Not wanted in the study: an ethical, medical and political analysis of the exclusion of pregnant women from clinical research studies

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Abstract: Review and analysis of current clinical research practice suggests a general trend towards excluding pregnant women from clinical research studies. Although exclusionary research practices are premised upon concerns for the well-being of the fetus and the pregnant women, such practices can also produce various inadvertent harms to both parties. In particular, exclusion of pregnant women from clinical research limits the quality of care provided to pregnant women by impeding individual access to innovative research protocols and by limiting data collection applicable to the pregnant population. A review and analysis of relevant historical, legal, ethical, clinical, scientific and political documents suggests that various changes should be made to current clinical practice. To produce many such changes there is a need for a comprehensive, progressive Canadian health policy to be used to guide and direct researchers and research ethics boards in the appropriate inclusion of pregnant women in clinical research studies.

Exclues des études cliniques; une analyse éthique, médicale et politique de l'exclusion des femmes enceintes des essais cliniques

Résumé: La revue et l'analyse des procédures courantes dans la recherche clinique suggèrent une tendance générale d'exclure des femmes enceintes des études cliniques. Bien que ces pratiques de recherche exclusives soient basées sur la protection des fétus et de la femme enceinte, ces pratiques peuvent aussi amener des conséquences néfastes pour la femme et son fétus. L'exclusion des femmes enceintes de la recherche clinique limite particulièrement la qualité des soins donnés à ces femmes parce que l'accès individuel au protocole de la recherche innovatrice est proscrite et la compilation des données concernant la population des femmes enceintes est limitée. La revue et l'analyse des documents historiques, éthiques, cliniques et politiques pertinents suggèrent la nécessite d'apporter des modifications importantes aux protocoles courants de recherche clinique. Une politique de santé canadienne claire et progressive aurait pour but apporter les changements nécessaires et de guider les chercheurs et les comités d'éthique de recherche sur l'insertion appropriée des femmes enceintes dans les études cliniques.

Chapter 1: A review of the historical exclusion of women from clinical research and description of the current role of pregnant women in research

1.1 Introduction

Considering that half of the Canadian population is female, and that the majority of this population will become pregnant at some point in their lives, it is important that health care providers are able to provide excellent health care during pregnancy. In Canada, health care provision during pregnancy is excellent, but is not optimal. The current exclusion of pregnant women from much clinical research[1] limits the quality of care provided to pregnant women by impeding individual access to innovative research protocols and by limiting data collection applicable to the pregnant population. Although there is no simple solution to this problem, there are ways in which the situation can be ameliorated. The focus of this thesis is to provide an overview of the exclusion of pregnant women from clinical research and provide suggestions as to improvements that could be made. Chapter one begins this discussion by providing the historical progression towards the current exclusionary practices. In chapters two and three the main controversies and challenges are examined and expanded upon from ethical, legal and scientific perspectives. Chapter four highlights pertinent policy related to the topic and suggests changes that could be made to improve current Canadian health policy.

[1] Within this thesis, 'exclusion of x' will be used to convey that a researcher *has* listed population x within their study protocol's exclusion criteria. The term 'inclusion' will also be used, yet, will convey that population x *has not* been listed within the exclusion criteria.

1.2 Historical exclusion of women from clinical research

To fully understand the current exclusion of pregnant women from clinical research, and understand the impetus behind such exclusionary practices, it is important to situate such exclusion within the broader historical practice of excluding women from clinical research. Such information is important not only because it provides a context for the current situation, but because the positive steps that were required to increase the inclusion of women within clinical research in the past can be used as a reference point when trying to deduce the future steps required to improve the situation for pregnant women.

It is generally accepted that the historical exclusion of women from clinical research was partially in response to research wrongdoings incurred upon this population and various other populations in the past (1;2). Although many cases could be cited to illustrate wrongdoings against such populations, one of the most well-known of such injustices was the prescription of thalidomide for pregnant women. Throughout the 1950s, physicians prescribed thalidomide to pregnant women as a means of reducing morning sickness and other ailments. Yet, after a decade of prescriptions, it was discovered that thalidomide was teratogenic (3). Following further inquiry, it was found that inadequate research standards had been in place and that the manufacturer had failed to report side effects (1). When the public (including physicians) became aware of the situation, physicians stopped prescribing the drug for pregnant women.

Unfortunately, in the 1970s, a similar finding occurred when researchers realized that the drug diethylstillbestrol (DES), that had been prescribed for pregnant women from 1938 to 1971, also produced harmful effects (4). The drug was prescribed to reduce

miscarriages for pregnant women, yet had the side effect of significantly increasing the risk of vaginal cancer for daughters of women who had taken DES (5). Like the thalidomide situation, the harmful effects of DES were blamed on inadequate testing by the pharmaceutical manufacturer (6). When the public became aware of the inadequate testing that occurred for both drugs, and the serious implications of this laxity, clinical research was viewed by many as a risky endeavor and a protectionist sentiment resulted (1;7).

In 1972, at about the same time as the DES and thalidomide results were exposed, the public caught wind of the US Public Health Service (USPHS) Syphilis Study (Tuskegee Syphilis Study) which had been ongoing since 1932 in the United States. The focus of these trials was the documentation of the natural progression of syphilis, with poor, Black, males as the primary study population. What made these trials particularly unethical was that the participants were not informed of their contagious, life-threatening, devastating diagnosis, and were not offered penicillin as treatment, even though its effectiveness had been proven years before (2). Despite knowledge of the study in political and scientific circles, the trial was only stopped when the public reacted to media accounts of the study with outrage. Yet, by this time hundreds of people had already died. The most significant long-term reaction to the information was further distrust in medical research, particularly by ethnic minority populations (8).

Examples like these explain why the public's perception of medical research was, and in some cases still is, negative. They also illustrate the large amount of influence and responsibility researchers possess. In response to these cases, and the prevalent mood of the public, researchers in the 1970s were genuinely concerned for the well being of

vulnerable populations, and feared being held liable for further research 'mistakes'. It was because of this apprehension within the clinical community that researchers began to exclude women and other vulnerable populations from their research studies. In particular, the United States government created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research – a group credited for establishing protections for a number of vulnerable populations (8).

During the 1970s, following the legalization of abortion in various European countries, much energy was devoted to the abortion issue in North America. The 1973 United States *Roe v. Wade* decision brought the issue to a head, as the courts decided to legalize abortion (1;9). Despite this victory for pro-choice advocates, pro-life advocates continued their fight for the rights of the fetus. Although attitudes regarding the status of the fetus clashed prior to the court decision, the conflict and energy following the court case was significantly heightened. The court case publicized and formalized issues concerning the rights of the fetus and therefore, concerns relating to fetal rights permeated much of society – including medical research (1).

1.3 Policy development regarding the inclusion of women

Since the 1970s, policy concerning the participation of women in clinical research has changed dramatically. The gradual shift from early exclusionary research policy, to current policy which encourages the inclusion of women, has been the result of work by public advocacy groups and publicly funded research studies. Understanding the driving forces behind early policy development suggests a means by which current policy can be

influenced and adjusted. Although various countries have addressed the inclusion of women in clinical research, the most influential health policy has come from the United States. Because of this, an account of the development of American policy – primarily by the NIH and FDA will first be highlighted.

Considering the predominant protectionist climate regarding female involvement in clinical research, and the heightened concern for the rights of the fetus, the stance taken in 1977 by the Food and Drug Administration (FDA) was not surprising (10). This stance was the official exclusion of women "of childbearing potential from Phase I and Phase II studies of new drugs until reproductive toxicity studies were conducted and some evidence of effectiveness had become available" (11). The rationale for this policy, as well as future exclusion policies, was on the basis of fetal protection and legal liability concerns (12).

Although researchers today are aware that, as research subjects, women are different from men due to their gender roles (socially-structured relations) and sex (sex-linked biology), such knowledge has not always been the norm (13). Prior to the 1980s, there was minimal scientific awareness of the biological differences between men and women (14). In fact, the approach to sex was that women were simply "men with estrogen" (13). Because it was believed that results from male data could be extrapolated to the female population, and also as a means of eliminating possible variability among research subjects, the majority of research studies were conducted upon a Caucasian male population. This tendency is particularly evident when one reviews research conducted within the fields of cardiovascular and aging research. As a result, the majority of previous research findings within these fields are applicable to the male population,

therefore often inadvertently excluding women from access to health knowledge and innovative treatments (15).

Attention to the importance of including women in medical research first arose when the scientific community began to appreciate the value of understanding how drugs and other therapies work in specific patient groups (10). Such revelations within the scientific community prompted various federal agencies to consider the importance of including diverse patient groups in clinical research. In 1983, as a means of evaluating the inclusion of women in clinical research, the FDA reviewed 11 drug trials pending approval. The result of this review was the finding that there existed major disparities in the representation of women and the elderly in particular disease categories, such as cardiovascular studies (16).

In response to the scientific revelation that men and women respond differently to some pharmaceutical agents, and due to the realization that women were not well-represented in studies, the long-accepted position of the FDA was called into question (10). In 1988, a new FDA guideline was created that called for analyses of "safety and efficacy data by gender, age and race" (17).

As a means of evaluating the representation of women in clinical research, the NIH created the Advisory Committee on Women's Health Issues in 1986 (1). Soon after its creation, the committee created a policy that "urged grant applicants to consider the inclusion of women in the study populations of all clinical research efforts" (18). Despite the positive direction of this new committee, a number of advocacy groups, such as the Congressional Caucus for Women's Issues (CCWI), and leaders such as Henry Waxman (Chair, Energy & Commerce's Subcommittee on Health and the Environment), felt that

very little action had resulted from the implementation of the policy. Such suspicions were confirmed by a number of publications reporting results of research that included few or no women, yet were often related to diseases and conditions which significantly affected women. One particular study used 20,000 males and zero females when evaluating the effects of aspirin on heart attacks (1). As a means of evaluating the true effects of earlier NIH policy, and to judge to what degree women really were being included in medical studies, the CCWI requested the 1990 production of the General Accounting Office (GAO) report. As suspected by the CCWI, this report confirmed the minimal impact of the policy, suggesting that it had been poorly communicated and misunderstood (1).

In addition to these political responses, various activist groups and legal bodies began to formally oppose the exclusion of women from clinical research. In particular, comprehensive work by the HIV Law Project demonstrated the extensive exclusion of women from AIDS clinical trials and urged that women be permitted to determine for themselves whether to enter clinical trials (1;10).

In response to such governmental and public criticisms, the NIH developed the *Women's Health Equity Act* in 1990, as a clearer, legally binding, document. Unfortunately though, President George Bush vetoed the Act in 1990 due to the inclusion of fetal tissue research guidelines (1).

Meanwhile, despite the political environment, there was growing acknowledgement within the legal system of the rights of pregnant women. In the 1991 case of the *United Automobile Workers v. Johnson Controls,* the Supreme Court of the United States ruled that pregnant women could not be excluded from employment solely

because work conditions posed a potential fetal threat (10). Although this case was not directly related to clinical research, the stance taken by the courts reflected a continued shift in legal opinion regarding both fetal and maternal rights. In turn, such changes in legal perspective likely influenced the attitude of the public, and eventually, the government.

When the political environment shifted, and President Clinton gained power, a new Act was created: the 1993 *NIH Revitalization Act* (1;19). This Act was legally binding and therefore carried more weight in the U.S. than previous documents. It clearly required the inclusion of women (and members of racial and ethnic minority groups) in NIH-funded clinical research, an analysis of study variables to determine whether particular variables affected certain subgroups (e.g. women) differently, and the creation of a database documenting results by subgroup (19;20).

As a means of evaluating the impact of the Act, the NIH performed a review of the inclusion of women in all NIH-funded 1994 Phase III studies. The results of this review were good, but not ideal, demonstrating that 57% of subjects were male, while 42% were female. Further independent studies, such as the one conducted by Ramasubbu et al. (2000), indicated that the inclusion of women was even poorer than that reported by the NIH (21). This study reviewed all trials published in the *New England Journal of Medicine* from 1994 to 1999 and found that, on average, only 24.6% of subjects were women. In response to such quantitative research, academics within the social sciences decried the exclusionary practices within clinical research. The seminal article taking this stance was that written by Rebecca Dresser, entitled: *Wanted: Single, White Male for Medical Research* (15).

As a result of such research and scholarly findings, the FDA followed in the footsteps of the NIH in 1998, as they introduced their first legally binding policy entitled: *Final Rule: Investigational New Drug Applications and New Drug Applications* (22). This policy allowed the FDA to refuse approval of any applicant if appropriate gender analysis was absent. Unfortunately though, this policy was somewhat lacking, as it did not require a formal analysis of gender data nor a discussion of gender differences. In response to this flaw, the FDA issued the *Clinical Hold Rule* in 2000, which provided the FDA with the power to place a hold on a study if a researcher excluded women without sufficient rationale (23;24).

In 2000, the first international standards for the inclusion of women in clinical trials were developed. Section E8 of the guidelines developed at the International Conference on Harmonization (ICH) detailed that the study population must reflect the target population (i.e. the population to which the intervention is aimed) and that pharmacokinetic information for subgroups must be reported within Phase I results (25).

In 2001, the GAO wished to gauge the progress of the various FDA and NIH policies and therefore conducted a review of all approved FDA applicants between 1998 and 2000. The results were positive, indicating that 52% of subjects were women (26). Despite such positive results, a number of independent researchers have examined whether women are adequately represented in clinical research and have found conflicting results to those suggested by the GAO (2). It appears as though the wide variance in study findings hinges upon the chosen definition used for 'medical research'. For example, researchers who calculate the proportion of women in all clinical trials (i.e. sex-specific and mixed gender) will logically produce significantly different results than

those studying the proportion of women in non-sex-specific trials (i.e. mixed gender) (2). Although there lacks a consensus opinion as to the proportion of women participating in clinical research, it appears as though women are currently better-represented in clinical research than they were in the past (27).

Although the situation for women today within the medical research setting is rather positive, there is continued interest in the rationale and logic behind current exclusion criteria. As a means of deducing the rationale behind current exclusion criteria, one researcher conducted a qualitative review of 26 research projects, and discovered three general reasons for current exclusionary practices (28). The author found that women were excluded from medical research either due to scientific reasons (lack of pertinent knowledge of the physiology and metabolism of women), historical reasons (tendency to repeat studies on former study populations – who most often were male), or economic reasons (insufficient budget to allow participation of men and women). Another similar study suggested that the main rationale for exclusion was that the effects of the drug on a potential pregnancy, embryo or fetus were unknown (29). Although such rationales for excluding women from research may not excuse unnecessary exclusionary practices, they provide insight into the reasoning of researchers who subscribe to exclusionary practices. Knowledge of such rationales can be useful when research ethics boards review research protocols and request changes. Specifically, such knowledge may aid research ethics boards in identifying unreasonable exclusionary practices and in requesting solid justifications for exclusion from researchers.

