Chapter 1
Missed Trials, Future Opportunities

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Pregnant women deserve more from clinical research. Justice requires a research agenda that adequately addresses the health needs of pregnant women, and fair inclusion criteria that support the safe and responsible participation of pregnant women in relevant research. In recent years, there have been successful global efforts to expand paediatric clinical research[1] and to achieve appropriate gender balance in clinical trials. Significant challenges remain, however, with respect to the fair inclusion of pregnant women in clinical research. Indeed, pregnant women continue to be routinely excluded from such research *without justification* beyond the generic belief that vulnerable foetuses must be protected from research-related harms and that one effective way to meet this obligation is to exclude pregnant women from clinical research.

At the present time, pregnancy care and advice are driven by the precautionary principle (Kukla 2005). This principle advocates action to reduce threats of potentially serious, irreversible harm, before there is strong evidence of such harm (Harremoës et al. 2002). With the precautionary principle there is a reversal of the standard burden of proof – advocates need to demonstrate safety, rather than critics needing to demonstrate predictable harm. Precaution is usually applied in cases where unintended harms (or accidents) would be potentially catastrophic, for exam-

[1] Following the US National Institutes of Health, clinical research includes: 1. Patient-oriented research (which in turn includes mechanisms of human disease, therapeutic interventions, clinical trials, or development of new technologies). 2. Epidemiological and behavioural studies. 3. Outcomes research and health services research. National Institutes of Health. Glossary. http://grants.nih.gov/grants/policy. Accessed 17 May 2016.

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ple nuclear power, genetic engineering, and pregnancy. The underlying philosophy is perhaps best summed up in the proverb 'better safe, than sorry'. For example, when large epidemiological studies showed no evidence of caffeine-related harm at low doses, but showed increased rates of miscarriage at moderate to high doses, the message communicated to all pregnant women was 'avoid all caffeine'. The absence of evidence confirming potential harm at low doses was not taken as evidence of safety. Using a precautionary approach, evidence of potential harm with moderate to high doses of caffeine suggested that pregnant women should avoid all caffeine (Lyerly et al. 2009). The precautionary principle is key to understanding the reluctance to include pregnant women in clinical research.

Two now classic cases changed the way we perceive risk during pregnancy. Indeed, the histories of thalidomide and diethylstilboestrol (DES) are among the more significant barriers to the routine inclusion of pregnant women in clinical research (see Langston 2016). Both of these tragedies, which highlight foetal vulnerability, continue to influence research today, despite the fact that neither of these cases were the result of research-related harm. In the 1950s, thalidomide was prescribed to pregnant women to treat nausea, without prior safety studies having been completed. Tragically, this resulted in severe birth defects in over 10,000 children (Macklin 2010). From the 1940s through to the 1960s, DES was prescribed to millions of women to prevent miscarriage. In 1971, evidence emerged linking DES to several adverse effects, including vaginal and cervical cancer in young women exposed to DES during foetal development (Swan 2000).

These examples, and subsequent research, have clearly demonstrated that the foetus is not 'a bun in the oven' that floats suspended in a bubble until it is born. The foetus grows out of the pregnant woman. Even before it implants, the blastocyst is receiving and responding to environmental cues (Armant 2005). Once the embryo implants, it begins to function as part of the pregnant woman. There is no clear boundary or distinction between the pregnant woman and the foetus. Understandably, this physiological inter-connectedness leads to a focus on the behaviours of pregnant women and the conditions they experience, as these may have profound and lasting effects on the subsequent child (or children).[2]

The precautionary principle as an over-riding principle governing clinical research involving pregnant women gained ground after the thalidomide and DES cases demonstrated foetal vulnerability. Precaution is now deeply embedded in the ethos of pregnancy and clinical research during pregnancy. Indeed, efforts to protect the foetus from potential, rather than demonstrated, harm include increasing prohibitions on acceptable behaviour during pregnancy that go well beyond clinical research participation (Kukla 2005). In this age of 'intensive motherhood', with the

