wrong. They didn't know quite enough about, um, how humans would metabolize it and how long the half life was in humans versus mice and rats. Humans did get malformation* (R06).

R06 emphasized the importance of well conducted and well interpreted animal studies as prerequisites for conducting research involving pregnant women.

7.5.3.2.2 Weighing risks and benefits

This category describes a basic strategy to evaluate a research project by considering its risks and benefits. Subcategories are: endorsing research with clear benefits, considering pregnant women's openness to risk, and considering problems of excluding pregnant women.

Endorsing research with clear benefits

All researchers wanted to see clear benefits of generating important knowledge in clinical research involving pregnant women. Being a basic scientist, R02 held that the research must be "*aimed at helping future women for future pregnancies to be more successful"*. Further, comparing human studies and animal studies, R02 argued that human research should impact on improving clinical care *"within five to ten years"* in contrast to animal studies which, "*in the next 20 years, will not lead to any sort of clinical interventions or anything like that*".

Researchers' understanding of the benefit of research was not limited to clinical benefits but also included extra medical attention as R05 commented on a study involving ultrasound:

> *I would say the reason, um, one benefit of doing this study is that it keeps an extra set of eyes and an extra scan, and extra measurements that could pick up something wrong early if there was something wrong. So that's a benefit, I think in my opinion, doing a human study* (R05).

Furthermore, knowledge was captured widely, not restricted to knowledge for society and future patients but also any piece of knowledge that might assist scientists to pursue future research and eventually lead to improving clinical care. R09 clarified:

> *Yeah, even some information may be useful to scientists' plans for a study, may not have an immediate impact on the health and well being of the patient but may provide useful information to scientists for trying something of maybe direct benefit to the patient* (R09).

Considering pregnant women's openness to risk

Most researchers suggested that acceptable risk may differ depending on the pregnant woman's conditions or the prospect of direct benefit to her and her fetus. As an extreme example, R04 stated that the woman might take some risk if that could "*preserve a pregnancy".* For including pregnant women in interventional research, R06 indicated the need to demonstrate a reasonable prospect of therapeutic benefits to the participating woman and/or fetus:

> *I think that, um well, the reasons for giving the drug to the woman have to be compelling in drug studies or some kind of intervention. There have to be really a benefit to her from whatever other data you have, whether animal studies or anything* (R06).

R07 also described whether or not to participate in a new vaccine study from the participant's needs in terms of health:

> *I guess it would depend on, like H1N1, pregnant women were more vulnerable. I think I would probably take the flu vaccine because pregnant women are more vulnerable. But if it was a new vaccine for something that was mostly affecting people over 65, then maybe I wouldn't be so willing to try a new vaccine* (R07).

The comparison of the two vaccines illustrates the significance of direct benefit to the participating woman and her fetus for taking risks of a new vaccine.

Considering problems of excluding pregnant women

Most researchers considered that the exclusion of pregnant women from research would generate problems in prenatal care. R04 argued for the need to conduct research with pregnant women due to the differences between pregnant and non-pregnant women:

> *They are definitely different. Huge physiological changes. So how are you going to know whether treatment works in pregnant women as well as in non-pregnant women unless you test it* (R04)*?*

Similarly, R06 indicated: "If *we never do studies with pregnant women, we have no idea what applies or what doesn't apply*". R04 expressed concern about the possibility of applying a treatment to pregnant women without having it tested with the pregnant population: "*You can make a case it's not fair to do tests only on non-pregnant women if you are going to be applying it to pregnant women".*

7.5.3.2.3 Considering complex nature of risk

This category explains the researcher's understanding and concerns about risk due to the complex nature of risk. Subcategories are: nothing is black and white, unknown risks, and wanting pregnant women to feel safe.

Nothing is black and white

R08 articulated that scientifically, nothing could be "*black and white*" in terms of risk. Whether something may or may not pose risk is simply a matter of dose or intensity.

> *The truth of the matter is everything has what we call an LD50 .... Anything, even water. If you drink too much water, it will kill you. So water even has an LD50. And it's surprisingly low. I think if you drink 5 liter of water a day, you will become very sick* (R08).

R02 pointed to the inconclusiveness of risk determination due to different opinions among experts regarding risks of flu vaccines:

> *There are some parents and doctors who are convinced taking the flu vaccine increases the risk of autism. And there are a large number of studies which also say that there is no clear evidence to suggest that* (R02).

R02 also referred to the differences of views on acceptable risks or safety among his colleagues. R02 "*personally want to stay out of"* his colleagues' research that "*need to be more invasive and probably ask for fetal cells that might be circulating in the womb, something like that".* Nevertheless, R02 endorsed the colleagues' research "*as long as there is a clear goal and know what they want to do".*

Unknown risks

Most researchers recognized unproven or unknown risks and other uncertainties involved in the course of research. For example, MRI is widely accepted by obstetricians for pregnant women with particular medical needs. Nevertheless, in discussing research involving MRI, R05 could not ignore the possibility of unknown risks in using MRI during pregnancy: "*I think the long term effects in MRI induced stress on the mom and the fetus is not really known*."

Regarding MRI, R08 referred to a higher intensity magnetic field used in some human research and commented on enrolling pregnant women in such research: "*I admit I will be cautious of the high intensity magnetic field"* because *"we don't know what the impact could be"*. R03 commented on a drug that had been prevalently used for years, which turned out to have adverse effects on the fetus: "*Paracetamol, acetaminophen, as you call it, or drugs that are very very current to use can have an effect on the fetus, can have endocrine disruptive properties."*

Wanting pregnant women to feel safe

A few researchers tried to be in the pregnant woman's shoes. R07 described women's concerns about adverse outcomes particularly in drug studies:

> *I think that when you are talking about medication, I think the overwhelming, um, the overwhelming thoughts of everyone is what are the, uh, how this is going to affect me and my baby* (R07).

R02 wanted to make sure that women would feel safe at any moments of research participation, particularly in research without any direct benefit to the participating woman. R02 emphasized the need to respect the woman's perception:

> *So if I say, you know, "We would like to draw blood from you every 30 minutes for five hours", right? Do you feel threatened by that? ... So I want them, for some research to help some other pregnancies, that they feel safe to participate for their own well being and for the well being of the unborn child* (R02).

R02 added that researchers must clarify to the participating woman that it is "*absolutely fine*" to withdraw if they felt unsafe.

R04 gave an interesting comparison of the two contexts to illustrate different perceptions regarding a piece of risk information described by the probability of an undesirable event happening:

> *If you say there's ten percent risk of premature labor, let's say, um, it's hard to know how they [pregnant women] interpret that in terms of their own situation. Ten percent sounds like a small number, but on the other hand, if you had a ten percent of winning a lottery, you might go for it* (R04).

R05 indicated the importance of informing and reassuring pregnant women about safety if the research indeed would not pose any risk to them:

> *If they can't be given that reassurance, they shouldn't go in the study, like they need to know that. So, right? And then, so, yeah, benefits of research, privacy, and knowing that there is going to be no harm done* (R05).

7.5.3.2.4 Connected with women, clinicians, and society

This category describes the need for input from women, clinicians, and society about what should be researched and how research should be conducted. Subcategories are: identifying research questions and review by professional and lay communities.

Identifying research questions

R05 commented that research questions must originate from the women's real life issues:

> *We need to learn from pregnant women, their habits, and what, nutritional habits, their habits with environmental factors, drugs, alcohol, etc., etc. because we need to learn from them, ... which then helps establish what basic scientists like myself to investigate* (R05).

R08 indicated more possibilities of research as a result of people's behavioral changes toward health:

> *Increasingly people are taking herbal medicines as well. Sort of plant derived medicines. And, uh, these are complex compounds, extracts that have many, many chemicals in them* (R08).

R08 added that we need to "*categorize things in terms of priorities"* to "*hit the most important ones"* among these emerging issues to be researched.

Review by professional and lay communities

Feedback from the professional community and the lay public was appreciated by a few researchers. R09 stood strongly by the peer review system for maintaining the integrity of research: "*So to me, I have faith in the system. Of course, nothing is perfect. There may be, from time to time, deficiencies, but overall I think I would trust the system*." R09 maintained that discussion must occur for each research project and that there should be no blanket rule to exclude any particular types of research with pregnant women or with any other populations:

> *To me, as long as it's a good question, as long as the study has gone through, uh, peer review in terms of science and also in terms of ethics consideration, I would be supportive. I don't have any preconceived, uh, opinion about drugs or anything* (R09).

R08 explicated the complexity of addressing ethical issues and the inherent limitation or inconclusiveness in doing so. R08 deferred ethical judgment to the general public:

> *Right and wrong is not always so transparent. ... I think ethics and morals are always a moving target and they are always open to evolution of thoughts and practice. ... It has to be something that a community, a society, a culture decides for itself* (R08).

7.5.3.2.5 Respecting the woman's decision

This category explains the researcher's attitude of leaving the final decision to the pregnant woman. This category is largely similar to the category identified with obstetric healthcare providers' views although subcategories show similarities as well as differences: providing pertinent information, assuming women's understanding insufficient, and respecting personal values and beliefs.

Providing pertinent information

All researchers thought full disclosure of information is mandated, including disclosure that there might be unknown risks:

> *I would, I mean disclosure has to be completely open. And you have to have open and honest conversation about, even though you may not know all the potential harms, you have to have a very honest conversation about that, of course* (R08).

Also, some researchers thought pregnant women could become unreasonably afraid depending on the way information was presented. R04 emphasized that the information should be provided in such a way to meaningfully support the woman's decision making:

> *I think as much information possible should be given so that the decision is not just based on irrational fear or lack of information. Information available should be provided to help make the decision* (R04).

Considering that clinician investigators might not always be "*unbiased and unemotional*" in providing information to the potential participant, R02 proposed:

> *I think there should be one neutral party involved. Somebody, like, say, you know, hospital might designate a certain person who has no interest in seeing the procedure being done and who has no interest in seeing whether the woman says yes or no* (R02).

Assuming women's understanding insufficient

While emphasizing the need for full disclosure of information, two researchers expressed concerns about the difficulty of lay persons to understand every detail of a scientific project. R04 described the downside of going too far into technical details:

> *It's important although very difficult to, uh, technical aspects, they probably won't understand and might get frightened, yes, because they don't understand. Yeah, may sound like something from another planet* (R04).

R02 expressed a dilemma arising from the gap between the ideal of full disclosure of information and the reality of the participant's limited understanding:

> *I think sometimes especially, you know, when research is complicated, it might be really difficult to, for a woman to, you know, a lay person in a community to fully grasp some of these things. ... But in my own research, I, uh, I would feel much better if they had some sort of understanding of what I am trying to do* (R02).

At a practical level, R02 felt the necessity to compromise, i.e. if the woman *"understands the risks involved, then that is fine"*.

Respecting personal values and beliefs

Several researchers expressed the need to respect the woman's personal beliefs and values in their decision making about research participation. R02 commented that "*religion or personal beliefs"* could be very important in the woman's decision making. To illustrate the importance of personal values and beliefs in the pregnant woman's decision making, R07 shared the gist of a conversation with colleagues about a friend's breast cancer treatment during pregnancy:

> *It was quite, um, it was a very interesting discussion and we all have very different answers to that question about who, like who has the bigger risk to be saved in that situation, right? And it also comes from culturally and, uh, where you are coming from and what your background is or what your beliefs are. So I think you are going to get a pretty wide range of answers to the question* (R07).

Although this example concerns a medical treatment, a person's backgrounds and the complexity due to the conflict of interest between the woman and fetus may pertain to the research context.

Several researchers referred to societal and familial expectations of successful pregnancy, which could influence the pregnant woman's values. R06 stated: "*I think there's huge expectation that you are going to have a healthy baby. It's great, yea*h." R01 feared that

pregnant women could be under societal pressure as *"almost the onus always goes on the pregnant woman"* for any adverse outcomes in pregnancy.

7.6 Discussion

The findings of the three groups of participants will be discussed to analyze their decision making processes about clinical research with pregnant women and how the results add to the body of literature. First, pregnant women's views will be discussed. Then, the views of obstetric healthcare providers and researchers in reproduction areas will be discussed together as some categories overlap while other categories show interesting differences which may be better analyzed through comparison.

