

Background and state of the issue: ethics of research in pregnancy

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Background and context

The purpose of this document is to give background information on the need for research during pregnancy in low- and middle-income countries (LMICs) and the main ethical issues related to this type of research to prepare for participation in the Global Forum on Bioethics in Research meeting. The document covers the following areas:

1. Ethical Issues Associated with Research in Pregnancy
2. Physiological Changes during Pregnancy
3. Lack of Research Evidence for Medications to Treat Pregnant Women
4. LMIC Pregnancy Research Needs: Infectious Disease and Non-communicable Disease
5. Previously Recommended Approaches

A few relevant recent (2010-2016) articles that are available online are cited for each topic for supplemental reading. For some topics (e.g. non-communicable diseases), information from high income countries (HICs) is provided because no equivalent information was found from LMICs where the topics are thought to be relevant. The 2010 report from the NIH Office of Women's Health workshop "Enrolling Pregnant Women: Issues in Clinical Research" and the article "Moving Targets: The Challenges of Studying Infectious Diseases among Pregnant Women in Resource Limited Settings" by Divala et al. (2015) offer broad introductions to both research and ethical issues and practical solutions employed to date.

1. Ethical Issues Associated with Research in Pregnancy

A number of major ethical issues are discussed in the literature related to research in pregnancy.

Access/fair inclusion: Pregnant women are often "over-excluded" from clinical and preventive intervention trials. In many settings, researchers must justify the inclusion of pregnant women and specify what special protections will be included in clinical trial designs, however, there is generally no requirement to justify their exclusion from a protocol. Pregnant women are sometimes included in implementation research (e.g. PrEP, Heffron et al. 2015). Paradoxically, exclusion of pregnant women from clinical trials will likely result in exposure of a larger number of pregnant women to medications for common medical conditions once successfully approved for marketing.

There are two possible issues of justice to consider in terms of access. In trials that offer the prospect of direct benefit to pregnant women, fair opportunity to access to those benefits may be deliberated. However, there is a broader issue regarding fair access of the pregnant population to the benefits of all research meant to advance medical knowledge for the general public. From the population health perspective, the inclusion of pregnant women in early trials that do not carry potential for direct benefit may also be considered.

A change in the presumption of exclusion of pregnant women to one of inclusion consistent with regulations may also increase the number of clinical trials and research studies that include pregnant women as such a change did for children after an NIH directive was issued in 1998 (Blehar, et al. 2013). However, five years after the U.S. policy change for inclusion of children in research, a survey of IRB chairs found that only 5% thought that a study of a drug found safe in adults presented minimal risk to children (Shah et al. 2004). Concerns about institutional legal liability and the variable interpretation of regulations and ethical standards by RECs are additional impediments that may be addressed by clarifying guidance, REC training or the formation of RECs with special expertise in research in pregnancy.

Vulnerability: Populations are considered vulnerable when their ability to protect their interests is compromised. There is consensus that special protections are required for the fetus during research, however, the ethical challenge is balancing these protections with the need to do the research required to provide medical care for pregnant women.

Some argue that “vulnerability” does not apply to pregnant women who are capable of protecting their own interests and giving consent. It has been suggested that pregnant women should be reclassified as a “medically and ethically complex” population with additional issues that should be considered because they are also responsible for protecting the interests of the fetus who cannot consent to research and has unique susceptibility to its risks (Blehar, et al. 2013).

While it is not the case that women are necessarily vulnerable by virtue of being pregnant, there are social vulnerabilities affecting pregnant women that should be mitigated in research design (e.g. stigma and threat of domestic violence related to HIV status, birth defects or fetal loss, substance abuse, etc.).

Consent: Respect for a potential research participant’s autonomous decision making is fundamental to ethics and law. While researchers are obliged to disclose all research related risks to the woman and her fetus to obtain consent for participation, in practice, full explanation and comprehension of risks is challenging. The role of co-parent (or intimate partner for research if there is a risk of exposure to an experimental agent) consent for participation of pregnant women in research is controversial. Approximately one third of young women in LMICs (excluding China) marry before age 18 and therefore, researchers need to consider the consent process and the need for support in decision-making for adolescent pregnant women in these settings. Paradoxical situations arise in research when a pregnant women less than 18 years old can only provide assent to enroll in a study while pregnant but the same women can give consent to enroll her newborn in the study. There is debate concerning whether women can provide full consent during the rigors of labor and delivery which may be especially pertinent for studies where prenatal medical services are lacking and a potential participant’s first contact with a research study is at this stage of pregnancy.

Special cultural considerations in some settings may apply to consent for research that involves disclosure of pregnancy in the first trimester, placental sampling, studies of stillbirth or neonatal loss and autopsy.

