Participation of Ghanaian pregnant women in an antimalarial drug trial: willingness, experiences and perceptions

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Background: With increasing orientation towards including pregnant women in clinical trials, investigators must conduct culturally acceptable research to aid recruitment and retention. There is limited information on experiences and meanings that pregnant women make of trial participation in Africa. This study reports experiences and perceptions of Ghanaian pregnant women regarding their participation in a clinical trial.

Methods: From October to December 2012, 45 in-depth interviews were conducted among pregnant women and their male partners regarding their experiences and perceptions of clinical trial processes as part of an anti-malarial drug safety and efficacy trial in pregnant women in the Ashanti region of Ghana. Analysis was by pre-determined themes and inductive analysis.

Results: Familiarity with the disease studied in the trial and trust in health workers favoured participation with the latter underlying acceptance of study drugs in the absence of symptoms. Adverse drug events were perceived as intrinsic sickness exhibited on the path to wellness. There were no cultural barriers to blood sampling during home visits but hospital-based sampling was preferred. Home visits were linked to participants having HIV infection.

Conclusion: This study contributes knowledge on sociocultural matters underpinning pregnant women's decisions regarding trial participation in an era of increasing drug trials involving pregnant women.

Keywords: clinical trials, experiences, Ghana, perceptions, pregnant women, willingness

Introduction

Pregnant women have traditionally been excluded from drug trials for fear of potential harm to the foetus/newborn, legal liability and stringent review board regulations, and therefore inferences regarding drug safety and efficacy in this population have been extrapolated from data in children and young male adults.^{1,2} Drugs lacking the rigour of scientific research in pregnant women continue to be used, rendering most cases of drug use in this population an unmonitored experiment and creating situations of scarce information regarding the best practices for recruiting and retaining pregnant women in clinical research.^{3–5}

Justified by a need to provide scientific evidence for the benefit of drug interventions used in this population, research guidelines are now being oriented towards including pregnant women in clinical trials.^{1,6} Consequently, pregnant women have been included in a number of clinical trials assessing the safety, efficacy and effectiveness of both preventive and treatment interventions.^{7–9}

Given the many new drugs in development, treatment options in pregnancy will increase and create more need for safety and efficacy evaluations in this population.¹⁰ Investigators must conduct research in a manner that is acceptable to pregnant women and ensure a successful informed consent process where relevant information on risks and benefits is presented and understood

within existing cultural contexts. A limited number of studies have sought to address issues of willingness and experiences of participation in clinical trials among pregnant women but these have mostly been in western Europe and USA.^{4,11–13} There is limited information regarding the experiences and meanings pregnant women make of clinical trial participation and factors that influence participation in sub-Saharan Africa, including Ghana. Only one study in Ghana on the user acceptability of intermittent screening and treatment for malaria in pregnancy compared with routine intermittent preventive treatment addressed certain elements of participants' social constructs of their participation.¹⁴ Deeper insights and information are needed to appreciate the mindset of pregnant women concerning trial participation in Africa and also design strategies for their inclusion.

A qualitative study, to capture the experiences and perceptions of pregnant women regarding clinical trial participation and factors influencing their willingness to participate, was conducted as part of a clinical trial comparing the safety, tolerability and efficacy of dihydroartemisinin-piperaquine and artesunate-amodiaquine for treatment of *Plasmodium falciparum* infection in pregnancy in Ghana.⁹

Materials and methods

The trial was conducted in the Bosomtwe and Bekwai districts in Ghana from July 2011 to October 2012.⁹ For this substudy, in-depth interviews (IDIs) were conducted with three different groups of people from October to December 2012. The first group comprised women who completed the trial and could be easily reached. The second group were non-study pregnant women with similar characteristics who accessed antenatal care (ANC) at St. Michael's Hospital during the trial period. This group was presented with verbal descriptions of the trial aims, procedures, risks and benefits and asked what would inform their decision to join or otherwise. The last group was made up of male partners of the women in the first group who were interviewed for their opinions regarding the trial participation of their wives/partners. Saturation was reached after interviewing 20 women in each of the first two groups but we only interviewed 5 male partners. The interviews with male partners were supplementary/pilot interviews to contextualise the experiences of women and as such saturation was not deemed necessary. Moreover, their availability was frequently a challenge and the study focused on women's perceptions and experiences.