7.6.1 Pregnant women

7.6.1.1 Protecting myself and my fetus

Protecting herself and her fetus appeared to be at the center of the pregnant woman's decision making process of whether or not to participate in clinical research. While safety was recognized important for both the woman and fetus, pregnant women were inclined to be more protective of the fetus. A potential priority given to fetal well being is reported in several studies. In a study examining women's reasons to participate in an obstetric anesthesia study, 79.5% of the consenters (n=166) strongly considered low fetal risk (Dorantes, Tait, & Naughton, 2000). Baker, Lavender, & Tincello (2005) investigated women who participated in multiple studies including observational and interventional studies during pregnancy. These authors found that even some women who participated in all research to which they were recruited were concerned about any potential compromise to fetal well being. However, these studies have not discussed why a pregnant woman would prioritize fetal well being.

The participant's sense of responsibility and perception of the fetus may be understood as an attachment, i.e. a person's special preference for some persons over others (Mercer, 2006). Rubin (1984) discusses that a maternal identity which gradually grows during pregnancy is interdependent with the formation of the woman's attachment to the child.

In the process of building a maternal identity, a fantasy of fear for anything to go wrong may become a source of the woman's protective attitude toward the fetus (Rubin, 1984). These theories on maternal identity and maternal fetal attachment may explain the pregnant woman's perception of preciousness or fragility of the fetus and the need to protect it as shown in the findings.

At the same time, societal expectations may be another factor to consider in explaining the woman's focus on fetal well being (Lupton, 1999a, 1999b, 2012; T. Miller, 2005). Based on the pregnant woman's narratives in Western societies, Miller (2005) indicates that the woman's anticipation of a motherhood reflects cultural norms of being a mother, such as "being there for others" (p.137). Miller (2005) argues that a woman may find it challenging to disclose experiences that are not in line with moral expectations of good mothering behaviors even before giving birth. The participant's sense of responsibility to the fetus may be understood as her wish to be a good mother. Lupton (1999a, 1999b, 2012), drawing on Beck's risk theory of reflexive modernization which interprets industrialized modern society as society where each individual is deemed responsible for his or her risk management (Beck & Cronin, 2009; Beck, Giddens, & Lash, 1994; Beck, 1992), argues that pregnant women are under pressure to make right decisions to address risks to herself and her fetus. In terms of the fetal value itself, Lupton (1999a, 1999b, 2012a, 2012b) points out that the fetus is considered much more valuable than the pregnant woman and thus fetal safety is given priority to the woman's needs. Lupton argues that medical technologies, such as ultrasound and laboratory tests have put pregnant women under surveillance, holding women accountable for achieving healthy pregnancy and producing a healthy baby (Lupton, 1999a, 1999b, 2012a, 2012b). The participant's protective attitudes and behaviors toward the fetus could also be explained by societal value of the fetus and the medicalization of pregnancy which facilitated objective monitoring of the course of pregnancy.

7.6.1.2 Pregnant women's need for information

The results of this study illustrated the pregnant woman's need for information to make her decision about research participation. In regards to information, previous studies investigating women's reasons to participate or decline participation in research discussed

whether pregnant participants were satisfied with the information about specific research studies in which they participated or which they considered participation. Several studies showed that pregnant women's satisfaction with the information is a factor that may positively influence their participation (Dorantes et al., 2000; East, Chan, Brennecke, King, & Colditz, 2006; East & Colditz, 1996; Halkoaho et al., 2010; Hutton, Wilkinson, & Neale, 1990; Rodger et al., 2003). Also, some studies pointed out the importance of the circumstance under which the information was provided, suggesting that the timing of information provision may affect the participant's satisfaction about the information (Baker et al., 2005; East et al., 2006; Ferguson, 2000; Halkoaho et al., 2010; Rengerink, Logtenberg, Hooft, Bossuyt, & Mol, 2015). For example, if the information was provided during labor, it may be difficult for a woman to understand and appreciate (Ferguson, 2000). Although previous studies do not report specific pieces of information that were provided, their results resonate this study in suggesting that pregnant women want information for considering research participation and that insufficient provision of information may compromise successful recruitment.

In terms of the importance of information for the woman's decision making, this study captured two issues that had been little discussed. Among the list of items which pregnant women in this study wanted to know was how their personal information would be protected. Only one previous study (Halkoaho et al., 2010) indicated concerns regarding personal health information being breached. Another study examining 166 consenters and 109 non-consenters regarding their reasons to participate or not in obstetric anesthesia research referred to pregnant women's concern about a lack of privacy during labor or delivery due to research participation (Dorantes et al., 2000); however not about protection of personal information per se. The result of this study uncovering the pregnant woman's privacy concern in terms of personal information may reflect a growing concern in society about protection of personal information (Taitsman, Grimm, & Agrawal, 2013). Another point to highlight is that some pregnant women were active information seekers, wanting to seek information beyond what would be provided from the researcher and to examine a variety of issues, such as safety. This could be due to the fact that all the participants were relatively well educated, potentially more cognizant of resources for information.

Further, women clearly had some hierarchy in considering the retrieved information, such as trust in the information from physicians and some doubt about internet sources. In a qualitative study on pregnant women's experiences of surveillance medicine, Hammer and Burton-Jeangros (2013) analyzed that a group of women who coped with risk through verbal reassurance perceived the obstetricians and gynaecologists as the most reliable information source, i.e. who would address risks raised by other less reliable sources such as friends, handbooks on prenatal issues, media, and the internet. The reliance on healthcare providers in the woman's decision making process will be discussed later (7.6.1.6).

7.6.1.3 Wanting to see benefits

Pregnant women in this study wanted to see benefits in research, such as direct health benefit to the woman or fetus and learning opportunities for the woman as well as scientific knowledge for future pregnant women. The results confirmed previous evidence noting pregnant women's perception of benefits which included contributing to science and future pregnant women (Baker et al., 2005; Daniels et al., 2006; Dorantes et al., 2000; East & Colditz, 1996; Founds, 2007; Gatny & Axinn, 2012; Hutton et al., 1990; Joseph, Neidich, Ober, & Ross, 2008; Kenyon, Dixon-Woods, Jackson, Windridge, & Pitchforth, 2006; Lamvu et al., 2005; McLeod, Barrett, Hewson, & Hannah, 2004; Mohanna & Tunna, 1999; Promislow et al., 2004; Rodger et al., 2003; Smyth, Duley, Jacoby, & Elbourne, 2009) as well as benefiting themselves and their fetuses through receiving medical treatment (Coulibaly-Traoré, Msellati, Vidal, Welffens Ekra, & Dabis, 2003; Kenyon et al., 2006; Lyerly, Namey, Gray, Swamy, & Faden, 2012; Rodger et al., 2003; Smyth et al., 2009; Smyth, Jacoby, & Elbourne, 2012), additional medical attention (Coulibaly-Traoré et al., 2003; Daniels et al., 2006; Gatny & Axinn, 2012; Lamvu et al., 2005; Promislow et al., 2004), and learning opportunities (Daniels et al., 2006; Founds, 2007; Gatny & Axinn, 2012; Lamvu et al., 2005; Promislow et al., 2004). These studies indicated the benefits among the reasons for pregnant women to participate in research.

Most pregnant women in this study felt more positive about research if there was direct benefit to themselves even though all women recognized that research would not guarantee any therapeutic benefit to the participant. In a study investigating pregnant

women's reasons to participate in a hypothetical study involving heparin administration, the researchers concluded that benefits to fetal health was the dominant factor (68%), followed by benefits to the woman's own health (27%) (Rodger et al., 2003). Gatny and Axinn (2012) argue that pregnant women's altruism could be overestimated due to the societal value of endorsing altruism, i.e. women may be inclined to mention helping others or contributing to society. Also, the result of a study investigating pregnant women's views on research involving two antibiotics in preterm labor suggested that the woman would be altruistic only if there was no risk to her and her fetus (Kenyon et al., 2006). Further, Smyth et al. (2012) indicated that self benefit may be the strongest motivation based on semi-structured interviews of 40 women with preeclampsia who participated in a placebo involving trial investigating prophylactic use of magnesium sulfate. Thus altruism may be the main motivation in observational studies where self benefit is not expected. However, in therapeutic research where all or some participants may receive benefit from treatment, self benefit may likely be the major reason to participate. This will be further discussed in the next section in relation to risk taking.

7.6.1.4 Focusing on safety

The results showed that pregnant women had much focus on safety assurance. This may be shown in their attitude toward accepting risk. These results confirm previous studies which identified risks as one of the main reasons for not participating in research (Baker et al., 2005; Dorantes et al., 2000; Hendrix et al., 2009; Hutton et al., 1990; Mohanna & Tunna, 1999; Rodger et al., 2003).

The results showed that pregnant women basically did not want any risk although a few pregnant women felt discomfort or minor transient symptoms to themselves, such as mild diarrhea, nausea, or feeling of sickness, acceptable. These minor transient symptoms described by pregnant women may likely fall under minimal risk stipulated in research ethics regulations. The US (Department of Health and Human Services, 2009) and European Regulations (Council of Europe, 2005) stipulate an upper limit of fetal risk as minimal risk in research without direct benefit to the participant and the Australian Regulation (National Health and Medical Research Council et al., 2007 (updated 2014)) allows no fetal risk in research involving drugs or medical procedures. None of the

regulations discussed in Chapter 5 specifically refers to an upper limit of maternal risk, which may be unreasonable, given that the woman and fetus influence each other in the course of pregnancy. In terms of the upper limit to fetal risk, the US Regulation which allows minimal risk for nontherapeutic research seems more permissive than the views of pregnant women who did not want any fetal risk; however, in terms of an upper risk limit to pregnant women, the research ethics regulations may be more lenient for not setting a limit. Thus some discrepancies exist between the views of pregnant women and these regulations.

Further, the results suggested that pregnant women were inclined to take risks in research only if any research intervention was the avenue to provide a possibility of solving the woman's or fetus's existing health problems. This may be consistent with previous studies on the pregnant women's views on a placebo randomized controlled trial (RCT) involving heparin injection (Rodger et al., 2003) or a new H1N1vaccine study (Lyerly et al., 2012). In both studies women weighed risks and benefits to themselves and their fetuses in considering participation in interventional research which involved risks. The results of this study further articulated that risk taking may occur only under exceptional circumstances where existing risks are serious and research participation has a prospect of containing those risks. Acceptable risk could be higher depending on the seriousness of the health condition to be addressed. Importantly, comparing clinical care and research, pregnant women in this study expressed lower risk tolerance in the research context compared with the clinical context where procedures would be performed for their medical needs. Although pregnant women did not explicitly refer to unknown risks as did obstetric healthcare providers and researchers, the pregnant woman's strategy to avoid anything unnecessary – even an additional ultrasound if solely for a research purpose - may imply their worries about unknown risks.

7.6.1.5 Considering personal values and beliefs

Many pregnant participants referred to personal values and beliefs in explaining their decision making process. The influence of personal values and beliefs on the pregnant woman's decision to participate in research has been little discussed to date although some discussions revolved around differences across ethnic groups (Lamvu et al., 2005;

Nechuta et al., 2012; vanDelft 2013) or individuals (Baker et al., 2005; Mohanna & Tunna, 1999; Smyth et al., 2012). A few studies discussed differences of pregnant women's attitudes across ethnicities which may represent different cultures with different values (Lamvu et al., 2005; Nechuta et al., 2012; vanDelft 2013). For example, a study investigating 311 pregnant women's attitudes toward research involving biological specimen collection indicated that Hispanics were less willing to participate in research involving blood collection (OR=2.16, CI: 1.15-4.04) than white women (Nechuta et al., 2012). Although authors do not analyze potential backgrounds of the results, one of the factors could be different cultural values shared by different ethnic groups. Also, in a study comparing 735 white pregnant women and 285 black pregnant women about their reasons to participate in research on pregnancy outcomes, black women were less motivated by contribution to knowledge (OR=0.44, 95% CI: 0.36-0.63) while they were more likely to participate for self benefit such as learning about pregnancy health (OR=3.12, CI: 1.88-5.55) and concern about their pregnancy health (OR=3.0, CI: 1.56-5.94) (Lamvu et al., 2005). As these results were adjusted for the woman's age, gravidity, pregnancy loss, education, marital status, and income, values prevalently held within an ethnicity could be a factor to be considered.

