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Pregnancy specific research

Case study 1: Ethical issues associated with consent for intrapartum clinical trials

Hema Dhumale MD, Professor of Obstetrics & Gynaecology at KLE University's J N Medical College, Belagavi, India

Research project

Postpartum haemorrhage (PPH) is defined as blood loss of 500ml or more within 24 hours of delivery. Blood loss of more than 1000ml is considered as severe PPH. Atonic PPH is the most common cause of maternal mortality and morbidity in low income countries, particularly in Africa and Asia where it contributes to 30% of maternal deaths. Maternal mortality and morbidity due to atonic PPH can be prevented by the use of prophylactic uterotonic agents during the active management of third stage of labour. Though oxytocin injection is the ideal uterotonic for this purpose, the requirement of strict cold storage for maintaining its efficacy prevents it from being used in many low and middle income tropical country settings. Carbetocin RTS (room temperature stable) has been considered as a promising intervention for reducing PPH in settings where cold storage is difficult to maintain.

This trial aims to evaluate the effectiveness of Carbetocin RTS 100 mcg, intramuscular (IM) compared to Oxytocin (10U), IM in preventing PPH in vaginal deliveries. This is a multicentre, non-inferiority, randomised controlled trial. Women with singleton pregnancy expecting to deliver vaginally will be approached early in labour (<=6 cms of cervical dilatation) for participation and written informed consent will be taken. There will be audio- visual (A-V) recording of the entire consenting process (only in India). All eligible consented women will be randomly assigned at second stage of labour when vaginal delivery is imminent, with allocation sequence to receive either a single dose of Oxytocin (10U), IM or a single dose of Carbetocin RTS 100 mcg, IM. Placental delivery in all women will be conducted by controlled cord traction immediately after cord clamping. Blood loss will be measured using BRASSV drape for one hour following delivery. The main objective of this trial is to determine if Carbetocin RTS is similar in efficacy to Oxytocin in preventing PPH.

Ethical issues concerned with consent for intrapartum trials

Informed consent is the heart of ethical research. For any consent to be ethically valid, it should meet certain critical criteria – disclosure and understanding of relevant information, decision making competency of the participants, voluntariness of the decision and indication of agreement (e.g. written consent).

Meeting all these criteria and obtaining ethically valid consent from labouring women while conducting intrapartum trials is challenging because there is little time available during labour to provide trial specific information necessary for the participant to understand and decide to sign the consent form. Moreover women during labour may be anxious and distressed due to labour pains which may be thought to interfere with the capacity to take decisions. Emphasis on these concerns will ultimately lead to exclusion of many eligible women in labour from intrapartum clinical trials.

The two main ethical issues regarding the consent process for intrapartum trials addressed in this case study are :-

1. Excluding women in established active stage of labour with cervical dilatation of more than 6 cms, on the grounds that she will be too distressed due to labour pains to provide informed written consent.

The ability of a woman in labour to understand new information and to make an informed decision varies widely. The nature of the intrapartum complication being studied in the trial also determines the time available for providing informed consent. Despite the arguments questioning the competency of labouring women to give informed written consent late in labour, there is evidence in the literature that most of the anticipated variables like labour pains, duration of labour, anxiety and opioid analgesics, may not interfere with the ability of women in labour to understand the information provided to them and make decisions.[1] Many women with these conditions are still capable of giving their own consent, so it should not be assumed that they lack capacity. Hence denying women in labour to get included in the trial based only on the cervical dilatation cut off <= 6cms (early labour) seems scientifically and ethically incorrect. There is also a recommendation in the literature to consider the obstetric care provider (doctor/ midwife) as the "gatekeeper" to assess the physical and emotional state of the labouring woman and to determine her competency to provide consent[2]. This could be a novel alternative approach.

2. Audio-visual (A-V) recording of consent process for intrapartum clinical trials in India.

The issue of audio- visual (A-V) recording of the informed consent process is unique and applicable only in India. In 2015, the Drug Controller General of India (DCGI) amended the earlier regulation and made A-V recording mandatory only for trials involving vulnerable population and trials related to new drugs[3]. It has not been determined whether pregnant women constitute a vulnerable population in India. A-V recording might add to the anxiety and distress of labouring women and also may make them feel vulnerable with respect to maintaining privacy and confidentiality, thus discouraging women from participating in intrapartum clinical trials.

Conclusions and recommendations

There is a need to develop standard outline of the intrapartum consent process with optional elements that can be adjusted depending upon the type of the trial and the participants.

1. Intrapartum women who have received the relevant trial information and signed the informed consent antenatally, should be eligible to reconfirm and sign the consent during any stage of labour as long as they remain eligible and competent to provide consent. In acute circumstances, such women may also be allowed to provide oral consent at the time of complication supplemented by signing the written consent at a later stage[4].

2. Intrapartum women who have not received the trial information antenatally, should be eligible to sign informed consent in early labour (<= 6 cms of cervical dilatation). Such women may still be allowed to sign informed consent even late in labour (>= 6 cms of cervical dilatation), provided they are considered competent to provide consent by the obstetric care provider (doctor/ midwife), taking into account their physical and emotional status on an individual basis.

3. There should be a waiver for A-V recording of the consent process for all intrapartum trials keeping in mind the socio - cultural factors and also the need to protect the privacy of labouring women.

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Case study 2: Ethical conflicts in clinical trials in preterm labor

Sofía P. Salas, Program of Ethics and Public Policies in Human Reproduction, Faculty of Medicine, Universidad Diego Portales, Chile

Background

Preterm birth, defined as birth occurring between 20 and 36 weeks of gestation, is a major cause of perinatal morbidity and mortality. Preterm complications are the leading cause of death among children under the age of 5, causing nearly 1 million deaths annually. The rate of preterm birth ranges between 5-18% of all deliveries. In low-income settings, nearly half of births occurring before 32 weeks of gestation result in death due to lack of cost-effective care[1,2]. The acute use of a tocolytic drug to prolong pregnancy for up to 48 hours can be useful to provide a window for administration of antenatal corticosteroid or in-utero fetal transfer to an appropriate neonatal healthcare setting. However, there is no clear evidence on which tocolytic drug is preferable[3]. The most frequently used tocolytic agents are beta-adrenergic agonists (betamimetics)[4]. Although betamimetics are effective in delaying birth for more than 48 hours, maternal side effects - cardiovascular adverse events are reported in nearly 80% of the women – must be weighed against the benefit of short prolongation of the time of birth for the newborn[1,3,5]. Other tocolytic agents are nitric oxide donors, calcium channel blockers and oxytocin receptor antagonists, such as atosiban.

