Chapter 2
Why Physicians and Women Should Want Pregnant Women Included in Clinical Trials

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Abstract *A direct consequence of the routine exclusion of pregnant women from clinical trials is pregnant women using over-the-counter and prescription medications in the absence of population-specific clinical trial data about the potential benefits and harms of these medications for themselves, their foetuses, and their future children. In our view, pregnant women are as entitled as other patient populations to robust clinical trial data about safety and dosing on the basis of which to make evidence-informed decisions. To this end, we maintain that pregnant women should be presumed eligible to participate in clinical trials. This chapter asks and answers the following questions: Why are clinical trials in pregnancy important from a physician's perspective? And, why are clinical trials in pregnancy important from a pregnant woman's perspective? Having addressed these questions, we next consider why pregnant women might choose not to participate in clinical trials, and what can be done to encourage their participation.*

There are many reasons why pregnant women are routinely excluded from clinical trials of medications and vaccines including the fact that manufacturers, regulators, sponsors, researchers, and research ethics review committees would prefer to avoid the scientific, legal, and ethical complexities and the costs associated with research in pregnancy. In this chapter, we do not review these reasons which are well documented by others (Lyerly et al. 2008; Shields and Lyerly 2013; see also van der Zande et al. 2016). Instead, we critically examine why access to robust clinical trial data detailing the safety and effectiveness of drugs used during pregnancy

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should be a high priority for physicians (and not just obstetricians)[1] and for pregnant women.[2] Physicians should want to provide their pregnant patients with the same standard of care they provide their non-pregnant patients, and pregnant women should demand no less. From this perspective, it is important to exert pressure on manufacturers, regulators, sponsors, researchers, and research ethics review committees to change the *status quo* so that pregnant women are presumed eligible to participate in all Phases of clinical research (Blehar et al. 2013).

In our view, pregnant women should not only be included in clinical trials specifically targeting pregnant women, they should also be included in clinical trials targeting the general population. In both instances, careful attention should be given to issues of trial design and to the timing of participation in research by pregnant women in order to build on knowledge gained from prior research in the general population (Baylis and Halperin 2012). We recognise that pregnant women may legitimately be excluded from specific clinical trials on scientific and ethical grounds, such as trials involving the use of drugs for which there is evidence of teratogenicity or evidence of foetal risk. However, the inclusion of pregnant women in clinical trials should be the rule, rather than the exception (see Kaposy 2016). This view is consistent with that of the World Health Organization (WHO) in the *International Ethical Guidelines for Biomedical Research Involving Human Subjects* of the Council for International Organizations of Medical Sciences (CIOMS). These guidelines state unequivocally that "[p]regnant women should be presumed to be eligible for participation in biomedical research"[3] (CIOMS 2002). Consistent with this directive, exclusion from a specific clinical trial would require an explicit rationale that references scientifically and ethically defensible exclusion criteria.

At the present time, a majority of pregnant women use over-the-counter and prescription medications in the absence of relevant clinical trial data confirming the potential benefits and harms of these medications for themselves, their foetuses, and their future children. Indeed, recent data confirm that more than 90 % of pregnant women in the United States take one or more over-the-counter or prescription medications for both obstetrical and non-obstetrical illnesses (Mitchell et al. 2011). As well, in recent years, the average number of medications taken during pregnancy has increased. For example, first-trimester use of prescription medications has increased by more than 60 % in the last 30 years and, during this same timeframe, the number of pregnant women taking four or more medications

[1] While many health care providers can be involved in the care of pregnant women, we focus on physicians as these are the health care providers authorised to prescribe medications. As well, though many of the claims advanced in this chapter apply equally to vaccines, our focus is on medications.

[2] Arguably, this claim applies to women and transgender men, some of whom have experienced pregnancy and some of whom may experience pregnancy. This is beyond the scope of this chapter.

[3] See Macklin (2010) for a brief discussion of ambiguity in the CIOMS guidelines. Also, at the time of writing the CIOMS guidelines are under review. Changes to the guidelines for research involving pregnant women are anticipated.

has tripled (Mitchell et al. 2011). We assume a similar practice pattern in many high- and middle-income countries.

The significant use of over-the-counter medications during pregnancy should not be surprising. Pregnancy occurs over nine months, and it would be unusual for anyone (including pregnant women) not to take any over-the-counter medications for the greater part of a year. Among the most commonly used over-the-counter medications are acetaminophen, ibuprofen, pseudoephedrine, and aspirin. Data from the Slone Epidemiology Center Birth Defects Study and the National Birth Defects Prevention Study show "that approximately two-thirds of women take acetaminophen and that approximately 1 in 6 women takes a decongestant or ibuprofen during pregnancy" (Werler et al. 2005).

