Global Forum on Bioethics in Research

Meeting report:

Ethics of research in pregnancy

Buenos Aires, Argentina

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Executive Summary

Grounding and Justification: The Global Forum on Bioethics in Research convened in Buenos Aires, Argentina in November 2016, to explore the "Ethics of research in pregnancy". With experts in bioethics, obstetrics and gynecology, epidemiology, public policy and clinical research from over 40 countries, the meeting used case study presentations and first hand experiences as the basis for discussion, covering both communicable and non-communicable disease and research in public health emergencies, such as the recent Zika epidemic. With a focus on research in low- and middle- income countries (LMICs) the meeting explored the reasons why pregnant women have been systematically excluded from research and how the ethical and legal issues can be navigated to promote and facilitate appropriate inclusion.

Summary: Regulations allow research with pregnant women but misunderstanding, myth and problematic culture stand in the way. While the default approach is that many researchers and Research Ethics Committees (RECs) continue to regard pregnancy as a near-automatic cause for exclusion, the real-life implications are that fewer than 20 US Federal Drugs Authority (FDA)-approved drugs are approved for use during pregnancy and since 1980 the mean time taken to determine a teratogenic risk for prescription medications approved by the FDA has been 27 years[1].

The very premise of clinical research is to find highly regulated, carefully controlled, morally responsible ways to generate evidence about how to effectively and safely treat sick people. This is as true for pregnant women as for any other population as 'sick women get pregnant and pregnant women get sick'[2]. Not performing research with pregnant women pushes and magnifies what should be a carefully controlled risk during research into the clinical setting. This leaves clinicians faced with making treatment decisions for pregnant patients with little evidence of efficacy and safety and causes tremendous anxiety and worry for pregnant women, their partners and health providers.

During the meeting, substantial consensus was reached that research with pregnant women is morally important given the critical need for providing women with safe and effective medical preventions and treatments during pregnancy. The recommendations below emerged from deliberations at the meeting and begin to address some of the key issues that need to be resolved to meet this moral imperative. Further details on each heading can be found in the corresponding section of the report.

Concept of vulnerability: Pregnant women should not be categorized as "vulnerable" as there is no evidence that their special circumstances reflect cognitive or physical impairment or that by default there is heightened susceptibility to harm for the mother and/or foetus through participation. The categorization as "vulnerable" has led to less research being conducted with pregnant women, which results in the population being more vulnerable to potentially harmful clinical interventions that lack a solid evidence base. There is a need to find alternate categories such as "special populations" to facilitate pregnant women's inclusion in research, while at the same time addressing any special needs they may have.

[1] Margaret P. Adam, Janine E. Polifka and J.M. Friedman 'Evolving knowledge of the teratogenicity of medications in human pregnancy' *American Journal of Medical Genetics* Part C (Seminars in Medical Genetics) 157:175–182 (2011)

[2] Quote from Françoise Baylis in, 'Canada's Clinical Trial Infrastructure: A Prescription for Improved Access to New Medicines' Standing Senate Committee on Social Affairs, Science and Technology. November 2012.

Minimal risk and the risk/benefit balance: Minimal risk is often considered a threshold for participation in research but there is uncertainty regarding how the concept should be applied in the context of research with pregnant women. A relative standard for minimal risk should be applied when deciding on the inclusion/exclusion of pregnant women, that is, the risks that the pregnant women in their particular situation would face, rather than referring to the general population or to pregnant women as a whole. Direct benefit to the mother or foetus should not be a prerequisite of participation, but risks to mother and foetus should be considered and weighed. As protocols are developed consideration should be given not only to the risks of participation but also to the risks to the pregnant woman and foetus if she is not included in the research. RECs should be encouraged to consider both the risks of participation and non-participation for the mother and foetus and researchers should be required to justify why pregnant women should be excluded from research if there is a possibility that the research can benefit the woman personally, the foetus, or pregnant women as a class of participants.

Cultural views and the need for engagement: Cultural views can pose a significant barrier to the participation of pregnant women in research. Robust engagement strategies are needed to reconcile cultural norms and beliefs with the ethical and clinical rationale supporting the need for research during pregnancy. Such engagement should include the community, healthcare providers, RECs and funders. GFBR participants were encouraged to act as advocates for research during pregnancy. Through broad and regular dissemination to their colleagues and institutions, GFBR participants can help establish the concept as a norm and through this 'socialisation' help shift perspectives in communities and institutions.

Consent and the role of family members: Consent in pregnancy should be obtained as early as possible with the option to revisit later during pregnancy including during labour. For certain interventions and/or due to the timing of enrolment obtaining consent during labour may be necessary. Strategies for beginning discussions about possible research participation earlier in pregnancy can mitigate some of the concerns about duress during active labour. The autonomy of pregnant women may be compromised by cultural norms such as the need to seek permission from other family members in the decision-making process. Since this is the cultural norm in many settings, it is acceptable to integrate the consultation and engagement of other relevant family members in the consent and enrolment process. The final consent should, however, be given by the pregnant woman.