Risks/potential benefits: A key ethical issue is how much risk it is acceptable to impose upon the fetus, which, like a child, cannot consent to participation in research. Many regulations and ethical frameworks give a two-stage analysis of acceptable risk. For research involving the potential or

prospect of direct medical benefit to the woman or fetus, risk proportionate to the potential benefit is acceptable. For research that does not involve the prospect of such direct medical benefit, risk to the fetus must be no more than minimal. However, the definitions of minimal risk and more than minimal risk in the context of pregnancy are unclear (Little 2016). To add to the confusion, adverse outcomes may be attributed to a research intervention despite a baseline rate of birth defects in a population due to unknown reasons (approximately 3% in U.S.) (Blehar, et al. 2014) and scientific journals are biased toward the publication of studies showing abnormalities compared to those showing health-outcomes. The adjudication of risks and potential benefits of a specific research project among a woman, fetus and future offspring is scientifically and ethically challenging. Of special interest to LMICs may be an analysis of public health (population level) risks and potential benefits of research studies in pregnant women.

Ethical study design: Creative, thoughtful research designs are needed to promote inclusion of pregnant women in clinical trials, especially in LMICs. For example, a tiered trial of the H1N1 vaccine was conducted in second and third trimester women after initial safety and efficacy information for the general population was available (Sperling et al. 2012).

Long-term follow-up: There are special challenges to the ethical design of research during pregnancy. Pregnant women are inherently a transient population with constantly changing physiology, therefore, appropriate comparison groups must be chosen carefully to ensure validity. Research often measures a balance of immediate maternal and fetal outcomes; however, longitudinal studies of child development and women's health which may be needed to detect risks to fertility, cognitive development, etc. present many difficulties. Public health intervention research on maternal and child health often takes place in homes, not clinics, in LMICs where health services are delivered by community health workers, traditional birth attendants and midwives. In these settings, researchers may need to pay special attention to the need for capacity building to meet standards of care in the country and ethical obligations to provide ancillary care during the study (Merritt, et al 2010).

Access to abortion: This is a complicated issue in countries that prohibit abortions. The draft CIOMS guidelines currently state: "As a general rule, health related research involving pregnant women that has the potential for serious harm to the fetus must be conducted only in settings where women can be guaranteed access to a safe, timely and legal abortion in the event that participation in the research makes the pregnancy unwanted." On the other hand, restricting research to such contexts may have untoward effects when a disease emergently presents specifically in a country that does not have good access to abortion.

2. Physiological Changes during Pregnancy

The enormous and continuous changes in the physiological state of pregnant women are relevant to the design of ethical research involving medications and vaccines.

Metabolism: Physiological changes during pregnancy (50% increase in kidney glomerular filtration rate, 40-50% increase blood volume, alteration in serum binding proteins) change drug metabolism so that research findings for non-pregnant women regarding dose, schedule and toxicity are not generalizable to pregnant women (Little, 1999, Chambers et al. 2008).

Immunological changes: The concept of pregnancy as a state of systemic immunosuppression to ensure tolerance of the semi-allogenic fetus is oversimplified (Kourtis, et al. 2014). Strong evidence exists that pregnant women are more severely affected by some infections such as malaria parasites, influenza, hepatitis E and herpes simplex viruses. Dramatic hormonal changes during pregnancy modulate different immune responses and may increase infection severity, especially in the third trimester, along with decreased lung capacity, urinary stasis and change in blood flow. However, adequate immunological responses and safety of many inactivated and live attenuated vaccines in pregnant women have been demonstrated (Keller-Stanislawski, et al. 2014). The safety and efficacy of new hybrid virus carriers, DNA vaccines and adjuvants are unknown.

Although many vaccines have been shown to be beneficial, current issues in vaccination of pregnant women may affect the context for approval of studies of new vaccines. Immunization of pregnant women can protect them directly against vaccine preventable infections and protect the fetus and neonate via antibodies transferred from the mother during pregnancy. In particular, tetanus toxoid vaccination is recommended for use in pregnancy in developing countries where elimination of maternal and neonatal tetanus remains a goal. Despite the recognized benefits, theoretical safety concerns result in vaccine refusal in communities and vaccination withheld from pregnant women by health care providers.

3. Lack of Research Evidence for Medications to Treat Pregnant Women

Increasingly, research is being conducted on conditions associated with pregnancy such as stillbirths (Freen et al. 2016). However, pregnant women become ill and sick women become pregnant. Despite the lack of specific approval of drugs for use during pregnancy, many pregnant women are treated for serious non-pregnancy related conditions with prescription medications.