Research Project

A study design aimed to compare effectiveness and safety of the oxytocin receptor antagonist (atosiban) versus a betamimetic (salbutamol) in the treatment of preterm labor was presented at a local institutional review board (IRB) in Chile affiliated with a private teaching hospital. To blind the study treatment, a double-dummy technique was used (the study medications had identical shape, size, and color). Inclusion criteria included maternal age between 16 and 44 years, singleton pregnancy, intact membranes, between 24 weeks and 34 weeks gestation; reported or documented uterine activity, and cervical dilation between 2 cm and 4 cm in an otherwise normal singleton pregnancy. Primary outcome was preterm birth (< 37 weeks); secondary outcomes were preterm birth within 48h of randomization, at least 2 doses of corticosteroid administered prior to delivery, and preterm birth within 7 days of randomization. Both groups received standard obstetric and neonatal care, and there were no other interventions associated with their participation in the trial, except for strict data registration and non-invasive neonatal follow-up.

Ethical issues

As stated by the CIOMS guidelines, pregnant women are considered vulnerable research subjects but should not be excluded from participating in clinical trials[6]. In this proposal, there is no doubt that the research is relevant to this population and that it can only be done in pregnant women with premature labor. There are some specific ethical issues raised by this protocol.

1. **Should this type of protocol be done in a developing country and under what conditions?** When the local IRB discussed this protocol, the first consideration was to determine if this protocol should be done in our teaching hospital. To answer this initial question, we considered the following:
a. The condition (premature labor) is prevalent in the country and current therapy with betamimetics has important health risks.
b. The existence of a well-implemented neonatal intensive care unit was mandatory.
c. Although expected to be more expensive than current therapy, the new drug could be made available in the country and therefore benefit the local population.

2. **When to consent?** Preterm labor is an acute and unexpected condition, which threatens neonatal survival. Pregnant women with premature uterine contractions, are usually anxious and in pain, and may not be in the best condition to participate in a full consent procedure. As an alternative, the local IRB suggested that the maternity ward that will be enrolling women with the condition should implement a pre-consent procedure during usual pregnancy checkups. This could allow enough time for women to consider enrollment and understand the known maternal risks and potential benefits for the newborn of using the standard treatment or the new drug before the condition is present. In the event that they started with premature contractions, only those that had initially agreed to be enrolled would be contacted for an abbreviated consent procedure.

3. **Balance between the interests of the mother and the infant.** Premature birth poses greatest health risks for the newborn, but treatment, particular with tocolytic agents, has cardiovascular risks to both the mother and the fetus. Therefore, it is important to address risk/benefit ratio for both mother and the child during a research protocol in pregnant women.

4. **Which are the obligations of the sponsor?** It is difficult to determine the duties of the sponsor towards the mother and the child in the event a premature delivery finally occurs. The local IRB considered that at least the study design should choose a site that has the best standard of care (i.e., access to intensive care unit, antenatal corticoid administration, and eventually surfactant use). It is also necessary to determine which of these treatments the sponsor should finance if a premature delivery occurs. The IRB considered that those complications inherent to the condition (i.e. associated to prematurity) should be paid by social security or private insurance, but in the event of adverse effects, the sponsor should have insurance to cover the expenses.

5. **Who should consent?** According to Chilean regulations, only the mother needs to consent to participate in this study protocol. However, local adaptations to include the father might be necessary in some other countries.

Conclusions

Inclusion of pregnant women as research subjects for acute medical conditions such as threatened premature labor raises important ethical questions that should be carefully analyzed by the local IRB, considering not only the way that informed consent process is conducted but also the timing of consent, as well as how this research can be implemented safely within local facilities.

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Case study 3: Research ethics in pregnancy in Laos

Authors: Vilada Chansamouth MD (presenter), Research Physician, Lao-Oxford-Mahosot Hospital-Wellcome Trust Research Unit (LOMWRU), Microbiology Laboratory, Mahosot Hospital, Vientiane, Laos; Rose McGready, Mayfong Mayxay and Paul N Newton

Background - Laos

Laos is a land-locked country in Southeast Asia with 49 ethnic groups. It has one of the lowest per capita incomes in Asia (1,756 USD in 2014), the highest maternal mortality ratio in mainland Southeast Asia (197/100,000 live births in 2015) and a high incidence of infectious diseases. Even though the number of maternal deaths in Laos has decreased over the last decade, progress has been slow. Medical research in Laos has increased since 2000. However, little research has been conducted in pregnant women to inform policy to reduce their mortality.

Brief description of the research project

My project was a community-based prospective cohort study to investigate causes and impact of fever in pregnant women, in Pakngum District, Vientiane, Laos. We determined whether fevers were significant causes of maternal morbidity, low birth-weight and preterm birth in this setting. We also investigated vertical transmission of infection, maternal death, foetal death, neonatal death and congenital abnormalities. We intended to include 1,000 Lao pregnant women of any age and any gestational stage during 18 months. The follow-up period started from the recruitment date to six weeks postpartum.

On recruitment, pregnant women were asked for 10ml of blood, 10ml of urine and nasopharyngeal and pharyngeal swabs as baseline samples. Screening for syphilis, full blood count testing and obstetrical ultrasound were performed on the recruitment date or as soon as possible. Causes of fever were investigated using specific diagnostic tests (serology test, PCR and conventional culture). Four biopsies of placenta (1x1x1cm), cord blood samples and blood samples from mothers were collected at birth.