[2] We explicitly avoid the language of 'lifestyle choices' here because many behaviours that affect foetal health are the result of external factors (for example, employment stress, financial insecurity, ill health, domestic abuse) or habits (for example, diet, exercise, sleep) that have little to do with conscious, intentional deliberation and choice. Pregnancy is certainly a time when women become more conscious of their behaviours and have higher motivation for changing behaviours (for example smoking, see WHO 2013). But, pregnancy also entails barriers to health-related behaviour change (Sui et al. 2013). Despite increased consciousness regarding the importance of behaviour during pregnancy, many behaviours are still driven primarily by habit, environmental stimuli, and unconscious motivations.

burgeoning growth in pregnancy and infant-related health advice (Lee et al. 2014), there are instructions on virtually all aspects of a pregnant woman's life. For example, pregnant women are routinely given advice on diet (e.g., eat plenty of green, leafy vegetables, avoid eating hummus), exercise (e.g., do this in moderation, don't go horseback riding), work, including unpaid housework (e.g., avoid exposure to dangerous chemicals, reduce work hours), sleep (e.g., not on your back during the third trimester), prescription and over-the-counter drugs (e.g., avoid most medications, take care with others), tobacco (e.g., stop smoking, avoid second-hand smoke), alcohol (stop drinking), recreational drugs (stop taking them), and sex (continue as comfortable) (see, for example, Baylis and Sherwin 2002, 287–288).

While some behaviours during pregnancy may pose immediate physiological harm to the developing foetus (for example, eating certain foods increases the risk of listeria, and sleeping on one's back during the third trimester restricts blood flow to the foetus), other potential harms operate via epigenetic programming during foetal development. Epigenetic programming can have significant and long-lasting effects on mental and physical health through the course of the future child's life (Gluckman et al. 2008). Sleep, stress, diet, drug use, and exercise can all affect the growing foetus. For example, it has been shown that stress during pregnancy, triggered by domestic violence, changes the cortisol receptors of offspring as observed during adolescence (Radtke et al. 2011). As well, the diet of pregnant women has been shown to correlate to epigenetic changes in DNA programming at birth that predict the child's vulnerability to later obesity and metabolic disease (Godfrey et al. 2011). Evidence of these sorts of correlations between the experiences of pregnant women and the future child's (or children's) health drive a distorted and erroneous view of the ethics of pregnancy according to which 'good' pregnant women are those who avoid all risks. The reality is much more complex, however. For example, for some pregnant women, many risky behaviours are unavoidable (e.g., driving, experiencing domestic violence), or difficult to define (e.g., healthy eating), or hard to change (e.g., weight management). More generally, few pregnant women could manage to follow the entire range of health advice they might be given (Baylis and Sherwin 2002).

Consider, for example, advice regarding diet. An overwhelming majority of pregnant women do not meet current pregnancy diet guidelines (Callaway et al. 2009; Blumfield et al. 2011). For instance, in New Zealand, only 3 % of pregnant women meet national dietary targets for all four food groups (Morton et al. 2014). In Australia, 2 % of pregnant women meet national guidelines for vegetable consumption and 10 % meet guidelines for meat consumption (Mishra et al. 2015). Achieving the designated behaviour is challenging to say the least. Further, recent clinical research shows that following pregnancy diet guidelines is sometimes unwise. For example, while pregnant women are susceptible to listeria food poisoning (and miscarriage) and are advised to avoid high risk food, clinical research has shown that following this advice results in pregnant women consuming fewer essential nutrients (Pezdirc et al. 2012). A similar story has emerged in relation to fish consumption in the United States. Pregnant women are instructed to limit fish consumption (Hibbelin et al. 2007) and to avoid specific species of fish during

pregnancy in order to reduce the threat of mercury-related adverse effects to the foetus. But avoidance in this context has proven to be misguided. Overall, dietary intake of omega-3 fatty acids by pregnant and postpartum women in the United States falls short of recommended 'safe' levels (Benisek et al. 2000). These examples demonstrate the influence of the precautionary principle in pregnancy. Pregnant women are told to avoid multiple behaviours, often based on theoretical risks or preliminary evidence. However, avoidance is often impractical, and in some cases counterproductive. The same problems can occur when the precautionary principle is applied to clinical research with pregnant women.