1.4 Pregnant women as a special subgroup

After decades of debate, policy change and practical adjustments, it appears as though nonpregnant women are better-represented within current clinical research. In addition to this improved representation, the controversy – as to whether or not women should be included – has been nearly resolved. The majority of researchers and policy-makers have come to realize that including women in research is absolutely necessary if they wish to apply their research findings to the general population. Because of this, researchers and policy-makers have made, and continue to make, great efforts to ensure that women are well-represented within clinical research.

Despite the increased inclusion in clinical research of women in general, a subgroup of this population remains underrepresented – pregnant women. Although this subpopulation has been discussed by researchers, ethicists and policy-makers for many years, the position taken by these bodies remains diverse and indefinite. Yet, unlike many debates which subside over time, it appears as though interest in this topic has instead increased over the past decade – as evidenced by the continued creation of relevant articles and recent development of policy documents (30-35).

1.5 Main rationales for exclusion of pregnant women

Initially, pregnant women were excluded from clinical research because they were grouped in with the general female population. As has been described above, women were poorly represented in clinical research up until the late 1990s and therefore, pregnant women were also poorly represented. Yet, as the general female population began to receive better representation within clinical research, the same could not be said

for pregnant women. Despite the gains made by the general female population, the subpopulation of pregnant women did not receive improved representation in clinical research. Instead, this group continues to face exclusionary research protocols, therefore continuing them along the same trajectory as that encountered previously by the general female population.

One of the most commonly cited rationales for excluding pregnant women has been concern that research studies may harm the fetus (29;32;36). This concern for the fetus is likely so well-defined and solidly ingrained in the minds of many researchers and administrative bodies because it was one of the primary reasons for the earlier exclusion of 'women of childbearing potential' (the main female population). Although the female population gained greater representation in clinical research by challenging this concern, the fundamental concern regarding the fetus remained unresolved. This lack of resolution is most likely due to the fact that women are usually only included in clinical research if they practice reliable birth control – therefore somewhat skirting the heart of the issue. Because this issue has not been resolved, and researchers are confronted with the pregnant subpopulation, the arguments concerning fetal harm and women's autonomy are re-evoked. This rationale for the exclusion of pregnant women from clinical research will be further explored in subsequent chapters.

Another rationale for the exclusion of pregnant women from clinical research is concern by researchers regarding legal liability (36). Much like the aforementioned rationale, this rationale concerns harm to the fetus, yet further captures the personal motivations of some researchers – a desire for self-protection or protection of the sponsor of the research. This rationale likely comes as a response to earlier research tragedies –

such as the thalidomide and DES prescriptions. Most researchers are aware of such violations and the consequences of such negligence for both the participants and institutions involved. With such knowledge in mind, many researchers fear being held legally responsible for possible developmental harms to the fetus. Although there is minimal proof that inclusion of pregnant women in research increases the risk of lawsuit for researchers (36), a number of researchers suggest that the fear of liability is a common concern among researchers, and therefore requires further exploration (32).

Further rationale for the exclusion of pregnant women from clinical research is that this population is physiologically different from the non-pregnant female population – therefore biasing data and invalidating study results (13;36). In response to such rationale, Hall asserts that the physiology of non-pregnant women "differs far more from the physiology of men, than the physiology of pregnant women differs from the physiology of non-pregnant women". Hall goes on to explain that if the "different physiology" argument were to be accepted, then exclusion of women from studies because of their sex would also have to be accepted (36). The physiological attributes unique to the pregnant population will be further explored in subsequent chapters.

1.6 Main rationales for inclusion of pregnant women

The general impetus behind the recent heightened interest in the inclusion of pregnant women in clinical research, is likely due to the realization by the public and medical professionals that very little data exist concerning the effects of medications on the pregnant population. The practical consequence of this situation is that when a woman becomes pregnant, and is faced with a health challenge, she and her physician

lack the information required to begin balancing the risks and benefits of various treatment options (10;37). The gravity of this situation has been emphasized by many researchers and government leaders. For example, a statement by a representative of the FDA's Office of Women's Health explained:

> Because so few drugs have been well-studied in pregnant women, prescribing medications is generally left to a health provider's individual experience. As a result, the scientific basis to treat women who begin a pregnancy with a chronic disease, or develop a pregnancy-specific medical condition is often inadequate. Moreover, the physiological alterations of pregnancy are rarely considered or addressed in descriptions of standard dosing regimens. (10)

Although it is generally agreed by all parties that more information about the effects of therapeutic agents upon the developing fetus would be highly advantageous, the means of collecting such information remains hotly debated. In particular, there are varying views as to what degree pregnant women should be included in clinical research. The ethical, scientific and political positions concerning this topic area will be explored in subsequent chapters.

Although there has been interest regarding the inclusion of pregnant women in clinical research for a number of years, the current increase in attention could partially be attributed to a change in the characteristics and behaviours of pregnant women. One such characteristic is the average age at which women are having children. Over the past decade the average age of first-time mothers in Canada rose from 26.9 years to 29.6 (38). It has been suggested that this increase in age increases the likelihood of women suffering from medical problems prior to, and during, pregnancy (32). Evidence by the FDA, collected between 1993 and 1994, suggests that this line of reasoning may be correct – citing that women less that 35 years of age took an average of three prescription

medications, while women over the age of 35 took an average of five prescription medications (32). Aside from assumptions relating to age, Statistics Canada reported an increase in non-prescription medication use by pregnant women from 1993/94 to 2001/02 (31). In general, it was reported that the proportion of pregnant women who use prescription medications in Canada is 27%, while 33% use non-prescription medicine (31). Considering these statistics, in combination with those that suggest an increase in medication use by the pregnant population, it is not surprising that the inclusion of pregnant women in clinical research is receiving greater attention now than it did in the past.

Further rationale for including pregnant women in clinical research is premised upon the "different physiology" argument outlined earlier. Yet, instead of using this idea as rationale for exclusion, various researchers have flipped it around and used it as a means of advocating for further inclusion of pregnant women in clinical research. Goodrum and colleagues assert that pregnant women are indeed physiologically different from the non-pregnant population, therefore leading to "alterations in drug distribution, absorption, and clearance" (32). Because of this difference in physiology, it is important that information is gathered regarding the "pharmacokinetics and pharmacodynamics of drugs as related to the specific physiology of the woman/fetal unit during pregnancy and the postpartum period." Although these researchers do not suggest what exact study type is most appropriate for collecting such information, they advocate for the general inclusion of pregnant and postpartum women in clinical research regarding obstetrical problems and preexisting chronic medical conditions (32). Further discussion of

scientifically and ethically appropriate study methods will be presented in subsequent chapters.

One of the most compelling arguments for inclusion of pregnant women in clinical research is that such inclusion allows access to advantageous research protocols (29;36). Although it may be hoped that individuals enter research studies as a means of benefiting the 'greater good', it appears as though there is greater recognition of the reality that much participation is stimulated by more individualistic motivations. Such motives may be the desire to obtain access to the most innovative (often unproven and unapproved) treatments or, more basically, receive health care services that may otherwise be unaffordable. One particular research area in which there appears to be strong support for the inclusion of pregnant women is that concerning life-threatening illnesses and conditions. Specifically, there appears to be major support for the inclusion of HIV-positive pregnant women in clinical research (39). Hall suggests that excluding pregnant women from such 'benefits' is discrimination on the basis of sex and hence, in the United States [and Canada] is illegal (36).

1.7 Conclusion

An understanding of the exclusion of women from clinical research is important because the challenges faced by women in the past are similar, if not shared, by the pregnant population. It is also hoped that an understanding of the historical experience of women in clinical research can be used to identify possible solutions to current problems faced by pregnant women within the clinical setting.

It appears as though the current representation of women within clinical research is satisfactory; however, the same cannot be said for pregnant women. As a result, pregnant women lack access to comprehensive, relevant, information regarding many therapeutic interventions and are denied entrance into potentially beneficial research studies. It is clear that pregnant women would benefit greatly from access to further information regarding their physiology and the effects of therapeutic interventions upon their pregnancies. Yet, does this mean that pregnant women should be included in clinical research? And if so, under what conditions should they be included? To answer such questions, a thorough, multidisciplinary, discussion is required. The following chapters will be used to provide such a discussion, referring particularly to relevant ethics, scientific and political literature, to enrich and substantiate the dialogue.

Chapter 2: A discussion of the ethical implications of excluding pregnant women from clinical research

2.1 Introduction

Underlying concerns regarding the exclusion of pregnant women from clinical trials are a number of ethical dilemmas. Although many of these dilemmas are readily apparent, many of them are more nuanced. A number of the guiding principles set out within the *Belmont Report* and the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (TCPS) will be used as a means of identifying and discussing the ethical issues which arise when pregnant women are excluded from, or included in, clinical research (40;41). However, before such an analysis can begin, it is important to outline the legal and moral status of the main players involved – the fetus and the pregnant woman.

2.2 Moral and Legal Status

When discussing the ethical issues which arise from the exclusion of pregnant women from clinical trials, one must first address the intimate relationship that exists between the fetus and the pregnant woman. In particular, one must consider whether these two entities can be considered as independent individuals. Although there is no definitive answer to this question, a review of Canadian jurisprudence and ethics literature can be used to outline the popular understanding of the legal and moral status of the fetus and the legal expectations of the pregnant woman.

2.21 The fetus – legal status

A review of the past century of Canadian law highlights the great challenges faced in determining the rights and legal status of the fetus. Although the status of the fetus is an issue which has come up in many legal cases, it appears to be most prominent in cases related to the legality of medical abortions. In Canada, abortion was illegal from 1869 until 1967, when Prime Minister Trudeau introduced amendment 251 to the Criminal Code of Canada, resulting in an easing of the earlier abortion laws. Under section 251, for a woman to obtain an abortion she was required to receive a certificate from a therapeutic abortion committee at an approved or accredited hospital. Although this amendment marked a shift in perspective regarding medical abortions, there remained a number of practical barriers to obtaining an abortion and therefore much tension surrounding the issue (42).

Since the legal changes proposed by Prime Minister Trudeau, the legal case that has likely had the greatest recent impact upon the abortion debate, and contributed most to our understanding of the legal status of the fetus, was the case of *R. v. Morgentaler* (43). In this case, a number of physicians were charged with illegally practicing abortions because they were performing abortions upon women without official therapeutic abortion committee certification – contrary to the requirements of section 251. In response to this case, the Supreme Court of Canada ruled that provision 251 of the *Criminal Code of Canada* unreasonably infringed upon the right to life, liberty, and security of the person as guaranteed by section 7 of the *Canadian Charter of Rights and Freedoms* and was not justifiable under section 1 of the *Charter*. Therefore, section 251 of the Criminal Code was struck down, and has not since been replaced by Parliament

(42). Although the result of this case implied that the court did not view the fetus as a person deserving of rights, there lacked any overt comment by the Supreme Court judges as to whether the fetus was considered a person or an individual. However, what was specified was that any rights that the fetus did possess could not override the pregnant woman's right to liberty and security of the person (44). Although subsequent cases have added details to the legal view of the status of the fetus, there is yet to be a court case or piece of legislation to contradict the stance taken by the Supreme Court in 1988.

In 1989, the *Morgentaler* decision was put into practice when the Supreme Court reviewed the *Tremblay v. Daigle* case (45). In this case, the applicant sought an injunction to prevent his former partner from having an abortion, arguing that the fetus had a right to life. The court refused the application, holding that the fetus is not a juridical person (46). Since this case, further cases have reinforced that the law does not view the fetus as a person. In *R. v. Sullivan and Lemay* [1991], the courts overturned the conviction of two midwives for criminal negligence, following the death of a fetus during childbirth (47). The basis for their decision was that under the Criminal Code of Canada, the fetus was not considered a person. A similar conclusion was drawn in *R. v. Drummond* [1997] when the courts did not convict a woman of murder after shooting a pellet at her pregnant womb – on the basis that the fetus she was shooting at was not considered a person (44;48). In summary, the Canadian legal system continues to lack legislation concerning abortion and does not recognize the fetus as a person or individual deserving of rights.

2.22 The fetus – moral status

While it is relatively clear that the fetus does not possess legal status and rights in Canada, the moral status of the fetus appears to be a more complex issue. It is important to discuss the moral status of the fetus because the existence of full moral standing is considered by many as equivalent to a right to life (49). L. Wayne Summer elaborates on the implications of the right to life, explaining that such a right imposes positive (to support life) and negative (to not deprive life) duties on moral agents, and therefore possibly the obligation to aid and not attack such moral beings (49). This right to life is important in the research setting because it can be deduced that if a fetus is granted a right to life, research protocols that threaten this right may be ethically problematic. Although the majority of ethics literature pertaining to the moral status of the fetus is written in the context of the abortion issues, similar ideas and arguments can be extrapolated to the fetus within a research setting.

Within the context of the abortion debate, scholars place the beginning of personhood anywhere from the time of fertilization to the time period following birth (50). Scholars such as John T. Noonan place personhood at conception, arguing that the acquirement of the human genetic code grants personhood. In addition to such arguments, various scholars have used arguments of 'potentiality' (the potential of the fetus to grow into a full human being with full moral status) as a means of granting personhood at conception or fertilization (50). In contrast, scholars such as Mary Anne Warren, use a list of properties (consciousness, self-motivated actions, reasoning activity, communication skills and rationality) as a means of determining personhood, and therefore argue that moral status can only be granted following birth (51). Similar

personhood properties were also proposed by Fletcher (self awareness, self control, a sense of the future, a sense of the past, the capacity to relate to others, concern for others, communication and curiosity) and Tooley (awareness of self as a continuing entity and the capability to have an interest in his own continued existence) (52;53).

Although the extreme viewpoints listed above play an important role in coloring the abortion debate, moderate approaches appear to be more widely accepted by the Canadian medical community, and capture some of the pivotal issues surrounding the moral status of the fetus (54). Common to the majority of moderate viewpoints is the desire to identify what property, or properties, grant personhood to the fetus. Some of the most compelling personhood arguments approach this identification of a fetal property within the life continuum – therefore considering what property is lost at the time of medical death, as a means of deducing what property must be acquired at the beginning of life. Anita Allen describes how Baruch Brody takes this approach, identifying the key property as a functioning brain:

> That is, the property whose acquisition confers the right to life in the first place is the same property that, when permanently lost, entails the loss of a right to life. This property is the possession of a functioning brain (50).

When Brody's approach is applied to our understanding of fetal development, the beginning of personhood is deemed to be at approximately 6-weeks gestation (50).

A further attempt to identify the property that determines personhood is that made by Summer. The argument made by Summer is particularly compelling because it suggests an approach which intertwines philosophical reasoning and scientific understanding. After considering, and rejecting, a number of possible properties (intrinsic

value, aliveness and rationality), Summer argues that the most appropriate property of moral status is sentience – the capacity for feeling or affect (49). The strength and uniqueness of this property is that it allows for a gradient in moral status, as opposed to a binary definition. As Summer explains, this gradient in sentience, and hence moral status, exists in many continuums – phylogenic, pathogenic and ontogenic. However, in relation to the moral status of the fetus, the sentience continuum of interest is the ontogenic continuum. At a certain point in development, the fetus shifts from lacking moral status, to possessing a *degree* of moral status (49). By reviewing scientific literature, Summer suggests that this acquisition of sentience occurs at some point during the second trimester, however, a precise week is not provided (49).