Interview guides were developed for the different groups with themes extracted from literature review and cultural context and piloted before use. The themes addressed reasons for willingness to participate, experiences and interpretations of trial processes, including home visits and blood draws at home. Two interviewers with previous experience in qualitative methods conducted the interviews in the Asante Twi language. The interviews, each lasting 30–60 min, were audio-recorded with the participants' consent. Recordings were transcribed verbatim into English and cross-checked for accuracy of translation and retention of meaning.

The transcripts were manually coded and analysed independently by JO and ROA. Analysis was according to both predetermined themes and inductive analysis performed simultaneously

to develop categories and themes. Disagreements were settled by consensus building through discussions of investigator perspectives to obtain best-fit interpretations with the study objectives in mind.

Results

The two groups of women had mean ages of 27 and 29 y, respectively. The majority of women in both groups had formal education up to junior high school, belonged to the Ashanti ethnic group, were married with at least two children and were Christians. The various themes garnered from the IDIs with all three groups of participants are presented under broader descriptions of willingness to participate, perceptions of the clinical trial process and experiences during the clinical trial, and underlying health and illness assumptions.

Willingness to participate

Familiarity with the disease under study appeared relevant to participation decision in both groups of women. Malaria was a familiar entity among participants. They knew the link between mosquitoes and malaria and the need to sleep under long-lasting insecticide-treated nets (LLINs). However, other 'causes' of malaria including certain foods and poor handwashing practices were also mentioned. Malaria was also expressed as a constant feature of pregnancy.

Beyond the knowledge of malaria, familiarity with artesunate-amodiaquine (the trial control drug) also appeared to favour participation among the non-trial women specifically:

The mosquitoes bite us and that is why we get malaria. At times, the food that we eat too can contribute to it...And the fruits that we eat of late too is a factor. The chemicals are too much...and they say every pregnant woman has malaria (GO-AA-002, aged 34 y, P3).

For both groups of women, trust in the knowledge/competence of ANC midwives seemed important in the decision to participate. Among trial women, trust in health workers also seemed to underlie their belief when told they had malaria parasites although they were not ill at the time of screening for malaria parasites:

What made me join is that the nurses [ANC midwives] told us when we go and we are told there is malaria parasite in our blood, we should not worry. We will be given medication for us to be fine (GO-EE-02, aged 34 y, P4).

Anticipated health benefits were also relevant for participation decision in both women groups. This was based on an understanding of adverse outcomes of malaria in pregnancy:

If there are malaria parasites in my blood, I will agree to join to protect me and my baby from getting malaria (GT-AA-006, G2P1).

Another facilitator for participation was conceptualisation of the trial as a worthy way to eradicate disease:

Yes please I will join...it is because you are helping to get rid of disease (GT-EE-05, G3P2).

Perceptions of the clinical trial process and experiences during the clinical trial

Next, participants' perceptions of trial processes, including study drugs and adverse events, home visits, blood sampling at home and monetary compensation, were recorded.

Study drugs were widely accepted among the trial participants even although they did not have symptomatic malaria and had only attended the ANC clinic for routine monitoring. This acceptance resonated among male partners and seemed to depend upon trust in the health workers/research team:

She went for check-up and they told her that she has malaria. You need not to disagree with them [health workers/midwives] when they tell you something like that...they test blood to check whether there is any disease in it. So you cannot dispute that fact (G3-AA-002, aged 42 y, husband of GO-AA-010).