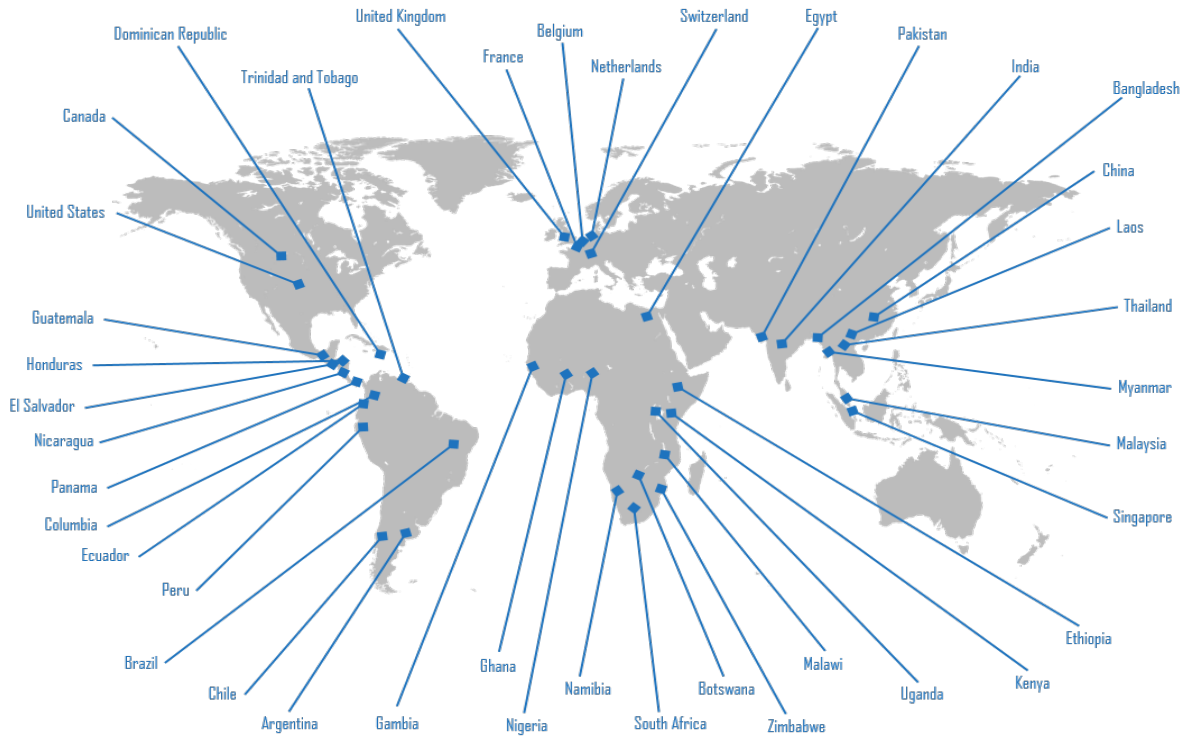
Law, policy and regulation: Regulations allow research with pregnant women but precautionary interpretation often stands in the way of inclusion by default. There is a strong need for international harmonisation and standardization from the regulatory perspective. For example, defining concepts such as 'minimal risk' and addressing situations where law conflicts with research possibilities (e.g. the recognition of pregnant minors as legally emancipated and able to consent to research). As gatekeepers to research RECs should be supported to better understand research in this context and lawyers should be recognised as active and influential participants in decision-making throughout the research process. It is important to demonstrate to researchers, RECs, lawyers and others that research with pregnant women is being responsibly done and that precedents have been set. Appropriate insurance and compensation plans should be put in place to mitigate the research sponsor's concerns should litigation arise out of any potential injury to the subsequently born child.

Public health emergencies: Settings of uncertainty such as public health emergencies accentuate the challenges associated with the inclusion of pregnant women in research. If endorsed by RECs, and deemed in

the best interest of the participant, the option to participate in clinical trials in emergency situations should be provided and recommended to pregnant women. The ultimate decision whether to follow these recommendations and participate in such a trial should be left to the woman. Having lost opportunities during the Ebola outbreak to assess safety/efficacy under rigorous scientific conditions there is a clear and urgent need for requirements for inclusion and exclusion to be agreed with regulatory authorities and manufacturers in advance of the next epidemic.

Introduction

The Global Forum on Bioethics in Research (GFBR) convened in Buenos Aires, Argentina in November 2016, to explore the "Ethics of research in pregnancy". With experts in bioethics, obstetrics and gynecology, epidemiology, public policy and clinical research from over 40 countries (see map of GFBR participants' countries below), the meeting delved into pressing ethical issues with respect to the inclusion and more particularly the exclusion of pregnant women from research. The meeting topic was chosen in light of experiences during the Ebola outbreak and its timeliness was all the more apparent given the 2016 Zika outbreak, which has deeply affected the Latin American region. It is a terrible irony that pregnant women, as the one group most in need of protection against the virus, is also the group routinely excluded from clinical trials of potential vaccines and treatments based on their condition. This situation has cast a spotlight on many broader ethical and practical issues for conducting research in pregnancy that extend right across cultures and contexts, and across high-and low- resource settings. This GFBR meeting helped bring some of these formidable challenges to the forefront of global discourse in bioethics and policy-making, and was intended to seed connections, new ideas, and create the benefits of bringing together multiple perspectives to make progress in addressing them in practice.



1. Concept of vulnerability

One significant barrier to the inclusion of pregnant women is their traditional categorization as "vulnerable". GFBR participants agreed that there is a need to move away from regarding pregnant women as vulnerable in the cognitive, decisional-capacity sense; pregnancy does not confer vulnerability per se in terms of regulatory concerns regarding consent or ability to protect oneself as it does not make women unable to understand, weigh information and make decisions. Rather, they are a special research population since pregnancy does pose scientific challenges and specific circumstances, such as risk of harm to the foetus and may require special protections. Some GFBR participants suggested that for late stage pregnancies the obstetrician has "two patients" and that the future interests of the child should carry some moral weight. The "two patient" problem in late stage pregnancy creates special ethical considerations for including pregnant women in research.