If pregnant women should avoid eating certain foods on the grounds of foetal risk, it may seem obvious that they should avoid participating in clinical research. Moreover, *prima facie* this might seem much easier than avoiding stress, unhealthy food, or other potentially harmful exposures during pregnancy. From an individual perspective, participation in clinical research is 'unnecessary' insofar as research is designed primarily to benefit future generations, rather than the research participants themselves. As well, in almost all cases, research participation during pregnancy is simple to avoid.[3] Protecting foetuses from research-related risks, by excluding pregnant women from clinical research, therefore appears like an easy win for all who are rightly concerned with foetal and maternal wellbeing, including pregnant women, their families, their clinicians, and the community more broadly.

But not so fast; there are at least two problems here. First, all clinical research in humans involves a trade-off between risk borne by current research participants and potential benefits to future generations who may gain access to safe and effective treatments stemming from research. It follows that we can protect foetuses – as a population – by accepting some risk to current foetuses in order to generate knowledge that improves foetal safety in the future. We routinely accept the need for these sorts of trade-offs when it comes to doing clinical research involving other research populations.

Second, pregnant women, clinicians, and the community often are unclear about the potential benefits and risks of offered or recommended treatments. Studies show, for example, that in some cases pregnant women over-estimate the risks of drugs and other treatments used in clinical practice (Nordeng et al. 2010). But other studies suggest that pregnant women may have undue confidence in interventions seemingly offered as part of clinical care. Pregnant women use on average 2.6 medications (prescription and non-prescription) during pregnancy (Mitchell et al. 2011). This is despite the fact that greater than 98 % of medicines have no, or insufficient, safety data or pharmacokinetic data to guide dosing during pregnancy (McCormack and Best 2014). Consider the ongoing and controversial clinical use of the drug dexa-

[3] There are some exceptions to this general rule, however. Consider, for example, a pregnant woman diagnosed with a life-threatening condition where receiving an experimental intervention in a trial may be in her and her foetus' best interests. Medications to prevent perinatal transmission of HIV are some of the best-studied drugs in pregnant women. Consensus around the high risk of untreated HIV was enough to overcome the standard aversion to clinical research during pregnancy. But much clinical research is optional and therefore framed as an unnecessary risk.

methasone (DEX) to prevent virilisation of female foetuses affected by congenital adrenal hyperplasia and to prevent miscarriage for IVF patients. There is significant ethical debate in the literature, not only about the objective of preventing virilisation, but also about whether there is sufficient data regarding safety and efficacy to offer DEX as clinical treatment. A number of influential medical societies have concluded that DEX should only be offered in the context of approved research protocols (Witchel and Miller 2012). Yet many patients who are offered or recommended DEX will be unaware of this controversy and assume that DEX is safe and well established (Dreger 2015).

Reluctance to enrol pregnant women in clinical research is understandable, and the underlying concerns about potential foetal harm are valid. The widespread exclusion of pregnant women from clinical research results in its own harms, however, as when clinical care is compromised due to a lack of evidence about how to safely and effectively treat conditions affecting women during their pregnancies. This can result in a variety of problems, including the prescription of unsafe drugs because the health care provider is unaware of the risks, dangerous delays in the provision of medical treatment, and refusal to prescribe clinically indicated drugs. The resulting sub-optimal clinical care affects both the pregnant women and their developing foetuses. As a matter of justice, pregnant women are entitled to high-quality evidenced-informed care (see Baylis and MacQuarrie 2016). Clinical research involving pregnant women is an effective means to this end.

In 2009, the *Second Wave Initiative* at Georgetown University started to develop an ethical framework to support the increased inclusion of pregnant women in clinical research (Lyerly et al. 2008, 2009, 2012; Little 2011). In the United States, the Office of Research on Women's Health supported work focused on overcoming barriers to the inclusion of pregnant women in clinical research (ORWH 2011). More generally, for some time now, a number of academics have been advocating for the fair inclusion of pregnant women in clinical research (Chambers et al. 2008; Lyerly et al. 2008; Baylis 2010; Macklin 2010).

To date, much of this literature has focused on the *why* of including pregnant women in clinical research. As recently summarised by Lyerly and colleagues (2008), the benefits of this research include: developing effective treatments for women during pregnancy; promoting foetal safety; reducing harm to women and foetuses resulting from suboptimal care; and allowing access to the benefits of research participation. Notably, while there is still much resistance to the idea of including pregnant women in clinical research, increasingly there are some who are convinced of the need for such research. They understand and endorse the *why*; they are committed to the development of safe and effective treatments for pre-existing conditions in women who become pregnant, for medical conditions of pregnancy, and for conditions that threaten the successful outcome of pregnancy. To make meaningful progress on this front, however, they need to know more about the *how* (Baylis and Halperin 2012).