Of the 1,084 pregnant women screened, 1,000 were recruited, 47 (4%) did not meet the inclusion criteria, 37 (3%) declined to participate and 15 (2%) did not complete the study. The frequency of fever in pregnant women was 10% and the most common cause was influenza, followed by kidney infection and rickettsial infections. Miscarriage, stillbirth, maternal and neonatal deaths and congenital abnormalities were found in this study.

Issues in enrolling pregnant women to the study in this setting

Whilst ethical issues can occur in any stage of a study it is important to be aware of them before starting the project. The common issues that we encountered in Lao pregnant women, were related to (a) level of education; (b) cultural norms about family decision-making; (c) mistaken beliefs about research procedures and medical care.

a. According to Lao Social Indicator Survey 2011-2012, only 69% of Lao women aged between 15-24 years are literate. In our study, 47% of women had completed primary school with no further education. We did not

examine health understanding in our study participants. However, level of education could affect the decision of a pregnant woman to participate in the study, adherence to the schedule of follow-up, and whether someone would withdraw from the study. For example, in the small community setting of our study, news of health issues such as miscarriage, stillbirth or a neonatal death spread quickly. If the women or their families do not understand and think that the study led to such problems then pregnant women might be less likely to participate in research and current participants might withdraw from the study.

b. In addition, Lao women are strongly influenced by their husbands and mothers in terms of their behavior during pregnancy and lactation. This is a sensitive situation in Lao society. We had to accept that these women could not join the study if their relatives did not agree in order to avoid arguments within families. Nearly one-third of women who declined to consent did so because her family refused: the pregnant woman herself did not actually decide. In our study, the blood test in fever cases is highly beneficial in obtaining a diagnosis but women and their families (mothers or husbands) had very strong opinions about losing blood during pregnancy. Some believed that even a small amount of blood sample could cause unhealthy mothers and babies.

c. Some pregnant women believed that traveling (including going to hospital when they were sick) could make bad things happen during their pregnancies. Some women decided not to give more samples (blood or placenta) later during the study. This affected the quality of the study, e.g. convalescent serology is important for objective diagnoses for some pathogens. Some pregnant women or their families believed that all medications could be harmful for babies. Some refused to receive any antibiotic or further investigations even when they were sick. This created a deep conflict of interest between trained health staff and participants, and was an ethical challenge for the study. In this study febrile pregnant women received access to full, free, care and treatment, which is better than what is normally available to them. Respecting the patient's right to refuse treatment could result in preventable maternal or neonatal death in situations when the patient (or her family) refuses consent because of misconceptions. To try to ensure that pregnant women receive the best treatment requires a significant investment in community engagement, or improved female education to shift thinking.

What could be done better?

Good engagement between the research team and study participants is the key to reducing the problems mentioned above. The research team has to be trained how to approach pregnant women and to give as much information as possible to ensure that the women understand the aims and methods of the projects. For example, some research team members may have been too rushed to enroll study participants, without clearly explaining the relevant study processes. Women appeared to find out later that they were going to be asked to give more blood samples and this might have led to them withdrawing from the study.

Giving more health information to the community will improve both educational issues and reducing traditional beliefs that modern public health suggests are harmful. However, we have to make sure that the research team gives the correct information to pregnant women, husbands, and other family members and respects their decisions.

Non-communicable diseases

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

Elezebeth Mathews, Assistant Professor, Department of Public Health and Community Medicine, Central University of Kerala, India

Background

India has the second largest number of individuals with type 2 diabetes mellitus (T2DM) globally and this is expected to double by 2030[1]. The highest prevalence rates are in the state of Kerala, India with prevalence up to 20% in a few regions[2].Several large efficacy trials in both high-income countries (HICs) and low middle income countries (LMICs) have shown that the risk of developing T2DM can be reduced by as much as 60% following lifestyle changes[3-7].

An internationally funded cluster randomized controlled trial of a lifestyle intervention program to compare lifestyle intervention versus no intervention was implemented in the rural areas of Kerala. The trial aimed to estimate the effectiveness of a culturally adapted lifestyle intervention in reducing the incidence of T2DM among high-risk individuals.

Individuals with a diabetic risk score greater than 60 were enrolled (after ruling out diabetes based on the fasting plasma glucose and 2hr- postprandial plasma glucose through oral glucose tolerance test). Only high-risk individuals who were either normoglycemic, having impaired fasting glucose (fasting plasma glucose concentration of ≥100 and <126 mg/dl)) or impaired glucose tolerance (2hr plasma glucose concentration of ≥140 and <200 mg/dl), were included in the trial. Exclusion criteria included prior diagnosis of T2DM, myocardial infarction, heart failure, stroke, cancer, epilepsy, arthritis or dementia, current use medications known to affect glucose tolerance (glucocorticoids, anti-psychotic drugs, and anti-retroviral drugs) and pregnancy.

The occurrence of gestational diabetes is increasing worldwide[8]. As last reported in 2004, the overall prevalence of gestational diabetes in India was 16.55%[9], with the lowest rate of 3.8% reported in the northern region of Jammu,[10] and the highest rate of 17.8% reported in the southern state of Tamil Nadu[11].

Compelling evidence suggests that gestational diabetes causes both long and short term health effects for the pregnant woman, her fetus, and future child. For the woman, there is increased risk of gestational hypertension and pre-eclampsia during pregnancy,[12] and a very high risk for T2DM after the pregnancy. For the offspring, there is the risk of macrosomia, neonatal complications and birth defects.[13] Long-term effects on the children include a higher likelihood of developing childhood obesity[14] and glucose intolerance in early adulthood[15]. Further, limited evidence suggests a higher likelihood of girls born to women with gestational diabetes developing gestational diabetes themselves[16] causing a vicious trans-generational cycle of 'diabetes-begets-diabetes'[17].

Ethical issues

a. Fair inclusion exclusion criteria

Although no reasons were stated for excluding pregnant women from this cluster randomized controlled trial of a community-based lifestyle intervention program, the possible reasons for this exclusion are: (i) As per the Indian Council of Medical Research(ICMR) "Ethical Guidelines For Biomedical Research on Human Participants"[18] pregnant women are considered as "special group", and the investigators might have decided to follow the national guidelines (ii) the community could attribute any complications that might arise during pregnancy to the trial (especially as internationally funded trials are viewed suspiciously following a previous incident[19], although lifestyle modification is non-invasive with no potential harm to the pregnant woman or the fetus (iii) due to the cultural practice of transient migration of pregnant women to their mother's house for delivery, there was a significant risk of loss to follow-up; (iv) the modality to identify "high risk for diabetes" would be different for pregnant women than for others.