As well, many pregnant women take prescription medications for acute or chronic obstetrical and non-obstetrical medical conditions. Among these women are those who are unable or unwilling to tolerate the side-effects of pregnancy. A serious example of this is women with extreme nausea and vomiting that results in weight loss and dehydration, and often requires hospitalisation. Moreover, there are women with underlying health conditions who require continued medical treatment during pregnancy. These women often will continue the use of their pre-pregnancy prescription medications (with or without changes in dosing). This includes women with diabetes, hypertension, epilepsy, asthma, depression, and anxiety. Among the most commonly prescribed medications in the first trimester of pregnancy are amoxicillin and other antibiotics used to treat a variety of infections (including bladder infections). As well, progesterone is commonly used throughout pregnancy to prevent preterm labour and in the first trimester to provide placental support in pregnancies resulting from assisted reproduction (Mitchell et al. 2011).

Three phenomena explain the increasing number of women taking medications during pregnancy, and the increasing number of medications being taken by them. First, women in high- and middle-income countries are delaying childbearing and, typically, older pregnant women have more health challenges than their younger counterparts (for example, hypertension, pre-existing diabetes, hypothyroidism) (Martin et al. 2012, 2015). Second, women with chronic health conditions for which physicians would have actively discouraged pregnancy are now choosing to become pregnant owing to improved management options for their underlying disease (for example, women with Crohn's disease, Factor IV Leiden, and congenital heart disease). Third, women with poorly controlled (i.e., difficult to manage) health conditions that previously precluded pregnancy are now able to become pregnant using fertility drugs (for example, women with obesity, polycystic ovarian syndrome, and uterine fibroids). Taken together, these discrete phenomena have resulted in an increase in the number of women with underlying health challenges that need to be managed during pregnancy. As one of us has noted previously, "pregnant women get sick, and sick women get pregnant" (Baylis 2010), and this is now happening in increasing numbers.

The problem for pregnant women who use over-the-counter and prescription medications is that, for the most part, robust clinical trial data confirming the safety and effectiveness of the drugs used during pregnancy do not exist. Data from

retrospective observational studies and adverse event registries are sometimes available to guide physicians and patients in making treatment decisions during pregnancy. Sometimes, however, there are good reasons to question the quality of some of these data and to demand additional research. Not only is there the problem of recall bias with retrospective studies but, in many cases, data are inconsistent among drug safety databases that pool all known studies, including animal studies and retrospective studies. As well, data may be inconclusive within any one registry. In such cases, available data may be of limited value (see Ballantyne and Rogers 2016; Healy and Mangin 2016). This makes it difficult for physicians to offer sound clinical recommendations based on a clear understanding and evaluation of the potential benefits and harms. This situation contrasts markedly with medications available to the general population, as these medications are approved for use following the completion of a series of clinical trials that typically move through four Phases.

As described by the US Food and Drug Administration, the aim of Phase I clinical trials is to establish the safety of a new drug (FDA 2014). Typically, 20–80 healthy volunteers are recruited to Phase I trials to study the pharmacokinetic and pharmacodynamic properties of a new drug in order to identify acute side-effects. Pharmacokinetics refers to the process by means of which the body absorbs, distributes, metabolises, and eliminates a drug. Pharmacodynamics refers to the biochemical and physiological effects that a drug may have on the body. If a new drug passes this Phase, a Phase II trial is the next step. With Phase II clinical trials, the number of research participants is greater than those involved in Phase I trials – between 100 and 300 participants. In this research Phase, patients who suffer from the disease or condition for which the drug is being developed, rather than healthy volunteers, are recruited. The goal is to determine whether the drug under study is efficacious in treating the condition and whether, in addition to the desired therapeutic effect, there are undesirable side-effects. Next, there are Phase III clinical trials that involve a larger number of research participants – somewhere between 1,000 and 3,000 people. This Phase allows for a more robust assessment of the efficacy and dosing of the drug. As well, more information can be gathered on less common side-effects because the drug is being studied in more people over more time. Phase III is also when a drug may be compared to an available competitor drug to assess relative value – that is, comparative efficacy and effectiveness. Once a drug has been approved, the research that follows is generally described as a Phase IV trial. In this fourth Phase, a new drug is assessed for long-term safety and effectiveness, while considering the different ways in which the drug may be administered. To be clear, post-marketing ‘research’ doesn’t resemble or recruit like the other research Phases described above.