Case study 3 demonstrated that pregnant women in certain social settings may be vulnerable in other senses. For example, they may be subject to "deferential" vulnerability – the social expectation to defer to what the family wants to do. In some countries the husband/father may have legal rights (or socially assumed rights). Even where there are no such rights, the women may not feel empowered to make decisions alone as it involves the best interest of the foetus and therefore needs her husband/partner and other family members to participate in the decision-making process. GFBR participants agreed that this is her choice to decide whom to involve in the informed consent process.

Case study 3: ***Research ethics in pregnancy in Laos***

Vilada Chansamouth, Lao-Oxford-Mahosot Hospital Wellcome Trust Research Unit

Cultural norms about family decision-making, levels of education and mistaken beliefs about research procedures impacted the recruitment and retention of pregnant women during a community-based prospective cohort study to investigate the causes and impact of fever in pregnant women, in Paknguem District, Vientiane, Laos. Good engagement between the research team and study participants and the community is key to addressing these issues.

The discussion mirrored the bioethics literature on vulnerability where there is a move away from labelling groups as vulnerable and focus on evaluating research with pregnant women from the lens of special scrutiny. That is to subject research with pregnant women to more thorough ethics review and to consider how to strengthen or provide more targeted forms of protection for different kinds of pregnant women – pregnant women who are well, pregnant women who are ill and so forth. In this regard, the meeting discussed various strategies for consent, such as for women in labour and in pain and in distress, and **there was a call for more empirical studies to examine how to improve the quality of consent for research with pregnant women**.

GFBR participants agreed that labelling pregnant women as vulnerable has led to less research being conducted, which actually makes the population more vulnerable to potentially harmful clinical interventions that lack a solid evidence base.

2. Minimal risk and the risk/benefit balance

Minimal risk: Minimal risk is often considered a threshold for participation in research but there is uncertainty about how the concept should be applied in the context of research with pregnant women. Should it be anchored to the general healthy population or be relativized to the proposed group of pregnant women for study? Also, assuming unborn children or foetuses are research subjects, how should we assess the daily risks of those in the womb to consider whether the study is minimal risk or not for the foetuses?

There was general broad agreement on using a relative standard for minimal risk, i.e., the risks that the pregnant women in their particular situation would face, rather than referring to the general population or to pregnant women as a whole, to ground minimal risk assessment. So for example, if research is being done on pregnant women who are ill, then risks should be anchored in this group rather than healthy pregnant women.

The risk/benefit assessment at all institutional levels regarding the inclusion of pregnant women should be based on robust safety and efficacy data, however, these decisions can oftentimes be influenced by divergent cultural norms and perception. **Community engagement is therefore critical in enabling appropriate design and conduct of research in pregnant women**. This should include family and community members, but also health and field workers, medical staff as well as policy-makers and regulators.

Further considerations were raised during the discussion:

- There is a clear need for standardization in order to have comparability of data across different geographical settings and population settings. A pregnant woman in a HIV or malaria endemic area is in a patho-physiologically different situation to someone, for example, in the UK, so researchers need to have a good understanding of the medical context.
- Safety monitoring and surveillance is required to gather data as the trial progresses.

The risk of inaction: As protocols are developed a key consideration should be not only what are the risks of participation but what is the risk to a pregnant woman if she is not included in the trial? The same question should be asked of the foetus. A central lesson from the meeting was that we want to make sure that we are attending to the health needs of the pregnant woman not just the foetus – as these interests are profoundly aligned. We often forget the risks of inaction and focus on the worries about taking the action but a clear message from the meeting was that we are as culpable for what we don't do as for what we do.

The broad research community needs to pay much more attention than it does to the risks of not doing research: RECs should be encouraged to consider both the risks of participation and non-participation for the mother and foetus and researches should be required to justify why pregnant women should be excluded from research if there is a possibility that the research can benefit women personally, their foetus, or pregnant women as a class of participants.

Risk/benefit balance: There was a consensus view that **pregnant women should not be restricted to participate in research only when there is a direct benefit to them or the foetus**. Not all research has direct benefits but are still crucial to undertake with pregnant women, for example, observational research, longitudinal studies and pharmacokinetic studies. None of these examples poses direct benefit to either the

pregnant woman or the foetus, but may be very important in the context of improving general health of a population. However GFBR participants recognised that there may be national legislation that prohibits research without direct benefit to pregnant women and only a minimal level of risk to the woman or the foetus may be acceptable for research that has no prospect of direct benefit.

Case study 2: ***Ethical conflicts in clinical trials in preterm labour***

Sofia Salas, Universidad Diego Portales

Inclusion of pregnant women as research subjects for acute medical conditions such as threatened premature labour raises important ethical questions. These should be carefully analyzed by the local REC, considering not only the way that informed consent process is conducted but also the timing of consent, the risk/benefit ratio for both mother and the child, how the research can be implemented safely within local facilities and defining the obligations of the sponsor towards the mother and child in the event a premature delivery does occur (e.g. choosing a site that has the best standard of care and having insurance to cover any adverse effects).

Case study 2 demonstrated the need to consider the risk/benefit ratio for both mother and the child during the development of a research protocol. Focusing on treatment of preterm labour the research study had to weigh the significant health risks that premature birth poses for the newborn against the administration of a treatment, in particular tocolytic agents that pose cardiovascular risks to both the mother and the foetus.