A range of adverse events including vomiting, dizziness and general weakness were elicited irrespective of the study drug taken. Adverse drug events were perceived as a familiar phenomenon in both groups of women. These did not seem likely to discourage trial participation in the non-trial women and were considered to be discomforts that must be tolerated to reach health:

These discomforts are normally associated with malaria drugs. For example the SP [sulphadoxine-pyrimethamine] malaria drug they give us at the antenatal is like that. Everybody complains about it. This is because, anytime you take it, you will fall sick for 3 days...you will have headache continuously and you will also vomit any food that enters your stomach. But after 3 days, then you feel okay again. Almost all the malaria drugs are like that (GT-AA-001, G1P0).

Home visits were used to capture adverse events and to sample blood. Each participant completing the trial schedule had six home visits. These were accepted by trial participants, their families and the wider community although there was some anxiety linked to non-familiarity with home visits targeting pregnant women specifically. Home visits were linked to the possibility that the women had HIV infection:

They said the illness might not be malaria...they said they have not seen such a programme before...that you are sick of malaria and health workers will visit you...they said it could be HIV/AIDS (GO-EE-06, P8).

Home visits were interpreted as a show of love and concern from the research team on the basis that only love for fellow

humans could drive such a venture. Others construed home visits as a government-driven programme to promote the welfare of pregnant women.

Blood samplings at homes were uneventful and none of the women in the clinical trial refused to participate. Similarly, there was no withdrawal from the trial on account of blood sampling at home. Neither the volume of blood drawn nor the pain of needle pricks seemed important compared to the frequency of sampling and perceived negative impact on foetal well-being. The non-trial participants had similar anxieties, such as people possibly claiming they have HIV, as well as concerns regarding the frequency of blood sampling.

Home-based blood sampling seemed aided by trial participants understanding of its relevance and a perception that they were being saved the time of having to travel to the hospital for the procedure to take place. However, some male partners expressed misgivings as to whether the blood being drawn was going to be used for the intended purpose. This mistrust underlined a preference for blood draws at the hospital compared to at their homes:

Taking of the blood at the hospital is better than if it is taken at home...someone might have a bad feeling about it that he [field worker] is using the blood for money rituals or something. Nobody knows if they will take the blood straight to the hospital or they will take it somewhere (G3-AA-002, aged 42 y, husband of GO-AA-010).

Study women interpreted trial processes, especially home visits, as an exhibition of concern for their health and reckoned there was no need for monetary compensation. The study drugs and the LLINs supplied were, in some cases, interpreted as compensation. However, others thought they should have been compensated in kind for their time and blood samples being taken.

Underlying health and illness assumptions

The meanings pregnant women attributed to adverse drug events were recorded. Non-trial participants were shown samples of the study drugs and they based their description of adverse events on previous use of the recognised drug, which in almost every case was artesunate-amodiaquine. Artesunate-amodiaquine was used long before dihydroartemisinin-piperaquine was introduced. Moreover, the latter is not approved for use in pregnancy.

One reason for the wide acceptance of the study drugs in both groups of women was the perception of a 'sick state' that is believed to be universal but may not always manifest physically. Hence, one did not necessarily need to be ill to take medication. This appeared to reiterate the expression of malaria as a constant feature of pregnancy and emphasised an acceptance of taking antimalarial drugs even when there were no symptoms of malaria.

Everybody is sick in any part of his or her body even though everybody is looking alright...: everybody is sick, just that you don't see it physically...If it has not put you on bed, you will never know that you are sick (GT-AA-02, G4P3).

Adverse events were variously conceptualised as a 'hidden sickness' that manifested after taking study drugs and this was likely to occur in those with perceived 'weak blood' that is overwhelmed by adverse events. It appears that 'hidden sickness' and 'sick state' are similar constructs of perceived illness states that are not physically expressed without a trigger.