This phased approach to the research and post-approval marketing of drugs for diverse patient populations typically does not occur for pregnant women. A direct consequence of not including pregnant women in clinical trials is that most drugs are used in this patient population not only without the benefit of robust evidence about safety and effectiveness (for pregnant women, their developing foetuses, or their future children), but also without population-specific information about the

pharmacodynamics and pharmacokinetics of the drugs to know how they are processed in a pregnant woman's body. This is a serious lacuna considering the major physiological changes that occur during pregnancy (Carlin and Alfirivic 2008).

During pregnancy, women experience increased plasma volume, body weight, body fat, metabolism, and hormone levels. For example, during pregnancy a woman's blood plasma levels increase by 50 % and her cardiac output increases by 30–50 %. Her blood pressure dips in the second trimester and potentially increases in the third. As well, her lung volumes are diminished. Her glomerular filtration rate increases by 40–50 % and her renal plasma flow increases by up to 65 %. As well, her gastrointestinal system has decreased motility. Arguably these changes "make it impossible to calculate dose and safety information by extrapolating from data on men and non-pregnant women" (Baylis 2010), and yet extrapolation is exactly what physicians do when they recommend or prescribe medications off-label as would be the case with any medication not labelled (i.e., specifically approved) for use in pregnancy (which is the vast majority of medications). Off-label prescribing occurs when a physician prescribes an approved medication for (i) an unapproved condition, or (ii) an approved condition, but in an unapproved patient population, or at an unapproved dose, or in an unapproved way (i.e., form of administration).

A current example of off-label prescribing in pregnancy is the drug ondansetron. This is an anti-nausea drug labelled to treat nausea and vomiting in chemotherapy and surgery patients. It is being prescribed off-label to pregnant women with extreme nausea and vomiting. It has been suggested that this drug may be responsible for birth defects (Anderka et al. 2012). A recent retrospective study, however, suggests that there are no significant side-effects with use of this medication during pregnancy (Pasternak et al. 2013). What is particularly challenging for physicians and pregnant women in this scenario is that the only evidence available is contradictory and substandard. Had pregnant women been included in meaningful ways in clinical trials of ondansetron, prior to the drug coming to market, there would be reliable, prospective safety data to guide decision-making. Instead, the only data available is contextual, retrospective, and limited.

Off-label use of medications *de facto* results in unmonitored and unregulated experimentation in an unsuspecting population – patients who do not appreciate that they are individually participating in a 'trial of one'. Here we use the term 'trial of one' to refer to a practice where a person receives an intervention outside of a formal clinical trial in a context where knowledge regarding the potential benefits and harms of the intervention do not satisfy standards for therapeutic use in the patient population of which the person is a member. A 'trial of one' is not the same as an n-of-1 study, which is far more rigorous and systematic. A common feature of a 'trial of one' is that the patient mistakenly believes that she is receiving a therapeutic intervention. This is an instance of therapeutic misperception[4] – believing that a

[4] The term therapeutic misconception refers to the mistaken belief that a research intervention in a clinical trial is a therapeutic intervention. The term therapeutic misperception introduced here, refers to the mistaken belief that off-label use of a drug, biologic, or device in a patient population for which data about safety and efficacy is lacking (experimentation rather than research proper) is a *bona fide* therapeutic intervention.

physician's willingness to recommend a medication off-label while relying on data from sources other than randomised controlled trials is as good as clinical trial data confirming safety and effectiveness. This perception is deeply problematic and clinical trials are specifically intended to supplant this kind of decision-making. Another common feature of a 'trial of one' is that data cannot be efficiently collated and analysed to produce generalizable knowledge to validate the intervention as therapeutic.

In support of our claim that pregnant women should be presumed eligible for proper and full participation in all Phases of clinical research (and should not find themselves routinely participating in 'trials of one'), we address the following questions: (1) Why are clinical trials in pregnancy important from a physician's perspective? And, (2) Why are clinical trials in pregnancy important from a pregnant woman's perspective? Having addressed these questions, we next engage the moral imagination to ask and answer two further questions that we believe will become relevant at some future time when pregnant women are routinely invited to participate in all Phases of clinical research: (3) Why might pregnant women choose not to participate in clinical trials? And, (4) What can be done to encourage pregnant women to participate in clinical trials?

2.1 Why Are Clinical Trials in Pregnancy Important from a Physician's Perspective?

The short answer to this question is that physicians who treat pregnant women, like all physicians, should practice and promote evidence-informed decision-making. For them to do so, they need robust evidence regarding the safety and effectiveness of therapeutic interventions for pregnant women and their developing foetuses. Only in this way, can physicians offer their pregnant patients sound professional recommendations regarding the use of over-the-counter and prescription medications.