As a means of determining a more precise threshold point it is useful to consult the most current scientific literature. Although few scientific papers refer to the fetus' 'sentience', many texts discuss the possibility of fetal 'awareness of pain'. Because an awareness of pain intuitively appears to be a component of sentience, it seems appropriate to use pain awareness as a scientific indicator of sentience.

Anatomical research indicates that the physical system required for the experience of pain is the cortical component of the central nervous system (55;56). Developmental data suggests that the requisite cortical layers, similar to those found in the adult brain, are intact at 26 weeks gestation (57;58). A comprehensive review of physiological literature by Derbyshire further confirms that the full biological system necessary for pain experience is intact and functional at 26 weeks gestation (59).

Although the physical components of the 'pain system' may be intact at 26 weeks, it is difficult to determine when, and if, the fetus has a psychological experience of pain.

Careful observation and testing of pre-term infants has informed our understanding of the possible psychology of the fetus at 26 weeks. Research of behavioral reactions and brain haemodynamic responses to noxious stimuli indicates that at 26-weeks gestation the neonate has the psychological ability to experience pain (60;61).

Despite such psychological research, Derbyshire and others question whether observations of neonates can be extrapolated to the fetus – due to the fact that the neonatal and fetal environments are very different (59;62). Derbyshire argues that factors in the womb affect the psychological state of the fetus, including: chemicals from the placenta which promote sleep and suppress higher cortical activation in the presence of external obtrusive stimuli, and attributes of the womb which buffer the fetus from tactile stimulation (59). Arguments such as this suggest that the fetus may perhaps not experience pain at all.

In recognition of the substantial controversy which persists, it appears as though the most prudent approach would be to assume that by the 26th week of gestation the fetus may experience pain, and therefore possesses one of the key components of sentience. When this scientific information is applied to Summer's argument, the threshold of sentience becomes 26-weeks gestational age. Using such rationale, it can therefore be argued that any fetus aged 26-weeks or older should likely be accorded a degree of moral status and is perhaps owed a certain moral right to life.

Although the majority of literature pertaining to the moral status of the fetus comes from discussions of abortion, a few authors have commented directly upon the status of the fetus in relation to research intended for the benefit of the pregnant woman. One of the most prominent discussions on this issue comes from McCullough et al. (37).

McCullough and colleagues argue that the previable fetus has dependent moral status – moral status conferred freely upon an entity by others, not as a matter of obligation. Therefore, the previable fetus is only granted moral status if, and when, the pregnant woman grants such status. However, once moral status is granted, or the fetus becomes viable, the fetus is considered a patient. At this point, the woman and her physician must balance beneficence-based obligations to the fetus against autonomy and beneficence obligations to the pregnant woman (37).

This perspective is fairly compatible with the views of Summer and others, because part of the argument uses viability as a means of determining moral status. Such compatibility exists because current medical literature sets fetal viability at about 23 weeks (63) – close to the approximate 26 week sentience cut-off discussed earlier. However, the second component of McCullough's argument – allowing the pregnant woman to grant moral status to the previable fetus – corresponds less with Summer and others, and is more difficult to apply in a practical research setting. Allowing the pregnant woman to grant moral status positions the woman against her fetus, therefore potentially creating a great psychological and intellectual burden for the woman (64). As a means of avoiding such great burdens it seems justifiable to set an overarching moral status standard, based upon viability or sentience – therefore placing such a time point at approximately 23 weeks gestation.

Within a practical research setting such a cut-off could be used by researchers and research ethics boards to outline, based on gestational age, which pregnant women could be offered entrance into a study. While such an approach may appear paternalistic – because late-term pregnant women would not be granted the choice as to whether or not

to enter clinical research – this moderate degree of paternalism is outweighed by potential benefits to the pre-person and pregnant woman. Having a clear, preset, cut-off point eases the burden upon researchers forced to determine when such a line should be drawn, therefore also protecting the developing fetus from variable, potentially harmful, research practices. Further benefit to imposing an overarching exclusion for pregnant women at 23 weeks and onwards, is that such an action removes responsibility from the pregnant woman, therefore avoiding the psychological stress involved in making such a decision. It should also be noted that, while general moral status may be determined by the researcher and research ethics board, prior to 23 weeks gestation the pregnant woman has implicit control over her fetus's moral status by agreeing or refusing to participate in the research study.

2.23 The pregnant woman – legal status

In Canada, the *Charter of Rights and Freedoms* accords pregnant women the same rights to life, liberty and security of the person as every other Canadian citizen (64). Although pregnant women are accorded the same rights as non-pregnant women in Canada, conflict has arisen when their actions were thought to negatively impact the life of their fetus. Because of this, the majority of Canadian legal cases which pertain to pregnant women deal with how their actions and lifestyle may affect or have affected their pregnancy. Because of the intertwinement of the pregnant woman and her fetus, issues of personhood resurface in many of these cases. Likely, the two most prominent Canadian cases concerning the legal status of the pregnant woman are: *Winnipeg Child*

and Family Services (Northwest area) v. G. (D.F.) [1997] and *Dobson v. Dobson [1999]* (65;66).

In *Winnipeg Child and Family Services v. G.,* Children's Aid was concerned that Mrs. G's glue-sniffing addiction would have a negative impact upon the health of her fetus. Therefore, when she refused to receive rehabilitation therapy, the director of Child and Family Services sought a court order to detain her in the residential therapy facility. When the case reached the Supreme Court of Canada, the judges decided that neither under tort law nor *parens patriae* (state acting as a parent to the child) could the woman be detained – because the law only respects the rights of the born person (67). It was explained that the pregnant woman and fetus are viewed as a single legal entity, and therefore it is nonsensical to allow action against the woman on behalf of her fetus (46). Further rationale for this decision included: the difficulty in drawing a line between offensive and allowable behaviour for pregnant women; the thought that lifestyle 'choices' are often not choices, but instead a product of unavoidable circumstances and illness; and the lack of evidence that a tort duty would decrease incidence of substance-abused children (67).

In the case of *Dobson v. Dobson,* a tort action of negligence toward the fetus during pregnancy was filed against Mrs. Dobson, on behalf of her child. It was claimed that Mrs. Dobson had driven recklessly during bad weather, causing a car accident which resulted in permanent physical and mental impairments to her son. The Supreme Court judges rejected the appeal, on the basis that a legal duty of care should not be imposed upon a pregnant woman (46). McLachlin J. elaborated on the decision, explaining that:

> … Virtually every action of a pregnant woman could affect a fetus, imposing a duty of care for prenatal negligence would have the potential to jeopardize the pregnant woman's fundamental right to control her body and make decisions in her own interest (46).

A review of the responses by the various Supreme Court Judges involved in this case indicates a general interest in not judging nor interfering with the lives of pregnant women, and a recognition that setting a 'standard of care' is an impractical goal.

Within the hospital setting, various rights and responsibilities of the pregnant woman have been outlined by the Canadian legal system. In particular, competent pregnant women have been granted the authority to refuse medical treatment – such as cesarean section births – even if such a refusal places the fetus's life at risk (64). This legal authority seems particularly relevant to clinical research as it further suggests the court's respect of the pregnant woman's autonomous choice regarding interventions that pose risk to the life of the fetus.

In summary, Canadian jurisprudence relating to the actions of women during pregnancy suggests that the legal system will not prohibit actions and lifestyle 'choices' which may harm the fetus. It appears as though the main rationale for this stance comes from the recognition that, under Canadian law, the fetus is not considered a person and therefore does not require protection. In addition to this, there is recognition of the slippery slope that would occur if the courts tried to dictate what actions were suitable for pregnant women and what were impermissible. Most refreshingly, comments made by many of the Judges suggest an implicit recognition that pregnant women (like all people) are not always in full control of their lifestyle choices, and instead can be greatly influenced by larger socioeconomic disparities and pressures.

2.3 Principled approach to the ethical dilemmas

To discuss the ethical issues which arise when pregnant women are excluded from clinical trials, a principled approach will be used as a framework. This approach is suitable because it provides a logical method for elucidating the key ethical dilemmas, and is compatible with the terminology and approach of previous literature concerning this topic. The particular ethical principles chosen to provide a framework for discussion are taken from the 2003 Canadian TCPS and the *Belmont Report* (40;41). These principles include: respect for persons, respect for justice and inclusiveness, and balancing harms and benefits.

2.31 Respect for persons

Discussion of the principle of respect for persons elucidates one of the key ethical challenges faced when one considers the exclusion of pregnant women from clinical studies. A review of various national and international health policies reveals a variety of related terms (e.g. autonomy, respect for informed consent…) used to convey a fundamental idea – respect for the individual. Within this chapter, the term "respect for persons" will be used – as taken from the *Belmont Report* (40). The *Belmont Report* has been chosen as the guiding policy document because it is one of the most well-recognized, international research ethics documents. Within the *Belmont Report*, "respect for persons" is described as a composite of two ethical convictions: "first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection" (40). Throughout this section of the

Report there is a clear emphasis upon the respect and protection of autonomy. An autonomous person is defined as any individual capable of deliberation about personal goals and acting in accord with such deliberation (40). The Report goes on to explain what is involved in respect of autonomy:

> To respect autonomy is to give weight to autonomous persons' considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others (40).

Much like the *Belmont Report*, the TCPS, highlights the need to respect and protect the individual. However, unlike the *Report*, the TCPS does not use the terms 'autonomy' or 'respect for persons', instead, two related terms are used: "respect for human dignity" and "respect for free and informed consent". These principles are defined as follows:

> **Respect for Human Dignity**: … [Respect for] the multiple and interdependent interests of the person – from bodily to psychological to cultural integrity. This principle forms the basis of the ethical obligations in research…
> **Respect for Free and Informed Consent**: Individuals are generally presumed to have the capacity and right to make free and informed decisions. Respect for persons thus means respecting the exercise of individual consent (41).

A review of the *Belmont Report* and TCPS suggests a common emphasis upon respect of individual autonomy, via various related means – protection of vulnerable individuals, empowerment through information and involvement in the decision-making process. A recent publication by the American College of Obstetricians and Gynecologists (ACOG) suggests that within a research context the principle of "respect for persons" is interpreted as the researcher's obligation to respect the right and capacity of their subjects to weigh the potential risks and benefits of research participation and decide for themselves whether to consent to participate in the research (68). Following this line of reasoning, it can be argued that when a pregnant woman is excluded from

research for 'non-scientific' reasons (e.g. because potential harm to her seems too great), her decision-making capacity is not being respected and therefore she is not being respected as an individual person.

2.32 Respect for justice and inclusiveness

The ethical principle of justice is one of the most relevant principles to consider when determining the ethical implications of the exclusion of pregnant women from clinical research. Justice, as defined by Beauchamp & Childress is: a group of norms for distributing benefits, risks and costs fairly (69). Within a research setting, the respect of Beauchamp & Childress's definition of justice may require that benefits such as access to information gained from research, as well as the inherent risks of participating in research, be distributed evenly among all members of the general population. The TCPS elaborates upon such a view of justice and describes the requirements for justice within a research setting:

> Justice connotes fairness and equity… Justice also concerns the distribution of benefits and burdens of research. On the one hand, distributive justice means that no segment of the population should be unfairly burdened with the harms of research. It thus imposes particular obligations toward individuals who are vulnerable and unable to protect their own interests in order to ensure that they are not exploited for the advancement of knowledge. History has many chapters of such exploitation. On the other hand, distributive justice also imposes duties neither to neglect nor discriminate against individuals or groups who may benefit from advances in research (41).

As suggested by the detailed description of justice provided by the TCPS, there exist many facets and approaches to justice. In relation to the exclusion of pregnant women

from clinical research, the most relevant approaches to justice will be discussed, including specifically: distributive justice, gender justice and economic justice.

Many authors discuss distributive justice when evaluating the ethical implications of the exclusion of pregnant women from clinical trials. For such justice to occur, the burdens and benefits of research participation must be distributed equitably (70). When this principle is applied to research studies that exclude pregnant women, it appears that distributive justice has not been respected – pregnant women are being excluded from both the benefits and burdens of research. This interpretation of distributive justice is echoed by Dresser, in her discussion of the role of women in research. Dresser argues that when women are excluded from research they are not only excluded from the benefits of research, but are unfairly imparted the burdens of research – by contributing tax dollars to publicly funded research (15). Although Dresser's discussion concerns women in general, the same argument can be made for the exclusion of pregnant women from clinical research.

Another approach to evaluating the exclusion of pregnant women from clinical trials is to view such exclusion from a gender justice perspective. Although there are many approaches to gender justice, the most comprehensive, contemporary, approach appears to be that suggested by K.L. Baird (1). Baird argues that previous approaches, such as those that aim to treat every individual as equal by removing gender (sameness model), and those that stress the differences between genders (difference model), are inadequate. Instead, there needs to be greater focus upon how women, as a diverse group, are disadvantaged by an absence of specific policies to meet their needs (1).

Baird argues that in order to achieve gender justice, three components must be satisfied: self-determination, equality of gendered consequences, and diversity. However, the component most relevant to the topic at hand is a subcomponent of self-determination – self-development. Within the context of healthcare, the need for self-development implies that people need the information and tools required to improve their health (1). Such information is most often gained from the publications of medical research. Therefore, when pregnant women are excluded from clinical trials, medical information pertaining to the effects of particular therapeutics upon pregnant women and their fetuses is absent. Because self-development is an essential component of Baird's gender justice requirements, the exclusion of pregnant women from clinical trials appears to inhibit full gender justice.

The economic justice approach described by Michael Walzer's spheres of justice is a further means of viewing the exclusion of pregnant women from clinical trials. The basis of this perspective is the belief that justice can only be achieved by an elimination of domination. Walzer's justice approach is adjusted to the health research setting and elaborated upon by Charles Weijer (70). Weijer provides a description of both the just state of being and a description of what produces an unjust state within a research setting.

According to Walzer, goods ought to be distributed according to need. For instance, food may symbolize sustenance or religious offerings; therefore, what is to be done with it depends on which meaning it is given (70). This perspective of justice is similar to distributive justice, yet instead of allocating goods uniformly, the allocation is based upon need. Instead of viewing goods as solely material and individual, he creates sets of goods: community membership, security and welfare, money and commodities,

hard work, free time, education, kinship and love, divine grace, recognition, and political power. These sets of goods each exist within their own sphere of justice and are governed by their own set of rules.