The issue of risk and benefit was also addressed in **case study 6** in the context of the PHASES Project. The Project is addressing key questions such as, are there ethically relevant differences between risks of interventions in trials in the context of prevention of foetal disease (as in prevention of mother-to-child transmission (PMTCT) programmes, which are widely seen as acceptable) versus the context of prevention of maternal disease (as in microbicides and pre-exposure prophylaxis (PrEP) the use of which is subject to conflicting guidance). Also, what ethical standard for acceptable foetal risk should be used in research studies that could potentially carry benefit to the foetus?

The issue of assessing and balancing risk and benefit for both mother and foetus is critical but complex and will need to be considered on a case-by-case basis informed by the most relevant data. Research should not be ruled out by default and the risks to the foetus of not having a healthy mother should be considered.

Case study 6: *Ethical considerations in developing an evidence base for PrEP in pregnant women*

Kristen Sullivan, University of North Carolina at Chapel Hill

Given the physiologic changes of pregnancy, research is critically needed to establish appropriate guidelines for safe and effective use of microbicides and pre-exposure prophylaxis (PrEP) and other preventives during pregnancy. The PHASES Project (Pregnancy and HIV/AIDS: Seeking Equitable Study) aims to develop ethically responsible, action-guiding recommendations for addressing evidence gaps through advancing HIV research in pregnancy.

3. Cultural views and the need for engagement

The case studies highlighted a number of cultural barriers to a pregnant woman's participation in research. This is a recurrent theme in international research or research with LMICs with strong traditions and worldviews differing from scientific worldviews or bioethical views which uphold individual autonomy or privacy as central values. Firstly, there may be cultural issues with how best to respect pregnant women as potential research participants through consent-taking. Should consent be taken only from the women as individuals or should it be widened to their network of relations who ultimately care for them and the resultant child? Although a country's law and international guidance may only recognize individual consent, in practice family decision-making or agreement may be the favoured approach.

Family may also be resistant to the study aim, such as lifestyle or nutrition interventions to prevent diabetes, on the belief that mothers-to-be should lead a sedentary lifestyle and consume high calorie food, as in **case study 4**. This was contrasted with an example from another culture where pregnant women are encouraged not to eat too much out of a concern that there will not be enough space for the foetus to grow.

Case study 4: *Should pregnant women be excluded from a community based lifestyle intervention trial?*

Elezebeth Mathews, Central University of Kerala

Despite strong scientific arguments for inclusion, pregnant women were excluded from a cluster randomized controlled trial that aimed to estimate the effectiveness of a culturally adapted lifestyle intervention in reducing the incidence of type 2 diabetes mellitus among high-risk individuals in Kerala, India. Reasons for this exclusion might include their classification as a 'special group' in the relevant Indian Council of Medical Research guidelines; concern that the community could attribute any complications that might arise during pregnancy to the trial, despite it being non-invasive; the risk of loss to follow-up due to the cultural practice of transient migration of pregnant women to their mother's house for delivery. Exclusion from the trial deprived pregnant women of the benefits of screening for high-risk status, and subsequent potential involvement in the lifestyle modification intervention.

Family may also be resistant to a study's research procedures, for example, blood draws to collect data on the belief that blood draws are just bad for mothers and the foetus, as in **case study 3**. This case also highlighted the deep conflict of interest and ethical challenge that can arise for the study staff when respecting the participant's right to refuse treatment even when sick – due to a belief that all medication could be harmful for the foetus – could result in preventable maternal or neonatal death.

There was agreement that robust community engagement needs to be done to reconcile cultural norms and beliefs with the ethical and clinical rationale for proposed research during pregnancy. GFBR participants recommended that research should be made as community specific as possible and that this process should start as soon before a trial as possible. It is not uncommon, for example, for different tribes in the same area to have very different norms and views so this must be considered. However, the degree to which traditional practices should or can be changed is unclear.

The following were suggested as strategies to reconcile respect for culture and health advancement through research:

- Involving the community in setting the agenda
- Engagement over the long term rather than short term basis
- Training of the study staff to have good rapport with the participants, bearing in mind this takes a long time to build
- Engagement with healthcare providers, including midwives, RECs and funders
- Engagement with men and partners
- Engagement with tribal leaders, chiefs, and religious leaders. An example was given from the Gambia where the placenta is sacred and so acquiring cord blood for research purposes was initially impossible. The researchers worked with religious leaders and now this research is going ahead.

In contrast to the case studies mentioned above, an example was given from the perspective of South African researchers who have found that over the years women are taking a more autonomous stance to their participation (including a move away from involving their partner or family in their decision-making). This is a

reflection of living in a dynamic society which leads to shifts in cultural views. While a fear of stigmatisation once resulted in women's reluctance to be involved in research, increasingly women have realised the potential benefits and are willing and often eager to participate. In this context the reason for non-participation of pregnant women in research has been largely due to the protective stance of RECs that, in their efforts to protect women, take a precautionary approach to pregnant women's participation. This example demonstrates that restrictive cultural views can also be held at the institutional level including not only the REC community but also research institutes and funding organisations.

GFBR participants were encouraged to act as advocates for research during pregnancy. Through broad and regular dissemination to their colleagues and institutions GFBR participants can help establish the concept as a norm and through this 'socialisation' help shift perspectives in communities and institutions.