Evidence-informed decision-making is a term recently introduced in response to the backlash against the concept of evidence-based medicine (Miles and Loughlin 2011). As defined by Sackett and colleagues "[e]vidence based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research" (Sackett et al. 1996). For years, many (mis) interpreted the reference to "best available external clinical evidence" in this definition of evidence-based medicine as requiring evidence from randomised controlled trials or meta-analyses. In an effort to underscore the fact that in some instances other types of evidence could satisfy the standard of 'best available external clinical evidence' (and thus appropriately guide clinical decision making) a new term was coined – evidence-informed decision-making (see Healy and Mangin 2016).

Currently, physicians who treat pregnant women rely on (often uncollated) data from animal studies, case reports, retrospective observational studies, adverse event registries, and some poorly supported meta-analyses. In some instances, this evidence suffices, as when a drug is clearly identified as causing harm through adverse events registries. In other instances, however, available evidence simply isn't good enough for the treatment of medical conditions complicating pregnancy. In some cases, without the benefit of evidence from randomised clinical trials, physicians are unable to offer their pregnant patients sound professional recommendations regarding the use of available drugs. Indeed, they are *de facto* precluded from practicing and promoting evidence-informed decision-making (Shields and Lyerly 2013). In many (if not most) instances, physicians treating pregnant women have few courses of action available to them. For pregnant women who are not taking medications, they can recommend over-the-counter or prescription medications based on 'no' or 'limited' evidence of potential benefits or harms. Alternatively, they can promote a philosophy of 'less is best' (Thall Bastow and Holmes 2016) and discourage pregnant women from taking any over-the-counter or prescription medications (consistent with the view that 'the safest pregnancy-related pharmacy is as little pharmacy as possible'). And, for pregnant women on a prior drug regimen, they can recommend the *status quo*, they can recommend a change in medication(s) or continuation of the same medication(s) but at a different dosage, or they can recommend discontinuation of the medication(s). Whatever physicians decide, however, they are invariably doing so in the absence of solid evidence.

As noted above, there are significant changes to women's physiology during pregnancy. In the absence of clinical trial data, in many instances, physicians won't know how these physiological changes affect the pharmacokinetics and pharmacodynamics of a drug in a pregnant body. For example, the known significant increase in plasma volume during pregnancy may dilute the concentration of a drug in the plasma. In addition, the amount of drug in the pregnant woman could be reduced further by the significant increase in glomerular filtration, and the subsequent renal processing of the drug which is then eliminated from the body in urine. The way in which a drug is metabolised is an important component of a clinical trial in which a drug's half-life is determined. The half-life of a drug – a measure of how long it takes for half of the drug to be cleared from active circulation – may be altered by these significant physiological variations. Understanding how a drug circulates in a pregnant body, and whether it crosses the placenta, is critical to evidence-informed decision-making.

In sum, physicians who care for pregnant women are regularly required to provide advice on the use of over-the-counter and prescription medications. Too frequently they do so in the absence of high-quality clinical trial data. This state of affairs is a direct result of intentional decision making on the part of manufacturers, regulators, sponsors, researchers and research ethics review committees to routinely exclude pregnant women from trial participation. Physicians should not accept this *status quo*, which effectively forces them to rely on lower standards of clinical evidence for the treatment of pregnant patients than would be the case for any other patient population. They should demand better for their patients and for themselves.

2.2 Why Are Clinical Trials in Pregnancy Important from a Pregnant Woman's Perspective?

Most pregnant women try to stay well during pregnancy, for their own sake, as well as the sake of their developing foetuses and future children. This can be a serious challenge, however, as when pregnant women take (or stop taking) medications without the benefit of good clinical trial data on toxicity and dosing.

Many pregnant women using prescribed medication(s) for underlying health conditions will modify the standard dosage of their prescription medication(s) when they become pregnant, or they will discontinue their prescription medication(s). Some pregnant women will make these decisions without seeking professional advice. Perhaps they rely on information available on the internet, or they simply act on their intuitions. Other pregnant women will ask their physicians to help them weigh the potential harms of untreated illness against the potential harms of their medications, but in many instances their physicians will be hard pressed to provide sound advice (see Wild and Biller-Andorno 2016). Such advice can only be available to pregnant women, if there are well-designed and executed clinical trials in pregnancy. A major barrier to such trials are current national and international research ethics laws, policies, guidelines, and practices that require the routine exclusion of pregnant women from clinical trials.

Without good clinical trial data on toxicity and dosing, there is the very real risk of under- or over-dosing. With under-dosing, the risk is that pregnant women and their developing foetuses will be exposed to the potential harms of the medication(s), without the corresponding potential benefits associated with addressing the underlying health problem. With over-dosing, the risk is that pregnant women and their developing foetuses will be exposed to greater potential harm than is required to manage the women's symptoms and achieve therapeutic benefit. Consider, for example, a medication that binds to receptors in a woman's body. Ideally, the appropriate dose of the medication would bind to these receptors without 'extra' drug free floating to potentially cause harm. With both under- and over-dosing, the harm-benefit ratio is skewed in a way that does not further the interests of pregnant women or their developing foetuses (see Little et al. 2016).