From an ethics perspective, pregnant women should have been eligible for inclusion in the trial. Pregnant women should have been screened for their high-risk status and given an opportunity to make an informed decision about research participation following the communication of information about the potential benefits and harms. Adopting a screening tool that is valid for pregnant women or enrolling pregnant women until the first trimester of pregnancy and assessing their risk status at that time could have been reasonable alternatives to exclusion. Legitimate exclusion could have been restricted to pregnant women with high blood glucose levels suggestive of gestational diabetes as per the standard criteria.

b. Favourable benefit-harm ratio

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. Their participation in the trial might have facilitated better health outcomes for the woman, her fetus and future child. It could also have contributed to a better understanding of the short- and long-term effects of lifestyle modifications on these populations. Furthermore, the inclusion of high-risk pregnant women would not have affected the primary research outcome of the study as it is the presence of the risk factors and the "high risk-status" that lead to gestational diabetes among pregnant women rather than the state of "pregnancy".

c. Community perspectives and experiences with research during pregnancy

Abstaining from smoking, engaging in regular physical activity, maintaining a healthy body weight, and a healthy diet[20-22] are related to a lower risk of gestational diabetes[23]. Alcohol and tobacco use is very low among women in Kerala. This is a good thing with respect to pregnancy. There are problems in India, however, with respect to the other three risk factors. In India it is widely believed that pregnant women should consume high calorie, energy dense food and restrain from any form of physical activity. The special diet is to meet the needs of two –the pregnant women and the growing fetus, and physical activity is thought to cause loss of pregnancy. These myths and taboos increase the risk of pregnant women developing gestational diabetes or diabetes

thereafter. Participation in a trial on adapted lifestyle interventions could have helped to challenges these myths and taboos.

Commentary on the issues, conclusions and/or recommendations for discussion or future research

Chronic non-communicable diseases, a major contributor of deaths in LMIC's, is lately recognized to have its onset in the womb, influenced further by environmental exposures. Unjustified exclusion of pregnant women limits the exploration and advancement of research on future disease prevention in the population at large. In most cases, there is no risk of harm to the pregnant women, her fetus and future child in participating in a lifestyle intervention study and pregnancy would in no way affect the primary research outcome. In this particular case, being part of the trial would have benefitted the pregnant woman, her fetus, and subsequent generations, with no foreseeable harm.

Yet with the prevailing community perspectives on pregnancy, the inclusion of pregnant women with no "visible health problem" in a trial would be difficult. Not addressing this issue will create knowledge gap in research evidence on the role of lifestyle modification in the prevention T2DM among pregnant women. Empowering the community and pregnant women to weigh the benefit for the mother and baby versus risk of participation in the trial, is crucial for them to make informed decisions on participation. This would also involve breaking irrational community perceptions regarding pregnancy.

A recommendation is for research funding organizations and ethical review boards to insist on justification(s) for exclusion of pregnant women from research.

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

Authors: Mala Ramanathan, Professor (presenter), Achutha Menon Centre for Health Science Studies (AMCHSS), Sree Chitra Tirunal Institute for Medical Science and Technology (SCTIMST), Kerala, India and K Sakeena

Background

According to the District Level Household Surveys[4] which provide reproductive and child health related data up to the district level in India, 24.7% of adult women aged ≥ 18 in Kerala, India reported blood sugar levels >140 mg/dl and 13.5% reported blood sugar levels >160 mg/dl[1]. For the District of Malappuram (within the state of Kerala), 14% of the women aged ≥ 18 reported blood sugar levels >140 mg/dl and 7.1% reported levels >160 mg/dl[2]. The burden of diabetes mellitus among adult women motivated a public health study on post-partum diabetes screening and follow-up for women with gestational diabetes mellitus (GDM) in the District of Malappuram[3].

This study had several objectives. The primary objectives were to examine the patterns of (and factors associated with) post-partum diabetes screening of women who had GDM during their most recent pregnancy, and to document patterns of post-partum morbidity among these women. A secondary objective was to understand health providers' perspectives on appropriate follow-up care for patients who had experienced GDM.

The study design used a mixed methods approach that included (i) a cross-sectional survey with a structured interview schedule for the GDM patients and (ii) in-depth interviews (using an interview guide) for health providers. The sample size for the study was 200 married women diagnosed with GDM during their most recent pregnancy in selected hospitals. The women included in the study were to have delivered three to six months before the date on which the survey was to be administered to ensure that all women had a minimum of 9 weeks post-partum experience to include in the morbidity study.

Ethical Issues

a. Fair inclusion exclusion criteria

The original study was designed to include 200 married women diagnosed with GDM during their most recent pregnancy in selected hospitals. This was important as GDM can affect all women who get pregnant and in India, procreation generally tends to follow marriage. There were significant challenges with the recruitment of married women under the age of 18. The risk of GDM follows the risk of type 2 diabetes mellitus in most populations and is associated with higher maternal age. Such risk among Asians was higher in the United States and Europe[4]. However, as the risk of pregnancy among women in younger ages is low, it is possible that reported prevalence of GDM could also be affected by the smaller share of pregnant women in younger ages. Therefore including women of all ages within the reproductive span is extremely important for an estimate of GDM.

In India, the *Prohibition of Child Marriage Act* stipulates that the legal age for marriage is 18 for a female and 21 for a male[5]. In the state of Kerala – a state known for high levels of literacy in general (and female literacy in

particular), better access to health care, and relatively higher ages at marriage – the prevalence of child marriage involving females under the age of 18 was 2.8% in 2012-13[6]. In the District Malappuram – the most densely populated of the 14 districts of Kerala and the district with the highest population growth rates – the prevalence of child marriage involving females under the age of 18 was 26.3% during this same time period and the percentage of all births in Malappuram to women between the ages of 15-19 years in 2012-13 was 6.2%[2].

b. Consent for emancipated minors

Typically, participation in research requires informed consent from adults (and emancipated minors) and assent from minors. In India, persons below the age 18 are not considered legal adults and the concept of emancipated minor is not legally recognized[7]. For this reason, research involving married adolescent girls is fraught with pitfalls.