This book interrogates both the *why* and the *how* of clinical research involving pregnant women. In this way, the book contrasts markedly from much of the existing literature in support of clinical research involving pregnant women, which focuses

predominantly on *why* the inclusion of pregnant women in clinical research is necessary. Particularly important with respect to the *how* are practical issues such as priority setting, research design, and research recruitment. Equally important, however, is research ethics oversight. This includes guidelines, and regulations, as well as their implementation through the work of research ethics review committees.

Research ethics oversight arose in response to unethical research over the last 80 years. For example, the Nazi medical research war crimes led to the *Nuremberg code* (Annas and Grodin 1992). The Tuskegee syphilis study in the United States led to the *Belmont report* (United States 1979). And, in New Zealand, the cervical cancer research at National Women's Hospital led to the *Cartwright inquiry* (Cartwright 1988) and the *Code of health and disability services consumers' rights* (New Zealand 1996, 2004). Public anger and dismay over the breach of trust by clinicians in these studies drove both the regulation separating clinical practice from research (United States 1979) and the insistence that vulnerable groups be protected from research related harms. This explains, in part, why contemporary research ethics guidelines (and legislation) continue to overemphasise the potential harms of research and underemphasise the social value of research. As a result, most guidelines (and legislation) have a distorted view of the dominant ethics of pregnancy focusing myopically on risk avoidance. This view informs the misguided belief that clinical research during pregnancy is either unnecessary or dangerous, rather than a social good. In combination, these perspectives effectively prohibit most clinical research involving pregnant women.

For example, the *Common Rule* in the United States lists pregnant women as vulnerable. But the concept of vulnerability is under-theorised in the literature and it is not clear what this vulnerability derives from or amounts to. For example, pregnant women and their foetuses are more physiologically vulnerable than non-pregnant adults, but are pregnant women also more morally vulnerable due to reduced capacity to consent, and if so, why? Many of the chapters in this book offer rich and diverse accounts of the concept of vulnerability. For example, the relationships between vulnerability and exploitation (see Ballantyne and Rogers 2016), vulnerability and informed consent (see Wild and Biller-Andorno 2016; Johnson 2016), and vulnerability and empowerment are explored in this book (see Ballantyne and Rogers 2016; Little et al. (2016).

While the pregnant woman is the so-called vulnerable research participant, the primary concern for many is the vulnerable foetus. Indeed, it is widely assumed that concerns about foetal vulnerability explain why research ethics review committees do not approve studies in pregnancy, why clinicians do not assist in recruiting their pregnant patients for such research, and why pregnant women do not volunteer to participate in such research. While concerns for foetal vulnerability are understandable, this book systematically challenges the continued routine exclusion of pregnant women from clinical research by arguing that routine exclusion is harmful, unfair, and illogical. The ethical alternative is fair, respectful, and responsible inclusion in appropriate clinical research.

1.1 Routine Exclusion Is Harmful

The use of medication during pregnancy (and lactation) is one of the least-developed areas of clinical pharmacology and drug research (Buhimschi and Weiner 2009). Changes in pharmacokinetics during pregnancy, correct therapeutic dosage, and compliance during pregnancy are not well understood. Due to a lack of robust evidence, many pregnant women are refused medically important drugs, are subject to dangerous delays in getting drugs, or are prescribed drugs that are thought 'safe' despite evidence of possible teratogenicity (see Baylis and MacQuarrie 2016; Ballantyne and Rogers 2016).