Further, potentially related to personal values, a UK study investigating post-partum women who participated in multiple studies during pregnancy reported women's wish for researchers to recognize the individual differences in terms of when or how they want to be approached by research staff (Baker et al., 2005). The authors (Baker et al., 2005) ascribed the result to the fact that research is less tailored to individuals compared with prenatal care in interacting and communicating with the woman. Although such difference may come from the nature of research being conducted as per protocol, consideration required for individual differences resonates the results of this study where many women referred to the influence of personal values and beliefs in their decision making.

7.6.1.6 Deciding with others

Pregnant women in this study wanted to consult others, particularly the partner in their decision making. Previous studies showed conflicting results regarding the influence of

others on the woman's decision making about research participation. Several studies reported family objection as one of the reasons for women to decline research participation (Daly, Toth, & Giebink, 2003; Dorantes et al., 2000; McLeod et al., 2004; Rohra et al., 2009) whereas a study with pregnant women considering participation in research involving a drug for preeclampsia showed that family opinions were not important for the woman's decision making (Smyth et al., 2012).

Previous studies also showed that healthcare providers' encouragement to participate enhanced women's participation (Founds, 2007) and that women's trust in healthcare providers positively influenced recruitment (Halkoaho et al., 2010; Joseph et al., 2008; Kenyon et al., 2006; Smyth et al., 2012). The woman's trust and reliance on healthcare professionals may in part reflect medicalization of pregnancy, which arguably began as early as in 1913 represented by publication of *Prenatal Care* by the US Children's Bureau (Barker, 1998). Indeed, the majority of women in developed countries present their body to a physician in the event of pregnancy (Miller, 2005). Also from the cognitive science perspective which is dominant in technical and scientific arenas, the expert opinion is more trusted than the lay opinions in addressing risk (Lupton, 1999a). Given that protecting herself and her fetus is at the top of the pregnant woman's agenda, it seems reasonable for the woman to consult healthcare professionals particularly regarding safety assurance.

This study may confirm the relational aspect of the pregnant woman's decision making about research participation although the pregnant woman's attitude and behavior could be influenced by multiple factors, such as complicated research procedures which may require advice from healthcare providers or the woman's relationships with family members or their family physicians.

7.6.2 Obstetric healthcare providers and researchers in reproduction areas

7.6.2.1 Main focus in their decision making processes

Obstetric healthcare providers had much focus on satisfying regulatory requirements. This may reflect many aspects of clinical practice that are highly regulated by

professional bodies such as the Royal College of Physicians and Surgeons of Canada or government agencies such as Health Canada. They appear to be bound by regulatory requirements for conducting human research as they are by clinical practice guidelines for their everyday practice. Despite much concern about safety of the participating woman and fetus, obstetric healthcare providers emphasized that involving pregnant women in research should not be considered exceptional. Their understanding is in line with the TCPS2 (Article 4.3) (Canadian Institute of Health Research, Natural Sciences and Engineering Research Council of Canada, & Social Sciences and Humanities Research Council of Canada, 2014) which describes pregnant women as eligible to participate and rather requires justification for their exclusion. By contrast, researchers in reproduction areas emphasized the differences between the general and pregnant populations as well as pregnant animals and pregnant humans. They had much focus on scrutinizing the scientific quality of prerequisite studies as well as their appropriate translation into pregnant human studies. Often referring to the critical nature of the events during pregnancy particularly for the fetus, researchers appeared more conservative, implying that adherence to regulatory requirements may not necessarily suffice.

Nevertheless, either adhering to regulations or scrutinizing the quality of prerequisite research may relate to liability concerns. Although it was only one clinician that explicitly mentioned the litigious and consumerist trend of society, the healthcare provider's focus on the adherence to regulatory requirements may suggest that they not only rely on these requirements as guiding principles but also as protection from liability by being in line with professional standards. Regarding the inclusion of pregnant women in research, several authors have suggested the need for more guidance from professional bodies and regulatory authorities to address medicolegal issues (Allesee & Gallagher, 2011; Brandon, Shivakumar, Lee, Inrig, & Sadler, 2009; Lyerly, Little, & Faden, 2008a). In an UK study investigating obstetric consultants' views on a RCT seeking an optimal mode of delivery for preterm breech, the reasons for not supporting the RCT included deviation from the standard of care and methodological concerns (Penn & Steer, 1990), both of which may lead to legal consequences. Also, in terms of researchers in reproduction areas, liability concern cannot be totally ruled out as they may not want

their work in basic science to be misinterpreted to provide a false safety assurance for human research.

7.6.2.2 Benefits of research and disadvantages of no research

Both researchers in reproduction areas and obstetric healthcare providers clarified that research must lead to improving prenatal care. These findings confirm the results of a qualitative study which identified seeking evidence-based alternative as a subtheme for obstetric healthcare providers' views regarding research testing knee-chest posture for breech presentation (Founds, 2007). However, in contrast to obstetric healthcare providers' focus on answering important clinical questions, the researchers' understanding of indirect benefit (knowledge) was broader. This may be understandable as most basic science studies usually do not produce results that are immediately clinically applicable yet important in the long term. A potential problem of this broader understanding of benefits may be that the justification of benefits could go too far where the research hardly relates to a remote goal of contributing to clinical outcomes. This could particularly be concerning if the research involves human specimens that require invasive procedures to be obtained.

In support of generating knowledge, both healthcare providers and researchers in reproduction areas indicated that the clinical disadvantages of excluding pregnant women from clinical research need to be considered. These findings support criticism on the paucity of research-based evidence resulting in suboptimal prenatal care (Baylis, 2010; Charo, 1993; Chervenak & McCullough, 2003; Kass, Taylor, & King, 1996; Lyerly, Little, & Faden, 2008b; Lyerly, Little, & Faden, 2008c; Macklin, 2010; Mastroianni, Faden, & Federman, 1994; Mattison & Zajicek, 2006; McCullough, Coverdale, & Chervenak, 2005; Minkoff, Moreno, & Powderly, 1992). However, considering the disadvantage of excluding pregnant women may be challenging.

Among the research ethics regulations discussed in Chapter 5, only the Canadian TCPS2 (Canadian Institute of Health Research et al., 2014) (Application of Article 4.3) explicitly considers the risks and benefits of excluding pregnant women. The CIOMS Guideline (Guideline12) (CIOMS, 2002) and Australian Regulation (National Health and Medical

Research Council, Australian Research Council, & Australian Vice-Chancellor's Committee, 2007 (updated 2014)) (Article 1.4) refer to fair participant selection, which may indirectly address the inappropriate exclusion of pregnant women. The Declaration of Helsinki (World Medical Association, 2013) also stipulates that appropriate access to research must be provided to groups that are underrepresented in research. Nevertheless, the Declaration of Helsinki (World Medical Association, 2013) also clarifies that the value of knowledge to be gained does not justify any compromise to the well being of research participants. Also, it seems difficult to evaluate and incorporate the disadvantage of excluding pregnant women into the risk benefit calculation as specific approaches to consider benefits and risks of excluding them seems unclear (Levine, 1988).

7.6.2.3 Pregnant women's desire for safety and risk tolerance

Safety and risk were discussed much by all participants across the three groups. Particularly, the word "safety" was heard a number of times from pregnant women and obstetric healthcare providers. In general, the term safety is widely used in the context of "protection from personal harm" (Miller, 1982) (p.5) in a variety of contexts, such as school safety, consumer safety, or aviation safety (Miller, 1982). Among the definitions of safety in the Oxford English Dictionary, one that suits the research context is "the state of being protected from or guarded against hurt or injury" (Oxford University Press, 2015).

In assuring safety, unknown risks are concerning as pointed out by many healthcare providers and researchers in this study. Moreover, as several researchers in reproduction areas articulated, determining whether something is risky or not may not be so straightforward or clear cut. The fear of unknown risk and the complexities inherent in risk determination may point to further difficulties and hesitation in including pregnant women in interventional research which is much needed for evidence-based care. Obstetric healthcare providers and researchers in reproduction areas assumed that the pregnant woman's openness to risk would be very limited and depend on her health conditions and the prospect of therapeutic benefits to herself or her fetus through research participation. Interestingly, their assumption was consistent with the findings from the

pregnant women's views in this study. These empirical results confirm the difficulty of conducting research with pregnant women if it involves any risk.

At a regulatory level, the US Regulation (Department of Health and Human Services, 2009) clearly supports these views by requiring direct benefits to the woman or fetus for justifying fetal risk although this regulation does not refer to how maternal risk should be justified. The TCPS2 (Canadian Institute of Health Research et al., 2014) also requires a favorable risk benefit ratio to the participant; however, remains open regarding risk benefit distribution between the woman and fetus. The Australian Regulation (National Health and Medical Research Council et al., 2007 (updated 2014)) may be stricter regarding the justification of fetal risk, requiring exclusively fetal benefit for any research influencing the fetus. The Council for International Organization of Medical Sciences (CIOMS) Guideline (CIOMS, 2002) (Guideline 17) stipulates that research involving pregnant women must meet the needs of pregnant women and/or fetuses as participants (direct benefits) and as a population (indirect benefits), which could indicate that research with pregnant women must always have benefit to the participants. Compared with the views of the three groups of participants in this study, these research ethics regulations are neither overly restrictive nor lenient in relation to risk.

7.6.2.4 Respecting the pregnant woman's decision making

Both obstetric healthcare providers and researchers in reproduction areas unanimously clarified that the pregnant woman's decision based on her understanding of information and personal values would be essential for research to happen. In terms of information provision, healthcare providers and researchers held high standards that are consistent with literature, i.e. sufficient and unbiased information must be provided to avoid any coercion (Appelbaum, Berg, & Lidz, 2001; Bowman, Spicer, & Iqbal, 2012). The result may indicate healthcare providers' and researchers' familiarity with the practice of informed consent which is considered critical in the ethical conduct of clinical practice and research (Appelbaum et al., 2001; Beauchamp, 2011).

Compared with obstetric healthcare providers, researchers in reproduction areas expressed more skepticism about the informed consent process in two aspects which

pertain to research with any populations. First, recognizing that clinician investigators could be coercive when approaching their own patients, a researcher participant in this study proposed a neutral party for recruitment. The pregnant women's views also support the researchers' concern as they overall expressed much trust in their physicians as the most reliable source of information, particularly regarding safety assurance, and felt comfortable to participate if their physician recommended. Previous studies also showed healthcare providers' positive influence on pregnant women's participation (Founds, 2007; Halkoaho et al., 2010; Joseph et al., 2008; Kenyon et al., 2006; Smyth et al., 2012). Thus the researcher's concern seems legitimate although it is ironical that a good clinical relationship could generate motivation and pressure for the patient to participate. Second, a few researchers were skeptical of the pregnant woman's understanding about research as they felt some pieces of information could be too technical for lay persons to fully understand. Interestingly, obstetric healthcare providers who have much more interaction with laypersons did not explicitly question the understanding of their patients or participants. Literature shows that informed consent has been discussed much in terms of the appropriate amount of information for enhancing understanding (Macklin, 1999). Specifically regarding the participant's understanding of information, a review of 30 empirical studies investigating the research participant's understanding revealed that participants who demonstrated sufficient understanding was 54% for the study objective, 50% for the voluntariness of participation, 47% for randomization, 44% for the right to withdraw from the study, 50% for risks, and 52% for benefits (Falagas, Korbila, Giannopoulou, Kondilis, & Peppas, 2009). A systematic review of 42 trials evaluating interventions, such as multimedia interventions or administering test and feedback, for enhancing the participant's understanding concluded that none of the interventions was significantly effective (Flory & Emanuel, 2004). These studies may support the researchers' concern captured in this study. The problems with the participant's voluntariness and understanding may raise a flag as the practice of consent may become a mere formality.