There was agreement on the need for an advocacy group to act as a liaison between the researcher, community, RECs, regulators and the funders. This kind of platform or body could work to protect participants' interests, so research can continue and advance the scientific field.

4. Consent and the role of family members

Consent during labour: **Case study 1** presented considerations for obtaining consent during intrapartum trials, drawing on experience gained during a trial in India. Dr Hema Dhumale explained that emphasis on concerns regarding the ability to obtain ethically valid consent from labouring women, who may be anxious and distressed due to labour pains, has ultimately lead to exclusion of many eligible women in labour from intrapartum clinical trials. Similar issues were raised by Dr Sofia Salas in **case study 2**, which focused on a trial to compare the effectiveness and safety of two tocolytic agents in the treatment of preterm labour.

GFBR participants agreed that consent should be obtained as early as possible but even in cases where it can only be obtained during labour this should not prohibit a woman's participation. The following strategies were suggested as best practice:

- A pre-consent procedure should be instigated during usual pregnancy checkups so women can consider enrollment and understand the risks and benefits (both maternal and to the newborn).
- Evaluation should be on a case-by-case basis and the level of pain should be a determining factor.
- A gatekeeper could be used to independently assess whether the woman is competent to give consent – this could be a health professional or a person nominated by the woman. Some GFBR participants considered this a more useful option, rather than the objective criteria of 6cm of dilation of the cervix, as described in **case study 1**.

Case study 1: *Ethical issues associated with consent for intrapartum clinical trials*
Hema Dhumale, KLE University's J N Medical College

Obtaining ethically valid consent from labouring women is challenging because there is little time available during labour to provide the information necessary for the participant to understand and provide written informed consent. Moreover, women during labour may be anxious and distressed due to labour pains which may interfere with the capacity to take decisions. Emphasis on these concerns has ultimately led to exclusion of many eligible women in labour from intrapartum clinical trials. A standard outline of the intrapartum consent process should be developed with optional elements that can be adjusted depending upon the type of the trial and the participants.

Autonomy: The autonomy (or not) of pregnant women to give consent varies widely between regions and countries; it is influenced by local culture, as well as existing legislation. For example, **case study 3** focused on Laos where women are strongly influenced by their husbands and mothers in terms of their behaviour during pregnancy and lactation; reportedly nearly one-third of women who declined to consent to research did so because her family refused. In some cultures, e.g. the Gambia, the child is seen as the man's property and this has implications for the pregnant woman's ability to make an independent decision regarding her participation. Yet in other cultures, e.g. in South India, a woman's first pregnancy takes place in her family home and the father can be a great distance away and so would not typically be involved in the consent process (subsequent births take place at the father's house and the mother-in-law will play a key role). There was a recognition that in some cultures social harms may come to women if a husband's wish is not respected.

Tensions over the mother's participation may be resolved if husbands are engaged early in understanding the aim and value of the research. **Case study 7** reported qualitative findings regarding the role of male partners in Kenyan women's decisions to participate in research and concluded that understanding and addressing partner concerns and clarifying the role of partners in decisions to participate in research are important factors for improving the ethical inclusion of pregnant women in research. It is important to recognise that many women across cultures voluntarily choose to involve partners in important decisions and this involvement does not undermine a woman's autonomy. However, a strict requirement of permission/consent from all male partners when not wanted by some women was not supported, as it would compromise the role of women as autonomous persons. There was also concern that requiring partner consent may present an additional barrier to the inclusion of pregnant women in research, further limiting women's access to potentially beneficial interventions for their own health, and/or for the developing foetus as in the case of HIV-prevention. Engagement with partners in studies and community engagement, particularly with men in the community, were thought to be important strategies for addressing these tensions.

Case study 7: ***The role of intimate male partners in women's consent for research during pregnancy: A case study from the Partners (PrEP) Demonstration Project***

Kenneth Ngure, Jomo Kenyatta University of Agriculture and Technology

Against the broader sociocultural backdrop, Kenyan women typically seek social support for important decisions during pregnancy from partners, friends, and family. Such social support is not viewed as compromising their autonomy as autonomy is understood as a relational concept, conditioned on social relationships and support for important decisions. However, it is important to distinguish the role of voluntarily sought social support from the view held by some men that women must always obtain a man's consent because they do not have the right to consent on their own.

There was a general view that if women were asked to have sole autonomy and were not able to consult family members, this would exclude a significant proportion of women. Since the need to engage other family members in the decision-making process is the cultural norm in many settings, it is acceptable to integrate the consultation and engagement of other relevant family members in the consent and enrolment process. However, the women would ideally be able to determine which – and to what extent – family members should be involved and the weight should be placed on the value of the study for the women over their family members' objections. Ultimately, the decision to participate in research should be the woman's decision.

5. Law, policy and regulation

Four perspectives were presented during the Policy and Regulation Panel: a global view, focusing on the Council of International Organizations of Medical Sciences (CIOMS) guidelines on research with pregnant and breastfeeding women, a view through the lens of US regulation, a regional view from Latin American, and a local perspective drawing on the experience of conducting research on the Thai-Burmese border.

Dr Rieke van der Graaf explained that the purpose of the CIOMS guidelines is to indicate how fundamental ethical principles and the Declaration of Helsinki can be applied effectively in medical research world-wide in different cultures, religions, traditions and socioeconomic circumstances, with special attention to LMICs. For example, the guidelines clearly state that pregnant women must not be considered vulnerable simply because they are pregnant but that specific circumstances, such as risk to the foetus, may require special protections. The distinctive physiologies and health needs of pregnant women are recognized and research designed to obtain knowledge relevant to the health needs of pregnant women is promoted, based on consideration of the best available relevant data. The aim of the improved guidelines, which were launched shortly after this meeting, is to provide clearer guidance for RECs and researchers.