As it stands, each pregnant woman who takes (or stops taking) medications invariably finds herself in a clinical 'trial of one'. In this trial, as compared with a standard clinical trial, she is not being carefully monitored for adverse events, the medication she is taking is not being formally assessed for effectiveness, there may be no clear safety parameters, and no clear stopping rules. As well, there is no long-term follow-up of children exposed to medications during foetal development. This kind of 'trial and error' is not in the best interest of pregnant women, their developing foetuses or their future children (see Healy and Mangin 2016). For this reason, pregnant women should demand inclusion in relevant, well-designed clinical trials. This is the only way to ensure that fewer pregnant women, foetuses, and future children are not at risk of harm, resulting from the off-label use of medications – medications that come to market without reliable data for use in pregnancy (Macklin 2010).

2.3 Why Might Pregnant Women Not Want to Participate in Clinical Trials?

To this point, we have explained why physicians should be motivated to advocate for research in pregnancy. From this it follows that they should be motivated to contribute to the design of scientifically and ethically sound clinical research involving pregnant women and, as appropriate, to encourage their pregnant patients to enrol in these trials. We have also explained why pregnant women should want to participate in such clinical trials– so as to secure potential benefits for themselves, their developing foetuses, and their future children as well as secure benefits for pregnant women as a class. We nonetheless recognise that many pregnant women may not want to enrol in clinical trials, having been told for many years that research participation is a risky activity that can result in serious harm to the developing foetus. The thalidomide tragedy, where thousands of children were born worldwide with significant limb deformities, is often cited in this regard (see Langston 2016). As has been noted repeatedly, however, it is not research participation but rather the failure to test thalidomide in Phase I and Phase II clinical trials that explains the tragedy (Macklin 2010). Had there been such research, significantly fewer children would have suffered the harmful side-effects of the drug. The trial would have been stopped after one or a few adverse events, and the drug would never have been marketed to pregnant women.

Notwithstanding these facts, it is important to understand the legitimate concern of pregnant women for foetal well-being so that it can be addressed pro-actively, thereby contributing to the sea change required to make the inclusion of pregnant women in clinical trials the norm. Indeed, understanding why pregnant women may resist participating in clinical trials is critical to strategising about the best ways to explain the benefits of research participation.

2.4 How Might Pregnant Women Be Encouraged to Participate in Clinical Trials?

Imagine a world in which the routine exclusion of pregnant women from clinical trials is no longer the norm. That is, imagine a world in which manufacturers, regulators, and sponsors require fair, respectful, and responsible clinical research in pregnancy for medications that might reasonably be used by pregnant women; a world in which researchers are motivated to pursue appropriate research in pregnancy; and a world in which research ethics review committees are able and willing to approve scientifically and ethically responsible clinical trials in pregnancy. How might pregnant women invited to participate in such research respond? (see Wild and Biller-Andorno 2016; Ballantyne et al. 2016)

Recent data on the views of pregnant women about participating in H1N1 vaccine trials suggest that there are discrete circumstances in which at least some pregnant

women perceive participation in a clinical trial as potentially safer than receiving so-called treatment in the standard clinical care setting (Lyerly et al. 2012). These are circumstances where the pregnant women and their developing foetuses are at significant risk of harm, knowledge about how to safely and effectively reduce the risk of harm is missing, the clinical trial promises careful monitoring, and is expected to produce generalizable knowledge. As these circumstances would apply to a number of pregnant populations, such as pregnant women with HIV (see Little et al. 2016) or pregnant women with diabetes, there is reason to think that in some circumstances some pregnant women might welcome the opportunity to participate in clinical trials.

Other pregnant women, however, might nonetheless be reluctant to participate in clinical trials because of perceived risk to their developing foetuses and future children. Consider, for example, a woman who suffers from significant inflammatory bowel disease. Her disease needs to be controlled in order for her to receive adequate nutrition, and subsequently nourish her foetus. Her treatment options include taking her usual medication(s) off-label and hopefully achieving an adequate dose in her body despite the fact that her body has significantly changed in pregnancy, *or* adjusting the dosage on her usual medication(s) in response to the physiological changes that accompany pregnancy, *or* not taking her usual medication(s). None of these options are ideal, and one or more of these options could potentially result in a growth-restricted foetus. Instead, the pregnant woman could be invited to participate in a Phase IV clinical trial where she would use her usual medication(s) in a managed way; the drug levels in her system would be in a therapeutic range; impact on herself and the developing foetus would be carefully monitored; and there would be long-term follow-up of the infant into childhood to look for potential long-term effects. Researchers following the child's progress would have access to information about other children who were exposed to the drug antenatally, and could look for patterns that persisted. Inclusion in such a trial would have clear benefits for the pregnant woman, her developing foetus, and other pregnant women who might benefit from the knowledge gained.