7.6.2.5 Involving others in the decision making

Obstetric healthcare providers and researchers in reproduction areas did not specifically refer to formal paternal consent. However, they endorsed the positive aspect of consulting others including the woman's partner in supporting her decision making. It seems interesting that despite no regulatory requirements, both healthcare providers and researchers maintained that the pregnant woman should consult others as needed. The pregnant woman's attitude also revealed that women would want to consult others rather than deciding by herself.

The stipulations on involving others particularly the fetus's father in the pregnant woman's decision making varies across research ethics regulations. At the one end, paternal consent is required (South Africa, (Medical Research Council of South Africa, 2002)) while at the other end, the woman's consent suffices for any research including research targeted toward the fetus or fetal tissues (Canadian Institute of Health Research et al., 2010). There are some variations, such as requiring paternal consent for research with fetal benefits (US, Department of Health and Human Services, 2009)), suggesting that paternal opinion is desirable (CIOMS, 2002), or allowing other stakeholders (not specified) to be involved upon the pregnant woman's request (Australia, National Health and Medical Research Council et al., 2007, updated 2014)). Although partner's or others' involvement in the consent process may support the woman's decision making, it could potentially hinder or delay the pregnant woman's decision making as it simply adds another step to the consent process, and may be controversial in relation to the woman's autonomy. However, the results showed that requiring paternal consent or opinion may not be totally disconnected from the views of pregnant women, obstetric healthcare providers, and researchers in reproduction areas. Nevertheless, if formal paternal consent is a regulatory requirement, all pregnant participants must involve their partner in the consent process regardless of their wish to do so. While this may be a contentious issue, research ethics regulations could rather leave the choice of involving others in the consent process to the pregnant woman as in the Australian Regulation.

7.7 Limitations and strengths

The findings must be interpreted in the light of limitations. The selection of participants was a limitation as obviously only those who were willing to participate in this study were interviewed. Pregnant women who participated may have positive rather than negative attitudes toward research with pregnant women compared with pregnant women in general as the participants agreed to spend their time for an interview for a research purpose. Previous studies on pregnant women's views on research participation suggested that whether the study looked at the consenters or decliners may generate a difference (Kenyon et al., 2006; Lyerly et al., 2012). The same issue applies to this study which involved consenters. Also, all pregnant participants were relatively socially advantaged women with tertiary education and a supportive partner and family members. These backgrounds could have influenced their views in considering clinical research participation compared with women with a lower level of education or unsupportive family members. Similarly, all obstetric healthcare providers and researchers in reproduction areas were those who agreed to participate amid their busy professional life. In addition, although the participants included three clinician investigators conducting research with pregnant women, none of their studies involved potential risk to the woman or fetus. It would have been valuable to interview clinician investigators conducting interventional research involving potential risk to the woman or fetus. A few such clinicians were identified and approached; unfortunately however, none of them were willing to participate.

Another limitation was the hypothetical setting of clinical research to be considered by the participants. In this study, the participants were not asked about participating in, conducting, or recruiting patients for a real research study. As indicated in studies on pregnant women, participants showed more favorable attitudes toward research participation if it was hypothetical (Daly et al., 2003; Lavender & Kingdon, 2009). The hypothetical setting could have influenced the results of this study in a way to collect data in favor of clinical research with pregnant women, particularly in terms of pregnant participants. On the other hand, obstetric healthcare providers and researchers would not be participants themselves and thus the setting might not have influenced their views as

much as it might have for pregnant women. Nevertheless, employing hypothetical settings enabled capturing the participant's feelings and attitudes toward clinical research with pregnant women in a variety of settings, which was suitable for answering the research question. Otherwise, most of the findings will be restricted to the participant's views and decision making regarding one particular study. Thus the hypothetical settings are limitations as well as strengths of this study.

Further, this study has significant strengths. This study examined three groups of stakeholders who would play different roles in clinical research with pregnant women. That is, pregnant women are potential participants; obstetric healthcare providers are either potential clinician investigators or recruiters as professionals in the circle of prenatal care; and researchers in reproduction areas are either potential investigators or investigators of prerequisite animal studies that could be applied to pregnant humans. Obstetric healthcare providers have been little studied and researchers in reproduction areas have not been studied to date despite the deep relationship with clinical research involving pregnant women. In addressing underrepresentation of pregnant women in clinical research, it is critical to expand the study population to other stakeholders besides pregnant women (Ngui, Warner, & Roberts, 2014; Shields, 2012).

Examining researchers in reproduction areas was valuable in this study as they were highly motivated to take part in the interview due to their interest in reproductive science and provided in-depth views on science, risk, and benefit. Particularly, their dissection of the complex nature of risk articulated the difficulties in conducting research with pregnant women who would not accept any risk except for very limited circumstances. It was also valuable to interview obstetric healthcare providers from a variety of specialties and professions. Seven out of ten healthcare providers practiced in specialties outside obstetrics, seeing pregnant women as their patients due to the woman’s non-obstetric conditions. Interviewing these clinicians was helpful as a paucity of research with pregnant women has been reported more in non-obstetric areas (Domínguez, Ramos, Torrents, García, & Carné, 2012). Particularly, as several physician participants recognized the need for more interventional research with pregnant women to guide their practice, they described specific examples of difficulties in prenatal care as well as the

risks that could be eliminated with research-based evidence. Together with their concern about securing safety, a dilemma inherent in enhancing clinical research with pregnant women was well described.

7.8 Implications of the results

The results have implications on prenatal/preconception care, policies on research with pregnant women, and education for healthcare providers, clinical investigators, and the general public.

7.8.1 Information provision in prenatal care and research

Interestingly, pregnant women often referred to clinical care and physicians in discussing clinical research with pregnant women. First, pregnant woman's risk tolerance for clinical care seems higher than that for clinical research based on their understanding that clinical care is required for their health and thus worth taking risks whereas research is not necessarily required for their healthcare. Nevertheless, clinical practice also involves uncertainties in terms of benefits and at times involves experimental treatments which are administered by clinicians' discretion and authorized by the patient's consent (Levine, 1988) in contrast to research which is scrutinized by third parties, such as committees for scientific and ethics review (Beauchamp, 2011). Clinicians' discussion with the patient about clinical procedures, particularly those that involve experimental components may require more caution in clarifying the risk benefit ratio to the patient as pregnant women appeared to trust physicians more than any other sources of information and expected them to make a fair assessment to act for their best interest. The pregnant woman's risk tolerance in clinical care and their trust in their healthcare providers suggest that healthcare providers must be very careful and responsible in how they communicate risks to pregnant women as they may likely be ready to accept most if not all clinical risks. This may apply to discussion with non-pregnant patients as well.

7.8.2 Policies on research with pregnant women

7.8.2.1 Identifying and prioritizing clinical questions

The experiences of obstetric healthcare providers strongly suggested the need for research to answer important clinical questions for improving prenatal and preconception care. Several obstetric healthcare providers voiced frustration due to the lack of updated evidence to support their daily practice and some of them gave examples of research that they would want to see. Some or most of these voices might not necessarily be systematically consolidated beyond sporadic discussions at practitioner levels.

The first step may be to identify areas in prenatal and preconception care where research evidence is lacking or requiring update. Professional bodies related to prenatal care, such as the Society of Obstetricians and Gynaecologists of Canada (SOGC) and College of Family Physicians of Canada could initiate a project that systematically collects, analyzes, and determines important clinical questions from a wide array of obstetric healthcare providers including non-obstetric specialties which do not have a high percentage of pregnant patients yet address important issues during pregnancy, such as psychiatry. Also, surveying pregnant women or women contemplating pregnancy may uncover their specific needs and concerns about prenatal care that may be outside the scope of healthcare providers. Recognizing the limitation of resources, the second step is to prioritize these research questions. Issues that involve more number of women or frequently occur, issues that could have serious consequences if not addressed, and issues for which research is feasible - as some research may not be feasible due to scientific, practical, financial, or ethical reasons - may be given priority over issues that are less frequent, not entailing serious consequences, or not feasible. Prioritization should be done at a policy level to make the most out of limited resources. Identifying what specifically needs to be researched for promoting pregnancy health may initiate changes to occur.

7.8.2.2 Guidance to the research community

Securing the safety of the pregnant woman and her fetus was unanimously considered critical by pregnant women, obstetric healthcare providers, and researchers in reproduction areas. This confirms the need to effectively address the safety and liability

concerns of clinical investigators and sponsors (Allesee & Gallagher, 2011). More specific guidance to the researchers, research ethics committees (RECs), and health related industries is required as research ethics regulations do not provide guidance that is specific enough. For example, consideration given to risks and benefits of excluding pregnant women (TCPS2, Application of Article 4.3) may require further guidance in terms of how this could be achieved.

Safety and liability concerns may be addressed through developing desirable study designs and standards for safety monitoring. Several authors have proposed study designs that may be relevant for including pregnant women, such as randomized controlled trials on a case by case basis (Goldkind et al., 2010) or with a higher level of monitoring compared with the general population (Baylis, 2010). The discussion of study designs and monitoring strategies should occur at a policy level to better address concerns of stakeholders including RECs that are also not exempt from liability (Icenogle, 2003; Robertson, 1980; Veatch, 1979). Although REC discretion is valuable in attending to specific circumstances, too much discretion may be open to a potential lack of consistencies within and across RECs (Kopelman, 2000; Resnik, 2005; Tauer, 2002).

The Canadian Institute of Health Research (CIHR) and SOGC may jointly draft a guideline for conducting interventional research involving pregnant women. Such a guideline should address (1) likely and unlikely risks at different stages of pregnancy, (2) desirable methods and frequency of maternal and fetal monitoring for various stages of pregnancy, (3) issues that should be discussed with the participant, and (4) strategies to address adverse events.

7.8.3 Education

7.8.3.1 Research ethics education

Although obtaining informed consent has been acknowledged as a professional standard in the medical community (Appelbaum et al., 2001; Rozovsky, 1990), several researchers in this study were skeptical about the layperson’s understanding of the information about research as well as voluntariness particularly when recruited by healthcare providers. The results suggest the need for further education for clinical investigators and research staff

to improve the consent process in clinical research for the participant's informed decision making.

Supporting a person's decision making through provision of a pertinent amount of information to optimize a person's understanding has been considered challenging in both clinical practice and research (Macklin, 1999). In research ethics literature, the letter of information (LOI) has been criticized for the lengthiness and complexity for a layperson to read through and understand (Davis, Holcombe, Berkel, Pramanik, & Divers, 1998; Holland, Browman, McDonald, & Saginur, 2013). Although the formal aspect of consent such as using a consent form to obtain written consent is important, research ethics education should also emphasize the substantive aspects, such as formulating a LOI that meaningfully facilitate laypersons' understanding and providing appropriate assistance in the course of recruitment to support their decision making. Otherwise, the consent process will become a mere formality, which is not desirable for both investigators and potential participants.

The results of this study also suggested potential coercion due to the clinical relationship and pregnant women's health problems. Ironically, a good clinical relationship could become a pressure for the patient to participate when recruited by healthcare providers. Also, pregnant women with no better choice than research participation to improve their health problems may be prone to give consent to research. Research ethics education for healthcare providers need to emphasize the power imbalance between the healthcare provider and patients (potential participants) as well as sensitivity to the patient's health context in relation to research participation.

7.8.3.2 Education for the general public

Education of the general public to promote their understanding about the importance of pregnancy health and the woman's autonomy seems critical in promoting research with pregnant women. First, the general public may be more interested in prenatal care and the need to improve prenatal care through research evidence if they understood more about the impact of prenatal health not only on fetal outcomes but also on a person's lifelong health. Second, it is the pregnant woman who should make the final decision on whether

or not to participate in research. Among the regulations discussed in Chapter 5, the Canadian TCPS2 (Canadian Institute of Health Research et al., 2014) clearly supports the pregnant woman's autonomy: "Research involving a fetus or fetal tissue shall be guided by respect for the woman's autonomy and physical integrity" (Application of Article 12.9). While the empirical findings showed that pregnant women give priority to the fetus and involve others in their decision making process, they should not be pressured by others to participate or not participate in research. The notion of the pregnant woman's autonomy should be shared by the general public to reduce societal, cultural, or familial pressure on the woman to decide in one way or the other.