Weijer explains that injustice can occur either if there is a failure to distribute goods within each sphere according to the norms dictated by each sphere, or if domination exists (transgression of the boundaries between the spheres). To apply such ideas to the medical research setting one must first outline what sphere medical research falls into and what norms are expected. Weijer explains that medical care and research fall into the sphere of security and welfare – goods that the community must provide. Medical research is placed in this sphere because providing medical care requires common effort – cooperation by all of society (70). One of the norms of this sphere is that goods, such as knowledge, must be provided equally to all members. In particular, the results of medical research must be applicable to the breadth of the community members afflicted with a particular illness (70). However, when pregnant women are excluded from medical research they are restricted access to the creation of, and hence the possible benefits from, medical knowledge. As a result, the norm of equal provision of knowledge has been violated, therefore satisfying one of the conditions of injustice.

The second component of injustice – domination – is defined as the conversion of one good into another when there is no intrinsic connection between the two (70). For instance, when money is used to buy votes, one good has been converted into another, and therefore domination has occurred (70). Walzer's theory dictates that when spheres cross without justification, injustice occurs. In the context of medical research Weijer explains that:

> …If an eligibility criteria selects (or excludes) subjects because of their standing in another sphere, without reference to the requirements of medical care or science, the criterion involves boundary crossing and is unjust (70).

In relation to the exclusion of women from medical research, Weijer suggests that women are excluded due to their reproductive physiology and concerns for the fetus. Although Walzer acknowledges that women play important roles in the family, he argues that these roles are allocated to the sphere of kinship and love (70). Weijer explains that such exclusion is unjust because it excludes women based on their connection to other spheres (e.g. the kinship and love sphere) rather than based upon a scientific rationale created within the security and welfare sphere.

Although the exclusion of pregnant women from clinical research appears to satisfy both conditions which lead to injustice, Weijer adds further practical guidance. He suggests that, due to the purposes of early studies, it is permissible to have strict eligibility guidelines for Phase I and II studies. However, he argues that Phase III studies should not be as restrictive - so as to allow the study population to represent patients in clinical practice. Despite this guidance, Weijer acknowledges the tension which exists between fastidious Phase III scientific method and the need for generalizability, and therefore suggests that exclusion criteria can be included as long as they are overtly justified (70).

2.33 Balancing harms and benefit

The principle of balancing harms and benefits is of great moral and practical importance and is a common theme in literature pertaining to the exclusion or inclusion

of pregnant women from clinical research. On a regular basis, researchers and research ethics boards are required to consider whether various research protocols successfully balance potential harms with potential benefits, while also maintaining minimal risk. As the TCPS explains:

> The analysis, balance and distribution of harms and benefits are critical to the ethics of human research. Modern research ethics, for instance, require a favourable harms-benefit balance – that is, that the foreseeable harms should not outweigh anticipated benefits. Harm-benefits analysis thus affects the welfare and rights of research subjects, the informed assumption of harms and benefits, and the ethical justification for competing research paths. Because research involved advancing the frontiers of knowledge, its undertaking often involves uncertainty about the precise magnitude and kind of benefits or harms that attend proposed research. These realities and the principle of respect for human dignity impose ethical obligations on the prerequisites, scientific validity, design and conduct of research. These concerns are particularly evident in biomedical and health research; in research they need to be tempered in areas such as political science, economics or modern history (including biographies), areas in which research may ethically result in the harming of the reputations of organizations or individuals in public life (41).

A fine balance is required to ensure the prospect of benefit while also reducing potential harms. Due to the subjective nature of this balance, it is the role of the researcher, followed by the research ethics board, to ensure that the prospect of direct benefit exists, while also maintaining the clinical equipoise which is essential to all research studies. Weijer and Crouch explain that Freedman's clinical equipoise exists when: "… there is an honest, professional disagreement in the community of expert clinicians as to the preferred treatment" (71). Freedman elaborates upon this idea, explaining how clinical equipoise can be approached within the randomized controlled trial setting:

> At the start of the trial, there must be a state of clinical equipoise regarding the merits of the regimens to be tested, and the trial must be designed in

> such a way to make it reasonable to expect that, if it is successfully concluded, clinical equipoise will be disturbed. In other words, the results of a successful trial should be convincing enough to resolve the dispute among clinicians (72).

When applying the harm-benefit principle to the current topic, one must first decide what parties will be considered in this balance. A review of current literature suggests that the two parties most commonly considered are the individual pregnant woman and the individual fetus. Although the balancing of potential harms and benefits appears to focus primarily upon the individual – the *current* woman and fetus – a consideration of *future* pregnant women and fetuses can also be integrated into the balance.

While it is fairly clear that the pregnant woman should be factored into the assessment of harms and benefits, the fetus poses a greater challenge. Because the Canadian legal system does not consider the fetus to be a person, it appears as though there is no legal obligation to consider the fetus in this balance. However, despite this legal stance, it is clear that the *moral* status of the fetus remains contentious. To add difficulty to the situation, unlike the abortion issue, research which may affect the fetus does not affect a single time point, but instead has the possibility of affecting development throughout pregnancy, childhood and into adulthood. With an understanding of the various positions held regarding the moral status of the fetus, and the possible developmental effects of research upon the fetus, it appears that the most logical and cautious approach to take would be to accord the fetus a degree of moral status from conception onwards. However, it will be the stance of this author to accord the fetus only a *degree* of moral status, and grant full moral status only at the time of

birth. Although this position will be contentious, review of current ethics literature and medical literature concerning fetal development suggests that this stance is reasonable.

To discuss harms and benefits in relation to pregnant women's involvement in clinical trials, it is necessary to discuss the harms and benefits of including pregnant women in research. Although the pregnant woman and fetus are intimately connected, earlier discussions in this chapter suggest that each can be considered separately – with the pregnant woman possessing full moral status, while the fetus is accorded a degree of moral status. Although this separation is artificial, it appears to be a useful approach and will be followed, at least provisionally, to analyze and evaluate harms and benefits.

To conduct a harm-benefit analysis, the *inclusion* of pregnant women in clinical trials will be considered. When pregnant women are to be included in trials, there is often great concern regarding possible harm to the fetus. This response is likely attributable to both historical events and our current understanding of the physiological relationship between pregnant woman and fetus. Anecdotal evidence suggests that strong emotional reactions to the inclusion of pregnant women in clinical research are due to a number of research mistakes in the past – such as the thalidomide tragedy in the early 1960s. Meanwhile, physiological research has allowed us to better understand how the actions of the pregnant woman can affect fetal development, and particularly, what chemicals can cross the placenta. Therefore, it is expected that fairly noninvasive interventions (i.e. intravenous sampling of maternal blood) would pose a low risk of harm, while more invasive interventions (i.e. clinical trials of novel pharmacologic agents) would pose a high risk of harm. In addition to this general evaluation of fetal harm it is absolutely necessary that the results of prior animal studies also be conducted and integrated into the

harm-benefit calculation. The effects of medication on fetal development will be discussed in greater detail in chapter three.

In addition to possible harm to the fetus, one must also consider harm to the pregnant woman. To begin with, these harms would be at least equivalent to the harms faced by a non-pregnant woman enrolling in research. Therefore, the expected harms faced by the pregnant woman would be expected to be proportional to the invasiveness of the intervention and the development stage of the research (e.g. Phase I, II or III). However, this harm may be greater than that expected for non-pregnant women because very little pharmaceutical data exists concerning pregnant women. Therefore, even during a Phase III study, it may be difficult to predict how the intervention might interact with the pregnant woman's physiological system. In addition to such physical harms, one must also consider the psychological pressures felt by the women – many women would likely feel a degree of guilt or stress for exposing their fetus to risky research.

When pregnant women are included in clinical research, there can be many benefits for the pregnant woman and the fetus. For the pregnant woman, the benefits depend on the type of research in which she is involved. If the research is intended to contribute to general medical knowledge only, the benefits for the individual woman will likely be minimal. However, for more developed research projects (non-invasive or invasive) – such as Phase III studies, the potential benefits to the woman herself may be great. For instance, participation in a cancer drug trial may provide access to some of the most cutting-edge therapeutic interventions, therefore possibly contributing to decreased mortality or a higher quality of life for the study subject.

Although 'future generations' will not be included as a separate party to consider, it is important to mention the benefits to future pregnant women when pregnant women are included in clinical research. A comment upon the implications of such inclusive research seems necessary because many scholarly articles concerning the inclusion of pregnant women, or women in general, mention this benefit. Although pregnant women should not feel pressured to join studies for the sake of future pregnant patients, the data gained from their participation in such studies can provide great benefits to future generations of pregnant women. When the sample of pregnant women is small, the data collected can be added to a pregnancy databank to which physicians can refer before prescribing drugs to future pregnant women. Such a databank would likely contain high quality data as it would be reported by the researchers – therefore hopefully making it more detailed and objective than those databanks containing maternal-reported information. However, if the sample size is large enough, results can also be used to draw significant conclusions regarding the interaction between the particular intervention and the pregnant physiology, or be used to gain a better understanding of the physiologic and pathological changes that can occur during pregnancy (68).

It should be noted that this type of beneficence can also be viewed as nonmaleficence. The ACOG suggests that inclusion of women in clinical research prevents possible harm because it avoids the inappropriate extrapolation of male data to the female population (68). This same line of argument can be used for pregnant women: including pregnant women in clinical research can avoid inappropriate extrapolation of male or non-pregnant female data to the pregnant female population. If pregnant women are not included in research, data are not generated for this population subgroup, and

clinicians are therefore forced to reference data from isolated case reports (i.e. their own previous experiences or reports by colleagues) or from the non-pregnant population. Basing treatment decisions on case reports can be very problematic due to the small sample size and bias. Basing treatment decisions on data taken from the nonpregnant population can also be problematic because the physiology of a pregnant woman is, in many regards, different than that of a non-pregnant person. For example, if a physician wishes to provide the most effective depression medication to his or her patient, yet all the clinical studies were conducted on a nonpregnant population, the physician may be forced to prescribe a drug that has not been tested on the pregnant population. As a result, the drug may negatively interact with a physiological process unique to the pregnant woman (e.g. the drug may negatively interact with the woman's elevated prolactin levels). Examples such as this highlight the importance of collecting data specific to the pregnant population.

In addition to maternal benefits, there can also be benefits to the fetus. In general, the amount of possible benefit to the fetus will likely correspond with the amount of possible benefit to the pregnant woman. This relationship is deduced by assuming that (outside the fetal research field) the research will not directly benefit the fetus, yet may have indirect effects upon the fetus. If the intervention has positive effects upon the woman's health, it may indirectly lead to a longer, healthier pregnancy – therefore producing a healthier, more fully-developed baby. Also, the better the mother's health, the better-equipped she is to care for her newborn, both physically and psychologically.

To come to a final balance of harms and benefits depends on information regarding the specific research studies. Although a case-specific approach is required,

there does exist a number of general guidelines which can be used to help categorize studies and provide directions. These guidelines generally come in the form of policy, and therefore will be discussed in greater detail in the ensuing policy chapter.

2.4 Conclusion

As a means of applying three relevant ethical principles to the exclusion of pregnant women from clinical research, it is important to discuss the legal and moral status of the fetus and the legal status of the pregnant woman. A review of Canadian jurisprudence suggests that the fetus does not gain legal status until birth, and therefore, the pregnant woman's lifestyle and choices cannot be legally restricted on the basis of protecting the fetus. Morally, the status of the fetus remains contentious. However, compilation of the work of philosophers Summer and McCullough, coupled with scientific data, suggests that the most prudent threshold for moral status is at 23 weeks gestational age.

With such a moral and legal basis, it is possible to thoroughly discuss the ethical principles of: respect for persons, respect for justice and inclusiveness, and balancing harms and benefits - as defined by the TCPS and *Belmont Report.* A review of the writings of various prominent authors, including Baird, Beauchamp, Childress, Dresser, McCullough, Walzer and Weijer suggest that the exclusion of pregnant women from clinical research clearly violates the principles of respect for persons, and respect for distributive, gender, and economic justice. Discussion of the principle of balancing harms and benefits suggests that a favourable balance can be struck when pregnant women are

included in clinical research, however, within a practical setting, such discussion of harms and benefits must be assessed on a case-by-case basis.

Chapter 3: The pregnant patient: A review of scientific knowledge and clinical practice

3.1 Introduction

Previous chapters have addressed the exclusion of pregnant women from research from relatively broad perspectives, using the historical exclusion of women from health research, and ethics and law to inform the discussion. This chapter will take the issue directly to a practical, clinical, perspective to see how physicians go about treating pregnant patients and what challenges are encountered. In particular, current clinical practice and teratogenicity knowledge will be reviewed, followed by a discussion of current and future means of collecting drug teratogenicity information. To provide background information and stimulate discussion of improved clinical practice, pertinent public health, epidemiological and basic science literature will be reviewed.

3.2 Drug use in pregnancy

Current data indicate that a large proportion of women use non-prescription and prescription medications during pregnancy, therefore suggesting that the provision of treatment and counseling to pregnant women by their physicians is a common clinical challenge. In particular, data collected from Canada's 2002/03 National Longitudinal Survey of Children and Youth suggest that 33% of women use non-prescription medications during pregnancy, while 27% use prescription medications during pregnancy (31). Further data taken from the 2003 Canadian Community Health Survey indicate that 62.2% of pregnant women surveyed reported medication use within the past month. The

most frequently reported medication being pain relievers, followed by cough/cold remedies, stomach remedies, 'other' medications, penicillin/other antibiotics, asthma medications and allergy medications (31). The results of these Canadian surveys are important because they provide very current data concerning the pregnant population and indicate a relatively high degree of prescription and nonprescription drug use within this population.

3.3 Clinical approach to pregnancy

When treating pregnant patients, Canadian physicians often refer to resources such as the *Physicians' Desk Reference* for guidance. Because fetal risk has often not been adequately established, many such reference manuals contain statements such as "use in pregnancy is not recommended…" (73). Also, because manufacturers almost never test their drugs on pregnant women before the drug is available on the market, most drugs are not labeled for use during pregnancy (73).

As a means of providing further information to physicians, the U.S. Food and Drug Administration (FDA) established the Use-in-pregnancy ratings. This system classifies medications into various alphabetical categories, based upon whether or not the medication has been scientifically tested, and whether it poses a threat to the fetus (31). This classification system is used for drug labeling and medical reference material across North America. The classification requirements are as follows:

Pregnancy category A	Controlled studies show no risk. Adequate, well-controlled studies in pregnant women have failed to demonstrate risk to the fetus.
Pregnancy category B	No evidence of risk to humans. Either animal findings show risk, but human findings do not; or, if no adequate human studies have been done, animal findings are negative.
Pregnancy category C	Risk cannot be ruled out. Human studies are lacking, and animal studies are either positive for fetal risk or lacking as well. However, potential benefits may justify the potential risk.
Pregnancy category D	Positive evidence of risk. Investigational or post-marketing data show risk to the fetus. Nevertheless, potential benefits may outweigh the potential risk.
Pregnancy category X	Contraindicated in pregnancy, Studies in animals or human, or investigational post-marketing reports, have shown fetal risk which clearly outweighs any possible benefit to the patient.