Current practice in India is that Ethics Committees require the assent of married adolescent females and the consent of their legal guardians[8]. Legal guardians of females below age 18 are nominally their parents. The problem with obtaining consent from the parents is that after the marriage, most girls move to their affinal homes and live with their husbands and in-laws. Neither the husband (assuming he is above the age of 18) nor the in-laws are recognized as legal guardians.

The study on GDM in Malappuram district chose to exclude married women below age 18 from the study. As the work was being undertaken for completion of a dissertation for the MPH Programme, the duration available for completing the study was limited. Practical difficulties involved in obtaining consent from the legal guardians (the parents) lead to this decision. Seeking consent from the parents was a legal option, but might have been seen as disrespectful of the marriage (even though the law does not recognize the marriage of girls below age 18). Moreover, attempting to obtain such consent was not without a time cost.

Commentary on issues and conclusions/recommendations

This pragmatic approach to the research unfairly excluded a group of women and their children who are particularly vulnerable to getting diabetes mellitus. These young women and their children would benefit from screening and advice on lifestyle modification to manage to prevent diabetes mellitus. What would be the consequences of public policy based on such unfair exclusions, particularly if this will be more likely to happen in LMICs?

Studies on reproductive health of adolescents require that confidentiality be respected, even if consent for participation is obtained from parents or legal guardians[9]. Ethics committees have allowed for a young adolescent to identify an adult living in her household whom she identifies has having her welfare at heart to provide consent on her behalf[10]. Making such an allowance for other studies among married adolescents, particularly when they will directly benefit from such participation is one possible solution to this unfair exclusion.

Alternatively, if there is recognition of a married adolescent as a mature minor this form of unfair exclusion can be avoided. In LMICs where married adolescents and/or pregnant adolescents are most likely to be found and benefit from engagement in research, lack of such recognition is problematic and at times unfair.

Such a policy has implications for studies elsewhere in India where the proportion of women married before age 18 is likely to be higher not lower than that found in Malappuram. In such circumstances, exclusions for such pragmatic considerations would affect the outcome measure and also exclude far more women than would happen in situations where marriages before age 18 are fewer in number. What are the likely implications for outcomes of research in such circumstances in terms of the trade-offs between research needs and ethical difficulties of inclusion?

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Communicable diseases

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

Authors: Kristen A. Sullivan PhD (presenter), PHASES Project Director, Center for Bioethics, University of North Carolina at Chapel Hill, USA; Margaret O. Little and Anne D. Lyerly

Brief Description of the Project

Approximately 17.8 million women are living with HIV worldwide[1], and millions more are at risk of infection. Given pregnancy rates in general, and the fact that unprotected intercourse is a leading HIV risk factor for women, many women in need of treatment for HIV or access to preventive regimes are pregnant. Although efforts to prevent maternal-to-child transmission of HIV have contributed to an evidence base for the use of established antiretrovirals during pregnancy, there is a dearth of data to guide care in other areas of pressing concern for maternal and child health, including prevention of HIV in pregnant women at risk for disease.

In 2013, we launched the PHASES Project (Pregnancy and HIV/AIDS: Seeking Equitable Study) aimed at developing ethically responsible, action-guiding recommendations for addressing evidence gaps through advancing HIV research in pregnancy. During the course of this project, we have engaged a vanguard of researchers in the HIV community who are working to advance HIV research with pregnant women, including prevention research utilizing microbicides and pre-exposure prophylaxis (PrEP)[2]. Here we present a case involving an expansion of a key preventive strategy to pregnant women, adapted from a protocol currently being developed by HIV researchers for potential implementation in sub-Saharan Africa.

Background

Pregnant women in sub-Saharan Africa are at significant risk of acquiring HIV, with incidence rates comparable to other high-risk groups. Additionally, maternal HIV infection occurring during pregnancy is associated with high rates of maternal-to-child transmission[3]. Nonetheless, major knowledge gaps on how to best prevent acquisition of HIV in pregnant women remain.

Pre-exposure prophylaxis (PrEP) has been shown to prevent HIV infection in numerous high-risk populations, yet little is known about its use in pregnant populations. Indeed, pregnancy has been an exclusion criteria from all major trials of PrEP in Africa[4], and women who become pregnant on such trials are required to discontinue medication. The result has been conflicting guidance on whether and when women at risk for HIV should use PrEP for prevention when they are pregnant. For instance, recent Southern African guidelines list pregnancy as a contraindication to PrEP[5], while WHO guidelines permit PrEP use in pregnancy alongside calls for further study[6]. Given the physiologic changes of pregnancy, research is critically needed to establish appropriate guidelines for safe and effective use of PrEP and other preventives during pregnancy.

Future study, however, is uncertain due to debate about when and under what circumstances pregnant women should be involved in trials of PrEP and other preventives, despite considerable evidence that the medications used in PrEP, including tenofovir (TDF) and tenofovir-emtricitabine (TDF-FTC) are safe in pregnancy. These drugs have been studied for prevention of maternal-to-child transmission among pregnant women living with HIV and Hepatitis B, and among women with incident pregnancy during PrEP trials and show no evidence of adverse pregnancy outcomes[7].

We propose for consideration the case of a prospective study of oral pre-exposure prophylaxis for pregnant women at risk for HIV in sub-Saharan Africa. This case is adapted from a study being developed by the IMPAACT Network[8], which is an observational cohort study comparing pregnancy outcomes among women at risk for HIV taking oral PrEP to women who decline PrEP during the antenatal period. If implemented, this will be the first large prospective study of PrEP in pregnant women.