1.2 Routine Exclusion Is Unfair

Ethical research must meet the demands of justice. Justice requires a research agenda that fairly addresses the needs of diverse populations, and fair inclusion criteria that adequately reflect the intervention's intended (i.e., targeted) or likely patient population. The widespread exclusion of most populations from clinical research except for young or middle-aged white males over the last 60 years has resulted in a disproportionate body of evidence regarding the health of young or middle-aged white men (Dresser 1992). Indeed, as a direct consequence of entrenched exclusionary practices, in some areas, current clinical guidelines continue to be based on clinical research that under-represents women and excludes pregnant women (Baylis 2010; Ballantyne and Rogers 2011; Baylis and Halperin 2012). Efforts to rebalance clinical research include policies advocating for, or requiring, more clinical research involving women (NIH 1994). As yet, however, pregnant women remain unfairly excluded from clinical research. Protective research ethics guidelines and regulations are motivated by concerns for the well-being of pregnant women and their foetuses. The net effect of these guidelines and regulations, however, is unjust – unjust because pregnant women thereby lack safe and effective treatment options, or lack information about the ways in which treatment options developed for non-pregnant persons might be appropriately modified for, and made available to, pregnant women.

1.3 Routine Exclusion Is Illogical

In some circumstances – for example pregnant women with an underlying health condition that requires ongoing treatment – the manner in which the precautionary principle is applied to clinical research involving pregnant women is illogical. Not only does exclusion from clinical research increase the risks to pregnant women as already argued, it may also increase the risks to developing foetuses. Here it is

worth repeating that the foetus is not 'a bun in the oven'. The foetus is a physiological, functional part of the pregnant woman. The foetus' presence significantly affects the pregnant woman's bodily processes and her health and wellbeing significantly affect the foetus in myriad and complex ways that we are only just beginning to understand. The physiological inter-connectedness of the foetus and the pregnant woman cannot be set aside. Excluding pregnant women with underlying health conditions that require ongoing treatment from clinical research does not protect developing foetuses from potential harm. When these pregnant women are excluded from clinical research, the risk of untested interventions is shifted from the context of a carefully controlled and monitored study, to potentially inconsistent off-label use in the context of clinical treatment (Baylis 2010; and Baylis and MacQuarrie 2016). In other words, research exclusion is precautionary about one sort of risk, and entirely ignores a parallel (and arguably greater) risk simply because the latter obtains outside the official realm of research.

More generally, it can be argued that the risk to pregnant women and their foetuses arises primarily from the lack of evidence about medical treatment during pregnancy, not necessarily from clinical research itself. Untreated or under-treated diseases, suboptimal care, and off-label prescription of untested drugs, can all pose harm to the foetus. A philosophy of extreme risk aversion may appear lofty, but it is unattainable and often counterproductive. Pregnant women need to make decisions involving complex trade-offs throughout their pregnancies, and these trade-offs often involve the use of medication (Lyerly et al. 2009). If precaution were really the guiding principle, then a thorough assessment of the risks and potential benefits of clinical research versus whatever intervention might be offered or recommended – which is sometimes nothing – would be required to determine which approach would be overall most precautionary.

1.4 The Book

Having discussed some of the background reasons for excluding pregnant women from clinical research, as well as some of the motivating reasons for advancing a discussion of both the *why* and the *how* of including pregnant women in clinical research, we now turn our attention to the ways in which this book contributes to the laudatory goal of promoting just research in this patient population. The book is original in three key ways. First, it provides bioethicists, clinicians, researchers, research ethics review committees, and health policy experts with an unparalleled depth of analysis regarding the ethics of clinical research involving pregnant women. To do so, it brings together many of the key authors in this field as well as experts in research ethics and vulnerability who have not previously applied their work to clinical research involving pregnant women. Second, the book incorporates innovative theoretical work in ethics and detailed disease-specific case studies that together highlight the complexity of clinical research involving pregnant women. The results of this integration include identifying conceptual priorities for future ethics research

and practical priorities for future clinical research. Third, the book includes a nuanced assessment of arguments both for and against including pregnant women in various kinds of clinical research. Analysis of the complex trade-offs associated with how, where, and when to safely include pregnant women in research are addressed across and within chapters, thus allowing readers to fairly consider arguments from multiple perspectives.

The book is divided into four parts. The first part advocates for fair, respectful, and responsible inclusion of pregnant women in appropriate clinical research. Here the authors describe the *status quo*, drawing on critical historical analysis of the thalidomide and DES scandals to help explain current exclusion practices. Françoise Baylis and Robyn MacQuarrie (2016) briefly describe problems arising from routine exclusion and then explain why clinicians and women should support clinical research in pregnancy. Lucy Langston (2016) argues that stigma around pharmaceutical use during pregnancy does not empower pregnant women or their clinicians to make good decisions about research participation or medical treatment during pregnancy. Chris Kaposy (2016) describes a new model of presumptive inclusion. These chapters paint a vision of a better model of pregnancy research and care that provides pregnant women with evidence-informed clinical care.