A further example of permissive regulation was given by Professor Anna Mastroianni drawing on practice in the US where pregnant women's participation in research is permitted under conditions specified in regulations and official guidance and is facilitated through local REC review with national regulatory oversight (e.g. the

Federal Drugs Authority (FDA)). Specifically regulation "Subpart B"[3] sets up an ethical framework and has extensive reach and international influence. Again, there is a presumption that pregnant women or foetuses 'may be involved in research' if certain conditions are met. Like the CIOMS guidelines, the regulations also address aspects of consent and risk/benefit (see Box1).

The permissibility of the regulation has, however, been stymied by regulatory and other legal obstacles. While the default approach is that many researchers and RECs continue to regard pregnancy as a near-automatic cause for exclusion, the real-life implications are that fewer than 20 FDA-approved drugs are approved for use during pregnancy and since 1980 the mean time taken to determine a teratogenic risk for prescription medications approved by the FDA has been 27 years.

Box 1 Selection provisions of the CIOMS guidelines and US Subpart B regulations

CIOMS guidelines:

- **Informed consent:** In no case must the permission of another person replace the requirement of individual informed consent by the pregnant or breastfeeding woman.
- **Risk and potential benefits:**
    - For research interventions or procedures that have the potential to benefit either pregnant or breastfeeding women or their foetus or infant, risks must be minimized and outweighed by the prospect of potential individual benefit (…)
    - For research interventions or procedures that have no potential individual benefits for pregnant and breastfeeding women:
      - the risks must be minimized and no more than minimal;
      - the purpose of the research must be to obtain knowledge relevant to the particular health needs of pregnant or breastfeeding women or their foetuses or infants.
    - When the social value of the research for pregnant or breastfeeding women or their foetus or infant is compelling, and the research cannot be conducted in non-pregnant or non-breastfeeding women, a research ethics committee may permit a minor increase above minimal risk.
- **Follow-up:** Short-term and long-term follow-up of the foetus and the child may be required in research involving pregnant and breastfeeding women depending upon the study intervention and its potential risks.
- **Abortion:** As a general rule, health-related research involving pregnant women that has the potential for harm to the foetus should 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.

US Subpart B:

- **Benefit/risk approach**: Where there is the prospect of direct benefit to the woman or foetus, risk to the foetus can be more than minimal but without that prospect the risk to the foetus should be no greater than minimal and the research purpose should be the development of important biomedical knowledge which cannot be obtained by any other means.
- **Paternal consent**: In general the father should be informed of reasonably foreseeable impact of the research on the foetus. However, if the research holds out the prospect of direct benefit solely to the foetus the father's consent is required in addition to the mother's (with exceptions e.g. incapacity).

[3]The official name is 'Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research'

Dr Carla Saenz described a tendency towards a restrictive regulatory approach in the Latin American region, which allows only a subset of what is ethical based on international guidelines, such as CIOMS. Underpinning this cautious approach is a lack of trust in the key players, including RECs and researchers and the result is the protection of pregnant women being interpreted as requiring exclusion due to vulnerability. In general this means inclusion only for pregnancy studies if there is minimal risk to the foetus but with extra provisions e.g. consent by others. In more extreme cases it is interpreted as inclusion in no circumstances. The Zika outbreak has thrown a spotlight on this restrictive approach; as an imperative to their own health and health of their offspring, and especially so in the context of the Latin American region, the need is urgent and different studies with pregnant women should be promoted.

Emancipated minors: Professor Phaik Yeong Cheah drew on her research experience to highlight a case where the law conflicts with research possibilities resulting in areas of uncertainty that discourage the inclusion of pregnant minors (see Box 2).

Box 2: Randomised trials of 3 artemisinin combination therapies for malaria in pregnancy, undertaken on the Thai-Burmese border in migrant clinics

Professor Phaik Yeong Cheah, The Mahidol Oxford Tropical Medical Research Unit

A number of ethical and practical challenges were faced during this research, including:

- The legal status of Burmese migrant women who had come to Thailand for better antenatal care
- The legal and cultural status of pregnant, emancipated minors from both Thailand and Burma.

These issues came to the fore in the case of a pregnant 15 year old from Burma, suffering from malaria who crossed the border to Thailand. Had she been a Thai citizen certain routes would have been available to confer emancipation (e.g. by registering her marriage at a district administration office with consent from one parent). However, given her unclear legal status in Thailand these options were not available. Professor Cheah explained that the issue of exclusion runs even deeper; the local community advisory board, which is aware of the prevalence of pregnant minors, was reluctant to widen the criteria to include any pregnant minors, even those from Thailand, due to cultural sensitivities. Ultimately, the ethical and legal challenges meant the sample size for the research was difficult to achieve and all under-age pregnant women were excluded.

In some countries, once married, a woman is considered emancipated and can be involved in research. However, even when emancipation is recognized in law, it may not be culturally acceptable. There may be cases where the legal guardian/parental consent can be waived, but that will only be possible if the country's legal system will allow it. An example was given from Uganda where a pregnant minor can participate if the REC decides that the research is not objectionable to the community and if there is a reason to target pregnant minors as a group. **Case study 5** gave a more restrictive example from India where RECs require the assent of married adolescent females and the consent of their legal guardians (typically their parents). However, this is practically and culturally problematic as after the marriage most girls move to their affinal homes and live with their husbands and in-laws. Neither the husband nor the in-laws are recognized as legal guardians and to seek the girl's parents' consent would be seen as disrespectful of the marriage.