In educating the general public, local health units hosting prenatal classes and professional bodies related to prenatal care may play a leading role. Professional bodies such as the SOGC may review and provide information about the importance pregnancy health for the woman and the fetus's lifelong health as well as the pregnant woman's right to decide whether or not to participate in research. Local health units may distribute the information in the community in a way suitable for the local contexts. Considering an increasing number of people using the social media that allows multidirectional communication (Kalampokis, Tambouris, & Tarabanis, 2013), Facebook and Twitter can be influential platforms for providing educational information or guiding people to venues providing such information. Advantages of the social media may be the accessibility to a large number of people and its power in enabling discussions on various topics in a timely manner. For example, potential harm of exposure to environmental chemicals during pregnancy is an emerging and controversial issue in terms of their toxicity to humans and human fetuses (Chapter 4). Active involvement in the discussion through the social media could motivate the general public to learn and think about the topics in pregnancy and the importance of clinical research with pregnant women in promoting pregnancy health.

7.9 Conclusions

For pregnant women, protecting herself and her fetus was most important in their decision making process regarding clinical research participation. They gathered information to make sure research would generate useful knowledge and that

participation would not harm the woman or fetus. Obstetric healthcare providers recognized the importance of satisfying regulatory requirements in endorsing clinical research with pregnant women. Although weighing risks and benefits was a basic strategy in examining a research project, obstetric healthcare providers had much focus on securing safety for the participating woman and fetus. Researchers in reproduction areas felt the need to carefully examine the science and interpretations of prerequisite studies behind research with pregnant women. Similar to healthcare providers, they weighed risks and benefits to evaluate research. Compared with healthcare providers, they were more skeptical about safety assurance as well as laypersons' understanding of the information. All groups appeared to share safety concerns and a dilemma between promoting clinical research with pregnant women and protecting the participating woman and fetus from harm. The results have implications on information provision in prenatal/preconception care, policies concerning clinical research with pregnant women, and education for the research team, healthcare providers, and the general public.

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Chapter 8

8 Conclusion

8.1 Introduction

A family of studies addressed questions related to the pregnant woman's informed decision making about health in clinical care and research with a focus on risk. In this last chapter, key findings and contribution of these studies to the body of knowledge in relevant areas will be articulated. Further, how these cluster of studies relate to one another in constructing a model that explains risk consideration in prenatal/preconception care as well as in clinical research involving pregnant women will be discussed. Finally, future research directions will be suggested.

8.2 Key findings of the four studies and their significance

8.2.1 Implications of applying the minimal risk concept in clinical research to clinical care (Chapters 3 & 4)

Two conceptual studies (Chapters 3 & 4) explored the potential of the minimal risk concept - a low risk standard codified in research ethics regulations – to be employed in clinical practice where a low risk standard is currently not established. Chapter 3 discussed why minimal risk may be appropriate to be applied to clinical care and how it may be useful for clinicians' practice in relation to providing risk information for the patient's informed decision making. Risks that clinicians need to discuss with the patient are not limited to those in clinical procedures but extend to health risks in everyday life such as substance use, sedentary life styles, or exposures to household chemicals. Considering a role of minimal risk as it relates to the modification of the informed consent process in research and the current lack of a low risk standard in clinical practice, applying minimal risk to clinical care may provide additional support in identifying risks that clinicians need to discuss with their patients.

Chapter 4 applied two minimal risk standards (one standard based on risks in daily life and the other based on risks in routine clinical examinations) to risk factors to be

considered in prenatal and preconception care. The results showed that cigarette smoking, moderate to heavy alcohol consumption, and folic acid insufficiency are above minimal risk and should be discussed with the patient in prenatal/preconception care while exposures to brominated flame retardants and phthalate plasticizers were difficult to determine whether or not they would be above minimal risk due to the insufficiency of evidence. The results also showed some limitations of the daily life standard of minimal risk in considering risks, such as risk of exposure to environmental chemicals that are ubiquitous in everyone's daily life.

The concept of minimal risk has been discussed extensively in research ethics in terms of the standards and their interpretations of the US regulation (Department of Health and Human Services, 2009). However, application of the minimal risk concept in research to clinical practice is a new proposal (Chapter 3). The application of the minimal risk concept to risks to pregnancy shown in Chapter 4 further clarified the usefulness of employing this low risk threshold concept for assisting clinicians' information provision in obstetrics and potentially across specialties. These two chapters provide a basis for developing new clinical practice guidelines using the minimal risk concept for assisting clinicians' practice in relation to risk discussion with the patient.

8.2.2 Critical review of national and international research ethics regulations on clinical research with pregnant women (Chapter 5)

The analysis of two international and four national research ethics regulations showed that these regulations involve factors that could overprotect pregnant women and fetuses, and potentially restrict important research with pregnant women. Endorsing the pregnant women's basic eligibility as research participants and requiring scientific justification for their exclusion may enhance their inclusion in studies that answer important clinical questions. Justification of fetal and maternal risk remains an issue to be solved. Strategies for balancing the risks and benefits among the woman, fetus, and society is a complicated matter which needs to be addressed in ethically convincing manners.

This chapter clarified differences across the six research ethics regulations in terms of pregnant women's eligibility as research participants and prerequisite studies, and thus adds to the body of literature which largely discussed the US regulation (Department of Health and Human Services, 2009), particularly its classification of pregnant women among the vulnerable populations that are addressed separately from the general population.

8.2.3 Views of pregnant women, obstetric healthcare providers, and researchers in reproduction areas on clinical research with pregnant women (Chapter 7)

The empirical study, employing constructivist grounded theory as a methodology, examined the views on clinical research with pregnant women from the viewpoints of pregnant women, obstetric healthcare providers, and researchers in reproduction areas. This study aimed to generate a substantive theory to explain the processes used by these three populations in determining conditions under which clinical research with pregnant women may be permissible. Twelve pregnant women, 10 obstetric healthcare providers, and 9 researchers in reproduction areas participated in an individual in-depth interview. In describing their decision making process, *protecting myself and my fetus* was identified most important for pregnant women. For healthcare providers, *satisfying regulatory requirements*, and for researchers in reproduction fields, *examining research with pregnant women* pertained throughout their decision making processes. The three groups of participants shared much concern about safety as well as a dilemma of promoting research for improving prenatal care and securing safety for the participating woman and fetus.

The results of pregnant women's views largely confirmed previous studies. However, this study further articulated that the pregnant woman's risk taking will be limited to exceptional circumstances in terms of her health problems and expected benefits through research participation. The pregnant woman's limited openness to risk was assumed by obstetric healthcare providers and researchers in reproduction areas. In contrast to pregnant women, healthcare providers and researchers had been little studied. Adding to previous studies that were mostly limited to examining healthcare providers' concerns,

this study revealed obstetric healthcare providers' basic strategy of following guidelines and regulatory authorities in securing safety as well as their need for research evidence to support their practice. Researchers in reproduction areas have not been studied to date, and thus this study brought valuable insights into their views which are characterized by placing emphasis on good science and careful application of prerequisite studies to pregnant women.

8.3 Relationship and implications of the four studies

The four studies comprising this thesis addressed issues related to the pregnant woman's informed decision making about her and her fetus's health in the context of clinical practice or research. Recognizing risk to maternal and fetal health as a critical factor in the decision making, these studies share discussions on risk, risk avoidance, and risk acceptance in either clinical practice or research. Despite the differences between clinical practice and research in terms of the objectives and uncertainties, it may be difficult to distinguish one from the other since some research may provide potential therapeutic benefits to participants while some clinical practice may involve experimental elements (Appelbaum & Lidz, 2008; Levine, 1979). Thus risk consideration in clinical care and research are not totally different, but could be rather similar (Chapter 3).

National and international research ethics regulations stipulate risks in research by (1) setting an upper limit, such as the *minimal risk threshold* for particular populations and purposes as well as (2) requiring a favorable *risk benefit ratio* through minimization of risks and maximization of benefits (Emanuel, Wendler, & Grady, 2000). These two approaches to restrict risk for participant protection apply to clinical research involving pregnant women as discussed in the critical review of research ethics regulations (Chapter 5). Among the regulations discussed, the US (Department of Health and Human Services, 2009) (45CFR46.204) and European (Council of Europe, 2005) (Article 18) regulations limit fetal risk to be within minimal risk in research without therapeutic benefits to the participating woman or fetus. On the other hand, requiring a favorable risk benefit ratio is among the overarching rules common to all populations, pregnant or non-pregnant (Emanuel, Wendler, & Grady, 2000). The *minimal risk threshold* and *risk benefit ratio* as codified in research ethics regulations regarding clinical research with

pregnant women (Chapter 5) may inform risk consideration not only in research but also in clinical practice for pregnant women.

Figure 5 illustrates a model mapping the results of the four studies summarized in 8.2. The arrows indicate influences. Chapters 3 and 4 discussed how minimal risk as an upper risk limit may influence clinical practice in relation to clinicians' information provision to women who are pregnant or contemplating pregnancy. Chapter 7 which examined the views of pregnant women, obstetric healthcare providers, and researchers in reproduction areas provided empirical evidence on acceptable risk in clinical research involving pregnant women.

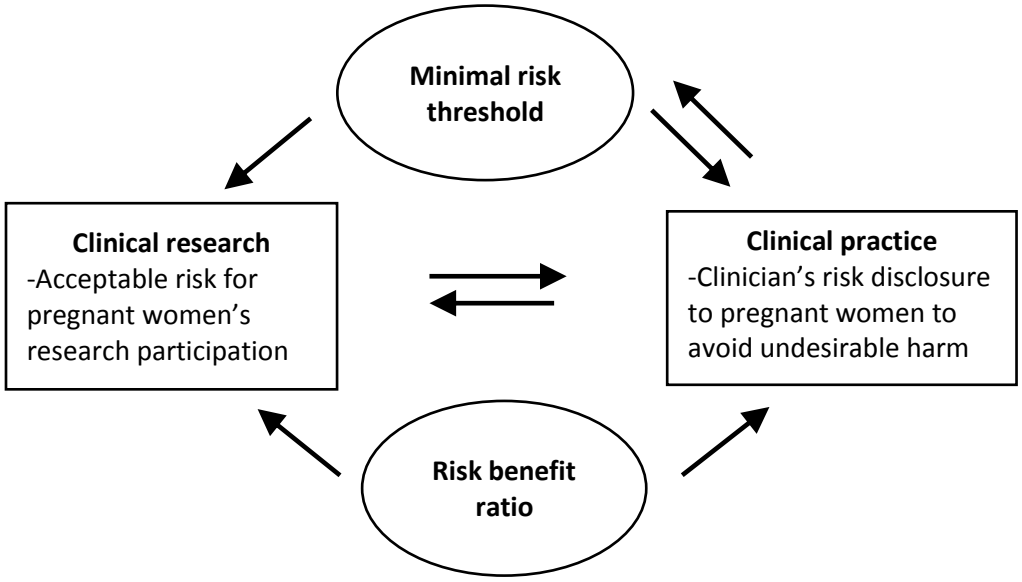

Figure 5. Risk consideration during pregnancy in clinical practice and research

The results of the grounded theory study (Chapter 7) suggested complex ways in which acceptable risk to pregnant women and fetuses are considered by pregnant women, obstetric healthcare providers, and researchers in reproduction areas. An important modification in terms of the upper risk limit is that the participants from all three groups basically wanted "no risk" although a few women seemed to accept minor transient

symptoms exclusively to themselves. In accepting risk, a major factor considered by all the three groups was to achieve a favorable risk benefit ratio under very limited circumstances where the woman or the fetus already had serious health conditions that could be improved through research participation. Thus, the empirical findings showed a more nuanced way in which these two approaches to risk restriction in research ethics regulations explain pregnant women's risk acceptance in clinical research (Chapter 7). On the other hand, in clinical practice, clinical procedures are, by definition, expected to satisfy a favorable risk benefit ratio for each patient as these procedures are primarily targeted toward improving the patient's health conditions. The findings suggested that the pregnant woman's risk tolerance in clinical practice may be higher compared with research participation (Chapter 7). This may be explained by the risk benefit ratio as research primarily does not guarantee any benefit to the participating woman or fetus, and thus acceptable risk in research usually cannot be as high as risk in clinical care where benefits are presumed to balance risks.