To be clear, off-label use of a medication is not safer (i.e., less risky) than use of the same medication within a clinical trial. In fact, the opposite is true insofar as a medication used within a clinical trial would be formally assessed for safety and effectiveness, the women and developing foetuses would be carefully monitored for adverse events, there would be clear safety parameters and stopping rules, and perhaps most importantly there should be long-term follow-up of infants exposed to medication during the trial. A similar point is made by Kristine Shields and Anne Drapkin Lyerly who note that: "Participation in an ethically designed Phase IV clinical study would be very much like treatment in clinical practice with the additional potential benefits of expanded informed consent, enhanced monitoring, and the patient's knowledge that she has contributed to the evidence base and has benefited other pregnant women" (Shields and Lyerly 2013).

Advocates of research in pregnancy (which should include physicians who treat pregnant women) need to help pregnant women (individually and as a class) to better understand the potential harms of using an over-the-counter or prescription

medication in the absence of robust clinical trial evidence regarding toxicity and dosage. These potential harms exist whether the medication is used outside or within a clinical trial. To be very specific about this, if a medication is potentially harmful to the developing foetus (under any circumstances, or in specific dosages, or at particular developmental stages), this fact about the medication does not change because the medication is administered within a clinical trial. Moreover, by participating in a clinical trial it is possible to improve the harm-benefit ratio by securing some of the potential benefits of trial participation described above. These benefits are significant, and they are not available to pregnant women using an over-the-counter or prescription medication off-label.

It is our belief that pregnant women can be helped to overcome the therapeutic misperception that off-label use of a medication is a *bona fide* therapeutic intervention. Moreover, there is reason to believe that at least some pregnant women who come to understand and appreciate the point about medications and geography – namely, that the risk profile of a medication depends upon the medication, not whether it is provided outside or within a clinical trial – are going to want to secure the potential benefits of trial participation as a way to counterbalance the potential harms of a medication otherwise taken off-label. They will appreciate that their fears about the use of medications during pregnancy cannot be allayed by participating in a 'trial of one'.

Now clearly the issue will be different for generally healthy women using over-the-counter medications as compared with women who have an acute or chronic underlying health condition for which they are using prescription medications off-label. It will also be different for women who are pregnant for the first time and women who have experienced one or more pregnancies. As well, it will be different for women in their first trimester and women in their second or third trimester. The point is that pregnant women should be empowered to make reasonable choices for themselves as they weigh the potential harms and benefits of trial participation as compared with the potential harms and benefits of off-label use of a medication.

Having helped pregnant women to better understand the benefits of trial participation, it will be important to meaningfully engage them in identifying research priorities. This exercise can help researchers design and implement clinical trials that first and foremost will address the health priorities of women who are, or who anticipate becoming, pregnant. Establishing research priorities that are relevant and important to the target population will be a key factor motivating their participation. Physicians can assist in this task by clarifying where they most need robust clinical trial evidence in order for them to offer competent care to their pregnant patients.

For example, with clinical trials targeting pregnant women, there might be early attention given to the top ten over-the-counter medications used by pregnant women. Many of these medications, including pseudoephedrine and ondansetron, do not have clinical trial data confirming their safe and effective use in pregnancy. For many (if not most) of these medications, there is clinical trial data on their use in the general population and some retrospective safety data that could be used to design randomised controlled trials. The aims of such trials would be to learn how widely used medications are metabolised in pregnancy, and what their impact is

on the health and well-being of pregnant women, their developing foetuses, and future children. Such information would enable physicians to provide pregnant patients with sound information in support of evidence-informed decision-making.

Another possible priority for routine research in pregnancy could be Phase IV clinical trials of prescription medications for chronic health conditions that are widely used by the general population but that could potentially threaten the health and well-being of women during pregnancy and, in turn, potentially threaten the health and well-being of their developing foetuses and future children. These would be clinical trials focused on the health needs of pregnant women who have experience with a medication prior to pregnancy, and who understand their bodies as an ecosystem where health challenges that affect them also affect their developing foetuses.

As with many aspects of health care, particularly in a western context, discrete medical symptoms are often addressed independently of the whole person within whom the symptoms manifest. This approach, while more simplistic (and thus more manageable), is deeply problematic and the problem is compounded when the person is pregnant. With a narrow focus on a pregnant woman's discrete medical symptoms one risks failing to properly attend to the physiological inter-connectedness of the pregnant woman and her foetus. It is important to take account of the fact that a threat to the pregnant woman's health is also a threat to the health of the foetus and future child(ren).