Current state of drug approval for use in pregnancy: The U.S. Food and Drug Administration (FDA) approved fewer than 15 non-pregnancy related medications for use during pregnancy (Haire 2001, Norwitz and Greenberg 2011). Of 500 drugs the FDA approved between 1980-2000, 91% had no determination of fetal risk (Lo and Friedman 2002). The average time for a drug to be categorized for risk in pregnancy is 27 years after market approval in the U.S. (Adam, et al. 2011).

Current exposure of pregnant women to unapproved drugs: It is estimated that at least 10% of women have a serious medical condition that requires treatment during pregnancy. This number is expected to increase as the average age of pregnancy increases in developed countries. In 2008, about 64% of U.S. pregnant women reported taking at least one prescription medication during their pregnancies and approximately 90% of pregnant women report using prescription and non-prescription medications (Mitchell et al. 2011). In the last 30 years, use of prescription medication during the first trimester increased more than 60% (Mitchell et al. 2011). Other commonly prescribed drugs include antibiotics to treat urinary tract infections, asthma, and hypertension and anti-nausea medications. In the absence of empirical evidence for most of these drugs, HIC prescribers routinely depend on case reports, pregnancy registries, observational studies or anecdotal clinical experience putting pregnant women at risk (Lylerly, et al 2011). These information resources are often not available to LMIC physicians.

Current regulation and historical context: According to many regulatory frameworks, the exclusion of pregnant women from clinical trials is not automatic, not unethical and not to be arbitrarily

determined. These frameworks vary in detail describing when inclusion is appropriate and when clear and compelling reasons for exclusion are present. The reticence to include pregnant women in clinical trials in HICs often stems from the historical tragic use of teratogenic drugs such as thalidomide and diethylstilbestrol during pregnancy (Allesee and Gallagher 2011).

4. LMIC Pregnancy Research Needs: Infectious Disease and Non-communicable Disease

Brief summaries of need and status for research on treatments for major LMIC infections (HIV/AIDS, tuberculosis, malaria, helminths, emerging viral epidemics) as well as non-communicable conditions (mental ill health, substance abuse, diabetes, hypertension, anemia) are described. Some interventions for conditions of pregnancy with proven efficacy in HICs, do not appear to work in LMIC populations (e.g. Althabe, et al. 2015). There is accumulating evidence that pregnancy provides a unique window into understanding fundamental mechanisms underlying links between a pregnant women's health, her later health and the future health of her children. Pregnancy may provide a "stress test" that unmask the possible risk of chronic diseases such as depression, diabetes and hypertension.

HIV/AIDS: Pregnancy increases the risk of HIV transmission to women by two-fold (Gray, et al. 2005). A new HIV infection during pregnancy increases the odds 15-fold for maternal to child transmission (Birkhead, et al. 2010). A substantial evidence base exists for use of anti-retroviral drugs for the prevention of mother to child HIV transmission.

New antiretroviral dosing studies for pregnant women lag behind the clinical use of these new drugs in which dosing was studied in non-pregnant individuals and toxicity is not known. Most microbicide trials excluded pregnant women (Macklin 2010, Abdool Karim, et al. 2010, with the exception of Cohen, et al. 2011, Little 2016). However, tenofovir gel trials served as a basis for a step by step framework developed for research on HIV prevention agents during pregnancy and lactation (Beigi, et al. 2013).

Tuberculosis: Tuberculosis is a leading cause of maternal mortality in high HIV prevalence settings. Maternal TB can result in premature birth, low birth weight, and congenital or neonatal TB infection or disease (Mnyani and McIntyre 2010). In pregnant women with HIV infection the risk of active TB disease ranges from 0.7% to 7.9% and HIV related TB accounts for 10% maternal deaths in some countries. TB in HIV infected pregnant women is difficult to diagnose (Hoffmann et al. 2013). (See diabetes section below.)

While the safety and efficacy of first line TB drugs has been established for pregnant women, management of HIV co-infection is complex because rifampicin and isoniazid reduce plasma concentrations of commonly used anti-retroviral drugs. Despite the high levels of multi-drug resistant TB strains worldwide, there is limited data on the safety of second line drugs during pregnancy and pregnant women have been excluded from trials of new classes of anti-tuberculosis drugs (McIlleron et al 2015).