In terms of information provision in clinical practice, the minimal risk threshold may be useful in informing clinicians' risk discussion with pregnant women (Chapters 3 & 4) whereas the risk benefit ratio may not seem to be as influential as in the research context. Nevertheless, the risk benefit ratio may have a different role in relation to the clinician's information provision. In considering discussions about health risks in daily life with the pregnant patient, clinicians may consider the risk benefit ratio in terms of the feasibility and outcomes of the woman's risk avoiding behavior (Chapter 4). For example, if a particular risk is unavoidable by individual efforts due to its ubiquity or changing behavior does not lead to substantive harm reduction, clinicians might not spend time informing the woman about such risks as her efforts to avoid risk may not bring benefits to her.

Further, Figure 5 illustrates the (1) influence of clinical practice on the minimal risk threshold and (2) interaction between clinical practice and research in relation to risk consideration. First, clinicians' practice may influence the concept of minimal risk since one of the minimal risk standards is based on the risks involved in routine clinical examinations as stipulated in regulations such as the US regulation (Department of

Health and Human Services, 2009) or Guidelines by the Council for International Organizations of Medical Sciences (CIOMS, 2002). Changes that occur over time in clinicians' practice may, in turn, reshape the minimal risk concept. In this sense, minimal risk is a dynamic concept with a flexibility of being redefined along with how clinical practice evolves. Thus, in implementing a clinical minimal risk concept for clinicians' information provision to the patient as proposed in Chapters 3 and 4, constant bidirectional influences between the minimal risk concept and clinicians' practice may occur when the concept is defined by referring to routine clinical examinations. Second, risk consideration in prenatal/preconception care and clinical research with pregnant women may influence each other. As mentioned, clinical care and research overlap in terms of procedures involved as well as therapeutic benefits and uncertainties (Appelbaum & Lidz, 2008; Levine, 1979). Moreover, research questions arise from clinical practice while research evidence is intended to inform clinical practice. Due to the common elements as well as the objectives that are intertwined, risk consideration in these two contexts could inform each other. This may lead to gradual remodeling of the risk consideration during pregnancy, encompassing clinical practice and research.

Finally, reflecting on these studies related to risk and decision making during pregnancy, I recognize an inherent gap between an ideal world and a real world of pregnant women's lived experiences. In crafting this thesis, I started off from the ideal end. The conceptual studies (Chapters 3, 4, and 5) are situated in the ideal world. For example, it would be assumed that unbiased information is always provided or accessible to everyone, all options are equally available to everyone, and the decision maker has adequate capacity to deliberate on the issue considered. By contrast in a real world, these assumptions are more or less modified. Information is filtered and not fairly distributed. Not all women have equal access to healthcare or health research. Women's knowledge about health differs across individuals. The woman's risk perception may differ depending on her health status, education, human relationships, religious and cultural backgrounds, or her attitude toward pregnancy among other factors. I began tapping into the real world as I moved on from the conceptual studies to conducting the grounded theory study (Chapter 7). Encountering participants, I realized the woman's strong desire for "no risk". This made me feel that a risk standard may not always help the woman's decision making, and

regulations may not adequately address the woman's concerns. Risks and benefits perceived by healthcare professionals and clinical investigators may not totally overlap with the woman's perception of risks and benefits. The discussions in the ideal world may be applicable to some women but may mean little to women who live mostly outside the assumptions of the ideal world. Having immersed myself in the data for more than a year, I find myself (and this thesis) standing with one foot in the ideal world and the other in a fraction of the real world. (A fraction as the women I interviewed were well educated, trying to do their best for pregnancy health, and had supportive relationships.) As regards to where I am at now as a researcher, I have ambivalent views. I feel that the ideal world hindered me from looking at the real world. At the same time, the ideal world helped me examine the real world with limitations. Thus what I might remind myself for future research is that the ideal world actually does not exist anywhere, yet it is one of the lenses through which I observe the real world and that the real world I encounter may gradually reshape the ideal world.

8.4 Future research directions

8.4.1 Influence of research ethics guidelines/regulations

As discussed in Chapter 5, differences exist across research ethics regulations in terms of the pregnant woman's eligibility as research participants, risk benefit distribution between the woman and fetus, upper risk limit to the woman and fetus, and paternal involvement in the consent process. However, the influence of regulatory differences on the conduct of research is unknown. For example, would classifying pregnant women as one of the vulnerable populations actually influence clinical investigators or research ethics committee (REC) members? Empirical research may be conducted to investigate the impact of regulatory differences on the attitudes of clinical investigators and REC members. Also, an empirical study may be conducted to compare the number and types (such as interventional or observational) of clinical research conducted with pregnant women across jurisdictions although many confounding factors exist, such as funding, education of researchers, and religious and cultural backgrounds.

8.4.2 Empirical research investigating application of minimal risk standards by obstetric healthcare providers

An empirical study may be conducted with obstetric healthcare providers to further explore the application of the minimal risk concept discussed in Chapters 3 and 4. Case studies as employed in Chapter 4 may be presented to the participants (obstetric healthcare providers) to determine whether each risk factor is above or within minimal risk for pregnant women and fetuses. Such a study may be required to validate the usefulness of the minimal risk standards, which may be necessary for developing clinical practice guidelines incorporating a clinical minimal risk concept for clinicians' information provision to the patient.

8.4.3 Views of other stakeholders on research with pregnant women

Regarding the inclusion of pregnant women in clinical research, more empirical research is needed with other stakeholders such as partners or other family members of pregnant women, REC members, and employees of health related industries and government agencies such as Health Canada and Canadian Institute of Health Research. In terms of research on the views of family members, a potential project may include educational components to inform the participants about pregnancy health and compare the participant's perception before and after educational interventions about pregnancy health. Such research may help in understanding the perception of family members who tend to be consulted by the pregnant woman. Further, such research could help in understanding the perception of the general public and in developing effective interventions to educate them about pregnancy health.

8.4.4 Distribution of risks and benefits among the woman, fetus, and society

Conceptual as well as empirical studies are required to further clarify acceptable distribution of risks and benefits between the participating woman, fetus, and society. The potential conflict of interest between the woman and fetus adds another layer to the conflict of interest between research participants who are exposed to risk and future patients who may benefit.

At a regulatory level, for example, the US regulation (Department of Health and Human Services, 2009) (45CFR46.204) justifies fetal risk if fetal or maternal benefits are expected. This may be highly controversial and the US regulation is silent on how maternal risk should be justified. Most regulations discussed in Chapter 5 leave clinical investigators, sponsors, and RECs with inadequate guidance. For example, the Canadian TCPS 2 (Canadian Institute of Health Research, Natural Sciences and Engineering Research Council of Canada, & Social Sciences and Humanities Research Council of Canada, 2014) (Article 4.3) considers distribution of risks and benefits among the woman, fetus, and society in terms of the inclusion and exclusion of pregnant women; however it does not provide specifically how such a comprehensive approach could be implemented. Without an ethical framework, the risk benefit distribution among the woman, fetus, and society or future pregnant women leaves questions and dilemmas among the stakeholders.

In seeking an appropriate ethical framework, Hansson (2007) indicates that no grand ethics theory fully articulates risk taking for others' benefit. In discussing imposition of risk to a person for others' benefit, Hansson (2007) proposes to use everyday intuitions to eliminate less defensible options based on the decision maker's values and available information. Hansson (2007) suggests that the reciprocity of exchanging risks and benefits for mutual convenience may be most defensible in the justification of risk exposures for others' benefit. However, it may be challenging to create a context where reciprocity of exchanging risks and benefits may apply. The ethical justification of imposing risk on an agent for the benefit of others require much research.

8.5 Conclusion

Risk is an important factor to consider in the pregnant woman's decision making in clinical practice or research participation. Research ethics regulation restrict risk by setting an upper limit of risk such as minimal risk or requiring a favorable risk benefit ratio. Formulating a risk threshold concept such as minimal risk in clinical practice may be useful in discerning risks that clinicians should discuss with pregnant women to support their decision making about clinical procedures as well as health risks in their everyday lives. Regarding clinical research with pregnant women, the empirical results suggested that pregnant women's openness to risk may be very limited and complex,

being dependent on their context, such as existing health risks and a prospect of benefit from research participation. At a policy level, much guidance is required to determine a justifiable risk benefit distribution among the woman, fetus, and society. This thesis has implications on risk communication in prenatal and preconception care and research, policies on clinical research with pregnant women, and education for healthcare providers, clinical investigators, research staff, and the general public.

References (Chapter 8)

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Appendices

Appendix A: Poster for pregnant women

Western

CIHR IRSC
Reproduction, Early Development
and the Impact on Health (REDIH)

Schulich
MEDICINE & DENTISTRY

Seeking to interview
Pregnant woman
for a research study

What do you think about research with pregnant women?

Pregnant women are often excluded from research. We would like to know your thoughts about research with pregnant women.

We invite you to participate in an in-person or telephone interview which may take approximately 25 minutes at a location convenient for you.

If interested or for more information, please contact:

Phone: Contact information omitted from published thesis

1-855- 1-855- 1-855- 1-855- 1-855- 1-855- 1-855- 1-855- 1-855- 1-855- 1-855- 1-855- 1-855- 1-855- 1-855- 1-855- 1-855- 1-855- 1-855- 1-855-

Contact information omitted from published thesis

Appendix B: Flyer for healthcare providers

Western

CIHR IRSC
Reproduction, Early Development
and the Impact on Health (REDIH)

Schulich
MEDICINE & DENTISTRY

Seeking to interview

Clinicians providing obstetrical care

(physicians, midwives, nurses)

What do you think about research with pregnant women?

Pregnant women are often excluded from research. We would like to know your thoughts about research with pregnant women.

We invite you to participate in an in-person or telephone interview which may take approximately 25 minutes at a location convenient for you.

If interested or for more information please call:

Contact information omitted from published thesis

Appendix C: Flyer for researchers

Western

CIHR IRSC

Reproduction, Early Development and the Impact on Health (REDIH)

Schulich MEDICINE & DENTISTRY

Seeking to interview

Medical Researchers

What do you think about research with pregnant women?

Pregnant women are often excluded from research. We would like to know your thoughts about research with pregnant women.

We invite you to participate in an in-person or telephone interview which may take approximately 25 minutes at a location convenient for you.

If interested or for more information please call:

Contact information omitted from published thesis

Appendix D: Semi-structured interview guide

Pregnant women

Thanks so much for participating in this interview.

Pregnant women are often excluded from research. I would like to know your feelings and thoughts about this issue.

1. How do you feel about research with pregnant women?
2. What types of research would you be willing to participate in during pregnancy? Why?
3. What would be your motivation to participate in research during pregnancy?
4. What would be the important factors for you to decide whether or not to participate in research during pregnancy?
5. If your doctor invited you to participate in research while you are pregnant, what kind of questions would you ask the doctor?
6. Which of the following research studies would you be willing to participate in during pregnancy?: A study which involves doing exercises, MRI for pregnancy related problems, drug for high blood pressure, flu vaccine, collecting blood samples, or follow up of your and your baby's health. Why?

Healthcare providers & medical researchers

Thanks so much for participating in this interview.

Pregnant women are often excluded from research. I would like to know your feelings and thoughts about this issue.