Ethical issues

The proposed case presents a trio of issues for consideration that are often at play when seeking to develop an approach to responsible research with pregnant women.

a. Are there are ethically relevant differences between risks of interventions in trials in the context of prevention of fetal disease (as in PMTCT, which is widely seen as acceptable) versus the context of prevention of maternal disease (which is the case with PrEP)?

b. What ethical standard for acceptable fetal risk should be used in research studies that could potentially carry benefit to the fetus? While the purpose of PrEP is to prevent maternal disease, success in that endeavor would also carry potential benefit to the fetus, namely, not being exposed to and potentially infected with HIV, and again not being gestated in the compromised environment of a woman infected with HIV. In such cases, what level of fetal risk is acceptable?

c. When in the development of new interventions should pregnant women be included in trials? Given the critical need for preventives used during pregnancy, this study raises the question about whether pregnant women should be included earlier and in studies designed to assess efficacy.

Commentary

There is an urgent need for HIV preventives during pregnancy; a prospective clinical trial of PrEP in pregnant women is an important step in meeting this need. Ethical issues needing consideration to responsibly include pregnant women in these trials include an exploration of acceptable risks in intervention trials for the prevention of maternal disease, determination of an ethical standard of acceptable fetal risk in the context of studies with potential benefit to the fetus, and the appropriate timing of the inclusion of pregnant women in research and development of new interventions. Discussion of these issues in the present case will also be helpful to guide strategies for other prevention modalities at various stages in development, such as the monthly vaginal ring and long-acting injections. Through this case study discussion among diverse global leaders in bioethics, we hope to further inform the development of ethically responsible, action-guiding

recommendations for addressing evidence gaps for research in pregnancy.

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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

Authors: Kenneth Ngure, Senior Lecturer, Department of Public Health, Jomo Kenyatta University of Agriculture and Technology, Juja, Kenya, (presenter), Susan Brown Trinidad, Kristin Beima-Sofie, Jared M. Baeten, Nelly R. Mugo, Elizabeth A. Bukusi, Renee Heffron, Grace John-Stewart, Maureen Kelley

Brief description of the research project

Pre-exposure prophylaxis (PrEP) with antiretrovirals is highly effective in preventing HIV acquisition. Pregnant women in high HIV prevalence regions are at significant risk of acquiring HIV and may benefit from PrEP to prevent their own HIV acquisition and subsequent HIV acquisition in their infant. However, previous investigational clinical trials of PrEP studies evaluating the use of PrEP to prevent HIV acquisition have excluded pregnant women due to concerns about fetal risk. The Partners Demonstration Project is an open-label demonstration project of PrEP use among HIV uninfected members of 1013 HIV serodiscordant couples Kenya

and Uganda[1]. There is significant interest in improving the evidence base for safety and efficacy of PrEP in pregnancy. The Demonstration Project gave women the opportunity to elect to continue taking PrEP if they became pregnant. A total of 30/34 (88%) women opted to continue PrEP during pregnancy and notably all women stayed in the project, regardless of their choice about PrEP during pregnancy. We conducted an ethics sub-study to characterize the biologic, social, biologic, and ethical considerations of a diverse group of key stakeholders with direct experience with PrEP use during pregnancy. In this research ethics case study we report qualitative findings regarding the role of male partners in Kenyan women's decisions to participate in the evaluation of a new intervention for HIV prevention during pregnancy.

Background

The majority of the world's 35.2 million people infected with HIV live in sub-Saharan Africa (SSA)[2]. Women account for more than 60% of HIV infections globally, and acute infection during pregnancy is associated with high risk of infant HIV infection[3]. Multiple studies in the African setting have reported high HIV incidence (1.3-10.7 per 100 women-years) during pregnancy[4-8], demonstrating the need for preventive interventions. Our work among HIV serodiscordant couples reported a two-fold increase in HIV acquisition during pregnancy[9], suggesting that in addition to unprotected sex, physiologic or social factors may further increase HIV acquisition risk during pregnancy. Implementation of PrEP in pregnancy has potential to avert HIV infections in pregnant women. However, many questions remain about drug safety during pregnancy and other important influences that might impact whether, when, and how PrEP becomes available to pregnant women in high HIV prevalence settings. In many countries with a high HIV burden, men play a key role in the health decisions of their female partners, and the experience of the Demonstration project illustrated the importance of understanding partners' perspectives when considering enrollment of pregnant women in PrEP intervention research.

Ethical issues

In our ethics sub-study we considered the following questions from the perspectives of women, male partners, and clinicians:

- How do male partners view the involvement of a female partner in research during pregnancy?
- What kinds of concerns do they have, and how do they view the role of women in decision making?
- Do men expect women to obtain permission from male partners or not, and what ethical rationale is offered?
- How do women think about partners' role in decisions about their own health and health during pregnancy?
- How do women and healthcare workers navigate social and cultural expectations when evaluating a new intervention for use during pregnancy?
- What, if anything, is exceptional about HIV in such decisions? For example, would a decision to evaluate a new malaria drug during pregnancy be considered differently by partners?

We observed a range of views among women about the need to involve male partners in decisions involving their own health, including decisions during pregnancy. Some women believed that male partners should be informed while others believed consent to participate was exclusively the woman's decision after getting the relevant information from health providers. Some women also mentioned wanting to discuss the issue of their

participation with friends and close family members. Most of the male partners reported that they should be consulted before women participate in biomedical research during pregnancy – with a few male partners reporting that their female partners should not participate without their permission to participate, using words such as '*must not*' and '*should not participate without permission.* Male partners also reported willingness to be involved in the research process in a supportive role, including accompanying the female partners to the health provider to discuss the safety of drugs during pregnancy, after which, an agreement would be reached between both partners and the doctor on whether the woman should participate in research while pregnant. Men and women shared many of the same ethical concerns about participation in research during pregnancy. When asked about how they weigh the health of the woman and potential risks to the unborn baby, both men and women were concerned about the risk of safety of the investigational product to the unborn baby and placed considerable value on health provider opinions and recommendations to understand these risks. Safety concerns to the pregnant woman were not paramount, possibly because this study was being conducted in the context of PrEP which had been found to be safe for the women.