Consider, for example, a woman who suffers from moderate asthma. Her illness is controlled as long as she takes her asthma medications. Upon learning of her pregnancy, however, she adopts what she considers a cautious approach and immediately stops all of her medications, for fear of risk to her foetus. In so doing, she is not alone. Recent research suggests that about 30 % of women with asthma will reduce or discontinue their asthma medications in the first trimester (Zetstra-van der Woude et al. 2013). This results in a significant worsening of her asthma, which is compounded by the changes in her respiratory physiology that naturally occur in pregnancy. These changes to her health ultimately result in the developing foetus being deprived of oxygen as it grows, resulting in a small for gestational age infant. In attempting to avoid the potential harms of the asthma medications, this woman would have inadvertently (and unintentionally) increased the harm to her developing foetus.

More generally, pregnant women with a chronic health condition, in consultation with their physicians, can guess at the best course of action with respect to drug use based on available evidence from case reports, adverse event registries, and so on. Alternatively, they can enrol in a clinical trial that aims to answer the research question: Should they continue their pre-pregnancy medication(s) regimen, continue their medication(s) but with a different dosage(s), or discontinue their medication(s)?

2.5 Conclusion

As noted at the outset, some pregnant women take over-the-counter and prescription medications during their pregnancy for which robust clinical trial data regarding use in pregnancy is lacking. These women may receive assurances from their physicians that the medications are 'likely safe even though they haven't been studied in pregnant women.' Other pregnant women do not take any over-the-counter and prescription medications fearing that the medications will harm their developing foetuses and future children. These women may receive assurances from their physicians that 'less is best' – a strategy used by some physicians to deal with their discomfort in prescribing under conditions of uncertainty.

This situation does not serve the best interests of pregnant women, their developing foetuses or future children, nor does it serve the interests of their treating physicians. Pregnant women are entitled to robust clinical trial evidence on the basis of which they can make evidence-informed decisions regarding their care. They can be helped to understand that current practice with respect to the use of off-label medications during pregnancy means that they are effectively participating in clinical 'trials of one', with very poor standards for recognising adverse events. If pregnant women were routinely included in clinical trials, the medications used would be formally assessed for safety and effectiveness, the women and developing foetuses would be carefully monitored for adverse events, there would be clear safety parameters and stopping rules, and perhaps most importantly there should be long-term follow-up of infants exposed to medications during pregnancy. While there are potential harms associated with participating in clinical trials, these can be counterbalanced by potential benefits.

In closing, we join others in insisting on the pressing need for fair, respectful, and responsible clinical trials in pregnancy to better understand and respond to the health needs of pregnant women, their developing foetuses, and their future children.

References

Anderka, M., A.A. Mitchell, C. Louik, M.M. Werler, S. Hernández-Diaz, S.A. Rasmussen, and National Birth Defects Prevention Study. 2012. Medications used to treat nausea and vomiting of pregnancy and the risk of selected birth defects. *Birth Defects Research, Part A: Clinical and Molecular Teratology* 94(1): 22–30.

Ballantyne, A., and W. Rogers. 2016. Pregnancy, vulnerability, and the risk of exploitation in clinical research. In *Clinical research involving pregnant women*, eds. F. Baylis and A. Ballantyne, 139–159. Cham: Springer.

Ballantyne, A., C. Barthow, and K. Wickens. 2016. Research into lifestyle changes in pregnancy. In *Clinical research involving pregnant women*, eds. F. Baylis and A. Ballantyne, 211–225. Cham: Springer.

Baylis, F. 2010. Pregnant women deserve better. *Nature* 465(7299): 689–690.

Baylis, F., and S. Halperin. 2012. Research involving pregnant women: Trials and tribulations. *Clinical Investigation* 2(2): 139–146.

Blehar, M.C., C. Spong, S.F. Grady, L. Sahin, and J.A. Clayton. 2013. Enrolling pregnant women: Issues in clinical research. *Women's Health Issues* 23(1): e39–e45.

Carlin, A., and Z. Alfirivic. 2008. Physiological changes of pregnancy and monitoring. *Best Practice & Research. Clinical Obstetrics & Gynaecology* 22(5): 801–823.

CIOMS (Council for International Organizations of Medical Sciences). 2002. *International ethical guidelines for biomedical research involving human subjects*. Geneva: World Health Organization. http://www.cioms.ch/publications/layout_guide2002.pdf. Accessed 3 Oct 2016.