Table 1: FDA Use-in-pregnancy ratings (United States Food and Drug Administration 1979) (74).

Despite the widespread use of this classification system, there has been a recent move to change the system due to various inadequacies. In particular, it has been argued that this system produces ambiguous statements that are difficult to interpret and may cause excessive anxiety for women. To overcome this weakness, the Teratology Society has proposed that the FDA replace the current system with one that summarizes and interprets available data and estimates teratogenic risk (75). These changes were proposed at an FDA hearing in 1997 and received public support, however, there is yet to be a formal change to classification practices (73).

In addition to problems with the framework of the FDA classification system, many authors have cited the practical inadequacies of the system. One such problem is that the FDA classification of medications often remains unchanged when new data concerning a drug are acquired (73). As a result, the classification system contains information that is out-dated and inaccurate.

Further criticism of the FDA system stems from the practical implications of the system. One study found the distribution of the drugs listed in the 1992 Physician's Desk Reference to be: 0.7% in A, 19% in B, 66% in C, 7% in D and 7% in X (76). This distribution is thought to be rather peculiar considering that there are many drugs which have been used in thousands of pregnant patients without showing potential for harm (77). Also, it has been argued that the default assignment of agents to FDA category C is misleading to physicians who consider this rating to indicate a degree of risk, as opposed to a lack of information from human studies (78).

These various criticisms of the current FDA classification system suggest that major changes are required to improve the framework of the system. However, underlying many of the 'structural' inadequacies of the system, there appears to be a lack of reliable data concerning medication use during pregnancy. As Koren and colleagues confirm; "physicians caring for pregnant women have very little information to help them decide whether the potential benefits to the mother outweigh the risks to the fetus" (73). Possible means of collecting information regarding medication use during pregnancy will be discussed in further sections.

As a means of overcoming the inadequacies of the FDA system, various pregnancy databanks and accessible information sources have been created. Three popular and current databanks which provide information regarding drug hazards during pregnancy are TERIS (Teratogen Information System), REPROTOX and TERAS (Teratogen Exposure Registry and Surveillance) (77). These databases hold a great deal of useful information, yet are not openly accessible – as a membership fee is often required. It would therefore be of great benefit if an equivalent free-of-charge database

could be established by a public, international organization such as the World Health Organization (WHO).

As a means of providing information directly to pregnant women, a number of Canadian and American agencies have developed accessible telephone and internet information sources. It is hoped that greater resources be devoted to such programs as they appear to provide an extremely comprehensive, accessible, up-to-date information source for both pregnant women and clinicians. One of the most well-known teratogen-information services available in Canada is the Motherisk Program (http://www.motherisk.org), developed by researchers and medical professionals at Toronto's Sick Kids Hospital (73).

3.4 Medication and the pregnant physiology

It has been established that pregnancy alters the four basic factors that determine the action of drugs on tissues: absorption, distribution, metabolism and elimination (77;79;80). These factors are what determine the pharmacokinetics of a drug – the time course of the biologically active forms of the agent relative to the incidence and magnitude of the toxicological response (81). The natural physiological changes that occur during pregnancy affect these four factors, and hence the pharmacokinetics of a drug. Such physiological changes that occur during pregnancy include: elevated cardiac output, various changes in blood-flow, an increase in gastric emptying, increase in pulmonary function, increase in plasma volume, changes in clearance and changes in oxidative and conjugative metabolism (34;77).

Although a great deal is known about the pregnant physiology, there remains very little information as to how pregnancy affects a woman's pharmacokinetics and dosage requirements (34;79). As a result, when physicians prescribe medications they are often uncertain as to the effects of the drug upon the pregnant women – let alone the drug's teratogenic effects. As a means of protecting the health and welfare of the pregnant woman it is important that greater research efforts be focused upon drug pharmacokinetics and dosage requirements during pregnancy.

3.5 Medication and teratogenesis

When physicians review medical resources to determine the effects of various medications upon pregnancy, the primary concern is usually whether a drug is reported to be teratogenic. Teratogenesis is defined as the dysgenesis of fetal organs as evidenced either structurally or functionally (82). Typical manifestations of teratogenesis include: restricted growth or death of the fetus, carcinogenesis, and malformations (77). Although various drugs are considered teratogenic, Schardein explains that timing of substance administration significantly affects teratogenicity. In particular, substances must be administered during organogenesis (the period of embryological differentiation) for teratogenesis to occur. In humans, this period of differentiation occurs at three to eight weeks gestation. After differentiation, the fetus becomes progressively less susceptible to teratogenic stimuli (77). Such information therefore suggests that depending on the stage of pregnancy, a pregnant woman may safely be able to participate in clinical trial research.

When medications are approved and placed on the commercial market, the majority of research used to create safety guidelines has been conducted within a male research subject population, or else, a nonpregnant female population. Because of this, there is usually very little information concerning fetal risk, and the majority of information is generated from animal studies (73).

Although there is a general perception that medication use during pregnancy is unsafe, current data suggests that fewer than thirty medications have been shown to be teratogenic when used in clinically effective doses (73;83). Our current understanding of teratogenic risk is based upon animal studies combined with retrospective studies. The following table was compiled by Koren et al. and lists all drugs with proven teratogenic effects in humans:

Drug	Teratogenic effect
Aminopterin, methotrexate	Central nervous system (CNS) and limb malformations
Angiotensin-converting-enzyme inhibitors	Prolonged renal failure in neonates, decreased skull ossification, renal tubular dysgenesis
Anticholinergic drugs	Neonatal meconium ileus
Antithyroid drugs (propylthiouracil and methimazole)	Fetal and neonatal goiter and hypothyroidism, aplasia cutis (with methimazole)
Carbamazepine	Neural-tube defects
Cyclophosphamide	CNS malformations, secondary cancer
Danazol and other androgenic drugs	Masculinization of female fetuses
Diethylstilbestrol	Vaginal carcinoma and other genitourinary defects in female and male offspring
Hypoglycemic drugs	Neonatal hypoglycemia
Lithium	Ebstein's anomaly
Misoprostol	Moebius sequence
Nonsteroidal anti-inflammatory drugs	Constriction of the ductus arteriosus, necrotizing enterocolitis
Paramethadione	Facial and CNS defects
Phenytoin	Growth retardation, CNS deficits
Psychoactive drugs (e.g., barbiturates, opiods, and benzodiazepines)	Neonatal withdrawl syndrome when drug is taken late in pregnancy
Systemic retinoids (isotretinoin and etretinate)	CNS, craniofacial, cardiovascular, and other defects
Tetracycline	Anomalies of teeth and bone
Thalidomide	Limb-shortening defects, internal-organ defects
Trimethadione	Facial and CNS defects
Valproic acid	Neural-tube defects
Warfarin	Skeletal and CNS defects, Dandy-Walker syndrome

Table 2: Drugs with proven teratogenic effects in humans (73).

3.6 Possible means of gaining further information

Although there exists a relatively extensive body of knowledge concerning the physiological changes that occur during pregnancy, and regarding the effects of known teratogenic drugs upon the fetus and neonate, there remain significant gaps in knowledge within other pregnancy-related topic-areas. In particular, there appears to be minimal human and animal teratogenic data and inadequate knowledge of the pharmacokinetics of drugs used during pregnancy. As a means of ameliorating this situation, it is important

that further teratogenic and pharmacokinetic information be collected via thoughtful, practical data collection methods.

3.61 General considerations

Before discussing what information collection methods could be pursued, it is useful to mention the pragmatic challenges and considerations common to all methods. One such consideration is that at least half of North American pregnancies are unplanned, therefore often resulting in the exposure of fetuses to drugs before women realize that they are pregnant (73;84). This finding is important when discussing information collection methods because it allows for the possibility of a great deal of retrospective study. In addition, it highlights the importance of having reliable teratogenic information accessible to pregnant women who find out that they have inadvertently exposed their fetus to medication. Current evidence suggests that when facing such a situation, many pregnant women consider and undergo abortions of otherwise wanted pregnancies (85;86). It is reasonable to conclude that more comprehensive, accurate, teratogenic information would prevent terminations of such otherwise-wanted pregnancies.

The baseline fetal malformation rate is another important factor to consider when discussing systems for the collection of teratogenic information. It is thought that the spontaneous occurrence of fetal malformations in the general public ranges from 1 to 5 percent. Epidemiological research indicates that very few drugs have the ability to increase the total malformation rate by a factor of more than two – thalidomide and isotretinoin being two such drugs (73). Therefore, it has been suggested that in a population where the baseline malformation risk is 3%, at least 220 control pregnancies

and 220 ‘exposed’ pregnancies would be required to demonstrate an increased risk due to exposure by a factor of 2.5, with a power of 80 percent (73). However, because most teratogenic drugs tend to change the baseline malformation rate by a factor of less than 2.5 it can deduced that a cumulative sample size of greater than 440 would be required to display significant results. Although such a large sample size is common-place in many studies directed at the general population, recruitment of a subsection of the general population – the pregnant population – would likely require great efforts.

3.62 Animal studies

One of the most important and practical means of collecting teratogenic information is through careful preclinical testing on animal models. By observing the effects of a drug upon a pregnant animal and her fetus, a great deal of useful teratogenic information can be collected. Although it may be ideal to have human data as a means of assessing fetal risk, animal data has proven to be very useful in predicting human risk. In fact, all drugs found to be teratogenic in humans have shown similar effects in animal populations, except for the drug misoprostol (73).

Despite the strong concordance between animal and human models when predicting teratogenic effects, it appears as though a number of drugs lack animal study data. Such a deduction is made as a result of the finding that the great majority of drugs are placed in Category C – a category used for drugs that have been shown to have negative effects upon animal models, or which have not been tested on animals. Although it is difficult to determine what proportion of drugs actually lack animal study data, it seems appropriate to assume that further animal studies need to be conducted.

A brief review of Canadian health policy suggests that there is no overarching requirement for testing on pregnant animal models prior to human clinical trial initiation, nor drug approval. It appears as though animal reproductive toxicity studies can be included in applications, but are not always required. The main documents referred to by Health Canada are the Canadian *Food and Drug Act* (and complementary regulations) and the International Conference on Harmonisation (ICH) *Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines* (87;88). Section C05.005e of the Canadian Food and Drug Regulations requires *disclosure* of animal testing results if tests have been conducted, however, it does not require *testing* on pregnant animals. This is consistent with the ICH document *Good Clinical Practice: Consolidated Guidelines E6* (GCP E6), which Health Canada endorses (89). The GCP E6 states that the information provided to the government for approval *may* include animal study information. Although section E6-7.3.5e of this document describes in detail how to conduct reproductive toxicity studies on animal models, it does not *require* such information for all products, stating that the information "should be described… when appropriate"(89). Considering that reproductive toxicity studies on animals can be fairly predictive of reproductive toxicity in humans, it may be useful to amend the Canadian Food and Drug Regulations or the ICH guidelines. Policy-makers should consider instituting a requirement that all new drug approval or clinical trial approval applications include information concerning reproductive toxicity in animal models and that drugs that are already on the market be reassessed in pregnant animal models if such information is lacking.

3.63 Teratology information services

The same resources used to inform women as to drug teratogenicity can be used to collect information. When pregnant women using medications voluntarily call information services for risk assessment counseling, exposure data could be recorded, and follow-up on the outcome of the pregnancy could easily be undertaken (73). Once such information is collected, it can be used in various retrospective epidemiological studies. Koren and colleagues suggest that the collaboration of various international teratology information systems could yield samples large enough to detect rare events (73).

In Canada, the most renowned information system is the Motherisk Program, located in Toronto, Ontario. As suggested by Koren and colleagues, this information system uses its counseling services as a means of also collecting teratology data – by inviting the pregnant women to take part in relevant studies conducted through the Motherisk research group. The Motherisk Program deserves a great deal of credit for its provision of accessible, evidence-based, counseling to pregnant women, and dedicated contribution to a greater research goal. However, despite such local achievements, there remains room for improvement – as an international method of pooling teratology data is yet to be established.

3.64 Clinical surveillance

A number of researchers suggest that information concerning human abortuses, and the woman's health state prior to the abortion, be systematically collected and studied as a means of providing clinical surveillance (77). If such a surveillance system included

both spontaneous and therapeutic abortuses, a large proportion of birth defects would likely be detected, ideally resulting in the recognition of defect clusters. It is hoped that such a surveillance system would also be rich enough to link the woman's medication use during pregnancy with the particular malformation, or else that detection of a defect cluster would prompt a comprehensive review of the woman's medication use during pregnancy. Although a comprehensive national abortuses surveillance system would likely be highly advantageous, the creation of such a system would be labour-intensive and require a great deal of sensitivity to the possibly emotionally upset women connected to the aborted fetuses.

In Canada, the Canadian Congenital Anomalies Surveillance System (CCASS) collects congenital anomaly data from medical records of therapeutic abortions conducted in hospitals. Although this surveillance system is certainly a good first step, the scope of collected information is extremely limited as it does not collect information regarding the woman's medication use, nor information from spontaneous abortions (90). Ideally, the CCASS would be amended to include the linked collection of data concerning the woman's medical history and health of the aborted fetus.

Another similar means of gaining teratogenicity information is through the development of national birth defect registries. It is estimated that, had the Swedish birth defect registry been operative in 1960, the teratogenicity of thalidomide could have been detected five months after the first malformed baby was born (77). Despite the current operation of such registries in many countries (including Canada), few teratogenic drugs have been identified through these registries. Also, it has been suggested that the time lag and effort required to collect such data is too great for practical application (77). Such

findings suggest that greater research into the functioning of current birth defect registries and identification of possible weaknesses may be of great value.

3.65 Epidemiological studies

3.651 Case reports

A case report is a detailed description of an individual patient, and when included in a scientific journal, can provide an important educational service by bringing unusual or rare conditions to the attention of other clinicians (91). Within the context of teratogen research, case reports can be very useful if very few pregnant women use an intervention, or if the malformations potentially caused by an intervention are very rare (73). If either of these factors are satisfied, a very strong association can be made by very few case reports. Warfarin, diethylstilbestrol and isotretinoin are examples of teratogenic drugs that satisfy one of these two factors, and hence, were successfully detected by case reports (73).

Although a number of teratogenic drugs have been detected through case reporting, great caution must be taken when interpreting case reports. If the medication is taken by many pregnant women (i.e. Benedectin), a small number of case reports of fetal malformations may simply reflect the incidence of spontaneous malformations (1-5%) found in the general population (73). Because of this, case reports cannot be used to prove a causal association, and instead should be viewed as a means of calling attention to unusual findings, and stimulating further scientific investigation (92).