Commentary

The under-inclusion of pregnant women in research continues to be a significant ethical problem. Within the Demonstration Project we observed two ethical tensions regarding the ethics of research involving pregnant women: how to improve the involvement of women in research during pregnancy while mitigating risks to the unborn child, and who should be involved in such decisions. The requirement of individual informed consent lies at the heart of ethically justified research to promote the rights of a participant as autonomous and capable of independent decision making. According to this principle, women have a right to make their own decisions about participation in research. However, little guidance has been offered for determining the role of intimate partner consent for research in socio-cultural contexts where it is often customary for partners to make other clinical decisions together during pregnancy and where men are viewed as playing a central role in decisions affecting family. Strict requirement of permission/consent from all male partners when not wanted by some women would compromise the role of female partners as autonomous persons. Furthermore, 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. Yet, some women and many partners viewed joint decision-making as important. One solution may be to consider women's views on this matter in the local context. 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. It will be 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.

Conclusions

Ethical guidance on the inclusion of pregnant women in research and the rapid uptake of novel HIV-prevention interventions needs to be relevant to the disease burden as well as considerate and culturally sensitive to male partners' concerns in contexts where the sociocultural norms support shared decision-making between

partners. 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.

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Public health emergencies

WHO experience: Ethical issues during emergency public health research on pregnant women

Melba Gomes, World Health Organisation Ethics Review Committee, Geneva

The goal of public health research is to determine the gaps and challenges in delivering health care, and improve efficacy, effectiveness and efficiency of interventions to improve health outcomes. Surely this also means improving health outcomes of pregnant women. It is therefore logical to include them in public health research that is relevant to their health needs. Unfortunately, because pregnant women are considered vulnerable, they are excluded from most research and consequently from the fruits of research. In efforts to identify effective medications (drugs or vaccines) the standard approach of excluding pregnant women from research is applied, even in public health emergencies that place them at higher risk of mortality than other populations. Through presenting the WHO Ethics Review Committee's experience in research, primarily in the context of public health emergencies, this presentation aims to highlight important ethical issues related to pregnancy – and encourage reflection and debate. Obligations to pregnant women when they are included in

observational studies needs clearer guidance. Among the challenges faced, exclusion of pregnancy in interventional research was the most intractable, involving scientific, ethical, and legal liability issues.

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 B. Krubiner PhD, Research Scholar, Johns Hopkins Berman Institute of Bioethics, Maryland, USA

Background

Over the past year, the Zika virus has spread explosively throughout Latin America and the Caribbean, with local transmission reported in 67 countries and an estimated 4 million cases expected in 2016 across the Western Hemisphere[1,2]. The rapid spread of the Zika virus (ZIKV) and its devastating impacts on the normal brain development of babies exposed prenatally led the WHO to declare Zika a Public Health Emergency of International Concern on February 1, 2016.

In response to this crisis, there has been extraordinary pressure on the research community to develop a vaccine as rapidly as possible[3]. Among the most promising Zika vaccine candidates are "live-attenuated" vaccines, which use weakened forms of the virus to induce immunity. Live attenuated vaccines can offer many advantages over other types of vaccine platforms, including that researchers can leverage work they have already done in develop live vaccines for other related flaviviruses like Dengue virus[3,4]. It is also possible that a live attenuated vaccine will be the preferred public health strategy for ongoing prevention efforts among women of reproductive age and children though mass vaccination campaigns[5]. This is because live attenuated vaccines typically require one dose to produce long-lasting protection, whereas killed or non-replicating vaccines often require multiple doses and often periodic booster doses[6] – issues that are especially critical in areas with challenged access to health care. Further, researchers are hoping to deliver a combined multivalent vaccine against both Zika and Dengue[3].

This raises a profoundly important question for the Zika vaccination strategy during pregnancy. Historically, live attenuated vaccines have been considered contraindicated among pregnant women, due to a theoretical risk that the weakened virus used could cross the placenta and result in fetal harm[5]. 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 fetal harm in the thousands of cases of inadvertent vaccinations given during pregnancy for diseases like Rubella, Polio, and Yellow Fever[4]. In the context of the Zika crisis, we must carefully consider the implications of a strategy that excludes pregnant women from participating in live vaccine trials and restricts their use in pregnancy in mass vaccination campaigns – particularly while alternative preventive strategies remain insufficient or unavailable.

On the one hand, there are the theoretical risks of using a live vaccine. However, as we have seen with previous vaccines, many women of reproductive age in Zika endemic areas who do not yet know they are pregnant will be inadvertently exposed in mass vaccination campaigns or may become pregnant shortly after vaccination

without waiting the recommended 30 days. Without safety data, we cannot know the impacts of this in a large-scale rollout. Furthermore, emerging evidence suggests that ZIKV has disruptive and destructive effects on the fetus across the pregnancy, not just at an early gestational age[7]. For pregnant women living in Zika endemic areas without prior exposure, it is possible that the benefits of a live attenuated vaccine to protect them from natural infection may outweigh the risks of vaccination. With pregnant women at the crux of Zika's most devastating consequences, it is imperative to consider how they fit into the Zika vaccine research agenda and help investigators navigate the complex ethical questions around whether, when, and how to include pregnant women in research activities. Our project aims to develop concrete, immediately actionable, consensus-driven guidance for conducting ethically responsible biomedical research with pregnant women in the context of the Zika epidemic.

Ethical issues

Given the realities of the Zika crisis, the devastating effects it can have on babies born to infected mothers, as well as the pace and direction of vaccine development and the public health response, many ethical questions arise with regard to live attenuated Zika vaccines:

a. Should pregnant women be allowed to participate in trials of live Zika vaccine candidates?
    i. How should we consider and weigh the potential harms and benefits of their enrollment?
    ii. Under what conditions would prospective enrolment of pregnant women in live vaccine trials – for Zika or other diseases – be ethically acceptable?
    iii. How might the inclusion or exclusion of pregnant women from this research influence the future access of pregnant women to an efficacious vaccine?
    iv. How can we ensure that pregnant women equitably share in the benefits of research?
b. Because many pregnant women would likely be given an efficacious live Zika vaccine (intentionally or unintentionally) during vaccine rollout, how can we ethically generate the best possible data on safety and efficacy to inform relevant health care decisions?
c. If a live attenuated vaccine is found to be efficacious and becomes available before any other more precautious alternative strategies are available, what should be offered to pregnant women living in areas of active Zika transmission?
    i. What ethical considerations are relevant in determining whether pregnant women should be offered a live-attenuated Zika vaccine?
d. How can and should local context, norms, values, and culture – both among pregnant women and broader Zika-affected communities – shape and inform the ethics analyses of these 3 questions?
        i. This includes, but is not limited to, access to family planning and reproductive services, access to abortion services, conceptions of disability and available services for people with disabilities, roles and shared decision-making among family members, health literacy, etc.