Malaria: Certain strains of *P. falciparum* malaria show tropism to the placenta that appears to mediate harm and are the focus of current research to develop a specific vaccine for pregnant women. Malaria Intermittent Preventive Treatment in pregnant women (IPTp) with anti-malarial drugs has been implemented broadly to prevent malaria morbidity and mortality (approximately

10,000 maternal deaths due to malaria associated anemia, 100,000 infant deaths due to low birth weight, also preterm delivery, congenital infection and fetal loss). High levels of parasite resistance to drugs currently used for pregnant women and lack new drugs approved for first trimester use are barriers to plans for mass drug administration to eliminate malaria worldwide (Huynt et al. 2015). The treatment of cases of malaria in pregnancy has lagged years behind the treatment given to non-pregnant patients. Despite observational studies of a large number of first trimester pregnant women after use of artemisinin combination therapy (ACT) demonstrating safety, WHO has not yet approved it to replace quinine (Moore, et al 2016). In addition, the pharmacokinetics of ACT and failure rate, suggests recommended doses based on insufficient research are inadequate in second and third trimester pregnant women with malaria (Mosha, et al 2014).

Helminth infections: Widespread hookworm infections in LICs put pregnant women at greater risk of severe anemia and higher mortality as well as contributing to reduced infant birth weight and increased mortality. The pathology related to female genital schistosomiasis is linked to infertility and increased transmission of HIV. There are limited data on the safety of the few available anti-helminthic drugs in pregnant women, although albendazole has been indicated by WHO for use in pregnant women after the first trimester in areas highly endemic for hookworm (WHO 2011). Women of reproductive age are currently excluded from public health mass drug administration campaigns to control helminth infections in LMICs (Hotex and Whitham 2014).

Emerging epidemic viral infections: Recently, viral infections that specifically impacted pregnant women have emerged and spread widely (e.g. H1N1 pandemic influenza, Ebola virus, Zika virus).

Pregnant women with influenza are at increased risk for hospitalization and death and are more likely to deliver preterm and low birth weight infants. During the 2009 H1N1 pandemic treatment with oseltamivir was recommended, however, due to limited data, higher complication rates occurred in pregnant women due to under-dosing (Goldkind et al 2010). In 2009 second and third trimester pregnant women were included in a tiered trial of H1N1 vaccine conducted after initial safety and efficacy information for the general population was available (Sperling, et al 2012).

The case fatality rate for pregnant women in the recent outbreak of Ebola virus in West Africa was estimated to be approximately 90% with near zero perinatal survival. A number of pregnant women received experimental intervention with convalescent plasma and ethical approval was obtained for emergency administration of favipiravir, an anti-viral drug (Black et al. 2015).

Zika virus has been confirmed as the cause of thousands of cases of microcephaly in babies born from infected mothers as well as other neurological pathology. Researchers are gearing up efforts to develop a preventive vaccine (Cohen <http://www.sciencemag.org/news/2016/02>), however, there are several surmountable barriers for developing these vaccines for pregnant women (Omer and Beigi 2016). Despite widespread use of DEET mosquito repellent, the only study of long term use during pregnancy comes from one malaria prevention project conducted with second and third trimester women (McGready et al 2001), leaving safe use during the first trimester, when the risk of harm due to Zika virus infection appears highest, unconfirmed.

Mental ill health: Major depressive disorder, one of the most common complications of pregnancy is associated with worse child outcomes- preterm delivery, low birth weight (Brandon, et al. 2016). Few mental health interventions have been tested in pregnant women. It is difficult to disentangle

pre-pregnancy depression from depression during pregnancy and postpartum. In the last 30 years, use of anti-depressants increased from less than 1% to 7.5% (Andrade, et al 2008, Mitchell et al 2011). The need for clinical trials of anti-depressants in pregnant women is controversial (Healy, et al. 2010).

Substance abuse and pregnancy: Substance abuse, such as alcoholism, in pregnant women may result in birth defects, stillbirths or infants with higher risk for sudden infant death syndrome (SIDS), neuro-developmental disabilities and other health issues. Research on substance abuse is difficult due to participant self report recall bias, stigma, low socio-economic status, low retention and other factors specific to local context that are compounded in pregnant women. Addressing these issues during the conduct of research is necessary to demonstrate the association of substance exposure to maternal and fetal outcomes as well as determine the biological basis of adverse outcomes that might be used to predict and prevent risk (for example, Dukes, et al. 2014)