3.652 Case series

Like case reporting, a case series analyses is also a descriptive epidemiological study, yet describes the characteristics of a group or cluster of individuals rather than individual cases (91). This type of study design is often used when trying to understand the physiological changes that occur during pregnancy, or how pregnancy influences a particular disease-state. When such studies are conducted, the 'disease' can be thought to be pregnancy, or else a disease encountered during pregnancy. An example of such a study was conducted by Ostensen and colleagues, on pregnant women with rheumatoid arthritis and ankylosing spondylitis (93). For this study, ten patients with rheumatoid arthritis and nine with ankylosing spondylitis were examined, and blood/urine sampling was performed before conception, at each trimester, and various weeks post partum. This investigation can be considered to be a case series study because no intervention was administered, participants were observed on an individual basis and the sample size was relatively small. Although case series studies can provide a rich data set, the small sample size, lack of controls and lack of researcher-administered intervention means that it is impossible to draw significant conclusions from this type of study alone.

3.653 Cohort studies

One of the most common epidemiological studies undertaken to determine a drug's teratogenicity is the cohort study. For this study design, subjects are classified according to exposure status at the time the cohort existed, and followed to present (retrospective study), or followed into the future (prospective study), so as to determine if the rate of development of the study disease is significantly different in the exposed and

unexposed groups (91). The data collected for such a study yields a relative risk – "the rate of occurrence of the outcome in the exposed population divided by the rate in the unexposed population" (92). A relative risk of greater than 1.0 means that the exposure is related to the outcome, while a value of less than 1.0 suggests that the exposure protects against the outcome (92). When determining teratogenicity, researchers aim to conclude whether mothers who took a particular drug during pregnancy have a larger number of malformed children than mothers who did not (73).

Although this type of study may be rather appealing, there are a number of practical challenges faced when conducting a cohort study with a pregnant population. One such challenge is recruiting a large enough study population. Scialli suggests that even if a particular drug was to increase the incidence of a particular abnormality by ten-fold, hundreds of women would be required to display a significant difference between the exposed and unexposed groups (92). Another challenge can be selecting a biologically and demographically comparable control group. Depending upon the particular exposure, researchers may have to find controls with similar disease-states, habits (i.e. smoking) and diets (92).

3.654 Case-control studies

Another common epidemiological study undertaken to determine a drug's teratogenicity is the case-control study (73). In this type of study, subjects are selected according to outcome status before exposure status is determined (91). When studying teratogenicity, researchers would typically deduce whether mothers of children with a specific malformation took a drug more often than mothers of children without the

malformation (73). The results of such a study would be expressed as an odds ratio. The odds ratio is the quotient of the ratio of the exposed and unexposed in the case group and the control group (91). The larger this value, the higher the odds are of exposure among the cases versus exposure among the controls.

One significant difficulty encountered by this study design (and to a degree, found in all retrospective study designs) is recall bias. Various studies indicate partial memory and bias in the way women remember the medications they took during pregnancy (73). In particular, a woman who has given birth to a malformed child may be more likely to remember her actions and medication use during the course of her pregnancy as a means of understanding what went wrong, when compared to a woman who has given birth to a healthy child (73). Such differential recall creates a bias, therefore leading to false positive associations. One means of reducing recall bias is to review medical or pharmacy records, so as to confirm reported exposures (92). Yet, if recall bias cannot be eliminated from the case group, Koren and colleagues suggest that the control group be composed of women who have also given birth to children with a malformation – yet different from that of the case group (73).

3.655 Randomized controlled trials

Inherent to all retrospective studies is an inability by the researcher to fully control exposure conditions. Specifically, the researcher is unable to randomly assign treatment/exposure to research subjects as a means of reducing confounding variables. Such confounders include: “nutritional and health status; maternal age, use of alcohol, tobacco, or illicit drugs; environmental toxins; history of miscarriages and stillbirths;

genetic history; use of multiple drugs including nonprescription drugs; gestational age at time of drug exposure; compliance; total dose…" (78). Such confounding variables can be virtually eliminated by a well-designed, randomized controlled trial (RCT) (91).

A RCT is one of the most commonly-used, comprehensive, prospective study designs and is designed to test the efficacy of an intervention on a group of volunteers. Specifically, it involves the random allocation of subjects into experimental and control groups for comparison purposes (91).

When pharmaceutical products are being developed, the most widely used study design is the RCT. As a means of expressing what stage of development a particular intervention is at, researchers and industry tend to use a 'phase categorization'. Drugs intended for commercial sale must proceed through Phase I, II and III clinical trials, and often continue on to Phase IV trials once placed on the market. A description of the purpose of each phase is presented by Health Canada as follows:

Phase I trials: Initial safety studies on a new drug, including first administration of the drugs into humans, usually conducted in healthy volunteers.
Phase II trials: Clinical trials to evaluate the efficacy of the drug in patients with medical conditions to be treated, diagnosed or prevented and to determine the side effects and risks associated with the drug.
Phase III trials: Controlled or uncontrolled trials conducted after preliminary evidence suggesting efficacy of the drug has been demonstrated.
Phase IV trials: All studies performed after the drug has been authorized by the regulator for the market, and related to the authorized indication.

Table 3: Classification of clinical trials (94).

When considering RCTs in relation to pregnancy, two general study categories can be discussed – pregnancy-related studies and non-pregnancy related studies.

3.655a Pregnancy-related studies

A brief literature review suggests that the majority of RCTs that include pregnant women are focused upon pregnancy-related topics. As a result, the majority of such pregnancy-related studies exclusively include pregnant (or recently pregnant) women. Although there are a great variety of pregnancy-related studies, the majority of such studies use one of two types of interventions – pregnancy-focused interventions or disease-focused interventions (adjusted for the pregnant physiology).

A pregnancy-focused intervention would be an intervention intended to improve any number of variables during pregnancy. These variables include: infant birth weight, infant morbidity, infant mortality, placental proliferation, gestational length, delivery complications and pregnancy 'side effects'. An example of such a RCT was that conducted by Klingler and colleagues, investigating the use of docosahexaenoic acid and folic acid upon placental apoptosis and proliferation (95).

A disease-focused intervention would be an intervention intended to improve treatment of a disease or condition that affects the general population yet can also occur during pregnancy. Such studies are important because they can help deduce whether a particular intervention is as effective in the pregnant population as in the general population, and also may lead to greater reproductive toxicity data. Possible diseases include, but are not limited to: diabetes, malaria, HIV/AIDS, arthritis, cancer and depression. An example of such a RCT was that conducted by Dombrowski and

colleagues, investigating the use of inhaled beclomethasone dipropionate versus theophylline to treat asthma during pregnancy (96).

A brief review of the literature suggests that the majority of disease-focused pregnancy studies use therapeutics that have received government approval for use in the general population. Therefore, the therapy has successfully undergone Phase I to III testing and is considered safe and effective for use in the general population. For example, Silverman and colleagues conducted a randomized controlled study of pregnant patients with asthma, using the approved drug budesonide (97). The existence of such studies suggests that health care professionals involved in research feel comfortable exposing pregnant women to at least some therapeutics considered to be safe for the general population. This situation is noteworthy because it contrasts the general trepidation displayed by healthcare professionals when asked to prescribe medications to their pregnant patients (outside of the research context). This seeming contradiction suggests that perhaps healthcare professionals are more comfortable prescribing medications to pregnant women within a peer-reviewed research setting, as opposed to the individual patient-physician setting. While there appears to be an acceptance of the use of approved drugs within a pregnant research population, it should be noted that, despite approval by Health Canada, such drugs have often undergone minimal reproductive toxicity testing. Of the data that do exist, the majority come from animal studies or retrospective epidemiological studies – the latter of which can often be frought with confounders and biases. Due to this lack of teratology data for many *approved* medications, healthcare professionals should be equally cautious when prescribing medications to pregnant women in research studies and outside of the research context.

Although this line of reasoning may appear logical, further research and discussion would be required to substantiate such deductions and suggestions. In particular, it may be useful to focus on studies of a particular ailment (i.e. asthma) and compare the different medications used (i.e. approved/unapproved for the general population) and whether pregnant women were included.

3.655b Non-pregnancy related studies

Unlike pregnancy-related studies, non-pregnancy related studies often investigate interventions intended for the general population's benefit (i.e. the effectiveness of Docetaxel for treating lung cancer). As a result, the research population is often intended to reflect the general population[2]. Because the target of such studies is the general population, there exist many non-pregnancy related studies. Yet, due to concerns regarding fetal harm, the great majority of these studies exclude pregnant women[3]. Although such an approach may protect researchers from possible liability (and fetuses from potential harms), it also means that pregnant women are not given the choice as to whether or not to enroll in possibly highly effective, innovative studies. For life-threatening diseases (i.e. cancer, AIDS…), where new therapeutic methods are continuously being developed, the desire to enroll may be particularly strong, and justified.

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[2] Because many women in our actual 'general population' are pregnant, it follows that there should also be pregnant women in the reflective 'research population' (*unless the target of the intervention is not the general population).

[3] It should be noted that, while many researchers aim to exclude pregnant women from their research, pregnant women are sometimes inadvertently included in research populations. This situation occurs when nonpregnant women (using contraceptive methods) are included in research, yet become pregnant due to failed contraceptive practices. As a result, fetuses can be exposed to potentially harmful interventions prior to knowledge of the pregnancy (73). Although such situations should be avoided, these unplanned pregnancies do often yield useful data concerning the effects of a particular intervention upon early fetal development.

Going against the trend, some researchers choose to include pregnant women in their study population – likely due to the realization that pregnant women are indeed members of the general population. An example of such a study was that conducted by Silverman and colleagues, investigating the use of budesonide to treat asthma in the general population (97). Unlike most general population trials, pregnant women were not excluded (unless they were U.S. residents). Because the researchers in many of the countries decided to include pregnant women, data from 313 pregnant women were analyzed (out of a sample of 7241 patients).

Studies that include pregnant women as part of the general population sample are often viewed as controversial because many such studies are seen as 'experimental', therefore suggesting that safety and efficacy are not well-established[4]. However, in reality, the majority of studies appear to be at the Phase III testing stage or even further progressed. Once a therapy has progressed to Phase III, a fairly high level of safety and efficacy for the general population has been established. However, despite this accumulation of safety information related to the general population, there is indeed minimal information concerning possible harms to the mother and fetus.

While such lack of information is concerning, it should also be noted, as alluded to earlier, that if research studies were only allowed following federal drug approval, minimal *additional* information concerning fetal harm would be known since the Canadian government does not require the presentation of data from pregnant animal models as a condition of drug approval. Therefore, when one wishes to judge safety

[4]Use of the term 'experimental', and its implicit association with a lack of safety and efficacy data, highlights the power of various term choices when presenting scientific information. In particular, the terms 'research', 'study' and 'experiment' are often used interchangeably in academic and popular media publications – yet, for many readers hold very different meanings.

based on animal data, it appears just as safe to include pregnant women in Phase I to III studies, as it is to include them in post-marketing studies. However, where the difference lies is in the amount of incidental human data – information gleaned from unplanned pregnancies within the general research population. It is also hoped that as a drug passes through the various Phases, researchers gain a better understanding of the mechanism of action of the drug and therefore are able to provide a more accurate hypothesis of possible risks to pregnant women.

Therefore, as a means of collecting as much relevant information as possible prior to enrolling pregnant women in studies, it would likely be of great benefit if the Canadian government required testing on pregnant animal models prior to Phase I initiation, and the completion of Phase II studies within the general population before including pregnant women in any type of study. To ensure the greatest amount of safety information possible, while also maintaining access to clinical research for pregnant women, it seems most reasonable to only allow pregnant women in Phase III general population trials, or Phase II or III special subpopulation trials (the subpopulation being the pregnant population) – both of which would follow the completion of Phase II trials within the general population.

If pregnant women are to be included in general population studies, one of the greatest challenges is ensuring that such studies are scientifically justifiable. As discussed by Weijer & Crouch, one must consider how many subjects from a particular subgroup must be included in a study to provide a sound basis for the treatment's generalizability to clinical practice (71). Researchers must therefore decide whether to include a sample

of subgroup members that is proportional to that found in the target population, or else a disproportionate sample, yet which allows a powerful subgroup analyses.

Weijer & Crouch conclude that if there is strong evidence that a "different response to treatment is likely in differing groups, then the trial must be designed to demonstrate efficacy separately in each of the relevant groups" (71). However, if there does not exist strong evidence that the subgroup would produce a different response to treatment, the study population should mirror the target population and post hoc subgroup studies should only be initiated if a subgroup responds significantly differently to treatment (71).

In the case of the pregnant population, it can be argued that the distinct pregnant physiology might produce a unique response to treatment, thus suggesting the need for subgroup analyses. To substantiate this hypothesis, evidence from case studies or basic science research could be cited. If researchers are to follow such reasoning, they would therefore be required to enroll enough pregnant participants to have the ability to demonstrate significant differences between case and control subjects. However, if a study proposes a novel intervention and there is not strong evidence that pregnancy would affect treatment outcome, it appears scientifically and ethically justifiable to simply create a study population that mirrors the target population. In such a case, a researcher would be required to enroll far fewer pregnant participants.

Due to the great variability in study questions and our limited knowledge of pharmacokinetics during pregnancy, it is difficult to suggest overarching policies for when and how pregnant research subgroup populations should be created. However, applicable to all clinical researchers should be a requirement that pregnant women be

included in clinical research (i.e. Phase II subgroup analysis, Phase III subgroup analysis or Phase III general population), or else, clear written justification if such inclusion is not undertaken. As a means of reducing the stress and complexity of such a major decision-making process, guidance materials should be developed by a team of researchers, community representatives and government personnel to be distributed to research coordinators.

3.7 Conclusion

As pregnant women continue to take medications during pregnancy, it is important that clinicians provide accurate information so as to protect the health of the pregnant woman and her future child. This information ranges from how the pregnant physiology reacts uniquely to therapeutic interventions, to whether the intervention is teratogenic. To provide such information, the majority of physicians rely upon a relatively small number of retrospective clinical studies or else compilations of data – such as the flawed FDA Use-in-pregnancy categories. Although these sources can provide a degree of guidance, it is clear that further information is required. Such information can be collected by the revised use of established methods of data collection, and through the development and promotion of new means of data collection.

One such established means of data collection is through testing on pregnant animal models. Although the concordance between animal and human fetal toxicity has been well-established, there remains a lack of government policy requiring testing on pregnant animals prior to clinical trial approval. Another important means of collecting

teratogenic information is through teratology information services – such as Canada's Motherrisk Program. While this Canadian example appears well-supported and effective, it is important that such support continues, and that efforts are made by such programs to share information with other local programs. In addition to such established means of information collection, a number of new programs should also be pursued. In particular, Health Canada should pursue the comprehensive collection of data concerning aborted fetuses, and relevant health, pregnancy and demographic information of the corresponding women.

In addition to animal testing and the use of teratology information services, there are a number of established epidemiological means of collecting information related to the effects of medication upon the pregnant woman and developing fetus. In particular, case reporting, case series studies, cohort studies and case-control studies can be used as a means of collecting information, or detecting possible negative outcomes. While such studies should be pursued and promoted, one must approach the results of such studies with great caution, as they can lack validity due to: small sample size, confounding variables and bias.