Case study 5: *Exclusion of married adolescents in a study of gestational diabetes mellitus*

Mala Ramanathan, Sree Chitra Tirunal Institute for Medical Science and Technology

In India, persons below the age 18 are not considered legal adults and the concept of emancipated minor is not legally recognized. In this case this resulted in a trade-off between the research needs and the ethical difficulties of inclusion; ultimately for pragmatic reasons pregnant adolescents were excluded. An allowance should be made for young adolescents to identify an adult living in her household whom she identifies has having her welfare at heart to provide consent on her behalf. Alternatively, recognizing a married adolescent as a mature minor would avoid this form of unfair exclusion.

There was a lot of variation between countries and regions regarding if and when emancipation can be recognised (in law or culturally) and there was no clear conclusion on how to recognise this concept to enable research with pregnant adolescents. GFBR participants called for:

- clarity and harmonization on this issue, particularly between research ethics guidance applying to children/minors and research ethics guidance applying to pregnant women
- flexibility for researchers to make a case specific judgement on whether a legally underage woman can be permitted to participate in a trial, an approach that would facilitate the conduct of multi-centre, multinational protocols which at the moment are difficult to perform as no single procedure fits all contexts.

Role of lawyers: Professor Mastroianni highlighted the influential role of lawyers throughout the research process; they give interpretation to the regulatory ambiguities and inconsistencies (e.g. how to define the concept of minimal risk and how risk between the mother and foetus should be balanced) and set precedents for future research. Legal risk management is also an issue, including liability concerns regarding the subsequently born child and whether the sponsor of the research should be responsible for any litigation that arises out of any potential injury to the child – which could last until the child is 18 years old. How this risk is mitigated depends on the availability of insurance and compensation and how comfortable the sponsor is to assume the risk; without these there is an obstacle to legal risk management as the lawyer's concern about liability is magnified. Lawyers will also look at the legal environment of any research site (both laws as written and laws as interpreted) and this additional legal complexity can be an obstacle for researchers and research funders and further discourage research with pregnant women. **Precedents should be shared in the literature showing where legal obstacles regarding the interpretation and inclusion of pregnant women in research have been successfully overcome.**

Role of funders and regulators: Funders and regulators have the authority to change the incentive structure of research with pregnant women and to promote a policy of inclusion.

Role of RECs: Serving as the gatekeepers to research, RECs are an important and influential aspect of the governance of research. Anecdotal accounts described RECs taking a 'better safe than sorry' approach, i.e. to minimize risks for the institution and funders and to prevent public backlash by excluding pregnant women or setting a high bar of protections that hinder research. Such a cautious approach to managing risks may be understandable in a climate in which lawsuits against health agencies are common, and the recognition that

harm or serious adverse events to women and the child may only manifest years later which heightens liabilities and potential damages. However, there are also risks to pregnant women if they are not included in research and RECs should be encouraged to take such risks into account.

Dr Saenz explained that in some Latin American countries, with categorical prohibitions set down in regulations, there is little scope for RECs to analyse and discuss research proposals involving pregnant women on a case-by-case basis. Indeed, it is often the case that RECs support deferral to the law as they often lack the training required to consider the difficult cases which fall outside their familiarity or comfort zone.

Practical measures were proposed during the discussion included:

- RECs should be supported to better understand research in this context with case studies used to demonstrate that research with pregnant women is being done
- Research should be undertaken to look at how REC members view their role and responsibilities in reviewing research with pregnant women.

Privacy considerations inhibiting participation: There can be times when other legal requirements can serve as a potential barriers to research. For example, **case study 1** described that in India, audio–visual recording of consent-taking is a legal requirement for trials involving new drugs and vulnerable populations. GFBR participants agreed that such a requirement does not encourage research enrolment insofar as it impacts the privacy of the women undergoing labour and may heighten their anxiety.

6. Public health emergencies

Ebola: In August 2014 the WHO convened an Advisory Panel to consider the ethical issues associated with research during the Ebola outbreak. Members included representatives from affected countries, drug companies and ethicists and they recommended that – for the first time – research on investigational drugs or vaccines should be authorized in the context of an ongoing epidemic. Specifically they recommended that "because of higher mortality rates, children and pregnant women should be considered particularly vulnerable to Ebola virus and given special protection in interventions to be considered…"[4].

Dr Melba Gomes reported on the work of the WHO Ethics Review Committee (ERC), which reviewed the majority of the Ebola protocols; a total of 19 including vaccines and treatment protocols were reviewed within a six month period with an average response time of 4.5 days. On the whole treatment protocols attempted to include pregnancy but this depended on insurance cover. Also, pregnant women were excluded if reproductive toxicity data indicated risk. On the other hand, all vaccine protocols excluded pregnant women. This exclusion applied in the initial phases (I and II) but continued in each amendment even when the ERC and the Data and Safety Monitoring Committee advised that pregnant women should be included. This created a dilemma for the WHO ERC given the emergency situation and high rates of mortality in Ebola virus patients and their foetuses: should they argue for the inclusion of specific groups, including pregnant women, knowing that this would delay implementation as researchers sought new approvals from the manufacturers and legal representatives or should they approve the protocol excluding pregnant women? This was a case of speed

[4] 'Ethical considerations for use of unregistered interventions for Ebola virus disease'. Report of an advisory panel to WHO 2014.

versus justice and ultimately the protocol was approved excluding pregnant women. The opportunity to assess safety/efficacy under rigorous scientific conditions was lost leaving the next epidemic with no data in pregnancy. Dr Gomes argued that there is a clear and urgent need for requirements for inclusion and exclusion to be agreed with regulatory authorities and manufacturers in advance before the next epidemic. This need was further highlighted by **case study 9**, presented by Dr Séverine Caluwaerts, which describe an individual case of how the practice of exclusion affect individuals and families.