Commentary

Navigating these challenging questions and the complex tradeoffs they present requires careful consideration of the following key principles and norms for ethical research, among others:

- Favorable risk-benefit ratio – and how to assess this with many scientific unknowns on both sides of the equation.

- Fair distribution of the risks and benefits of research – both the potential benefits of research participation as well as the longer-term prospects of benefit from a licensed live vaccine
- Respect for persons, recruited participants, and study communities.
- Scientific validity of studies – given that enrolling pregnant women may complicate the analysis and that, in some cases, there may not be sufficient numbers of pregnant women enrolled to draw statistically significant conclusions.

Through a discussion of this case study among global leaders in bioethics, we hope to further inform the development of consensus-driven, actionable guidance on the specific issue of participation of pregnant women in live vaccine trials and subsequent use of live vaccines by pregnant women.

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

Séverine Caluwaerts MD, Gynaecologist with Médecins sans Frontières and Prince Leopold Institute of Tropical Medicine Antwerp, Belgium.

Case study: Nubia's mother

A 25-year old woman patient tested positive for Ebola disease in Forécariah province, Guinea. She was seven months pregnant in her third pregnancy. She was also a follow-up household contact of a known Ebola case—a woman who succumbed to the disease. Because she was pregnant she had not been eligible for vaccination.

The Forécariah centre where she was diagnosed did not want to keep the patient because she was pregnant. They considered caring for a pregnant woman with Ebola too complex and referred her to the Médecins Sans Frontières (MSF) managed Ebola Treatment Centre in Nongo. Mortality of pregnant women in previous epidemics with the Ebola Zaire strain was 90% according to the limited data available; in the current West African epidemic Ebola-related mortality in pregnant women was estimated at that moment to be around 70-80%. The patient also had a very high Ebola viral load, which increased her mortality risk even further.

A randomized clinical trial of the experimental product ZMapp was ongoing in Guinea. From the moment the patient was confirmed positive for Ebola infection, MSF tried to obtain ZMapp outside of the randomized clinical trial for her. In this trial patients were randomly allocated to either receiving only standard supportive care or to receiving ZMapp in addition to standard supportive care. MSF thought that it was unethical to have a 50% chance of denying this patient a potentially life-saving treatment considering her extremely high chance of dying. Additionally in the case of this patient 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—these were the last cases of the epidemic.

ZMapp outside clinical trial was refused. The decision was then made to administer Favipiravir, an experimental antiviral drug that had shown limited success in previous small human studies. In agreement with the company (Toyama, Japan) emergency use of Favipiravir in pregnant Ebola-positive patients was allowed. Four days after admission to the treatment centre, the patient went into spontaneous labour and delivered an apparently healthy baby girl of 3kg, called Nubia. The patient deteriorated after delivery and died 7 hours later of postpartum hemorrhage complicated by disseminated intravascular coagulopathy as a consequence of Ebola.

Nubia was also diagnosed as Ebola-positive. For the newborn, MSF did not encounter any problem in obtaining the ZMapp outside clinical trial and Nubia received the first dose the day after her birth. In total she received 4 doses of ZMapp, GS5734 (an experimental broad-spectrum antiviral), and white blood cells (buffy coat) of an Ebola survivor.

Nubia recovered and survived. She left the Ebola treatment centre after more than one month and is still coming weekly for surveillance and follow-up.

Ethical issues

a. Access to experimental drugs for pregnant women

In the Brincidofovir trial in Liberia (stopped prematurely) it was impossible to obtain permission to use the drug in pregnant women. For Favipiravir after negotiations monitored emergency use was allowed. ZMapp was only available if the woman were enrolled in a clinical trial.

b. Trial design

MSF thought that randomized placebo-controlled trials of experimental treatments were unethical. In the trials run in MSF managed Ebola treatment centres, historical controls were used instead of randomization to

treatment or placebo both in order to have quicker results and to avoid denying patients a potentially beneficial drug.

c. Pregnant women were excluded from Ebola vaccination

Nubia's mother contracted Ebola in October 2015. At that time it was clear that the vaccine was protective against Ebola (the results were published in August 2015). There was a risk of potentially causing harm if the patient were vaccinated—no data existed on the effects of the vaccine in pregnancy. On the other hand, the vaccine could potentially have saved her.

d. Exclusion of the patient from decision-making

There was no involvement of the patient in the decision to vaccinate or not. This poses some questions about supporting the autonomy of the patient in decision-making about her medical care.

Some concluding thoughts

It seems unjust that being pregnant can worsen a patient's prognosis because she is therefore denied access to experimental drugs in an epidemic as deadly as Ebola. More patient-centered and patient-beneficial discussions are needed instead of the self-protective and medicolegal attitude of researchers and pharmaceutical companies.

Nubia's mother was at very high risk to contract Ebola and she was never asked if she would want to receive this vaccine whose effects on the foetus were unknown. Additionally no standard pregnancy testing was carried out during Ebola vaccination campaigns so there were definitely pregnant women accidentally vaccinated. From personal communication: no foetal malformations in the accidentally vaccinated women were seen.

Nubia's mother could not get access to ZMapp despite her very poor prognosis (MSF wanted her to receive the drug, but the centre refused access outside the clinical trial which would have meant a 50% chance of receiving placebo). Nubia herself received ZMapp a few hours after her birth. Nubia's mother was denied a potentially beneficial drug while Nubia received the drug without delay. It seems that the baby was privileged compared to her mother.

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[1] http://www.gfbr.global/past-meetings/11th-forum-buenos-aires-argentina-3-4-november-2016/