1. How do you feel about research with pregnant women?
2. What types of research do you think would be acceptable to include pregnant women? Why?
3. What would be the important factors for you to determine whether a particular research study is acceptable for including pregnant women?
4. If you were to recruit pregnant women in your research, what kind of information do you think would be important for pregnant women to know?
5. In which of the following research studies would you consider enrolling pregnant women: A study which involves doing exercise?, MRI for pregnancy related problems?, Drug for high blood pressure?, Flu vaccine, collecting specimens such as placenta, blood or urine?, Epidemiological studies such as follow up of women's and fetus's or child's health? Why?

Appendix E: Example of data, code to a category (Pregnant women)

Category	Sub-categories	Codes	Sub-codes	Data
Seeking information	Asking relevance to myself	Asking why I want to participate		I guess if I was pregnant just for the, just for being included in research, like I would want to have the purpose or benefit for me (PW03) why do I want to do it (PW07)
	Seeking further information	Consulting others	consulting different people depending on the nature of research	I would try and find somebody who has done it or has some insight on it to see what they thought or their kind of information that they can maybe help with (PW12)
			Consulting friends with children	then discuss with my friends because I do have a couple of friends who each has three kids (PW12)
			consulting my doctor	So it's the new vaccine, depending on what vaccine it was and if it's studied with humans and there were animal studies, I'll consult the physicians about their thoughts about it again (PW05) I think the doctors have an amazing wealth of information (PW03)
		Researching information by myself	Going on the internet	I actually google a lot. I work quite a lot on the internet (PW12)
			experiencing difficulty discerning information	And for anti-depressants, are they safe to be on anti-depressants? There was so much conflicting information PW04) I think there's, there is a lot of information probably about everything and I just don't know (PW07)

	Wanting to know what the research is about	wanting explanation in common language		The details in common language because I would never understand the doctor language (PW03)
		wanting full disclosure		I like to, yeah, find out all the details first (PW04)
		wanting to know risks and benefits		I would ask about the potential risks for the baby and mother, and potential benefits (PW01) If it might cause physical harm to yourself or physical harm to your baby (PW04) probably the risks for sure. That would be number one on my priority list (PW12)
		wanting to know the background and goal		Like why are we doing it (PW07) What they are looking for (PW06)
		wanting to know the cost for participation		cost, like you have to do parking, anything like that (PW10)
		wanting to know requirements to be in the study		I would want to know what was required to be in the study (PW12)
		wanting to know the research process		what specifically would be involved in the process of, in the course of participation (PW01) what you would be going through and the whole process (PW03) What I have to do (PW06)
		wanting to know the sponsor	wanting to know the sponsor's purpose	Who's behind this research? Who's it for? (PW07) It could be just benefiting the drug company (PW07)
			not trusting drug companies	they can lie to you because they just want to make money (PW07)
			Wanting to know the bias	If things are medically examined, you know, if you don't really have a bias on money, I hope (PW07)

Appendix F: Example of data, code, to a category (Healthcare providers)

Category	Sub-categories	Codes	Sub-codes	Data
Giving priority to safety	alarming unknown risks that can change the balance	considering on-going aspects of research		There's a lot of unknowns that I'm not fully aware of (HP06) a lot of unknowns for looking at effects of medication on pregnancy (HP08)
		recognizing it difficult to know long term consequences		some of the chemicals we give to the patient, it could have a lot of long term consequences for the child, which we will know about, but probably won't know about for that particular individual, um, because by the time that child grows up and whatever I may be retired (HP01)
		seeing pregnancy as having to be prepared for unknowns		I think pregnancy in itself involves a degree of uncertainty whether it's first baby, second baby, tenth baby (HP04)
		understanding safety as covering known and unknown risks		safety should cover the risks we know and risks we don't know (HP06)
		wanting to avoid anything with unknown risk	assuming women would accept calculated risk	If there's risk, it's calculated risk. Then, and you know, with dose that doesn't cause any harm, women would be willing to do something like that (HP04)
			avoiding treatment if too many unknowns	when there's too much risks of unknown, too much that we don't know, that increases unsafety, the lack of safety, in treatment or project and is difficult to regain that balance (HP06)
			feeling uncomfortable with things unknown	if there's not enough information and the risk of the unknown is considerable, far greater than the possible benefit, you should decide "do not" treat or expose to

				experimental (HP06)
			presuming some risk in any research	I would be, you know um, comfortable discussing the new flu vaccine, providing that they know there's unknown risk (HP04) the risk of unknown will have to be particularly highlighted (HP06)
	avoiding exposure to any risk	assuming safety matters for women		I think safety to um mom while she is pregnant and safety to the baby (HP05)
		assuming women's generosity if no risk		I think that's when the um, I forgot the word again, uh, generosity they might have toward the general population of wanting to do something that benefits someone else. I think that stops there because it might personally affect (HP03)
		feeling comfortable if no known risk		I think not many pregnant women are going to enter into a study if there's risk to their baby to do so (HP03) I would not put my baby at risk (HP05) One is collecting placenta will imply no risk as it will be disposed. So instead of disposing placenta, collecting the placenta for research, I will not really, would not see any concerns with regard to that.(HP06)
		not wanting to add risks during pregnancy		If they already take something, why they would change or why they would add another medication, or have some change in their meds (HP09)
	Living in a culture of blame	feeling liability as a huge drive		I think liability drives a lot of our decisions nowadays. There's a big worry about liability and how this is going to be blamed on me and, you know, people are afraid, I think. (HP02)
		thinking feasible		anything you can do a study

		research may differ across countries		about, can be studied, and will get studied eventually, depending on what country you are and what the ethics (HP09)
		thinking feasible research may differ depending on ethics		there is a lot of research done on the bodies and the fluids and the um uh, yeah the tissues of the babies that were aborted for that exact reason because they are um it is, I mean I've never been involved in any kind of research like that so I have no idea what ethics parameters are around all of that.(HP03) I think if you are looking from a researcher's perspective, there are barriers to involving pregnant women because of ethics board approvals where there's going to be a lot more stringent um and potentially strict guidelines or refusals for ethics permissions (HP03)

Appendix G: Example of data, code to a category (Researchers)

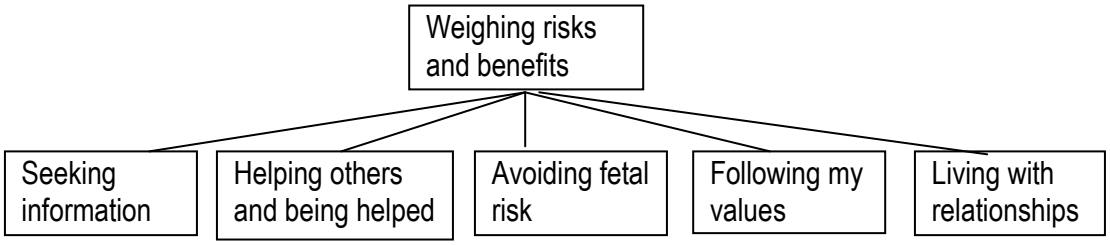
Category	Sub-categories	Codes	Sub-Codes	Data
Considering complex nature of risk	being concerned about unknown risks	looking at short and long term safety		it warrants me to do studies to see if nicotine alone is bad, short or long term (R05) there's a risk that your kidney, or may not develop, may have increased risk of developing diabetes when you get older if you do this treatment but that you may be able to save your life in a short term (R07)
		struggling to know about things untested		if it's not tested, it means we don't know much about it (R03) A new vaccine is by definition a little bit unknown (R04)
	Recognizing nothing is black and white	distinguishing own risk perception from others	endorsing colleague's research despite risk	if they are fine with doing that kind of research and ok with asking pregnant women to be involved in that kind of research, that is ok. Uh, but I personally couldn't do it (R02)
			Indicating conflicting opinions	There are some parents and doctors who are convinced taking the flu vaccine increases the risk of autism. And there are a large number of studies which also say that there is no clear evidence to suggest that (R02).
		indicating everything has LD50		So water even has an LD50. And it's surprisingly low (R08)
		never being 100% sure about outcomes		I think the long term effects in MRI induced stress on the mom and the fetus is not really known (R05) you have to monitor to make decisions which were not quite possible at the beginning when you were setting it up but as the data were accumulating (R06)
	Wanting women to feel safe	assuming risk can be a difficult concept	Assuming no mathematic formula for risk	I don't know what the threshold would be. It's not a mathematic formula, I don't think (R08)
			finding it difficult to define significant risk	Now, the problem is the word significant. That's a difficult word to define and it could be applied in a way that anything beyond no harm is significant. That's a worry

				(R08)
			struggling to describe acceptable fetal risk	I mean there is no acceptable service safe level that I would think (R08) the fetus already has, um, vulnerability to begin with (R05) I think I'm not really sure how to answer like what's acceptable risk. I think it's such a personal, such a personal decision, right? (R07)
			thinking adverse events could be rare	Um, you know, um with non-pregnant people, we had flu vaccines for decades and I know the risk there is very low (R04)
		limiting the types of research with pregnant women	thinking exercising research can be prospective	I think this is really ok as long as exercise, again, doesn't endanger the pregnancy (R03)
			thinking most pregnancy studies have no direct benefit	when you think about a lot of pregnancy studies we currently do, I think a lot of them I would be a little bit, there's a higher proportion of them that are for indirect benefit (R07)
			thinking RCT for interventions unacceptable	I don't think we can do a randomized controlled trial where we would give a group of women the drug, a group of women the placebo, um because I would be concerned about the effects. And, and, you know, I think in that case, it would cross over a line that would worry me (R08)
			thinking RCT of relatively benign intervention is ok	So if the external intervention is relatively benign, let's say not therapeutic or drug oriented, but something like um a nutritional study where you might improve maternal or fetal nutrition through uh a better diet and things like that or exercise kind of regime. I could see that being a valid and very important and quite useful approach (R08)
			thinking retrospective data provides fetal data	collects a lot of post hoc data, pregnancy outcomes and then retrospectively sort of looks back at a variety of factors that could have had impact on pregnancy outcomes and child's development (R08)

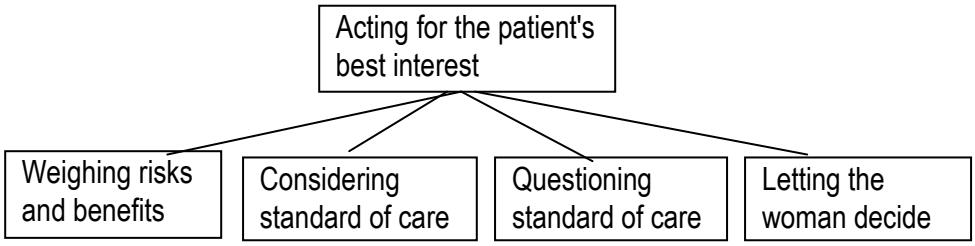
		Thinking as a person		I can’t answer my brain on one side and my heart on the other. I’m giving an answer that is consistent for both (R03) I feel like I have the same morals and standards, or whatever, uh or concerns whether it’s X the scientist or X the father to be, right? (R05) To me, if, uh let's think about research with pregnant women as a scientist and research with a pregnant person that may be related to me, like a family member, I don't differentiate (R09)
		thinking in pregnant women's shoes	assuming difficult decisions for women	it might be really difficult to, for a woman to, you know, a lay person in a community to fully grasp some of these things (R02)
			assuming women have other issues	pregnant women have their own issues (R04)
			assuming women's reluctance to make a decision	I understand that, uh, people can be reluctant about it (R03)

Appendix H: Examples of earlier models of the participant's decision making process regarding research with pregnant women

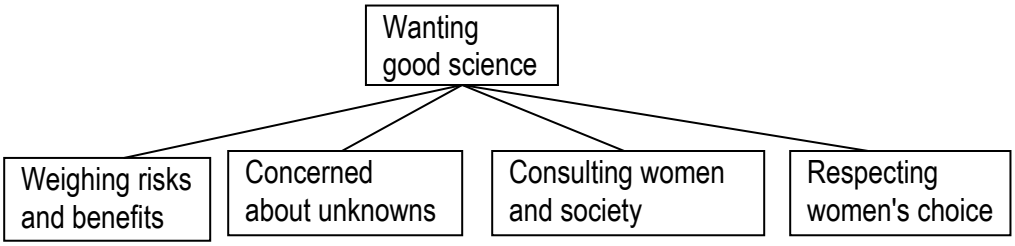
Pregnant women's decision making process