The second part reviews current justifications for the exclusion of pregnant women from clinical research and thereby exposes contemporary barriers to such research. Indira van der Zande and colleagues (2016) provide a systematic review of reported reasons for exclusion and suggest practical solutions to some of these barriers. Next, Carolyn Ells and Caroline Lyster (2016) explore the role of research ethics review committees as barriers to clinical research. They highlight problems with current research ethics guidelines and then offer guidance for improved ethics oversight as an alternative to the routine exclusion of pregnant women from clinical research. A crucial piece of the puzzle is pregnant women's own views about evidence, risk, and research. Verina Wild and Nikola Biller-Andorno (2016) present empirical results from a qualitative research study involving pregnant women in Germany regarding their thoughts and experiences with decision-making during pregnancy. They confirm that pregnant women are initially averse to the vague idea of research, but are more willing to participate in clinical research when the burdens and potential benefits of specific trials are explained to them.

Part three describes ways forward in how to undertake fair, respectful, and responsible inclusion of pregnant women in clinical research. These chapters probe important theoretical problems at issue in research involving pregnant women and how these can be overcome. Here the authors push the boundaries of our understanding of key concepts of vulnerability, risk, and equipoise and describe the normative nature of the maternal-foetal relationship in terms of moral status, autonomy, and guardianship of foetal interests. These chapters also scrutinise different research methods in order to better understand the goals, parameters, and limitations of competing processes of evidence generation. Angela Ballantyne and Wendy Rogers (2016) argue that while pregnant women may experience inherent, situational, or pathogenic vulnerability, in general they are not at risk of exploitation during clinical research. L. Syd Johnson (2016) also explores the notion of vulnerability, but from a different tack. She views the

classification of pregnant women as vulnerable research participants as a direct threat to pregnant women's autonomy. Rebecca Kukla (2016) focuses on equipoise and uncertainty in clinical research, underlining the importance of empowering pregnant women to make informed, autonomous decisions about research participation by including them in the early phases of research design. Finally, David Healy and Derelie Mangin (2016) highlight the shortcomings of a specific research design, namely the randomised controlled trial. In their view, when randomised controlled trials are used indiscriminately, their adverse effects may outweigh their benefits. Together these chapters suggest elements of an ethical framework for the future of clinical research involving pregnant women.

Part four moves the discussion from a careful review of theoretical and conceptual issues to a discussion of practical issues embedded in specific case studies that span the range of low to high risk research interventions. For example, Angela Ballantyne and colleagues (2016) write about clinical research on the use of probiotic supplements, which can be thought of as a lifestyle intervention. Ruth Farrell and Rebecca Flyckt (2016) write about clinical research involving reproductive medicine with a focus on uterine transplantation, the newest assisted reproductive technology which involves a complex combination of new and established fertility procedures and surgeries. In between these chapters, there is a chapter on clinical research involving women with, or at risk of contracting, HIV by Margaret Little and colleagues (2016), a chapter by Richard Ashcroft (2016) on clinical research involving maternal gene transfer with a view to improving foetal growth, and a chapter by Lisa Harris (2016) on clinical research involving women seeking abortion services. Together, these chapters show that clinical research can sometimes be effectively carried out under the existing oversight mechanisms, but they also highlight where guidelines and regulations unnecessarily hinder clinical research in pregnant women. Drilling down into the detail of specific cases brings to life the complexity and nuance of the ethical challenges facing clinical research involving pregnant women and showcases some inventive solutions to some of these challenges.

Taken together, these chapters represent a rich and diverse investigation of the ethical challenges associated with integrating pregnancy into the global clinical research agenda. Many chapters tell stories of the work of ethicists and researchers addressing questions of clinical importance for pregnant women. Their successes and innovative solutions to the restrictive regulatory environment should give us hope. The scholarship here challenges us to keep dismantling the harmful, unfair, and illogical barriers to the inclusion of pregnant women in clinical research and to build a framework for fair, respectful, and responsible clinical research during pregnancy.

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