Unlike the aforementioned epidemiological studies, RCTs allow a great deal of control over the research setting, and therefore can produce relevant, valid results. Although a number of pregnancy-related and non-pregnancy-related RCTs have been pursued, there remain relatively few such studies. As a means of promoting the creation of such studies, greater guidance material should be provided to researchers concerning which Phase pregnant women should be included, what data are required before allowing

such entrance, the proportion of women required in such studies, and how statistical analysis should be undertaken.

A review of current clinical practice and the various means of collecting pregnancy information suggest a need for greater information concerning the effects of medication upon the pregnant woman and her fetus. Fortunately, there are many pre-established and novel means by which such information can be collected. However, what is lacking is institutional guidance and encouragement for such research – by means of relevant, effective policy. The following chapter will discuss current international and national policy and propose changes to current policy practice.

Chapter 4: Canadian health policy related to the exclusion of pregnant women in clinical research

4.1 Introduction

A number of specific international and local policies direct and restrict the conduct of clinical research in Canada. Whereas preceding chapters have discussed the legal, ethical and clinical implications of including or excluding pregnant women in research, the purpose of this chapter will be to present and assess the overarching policies that incorporate such ethical thought and dictate the practical conduct of clinical research. The work accomplished in this chapter is important because, not only does it provide a thorough review of current policy, it also suggests novel, improved policy, which could be adopted within the Canadian context.

4.2 Policy concerning inclusion of women in clinical research

A review of current United States and Canadian health policy – such as that produced by the NIH, FDA and Health Canada – suggests that researchers are required to include women in clinical studies and perform a gendered analysis when appropriate (1;71). At a greater jurisdiction than such national policies exists international policy, such as that created by the International Conference on Harmonization (ICH). This international group was created in 1990 for the purpose of harmonizing regulations concerning the approval and authorization of new medicinal products (98). Current policy produced by the ICH requires that the study population of later-phase studies reflect the

target population, therefore implying that if a therapeutic intervention is intended for use in the female population, it should be tested on women:

> The variability of groups of patients or healthy volunteers studied in early trials may be limited to a narrow range by strict selection criteria, but as drug development proceeds, the populations tested should be broadened to reflect the target population (Section E8. 3.2.2.1) (99).

Further indication that the ICH expects that women be considered part of the general population, and therefore included in studies, comes from a review of Section E8 3.1.4.3. This section lists the various groups that should be considered separately from the general population – women are not on this list. In addition to such policy positions, empirical research, such as that highlighted in chapter 1, suggest that women are currently being adequately represented in clinical studies (2;100). Although health policy may now encourage the inclusion of women in clinical studies, there is a diversity of policy positions regarding the inclusion of pregnant women.

4.3 Policy concerning the inclusion of pregnant women in clinical research

When discussing health policy related to the inclusion of pregnant women in clinical research, it is useful to first consider towards which groups such policy is geared, and for what purpose such policies are created. In Canada, there are two main groups of researchers to which such pregnancy-related policies are targeted – private researchers (working through for-profit, private institutions) and publicly funded researchers (working through publicly-funded institutions). When developing new drugs, or conducting post-marketing research, private researchers must comply with the various governmental research policies that correspond with the country in which they conduct

their research, as well as the local policies imposed upon them by the institute at which they conduct their research. Like the private researchers, public researchers must also comply with national and local policies. In addition, they are also required to comply with the policies created by their respective funding agencies – such as Canadian Institutes of Health Research (CIHR), Social Sciences and Humanities Research Council (SSHRC), Natural Sciences and Engineering Research Council (NSERC), Genome Canada and Fonds de la recherche en santé Québec (FRSQ). Although the private and public research groups have distinct motivations and characteristics, there is often much practical crossover between the two groups since many public researchers choose to be involved in pharmaceutical research in addition to their own research.

4.31 International Policy

Above various national, provincial and institutional policies, there exists international policy, applicable to all clinical health researchers conducting research in countries that adhere to such policies. One of the most current, well-recognized policies is that produced by the International Conference on Harmonization (ICH). This document is important to the Canadian health research context because Health Canada has adopted many sections of the ICH policy, one of the most prominent sections being *E6: Good Clinical Practice* (89).

As noted above, the ICH requires that as a study proceeds, the research population reflect the target population (99). This requirement implies that if pregnant women are

part of the target population for the particular intervention they should be included in the research population.

In addition to the requirement that the study population reflect the target population, the ICH also outlines three special populations which require unique consideration: pregnant women, nursing women and children. This special population section is found in document E8 of the ICH guidelines, and has been adopted by Health Canada. Regarding pregnant women, the ICH requires that this special population be excluded from clinical trials, unless the trial is for a drug used during pregnancy. Section E8 3.1.4.3a reads as follows:

> In general, pregnant women should be excluded from clinical trials where the drug is not intended for use during pregnancy. If a patient becomes pregnant during administration of the drug, treatment should generally be discontinued if this can be done safely. Follow-up evaluation of the pregnancy, foetus, and child is very important. Similarly, for clinical trials that include pregnant women because the medicinal product is intended for use during pregnancy, follow-up of the pregnancy, foetus, and child is very important (Section E8. 3.1.4.3a) (101).

Further detail regarding the inclusion of pregnant women in clinical research is outlined in section M3 of the ICH guidelines, which requires that reproductive toxicity, genotoxicity and retrospective data be collected prior to trial initiation:

> Prior to the inclusion of pregnant women in clinical trials, all the reproduction toxicity studies and the standard battery of genotoxicity tests should be conducted. In addition, safety data from previous human exposure are generally needed (Section M3 9.4) (102).

Thus, the ICH seems to view the inclusion of pregnant women in pregnancy-related studies as acceptable as long as great care and comprehensive study is included prior to and following inclusion. However, there remains a degree of ambiguity concerning what

types of clinical studies pregnant women should be included in, and what amount of data must be presented before pregnant women are included. In particular, it is unclear whether a "drug [that is] intended for use during pregnancy" is a pregnancy-specific drug, or is any drug used by the general population and possibly also used by the pregnant population (i.e., a drug used to treat depression) (101). As a means of avoiding misinterpretation, it would be of great benefit if the ICH added greater detail to their guidelines. Although there does exist ambiguity in the ICH guidelines, these documents remain the most internationally-recognized form of research guidance and provide a useful foundation upon which various national policies have been created.

4.32 United States National Policy

One of the most influential national policies concerning the inclusion of pregnant women in research comes from the United States. This policy is useful not only because it is well-written and comprehensive, but also because it is intended for a research context relatively similar to that found in Canada.

The particular policy of interest is that included in the U.S. Code of Federal Regulations (CFR). 45 CFR 46 was updated by the United States government in 2001, and allows for the inclusion of pregnant women in research as long as a number of conditions are met (103). To include pregnant women in research, this policy requires: prior animal and human studies; direct benefit to the woman or fetus, or else, minimal risk; informed consent; and no undue influence or conflict-of-interest. The following is an excerpt from CFR 46:

§ 46.204 Research involving pregnant women or fetuses.
Pregnant women or fetuses may be involved in research if all of the following conditions are met:
(a) Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;
(b) The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;
(c) Any risk is the least possible for achieving the objectives of the research;
(d) If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions of subpart A of this part;
(e) If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A of this part, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.
(f) Each individual providing consent under paragraph (d) or (e) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
(g) For children as defined in §46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of subpart D of this part;
(h) No inducements, monetary or otherwise, will be offered to terminate a pregnancy;
(i) Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and
(j) Individuals engaged in the research will have no part in determining the viability of a neonate (104).

What makes this policy particularly strong is that it provides detailed direction, while also incorporating rich, progressive, scientific (e.g. requirement for testing on

pregnant animal models) and ethics reasoning (e.g. comprehensive direction regarding risk/benefit analysis and autonomous informed consent). Unlike many other policies, this document advocates for the inclusion of pregnant women in research – as long as various conditions are met. Due to these strengths, the 45 CFR 46.204 will later be used as a framework for the proposed Canadian policy.

4.33 Canadian National Policy

In Canada, there exist a number of policies created to provide direction to researchers when developing and conducting clinical research[5]. Within these documents there is often reference made to the expected inclusion of women in research, and sometimes even specific reference to pregnant women.

Health Canada, and other complementary government agencies, are responsible for the creation and enforcement of the broad policies applicable to both public and private drug and health device research involving human subjects. Before conducting clinical trials on human subjects, all researchers must receive clinical trial authorization. To receive such authorization, the Therapeutic Products Directorate (TPD) of Health Canada has outlined a number of policies and regulations to which researchers must comply. The international policies adopted by the TPD are the ICH's *E6: Good Clinical Practice* (adopted by Health Canada under the title: *ICH Guidance E6: Good Clinical Practice: Consolidated Guideline*) and the World Medical Association's *Declaration of Helsinki* – both of which require various research standards, yet do not specifically

[5] It should be noted that there also exists national and provincial jurisprudence concerning research standards and requirements. In Canada, such law supersedes, and often heavily influences, national and provincial policies.

discuss the role of pregnant women in research[6] (89;105). The two national documents that must be adhered to are the *Food and Drugs Act and Regulations* and the *Therapeutic Products Regulations* – both of which require detailed standards, yet do not address the role of the pregnant population in clinical research (87;106). In addition to such large policy documents, there is also a wide range of isolated guidelines and regulations available on the Health Canada website and through the national parliamentary newspaper (the *Canada Gazette Part I & II*) – all of which must be respected by researchers (107).

One such isolated national policy is that found in the *Therapeutic Products Programme Guidelines,* entitled: *Inclusion of Women in Clinical Trials* (33). Not only is this document useful because it discusses the role of pregnant women in research, but it is also written in a very comprehensive, accessible manner. In particular, the document includes an insightful statement of purpose, as it acknowledges the need to recognize and study the various physiological changes that occur during a woman's life:

> … Since physiological changes and hormonal levels during child-bearing years and menopause, as well as the use of oral contraceptives or hormone replacement therapy, may affect the efficacy and safety of a drug, the influence of these parameters should be studied during drug development (33).

Further in the document is a section entitled 'Definition of the Population' in which a direct reference is made to the pregnant population:

> A decision to enroll pregnant or lactating women in a specific trial must be individualized and based on a careful risk/benefit assessment taking into consideration the nature and severity of the disease, the availability and results of preclinical animal data, the availability and risks associated with

[6] Although the TPD refers to many of the ICH documents on their website (i.e. section E8, etc.) the TPD does not appear to *require* compliance with these ICH documents as a component of their clinical trials approval process.

> alternative therapy, the stage of pregnancy and the potential for harm to the fetus or infant (33).

This document is important because it displays a clear willingness by Health Canada to include pregnant women in trials, so long as various factors are taken into consideration, such as: severity of disease, animal data, alternative therapies and pregnancy stage. What makes the document particularly unique is that, not only does it consider possible risks to the fetus, it also implicitly acknowledges the possible individual benefits accorded to the pregnant woman.

4.34 Institutional Policy

In addition to the overarching government policies and guidelines, researchers must abide by various institutional guidelines. For example, researchers working for private pharmaceutical companies in Canada are not only required to follow Health Canada policies, but must also adhere to the specific policies and guidelines created by their particular institution.

Similarly, publicly-funded researchers must abide by both national policies and institutional policies. These institutional polices include those dictated by the researcher's funding agency, as well as those dictated by their physical place of research (i.e. university, hospital, public research institute). The latter set of policies will not be discussed in this paper because of the diversity of such policy and hence the inability to draw cohesive, meaningful conclusions regarding such policy.

In Canada, the three main research funding agencies - the Canadian Institutes of Health Research (CIHR), Natural Science and Engineering Research Council (NSERC)

and Social Sciences and Humanities Research Council (SSHRC) have their own agency-specific policies, and also share a number of comprehensive, tri-agency policies. The policy most relevant to the topic at hand was created in 1998 (with minor amendments since) and is entitled: *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (TCPS) (41). The TCPS sets out ethical norms and requirements for conducting research involving human subjects and provides guidance for the conduct of research ethics boards that oversee researchers receiving funding from one of the tri-councils. Despite its origin within the three main publicly-funded research agencies, the reach of the TCPS extends to most academic and clinical researchers, and also some private research. This extension in application is because section i.1 of the TCPS requires that every institute receiving Tri-Council funding must ensure that all of its researchers comply with the TCPS (108). For instance, if a hospital houses *any* researchers funded by one of the Tri-Councils, *all* researchers (both private and public) at the hospital must comply with the TCPS. Therefore, if privately-funded (e.g. pharmaceutical) research is conducted in a pubic hospital/institution that receives tri-council funds, then this research must comply with the TCPS (108).

The TCPS includes guidance regarding the inclusion of pregnant women in research. The main message being that pregnant women can be included in research, yet that research ethics boards should first evaluate whether the benefits to the woman and fetus outweigh the potential harms. This is described in Article 5.2 and its explanatory text:

> Article 5.2: Women shall not automatically be excluded from research solely on the basis of sex or reproductive capacity. [bolded in original document]

> Like Article 5.1, Article 5.2 imposes obligations of equitable treatment of potential subjects on REBs and researchers. While some research is properly focused on particular populations that do not include women or only include very few women, in most studies women should be represented.
>
> The Article is also clear about presumptive or automatic exclusion from research on the basis of sex or reproductive capacity. If in the past many women have been automatically excluded from research on such grounds, Article 5.2 rejects such an approach as a discriminating and unethical use of inclusion or exclusion criteria. Rather, in considering research on pregnant women, researchers and REBs must take into account potential harms and benefits for the pregnant woman and her embryo, foetus or infant. The ethical duty to assess the harms and benefits of research thus extends to the special case of research involving pregnant or breast-feeding women (41).

4.4 Comment upon current policy

A review of international, national and institutional policy relating to the inclusion of pregnant women in research suggests that attention is being paid to this important issue and that governing bodies are open to the inclusion of pregnant women in research. However, despite the useful policies that exist, there remain various weaknesses and inadequacies. In particular, as discussed earlier, the ICH guidelines lack specificity regarding what type of research pregnant women can be included in and what type of prior findings would prevent study on the pregnant population from proceeding.

In contrast to the international policy, the national guideline entitled *Inclusion of Women in Clinical Trials* takes a more inclusive stance and highlights the need for a risk/benefit assessment. This position, and the various suggested considerations, are innovative, yet would likely be of greater practical use if detail was added to each consideration and if more considerations were generated.

Much like the *Inclusion of Women in Clinical Trials* policy, the TCPS also displays a willingness to include pregnant women in research, and emphasizes the need to balance harms and benefits. Yet, unlike the Health Canada policy, the TCPS policy has an even greater lack of detail and concrete guidance for researchers and research ethics boards.

It is clear that improvements could be made to the international, national and institutional policies used by Canadian researchers. In general, these policies are flawed because they lack comprehensive and accessible guidance for the researchers and research ethics boards at which they are aimed. Although many changes could be made at various policy-making levels, it is likely that the most ideal and productive policy changes would come at the national level – as such policy would be applicable to all researchers conducting clinical research in Canada, regardless of institute, funding source or province. The following section will outline the possible elements of a new national policy suitable for the Canadian clinical research context.