Adult and gestational diabetes: Worldwide, the burden hyperglycemia during pregnancy is estimated to be 170 cases per 1000 live births, on par with other maternal morbidities. This burden is expected to increase due to the increasing prevalence of obesity and Type 2 diabetes. 92% cases of hyperglycemia in pregnancy occur in developing countries with the highest prevalence and number of cases in South/East Asia, particularly India (27.5%) (Guariguata, et al 2014). The prevalence rates are similarly high in the Middle East and North Africa (22.3%) while the African region has the second highest number of cases (6 million) followed by the Western Pacific region (4.3 million). Pre-existing diabetes as well as gestational diabetes is associated with serious complications for mother and child related to metabolic disruption and obstructed labor. There are significant barriers to diagnosis and treatment of adult (84% undiagnosed diabetics worldwide live in LMICs) and gestational diabetes in LMICs (Nielsen, et al. 2014). A causal relationship between gestational diabetes and postpartum development of diabetes in mother and possibly child is recognized but not understood. As a triple threat to pregnant women, diabetes also increases the risk of active tuberculosis by three fold, diabetics have poorer responses to TB treatments and TB worsens glycemic control in clinical management of diabetes (Lonroth, et al. 2014). The reported increase in diabetes prevalence in India 1998-2008 may have caused an estimated additional 1 million tuberculosis cases.

Adult hypertension and preeclampsia: The average prevalence of preeclampsia in LMICs is 4% (ranging from 1-8% Bilano et al. 2014) and it accounts for approximately 333,000 maternal deaths, 6 million perinatal deaths, 8 million pre-term births and 20 million low birthweight infants. Women diagnosed with preeclampsia have a 4 fold increased risk for maternal death. The etiology of preeclampsia is unknown although in LMICs chronic hypertension, obesity and severe anemia increase risk by three fold while cardiac or renal disease, diabetes, being nulliparous or older than 30 years increased risk by at least two fold. It is now recognized as an indicator of a women's risk for later cardiovascular disease (Ray, et al 2005).

Anemia: Approximately 500 million women in LMICs are anemic. Iron deficiency, the most common cause for estimated 50% all anemia worldwide, is correlated to increased risk of pre-term labor, low birth weight, child and maternal mortality. Among the highest risk populations worldwide are postpartum women. The magnitude of the gender gap in anemia burden widened between 1990 and 2010 in all regions and throughout adulthood. Anemia in women in LMICs was due to the a

higher prevalence of hookworm, sickle cell disorder, thalassemia, malaria, chronic kidney disease, schistosomiasis found in men and much of the excess anemia in women was due to gynecologic conditions which cause iron deficiency such as uterine fibroids and maternal haemorrhage (Kassebaum, et al. 2014). While the evidence is unclear for other infections, iron supplementation in pregnant women may result in increased risk of malaria and is recommended only in combination with malaria prevention measures (Sangare, et al. 2014).

5. Previously Recommended Approaches

The current guidance for researchers and ethics review committees specific to research in pregnant women does not address many specific barriers to research studies in this population. Although not a substitution for clinical trials, opportunities for gathering data that impose no additional risks such as opportunistic pharmacokinetic studies, cohort registries and case control surveillance studies are often overlooked or problematic due to the quality of the data. Conducting research to link exposures to adverse outcomes in LMICs is more difficult. There are no incentives from research funders or regulators for the inclusion of pregnant women in research as was done to encourage research in children or interventions for orphan diseases.

Existing guidance: UNAIDS Ethical Considerations in Biomedical HIV Prevention Trials (2012) Guidance Point 9 encourages the inclusion of women in HIV clinical trials including those who are “sexually active and may become pregnant, be pregnant or be breastfeeding” because they should be future recipient of safe and effective HIV prevention interventions. In 2010, experts were convened to delineate a framework for the study of safety for HIV prevention agents in pregnancy and lactation in light of guidance for testing vaginal microbicides published by the U.S. FDA (Beigei, et al.).

American College of Obstetricians and Gynecologists issued a Committee on Ethics Opinion on Ethical Considerations for including Women as Research Participants in November 2015 that supported the recommendations of the 2010 NIH Office of Women’s Health workshop “Enrolling Pregnant Women: Issues in Clinical Research” (Blehar et al. 2013).

In the 2013 guidance from Health Canada includes considerations for inclusion of women in clinical trials and analysis of sex differences.

In 2001, the wording of the U.S. regulations was changed to indicate that pregnant women may be involved in research if ten stated conditions are met (see Table 1 Blehar, et al 2013). The FDA also issued guidance on pharmacokinetic studies during pregnancy, clinical lactation studies, and pregnancy exposure registries (links in Blehar, et al. 2013).

Pregnancy exposure registries: Many pregnancy exposure registries exist including the Maternal Newborn Health Registry (Goudar et al 2012) created by a research network and a list of pregnancy exposure registries for 57 drugs and multiple drugs for epilepsy, autoimmune disease, asthma, cancer, HIV/AIDS and transplants set up for post-FDA approvals found at www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm134848.htm. However, these registries are rarely set up to record exposures to drugs used to treat common tropical and neglected diseases found in LMICs.

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