Case study 9: ***Pregnant women and experimental drugs in the 2014-2015 Ebola epidemic – the MSF experience***

Séverine Caluwaerts, Médecins Sans Frontières (MSF)

This case study describes the experience of a woman who was excluded from vaccination, despite it being clear at the time she contracted Ebola that the vaccine was protective. Exclusion from vaccination was due to the lack of documented evidence about its use in pregnant women and on the basis of the risk of potentially causing harm. MSF considered it unethical to recruit the patient to the ZMapp randomized clinical trial, given the 50% chance of denying a patient a potentially life-saving treatment. ZMapp was requested outside of the scope of the trial but was refused. Despite a subsequent agreement with a different company for emergency use of Favipiravir (an experimental antiviral drug that had shown limited success in previous small human studies) the patient died a few days later after going into spontaneous labour. The baby received ZMapp outside of the clinical trial and survived. In the case of the mother randomization was not relevant as finding a new patient with the same characteristics (age, pregnancy history, viral load, etc.) in the epidemiologic situation at that time was very unlikely. Given this and the backdrop of high mortality, how can denial of access to experimental, potentially life-saving drugs be justified? Dr Caluwaerts reflected that it seems that the baby was privileged compared to her pregnant mother.

Zika: Dr Gomes also reflected on experiences in relation to the Zika virus (ZIKV) which spread rapidly throughout Latin America and the Caribbean leading the WHO to declare Zika a Public Health Emergency of International Concern on February 1, 2016. A number of cohort studies are planned, e.g. case-control, to look at the risk factors for microcephaly and prospective longitudinal cohorts of newborns and infants born to ZIKV exposed pregnancies. These studies will face a number of ethical issues such as, what is the standard of care - does this include ultrasound, diagnostic tests and therapeutic abortion, if it is legally or culturally acceptable? If standard of care does not include ultrasounds but research does, what happens when abnormalities are identified? Who bears responsibilities and for how long?

In **case study 8**, Dr Carleigh Krubiner gave a detailed consideration of the issues associated with testing the most promising Zika vaccine candidates – live-attenuated vaccines – in pregnant women. Her work investigates how pregnant women fit into the Zika vaccine research agenda and aims to help investigators navigate the complex ethical questions around whether, when, and how to include pregnant women in research activities, especially in relation to live-attenuated vaccines. Challenging ethical questions remain involving complex tradeoffs regarding their participation in research, e.g. weighing potential harms and benefits of enrollment, the ethical acceptability of prospective enrolment, how to generate the best possible data on safety and efficacy and questions of how pregnant women can equitably share in the benefits of research.

Case study 8: ***Addressing the needs of pregnant women in the Zika response: testing and using a live attenuated Zika vaccine with pregnant women?***

Carleigh Krubiner, Johns Hopkins Berman Institute of Bioethics

Pregnant women are at the crux of Zika's most devastating consequences and so it is imperative to consider how they fit into the Zika vaccine research agenda. Live-attenuated vaccines are the most promising vaccine candidates but they present a number of ethical challenges and historically have been considered contraindicated among pregnant women due to a theoretical risk that the weakened virus used could cross the placenta and result in foetal harm. Yet, despite concerns about these theoretical risks – resulting in precautionary policies to restrict their testing and administration in pregnancy – there has been no evidence of foetal harm in the thousands of cases of inadvertent live-attenuated vaccinations given during pregnancy for diseases like Rubella, Polio and Yellow Fever.

In discussion it was agreed that:

- **International guidelines for emergency research with pregnant women during epidemics should be developed based on the experience in past epidemics.** Study files with templates for emergency research consent should be developed and be in place prior to future epidemics. There is a need for harmonisation in regions since epidemics cross national borders.
- **Trial insurance needs to be in place and adapted to emergency situations to reduce manufacturer risk**. Alternatively**, national insurance and compensation plans could be developed prior to future epidemics to ensure access to participation for pregnant women**; such a scheme would mean manufacturers are not responsible for any side-effects and any compensation in the event of an averse outcome would come from a government fund.
- **Drug manufacturers need to be more actively engaged in an ongoing dialogue** to enable not only research but also development that better fits the needs of pregnant women. The global health community needs to more actively engage with manufacturers to establish an ongoing dialogue and enable research and development that better fits the needs of pregnant women.
- In the same way that influenza had a significant effect on the advent of maternal immunization, the Ebola and Zika outbreaks are catalytic events that have the power to bring people together. There is an opportunity to identify jointly what the next steps should be and **these discussions should include wide public private engagement and consultations, e.g. bringing the manufacturers, the global health policy-makers such as WHO, but also the community to the same table.** Bringing all these different experts together could have a powerful effect as each group has a passionate understanding of what the drivers are for the decision-making processes in each of these different entities.

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