4.5 Proposed policy

Although current Canadian policy is fragmented and lacks much detail and practical guidance, the existence of such policies demonstrates a positive first step, as they highlight a willingness to include pregnant women in clinical research. For this reason, the proposed policy will incorporate much of the information found in current American and Canadian policy. However, before a national policy can be created, it must first be decided whether, and under what circumstances, pregnant women should be included in clinical research.

4.51 Policy statement

As argued in earlier chapters, it is the position of this author that pregnant women should, under certain circumstances, be included in clinical research. To respect pregnant women's autonomy and uphold the principle of distributive justice, it is necessary that we create inclusive policy documents. However, included in this stance is the recognition of the fetus as an entity perhaps deserving of consideration as a research subject. Previous chapters have outlined that in Canada the fetus does not have legal status before birth and likely can only be accorded moral status from 23-26 weeks gestation onwards. Moreover, scientific literature indicates that the greatest teratogenic effects occur during differentiation (3-8 weeks gestation), while the fetus becomes progressively less susceptible to teratogenic stimuli following the 8 week time point.

A review of relevant ethics and medical literature suggests that it may be useful to set fetal inclusion or exclusion restrictions based upon gestational age. To err on the side of caution and avoid possible harms to the differentiating (3-8 weeks) or viable (23rd week onwards) fetus, it seems most logical to only allow clinical research (not intended for the direct benefit of the fetus) between the beginning of the 9th week of gestation and the end of the 22nd week[7].

Based on the aforementioned ethical and scientific reasoning, it seems reasonable that the proposed policy begin as follows:

[7] Note that this stance is also consistent with the *Inclusion of Women in Clinical Trials* policy, which requires consideration of "the stage of pregnancy" when deciding whether to include pregnant subjects (33).

Inclusion of pregnant women in clinical research
1. A pregnant woman may be included in clinical trials research between the beginning of the 9th week of gestation and the end of the 22nd week of gestation, as long as the following conditions are met:

4.52 Preclinical study

As outlined in chapter 3, animal studies can predict with a great deal of accuracy whether a drug will be teratogenic to humans. Therefore, it is important that researchers collect and present previous animal and human findings to Health Canada before beginning research in the pregnant population. This requirement is seen throughout current policy documents: CFR 46.204a, ICH M3 (requirement for "reproduction toxicity studies"), and the *Inclusion of Women in Clinical Trials* (consideration of the "results of preclinical animal data"). So as to avoid ambiguity, the term 'minimal harm' has been replaced with a phrase describing the specific harms. This specification was adapted from policy suggestions by McCullough *et al.* (37). The new Canadian policy should therefore include the following condition:

a) Statistically valid preclinical studies on non-pregnant humans (phase I and II studies) and pregnant animals have been conducted, and the results indicate no documented death or documented serious, far-reaching, and irreversible injury to the fetus or pregnant woman due to the intervention.

4.53 Prospect of benefit

Although both the national and institutional Canadian policies refer to risks and benefits, the U.S. policy is the only one that details what types of benefits must exist. This detail is important because it provides extra guidance and support to research ethics

boards when trying to evaluate study designs. A modified version of the CFR 46.204 has therefore been included in the proposed Canadian policy:

> b) Interventions or procedures hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means.

Despite the utility of this section, it includes a somewhat ambiguous, yet seemingly unavoidable, phrase: "risk to the fetus is not greater than minimal". This ambiguous phrase is interesting because it highlights a common challenge faced in both law and ethics – quantifying and defining risk[8]. Although this phrase may produce uncertainty for researchers and research ethics boards, it has been included in the section because it provides flexibility to the policy and is intended to emphasize the benefits of a casuistic analysis.

In addition to challenges encountered when evaluating risk, the statement "prospect of benefit" also requires special consideration. This statement is challenging because it implies that there should be a possibility of benefit – when in reality clinical research often begins with very little evidence that an intervention will be beneficial. Although such uncertainty is necessary (if clinical equipoise is to be upheld), one can still require evidence of the possibility/prospect of benefit. To ensure the prospect of benefit, the proposed research study should ideally be similar to previous successful research studies (perhaps changing one variable) or established interventions. However, in the

[8] It should be noted that the most prominent document defining minimal risk is the United States' 45 CFR 46.102(i), which defines minimal risk as "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life" (109). Although it is difficult to directly apply the contents of this document to the fetus (as the fetus' "daily life risks" are very different from those of the general population) this document can be a useful starting point and reference for discussions of fetal harm and minimal risk.

case of innovative research studies – which are often not premised upon established interventions – a combination of previous, peer-reviewed studies or publications, and clinical need, could be used as rationale for the study.

4.54 Harm-benefit assessment

As endorsed by the Canadian and American policies, researchers and research ethics boards should conduct a harm/benefit assessment before pregnant women are included in clinical studies. However, what is lacking in these policies is guidance as to the interpretation of such an assessment, especially when harms and benefits may serve the pregnant woman and fetus differently. For example, if there are significant risks to the fetus, yet great potential benefits to the woman, should a study proceed? Unfortunately, given the diversity of clinical research, it is unrealistic to assume that a policy could be created that provides guidance of this nature for every specific situation. Instead, researchers and research ethics boards must conduct an assessment, by applying the values and principles highlighted in the policy, in a case-by-case manner. Despite this need for a case-by-case approach, one recommendation that can be advocated by policy is consideration of both the woman and the fetus. Although the fetus may not be granted equal moral status (and hence equal consideration) as that of the woman, the fetus should also not be dismissed (nor, conversely, solely considered) during the harm-benefit assessment.

As a means of promoting a rich case-by-case evaluation, various subsections can be added to the policy. Many of the following subsections under c have been inspired by the creative aspects of previous policy:

c) The foreseeable potential benefit to the woman and the fetus outweigh the foreseeable potential harms to the woman and the fetus. Factors to consider:
i) Nature and severity of the pregnant woman's disease (33).
ii) Availability of and risks associated with alternative therapy (33).
iii) Risk is the least possible for achieving the research objectives (110).

4.55 Rationale for exclusion

The final element which must be included in the proposed policy is a statement concerning exclusive research practices. Not only should researchers protect pregnant women and fetuses from excessive harm, they should also allow these subjects access to novel research – as outlined within the earlier discussion of distributive justice. Anecdotal evidence from colleagues suggests that pregnant women are often excluded from clinical research without explicit justification by researchers. Therefore, within the proposed policy it is very important to require that researchers justify their exclusionary practices. The final policy statement will read as follows:

2. If a researcher decides to exclude pregnant women from their research it is the responsibility of the researcher to provide thorough, convincing and explicit rationale for such exclusion. Such rationale must be included in all Health Canada health research applications and in the research ethics board application. The rationale would typically include data from animal and human studies, as well as other relevant scientific literature.

4.56 Full policy

Inclusion of pregnant women in clinical research

1. A pregnant woman may be included in clinical research between the beginning of the 9th week of gestation and the end of the 22nd week of gestation, as long as the following conditions are met:
a) Significant preclinical studies on non-pregnant humans (phase I and II studies) and pregnant animals have been conducted, and the results indicate no documented death or documented serious, far-reaching, and irreversible injury to the fetus or pregnant woman due to the intervention.
b) Interventions or procedures hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means (111).
c) The foreseeable potential benefit to the woman and the fetus outweigh the foreseeable potential harms to the woman and the fetus. Factors to consider:
i) Nature and severity of the pregnant woman's disease(33).
ii) Availability of and risks associated with alternative therapy (33).
iii) Risk is the least possible for achieving the research objectives (112).

2. If a researcher decides to exclude pregnant women from their research it is the responsibility of the researcher to provide thorough, convincing and explicit rationale for such exclusion. Such rationale must be included in all Health Canada health research applications and in the research ethics board application. The rationale would typically include data from animal and human studies, as well as other relevant scientific literature.

4.6 Conclusion

A review of current Canadian health policy indicates a general receptiveness to including pregnant women in clinical research. Although the international policies officially adopted by Health Canada remain fairly restrictive and ambiguous, the combination of policies applicable in Canada provide direction and progress where international policy is lacking. However, despite such progress, there remains a lack of detail and guidance within the individual policies. In addition, due to the scattered jurisdictions (e.g. national, institutional, etc.) of the policies, they are difficult to access and are not well-promoted by Health Canada. Such inadequacies can only be overcome

by the creation of an overarching, cohesive health research policy created by Health Canada, applicable to all health research in Canada.

Although there is a clear need for such policy change, there also exist many foreseeable challenges to the creation and implementation of such a policy. In particular, before a new policy is pursued, a very thorough review of current Canadian law and policy would be required in order to avoid contradictions and tensions between established documents and new policy. Once a new policy is created, great efforts would also need to be made to ensure that researchers, research ethics boards and government personnel were aware of policy changes, and had access to the resources and support required to help them adjust their practices in order to comply with the policy changes.

The sweeping exclusion of pregnant women from clinical research is a violation of their autonomy and basic principles of justice. Such exclusion has the potential to harm current pregnant women and pregnant women in the future. For these reasons, the exclusion of pregnant women should not be taken lightly. Instead, policy change must be pursued swiftly, yet with great care, so as to ensure that the research exclusion faced by women in the past is not repeated with the pregnant subpopulation.

Chapter 5: Conclusion

The aim of this thesis is to provide an overview of the exclusion of pregnant women from clinical research and suggest improvements that could be made to current practice. To provide a rich and comprehensive overview, information from various disciplines was incorporated, including: history, law, ethics, clinical medicine, basic science and policy.

The historical exclusion of women from clinical research provides a background for the current exclusion faced by pregnant women and highlights the shared struggles of these two groups. The most prominent of these struggles is the lack of access to relevant health information – due to the use of research populations that do not reflect the target population. The policy response regarding the general female population was included because pregnant women represent a subset of the general female population, and therefore share many of their challenges and accomplishments. Review of the development of policy pertaining to the general female population highlights the importance of dedicated advocacy groups and the requirement for solid policy documents created at the national level, such as the FDA's *Clinical Holds Rule* and NIH's *Revitalization Act.*

To explore the ethics of excluding pregnant women from clinical research it was important to first discuss the legal and moral status of the fetus and the legal status of the pregnant woman. A review of relevant Canadian jurisprudence suggests that the courts only grant legal status to the fetus following birth. Complementing this position is the court's approach to the legal rights and duties of the pregnant woman. The courts have shown that they will not interfere with the actions or choices of the pregnant woman,

even if such actions are harmful to the developing fetus. Although a definition of the moral status of the fetus is less clear than the legal status, a review of prominent philosophy and ethics literature suggests that moral status can reasonably be granted from 23 weeks gestation onwards.

With the moral and legal status established, it is possible to discuss the ethical principles and challenges encountered when pregnant women are excluded from clinical research. The relevant principles, as defined by the *Tri-Council Policy Statement* and the *Belmont Report*, include: respect of persons, respect for justice and inclusiveness and balancing of harms and benefits. A review of the writings of Beauchamp, Childress, Dresser, McCullough, Walzer and Weijer suggests that the exclusion of pregnant women from clinical research violates the principles of respect for persons and justice (distributive, gender and economic). When one considers the immediate and future risks and benefits to the pregnant woman and fetus, it appears that, with a carefully created study design, a favorable balance can be struck when pregnant women are included in clinical research. However, while such theoretical conclusions can be drawn, it is important to evaluate research studies on a case-by-case basis.

To understand the challenges faced by pregnant women within a clinical setting, chapter three reviews current clinical practice and the research conducted to inform such practice. Review of clinical practice suggests reliance upon a relatively small number of retrospective studies or else compilations of data – such as the flawed FDA Use-in-pregnancy categories. As a result, pregnant women and their physicians lack comprehensive information concerning the effects of interventions upon the pregnant physiology and the developing fetus. This situation can be greatly improved by the

pursuit of further animal testing, continued provision of teratology information services, and the creation of comprehensive clinical surveillance.

As a means of detecting possible teratogenic agents, various retrospective epidemiological studies should continue to be augmented and pursued, including: case reporting, case series reports, cohort studies and case-control studies. Despite the merits of such aforementioned measures, the most unbiased, useful information would likely come from the pursuit of further randomized controlled trials. Yet, to effectively and ethically pursue such studies, better guidance materials are needed for researchers concerning: the phase at which pregnant women should be included, what data is required before allowing such entrance, the proportion of pregnant women required in such studies, and how statistical analysis should be undertaken.

Review of national and international policy indicates a shift towards an acceptance of the inclusion of pregnant women in clinical research. However, despite such progress, there is a lack of detail present in many such policy documents and a lack of cohesion among the various Canadian policies. As a means of providing strong direction and support to researchers and research ethics boards, a clear, detailed national policy must be created. Included in this policy must be specific direction regarding: prior animal testing, balancing of risks and benefits and the allowance of exclusionary research practices. It is hoped that such policy would encourage the further inclusion of pregnant women in clinical research, thus allowing pregnant women access to innovative research and the generation of information relevant to the pregnant population.

It is clear that pregnant women and health care professionals would benefit from access to greater information regarding the effects of interventions upon the pregnant

physiology and developing fetus. To collect and share this information, a number of practical steps could be taken, including: the creation of comprehensive clinical surveillance, maintenance of teratology information services and the pursuit of a variety of scientific data collection methods. However, to produce such change requires the mobilization of the Canadian government, health providers, and health researchers.

To mobilize government, further data collection related to this topic is required. In particular, there is a need for the quantification of current exclusionary practices. Such quantification can be achieved by reviewing current clinical research protocols, recording and tallying the inclusion and exclusion factors included in such protocols, and by following those studies that have chosen to include pregnant women. In addition to such quantitative research, qualitative study could also be pursued. Such qualitative research could include interviews with clinicians so as to determine the challenges they face when treating pregnant woman and so as to identify the clinical areas in which data is particularly lacking.

To mobilize health providers and health researchers, both parties need to become more involved in discussion of the issues at hand. This could be promoted through the creation of accessible academic publications and the pursuit of interdisciplinary working groups. In parallel to such projects, detailed, accessible policy should be created. To produce such policy, experienced policy-makers, research ethics boards, and clinicians should be consulted. In particular, policy should be drafted concerning: the implementation of an improved clinical surveillance program, the compilation of clinical information (e.g. an improved system of rating drugs) and the inclusion of pregnant women in clinical trials.

What makes the collection and dissemination of pregnancy-related health information difficult is that it requires confronting longstanding and novel scientific, ethical, and administrative challenges. However, if we wish to provide excellent health care to Canadian women during pregnancy, it is absolutely necessary that we confront these issues and seek creative and effective methods of information collection. It is hoped that the continued academic and practical pursuit of this topic will allow us to avoid a continuation of the historical wrongs incurred upon the general female population within clinical research.

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