Obstetric healthcare providers' decision making process



Researchers' decision making process



Appendix I: Approval by the Health Sciences Research Ethics Board, Western University

Western Research

Research Ethics

Use of Human Participants - Initial Ethics Approval Notice

Principal Investigator: Dr. Jeff Nisker
File Number:105122
Review Level: Delegated
Protocol Title: Participation of pregnant women in clinical research: Views of pregnant women, healthcare providers, and medical researchers
Department & Institution: Schulich School of Medicine and Dentistry\Obstetrics & Gynaecology,London Health Sciences Centre
Sponsor: Canadian Institutes of Health Research

Ethics Approval Date: May 13, 2014 **Expiry Date:**August 31, 2015
Documents Reviewed & Approved & Documents Received for Information:

Document Name	Comments	Version Date
Other	References	
Other	Interview Guide (received March 7/14)	
Other	Demographic Data Form (received March 7/14)	
Western University Protocol	Western Protocol(clean copy)	2014/04/08
Other	Telephone script(Clean copy)	2014/04/08
Advertisement	Poster-researchers(clean copy)	2014/04/08
Advertisement	Poster-pregnant women(Clean copy)	2014/04/08
Other	Poster-healthcare providers(Clean copy)	2014/04/08
Letter of Information & Consent	LOI(clean copy)	2014/04/08
Advertisement	Flyer-Researchers(clean copy)	2014/04/08
Advertisement	Flyer-pregnant women (Clean copy)	2014/04/08
Advertisement	Flyer-healthcare provider (clean copy)	2014/04/08
Advertisement	Documentation of oral consent (Clean Copy)	2014/04/08
Advertisement	Contact Phone Message (Clean Copy)	2014/04/08

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced revision(s) or amendment(s) on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the University of Western Ontario Updated Approval Request Form.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

The Chair of the HSREB is Dr. Joseph Gilbert. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Signature omitted from published thesis

Ethics Officer to Contact for Further Information

Erika Basile (ebasile@uwo.ca)	Grace Kelly (grace.kelly@uwo.ca)	Mina Mekhail (mmekhail@uwo.ca)	Vikki Tran (vikki.tran@uwo.ca)

This is an official document. Please retain the original in your files.

Western University, Research, Support Services Bldg., Rm. 5150
London, ON, Canada N6A 3K7 t. 519.661.3036 f. 519.850.2466 www.uwo.ca/research/services/ethics

Appendix J: Approval by Lawson Health Research Institute

LAWSON
HEALTH RESEARCH INSTITUTE

LAWSON FINAL APPROVAL NOTICE

LAWSON APPROVAL NUMBER: R-14-164

PROJECT TITLE: Participation of pregnant women in clinical research: Views of pregnant women, healthcare providers, and medical researchers

PRINCIPAL INVESTIGATOR: Dr. Jeff Nisker

LAWSON APPROVAL DATE: May 14, 2014

Health Sciences REB#: 105122

Please be advised that the above project was reviewed by the Clinical Research Impact Committee and Lawson Administration and the project:

Was Approved

Please provide your Lawson Approval Number (R#) to the appropriate contact(s) in supporting departments (eg. Lab Services, Diagnostic Imaging, etc.) to inform them that your study is starting. The Lawson Approval Number must be provided each time services are requested.

Dr. David Hill
V.P. Research
Lawson Health Research Institute
All future correspondence concerning this study should include the Lawson Approval Number and should be directed to Sherry Paiva, Research Administration Officer, Lawson Approval, Lawson Health Research Institute, 750 Baseline Road, East, Suite 300.

cc: Administration

Appendix K: Letter of information & consent form

Principal Investigator: Jeff Nisker, MD, PhD
Department of Obstetrics &Gynaecology
Western University

Contact information omitted from published thesis

LETTER OF INFORMATION & CONSENT FORM

Study title: Participation of pregnant women in clinical research: Views of pregnant women, healthcare providers, and medical researchers

Investigators
-Jeff Nisker, MD, PhD, Professor, Department of Obstetrics & Gynaecology, Schulich School of Medicine & Dentistry, Western University
-Kyoko Wada, MD, PhD Candidate, Department of Health & Rehabilitation Sciences, Faculty of Health Sciences, Western University
-Barbra deVrijer, MD, Associate Professor, Department of Obstetrics & Gynaecology, Schulich School of Medicine & Dentistry, Western University
-Marilyn Evans, RN, PhD, Associate Professor, Arthur Labatt Family School of Nursing, Western University

1. Invitation to participate
You are invited to participate in a study exploring the views of pregnant women, clinicians providing obstetrical care (physicians, midwives, and nurses), and medical researchers about research with pregnant women. Approximately 20 pregnant women and 20 clinicians and medical researchers will be enrolled in this study.

2. Purpose of this Letter
The purpose of this letter is to provide you with information to decide whether or not to participate in this interview study.

3. Purpose of this Study
Pregnant women are often excluded from clinical research. The purpose of this study is to understand the views of pregnant women, clinicians providing obstetrical care (physicians, midwives, and nurses), and medical researchers on clinical research with pregnant women.

4. Study Procedures
If you give consent to participate, you will be interviewed about how you feel and think about this topic. For example, pregnant women may be asked “What kind of research would you be willing to participate in while pregnant?” or “What would be your motivation to participate in research during pregnancy?” Healthcare providers and medical researchers may be asked “How do you feel about including pregnant women in research?” or “What types of study do you think would be acceptable for including

pregnant women?" The interview is anticipated to last for approximately 25 minutes, which will be audio-recorded with your permission and transcribed for analysis. The interview will take place at London Health Sciences Centre (LHSC), Victoria Hospital, London, Ontario, or a location convenient for you. If a face-to-face interview is not feasible, interview over the telephone may be considered.

5. Possible Risks and Harms
There are no known risks for participating in this study.

6. Possible Benefits
You will not directly benefit from participating in this study. However, information obtained from this study may provide benefits to society or future pregnant women as such information may influence policy making to enhance important research with pregnant women.

7. Compensation
You will not be compensated for your participation in this research.

8. Voluntary Participation
Participation in this study is totally voluntary. You may refuse to participate, refuse to answer any questions or withdraw from the study at any time without giving any reason and without any influence on your healthcare or employment. If you choose to withdraw from this study after the interview, you may contact the researcher at leave a message, and all of the data you provided will be withdrawn.

Contact information omitted from published thesis

9. Confidentiality
Confidentiality of what you share with us in this study will be maintained to the highest level possible. All information will be coded and your code interface will be kept at LHSC, Victoria Hospital in a locked cabinet under the responsibility of Dr. Jeff Nisker. All coded data will be kept in a password protected computer and accessed only by the research team members of this study. The results of the study may be published in academic journals or communicated at conferences and part of your interview may be cited in the publication or presentation, but in such a way that it will be impossible to identify you. The study data will be kept in a secure computer in Dr. Nisker's office for 5 years after the publication of the results.While we will do our best to protect your information there is no guarantee that we will be able to do so.
Unless you have provided specific authorization or legally required, the information you provide will not be made available to any third parties. However, for the purposes of ensuring the proper management of the research, a member of the Health Sciences Research Ethics Board at Western University may contact you or require access to your study-related records to monitor the conduct of this research study.

10. Contact for Further Information
If you require any further information regarding this study or your participation in the study, you may contact I
your rights as a research
Office of Research Ethic

Contact information omitted from published thesis

Consent Form

Study title: Participation of pregnant women in clinical research: Views of pregnant women, healthcare providers, and medical researchers

Study Investigators:

Jeff Nisker,MD, PhD, Professor, Department of Obstetrics & Gynaecology, Schulich School of Medicine & Dentistry, Western University
Kyoko Wada, MD, PhD Candidate, Department of Health & Rehabilitation Sciences, Faculty of Health Sciences, Western University
Barbra deVrijer, MD, Associate Professor, Department of Obstetrics & Gynaecology, Schulich School of Medicine & Dentistry, Western University
Marilyn Evans, RN, PhD, Associate Professor, Arthur Labatt Family School of Nursing, Western University

I have read the Letter of Information, have had the nature of the study explained to me, and I agree to participate. All questions have been answered to my satisfaction.

☐ I give permission for the interview to be audio-recorded.

Participant's Name (please print):_____

Participant's Signature: _____

Date: _____

Person Obtaining Informed Consent (please print):

Signature: _____

Date: _____

Appendix L: Script for setting up an interview and seeking oral consent

Hello, may I please speak with (*insert the first name of the potential participant here*).

-*If potential participant is not home:* When do you think (*insert the name of the potential participant here*) will be back? …. I will call again then. Thanks.

-*If potential participant is on the phone proceed with the following script:*

Hello, my name is Kyoko Wada from Western University.
I am calling today because you left your name and phone number regarding the research study entitled "Participation of pregnant women in clinical research: views of pregnant women, healthcare providers, and medical researchers". This study is supervised by Dr. Jeff Nisker at Western University, and is looking at people's thoughts about research with pregnant women. We are interested in interviewing pregnant women, clinicians providing obstetrical care (physicians, midwives, and nurses) and medical researchers. The interview will take about 25 minutes, and will be audio-recorded and transcribed for analysis. Would you be interested in hearing more about this study?

-*No*: Thank you for your interest in our study. Have a nice day. Bye.

-*Yes*: Are you a pregnant woman, physician, midwife, nurse, or medical researcher? _____ Thank you.

I would like to set up an interview with you. Would you prefer phone or in-person?

-*In-person interview*:

Set up date, time, and location. _____

Do you have any questions?

-*Phone interview*:

I am now going to read you the Letter of Information over the phone. (*Read LOI*)
Do you have any questions?

Conduct oral consent
Do you agree to participate in this study?
Do you give permission for the interview to be audio-recorded?
(If yes, proceed with the interview)

Appendix M: Documentation of oral consent (telephone consent)

Documentation of oral consent

Study title: Participation of pregnant women in clinical research: Views of pregnant women, healthcare providers, and medical researchers

Investigators:
Jeff Nisker, MD, PhD, Professor, Department of Obstetrics & Gynaecology, Schulich School of Medicine & Dentistry, Western University
Kyoko Wada, MD, PhD Candidate, Department of Health & Rehabilitation Sciences, Faculty of Health Sciences, Western University
Barbra de Vrijer, MD, Associate Professor, Department of Obstetrics & Gynaecology, Schulich School of Medicine & Dentistry, Western University
Marilyn Evans, RN, PhD, Associate Professor, Arthur Labatt Family School of Nursing, Western University

_____ (Participant's name) has been informed about the nature of this study, has had the opportunity to ask questions and has them answered, and has agreed to participate.

Permission given by the participant for the interview to be audio-recorded.

_____
Person obtaining consent (Printed)

_____
Person obtaining consent (Signature)

_____
Date & Time

Appendix N: Curriculum vitae

Curriculum vitae
Kyoko Wada

Post-secondary education and degrees

-University of Tsukuba Medical School, Tsukuba, Ibaraki, Japan, 1988-1994, MD.
-Monash University, Clayton, New South Wales, Australia, 2006-2008, MA.
-Western University, London, Ontario, Canada, 2011-2015, PhD.

Research Fellowship

-Bioethics research fellowship in the Departments of Psychiatry and Anesthesia & Perioperative Medicine, Western University, 2009-2011

Honours and Awards

-CIHR Training Program in Reproduction, Early Development, and the Impact on Health, 2011-2014
-University of Tsukuba Medical School Scholarship 1992-1994

Volunteer Work

Ethicist, Western University, Health Sciences Research Ethics Board, 2010-present

Publications

1. Wada K, Nisker J. Implications of the concept of minimal risk in research on informed choice in clinical care. *Journal of Medical Ethi*cs 41(10):804-808, 2015. doi:10.1136/medethics-2014-102231.
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4. Rudnick A, Wada K. Introduction to bioethics in the 21st century. In: Rudnick A ed. *Bioethics in the 21st century*. InTech, 2011. pp.1-7.
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