FDA (US Food and Drug Administration). 2014. *Inside clinical research: Testing medical products in people*. http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143531.htm. Accessed 1 Apr 2016.

Healy, D., and D. Mangin. 2016. Does my bias look big in this? In *Clinical research involving pregnant women*, eds. F. Baylis and A. Ballantyne, 197–208. Cham: Springer.

Kaposy, C. 2016. Presumptive inclusion and legitimate exclusion criteria. In *Clinical research involving pregnant women*, eds. F. Baylis and A. Ballantyne, 51–62. Cham: Springer.

Kukla, R. 2016. Equipoise, uncertainty, and inductive risk in research involving pregnant women. In *Clinical research involving pregnant women*, eds. F. Baylis and A. Ballantyne, 179–196. Cham: Springer.

Langston, L. 2016. Better safe than sorry: Risk, stigma, and research during pregnancy. In *Clinical research involving pregnant women*, eds. F. Baylis and A. Ballantyne, 33–50. Cham: Springer.

Little, M.O., A.D. Lyerly, A.C. Mastroianni, and R.R. Faden. 2016. Ethics and research with pregnant women: Lessons from HIV/AIDS. In *Clinical research involving pregnant women*, eds. F. Baylis and A. Ballantyne, 227–246. Cham: Springer.

Lyerly, A.D., M.O. Little, and R. Faden. 2008. The second wave: Toward responsible inclusion of pregnant women in research. *International Journal of Feminist Approaches to Bioethics* 1(2): 5–22.

Lyerly, A.D., E.E. Namey, B. Gray, G. Swamy, and R. Faden. 2012. Women's views about participating in research while pregnant. *IRB: Ethics and Human Research* 34(4): 1–8.

Macklin, R. 2010. Enrolling pregnant women in biomedical research. *Lancet* 375(9715): 632–633.

Martin, J.A., B.E. Hamilton, S.J. Ventura, M.J.K. Osterman, E.C. Wilson, and T.J. Mathews. 2012. Births: Final data for 2010. *National Vital Statistics Reports* 61: 4–6.

Martin, J.A., B.E. Hamilton, M.J. Osterman, S.C. Curtin, and T.J. Matthews. 2015. Births: Final data for 2013. *National Vital Statistics Reports* 64(1): 1–65.

Miles, A., and M. Loughlin. 2011. Models in the balance: Evidence-based medicine versus evidence-informed individualized care. *Journal of Evaluation in Clinical Practice* 17(4): 531–536.

Mitchell, A.A., S.M. Gilboa, M.M. Werler, K.E. Kelley, C. Louik, S. Hernández Díaz, and National Birth Defects Prevention Study. 2011. Medication use during pregnancy, with particular focus on prescription drugs: 1976–2008. *American Journal of Obstetrics and Gynecology* 205(1): 51.e1–51.e8.

Pasternak, B., H. Svanström, and A. Hviid. 2013. Ondansetron in pregnancy and risk of adverse foetal outcomes. *The New England Journal of Medicine* 368(9): 814–823.

Sackett, D.L., W.M.C. Rosenberg, J.A. Muir Gray, R.B. Haynes, and W.S. Richardson. 1996. Evidence based medicine: What it is and what it isn't. *BMJ* 312(7023): 71–72.

Shields, K.E., and A.D. Lyerly. 2013. Exclusion of pregnant women from industry-sponsored clinical research. *Obstetrics and Gynecology* 122(5): 1077–1081.

Thall Bastow, B.D., and J.L. Holmes. 2016. Teratology and drug use during pregnancy. *Medscape*. http://emedicine.medscape.com/article/260725-overview#aw2aab6b3. Accessed 1 Apr 2016.

van der Zande, I.S.E., R. van der Graaf, J.L. Browne, and J.J.M. van Delden. 2016. Fair inclusion of pregnant women in clinical research: A systematic review of reported reasons for exclusion.

In *Clinical research involving pregnant women*, eds. F. Baylis and A. Ballantyne, 65–94. Cham: Springer.

Werler, M.M., A.A. Mitchell, S. Hernández-Diaz, and M.A. Honein. 2005. Use of over-the-counter medications during pregnancy. *American Journal of Obstetrics and Gynecology* 193(3 Pt 1): 771–777.

Wild, V., and N. Biller-Andorno. 2016. Pregnant women's views about participation in clinical research. In *Clinical research involving pregnant women*, eds. F. Baylis and A. Ballantyne, 119–136. Cham: Springer.

Zetstra-van der Woude, P.A., J.S. Vroegop, H.J. Bos, and L.T. de Jong-van den Berg. 2013. A population analysis of prescriptions for asthma medications during pregnancy. *The Journal of Allergy and Clinical Immunology* 131(3): 711–717.