You see when I went to the hospital, I was not sick...But when I started taking this drug, I was not feeling well at all. It has rather exposed all my hidden sickness. I became discouraged. I even said that I will stop taking the drug. Because I was strong before I took the drug. After I took the drug, it revealed all my hidden sicknesses in my body (GO-AA-010, aged 43 y, P4, who took DHA-PPQ).

I will take it if they give me another one. I believed that my blood was very weak for that drug and that was why I had all such experiences. I have to take it the next time they give me so that it clears all the malaria parasites from my blood (GO-AA-010, aged 43 y, P4).

Some participants also perceived adverse events as an independent entity that should be separated from drugs during their manufacture so as to render them more comfortable to take.

Discussion

The current study is one of the first to address willingness and perceptions regarding pregnant women's participation in clinical trials in Ghana. The findings have implications for participant recruitment and retention and remain relevant today despite it being 8 y since the data were collected. The inclusion of pregnant women in research borders on justice and there is limited literature regarding the perspectives of pregnant women themselves and their decision-making regarding research participation. IDIs were used as they permit greater trust and disclosure from participants and also avoid potential distractions that are associated with focus group discussions.

Holding simultaneous biomedical and locally construed notions of causes of malaria has been reported in previous studies and incongruence between these two can pose challenges for disease control if not tactfully handled.¹⁵⁻¹⁷ In the context of recruiting and retaining study participants in drug trials, it may be easier for participants to understand study information if their concept of disease causation aligns with known biomedical causes.

Malaria was conceptualised as an integral part of pregnancy presumably because most pregnancy-related complaints are similar to malaria symptoms. Study participants were knowledgeable about the consequences of malaria in pregnancy, presumably from study information given and health education provided during ANC. Relating malaria to poor handwashing habits is probably the result of mixed messages regarding health information given to pregnant women.

Perceived health benefits and trust in health workers, as facilitators for trial participation, agree with those reported in other studies.^{4,11-13,18,19} Recruitment into the trial was conducted in a hospital and involved ANC midwives who had previously delivered

routine care to most of these participants. This relationship may underlie the trust exhibited in the health workers/research team and contributed to participants' acceptance of study drugs and procedures.

Perceived health benefits in clinical research need to be examined cautiously in light of the ethical challenge of therapeutic misconception, where participants misinterpret the different goals of clinical research (contributing knowledge) and routine health-care provision (best patient care) and attribute personal benefit to research procedures.²⁰ In this context, health workers and researchers may experience conflict between their allegiance to providing the best patient care and to producing generalisable knowledge and thus risking therapeutic misconception.²¹ Adequate disclosure of research objectives in the informed consent process is necessary to address this issue. Contrary to other study findings, contributing to science was not proposed as a facilitator of trial participation.^{13,22,23} Indeed, advancing science is more likely to be given as a reason for study participation by well-educated people and the majority of participants in the current study were recorded as being of a low educational status. While it may be useful to emphasise the contribution to science in a study involving highly educated pregnant women, this may not be a convincing argument to present to pregnant women of a low socioeconomic status. Conceptualisation of the trial as a good way with which to eliminate disease may be regarded as fulfilling the ethical justification of 'social value' in conducting health research involving people. The description 'good' may be perceived as the trial having social value.

Study drugs were not seen as causes of adverse events but vehicles through which perceived 'hidden sickness' was expressed. Adverse events were also blamed for having 'weak blood'. In this sense, study drugs were perceived as being overwhelming for a comparatively weak 'blood/body system'. The concept of 'strong/weak blood' exists in other situations in the study area. For instance, when a newborn baby has a strong physical resemblance to one parent, that parent is said to have 'strong blood'. The concepts of 'weak blood' and 'hidden sickness' connote a 'body system' that does not measure up to some perceived standard. While no direct reference was made to pregnancy being an underlying factor for 'hidden sickness' and 'weak blood', it is reasonable to presume that pregnant women formed these descriptions with their pregnancies in mind. Discomfort/adverse events associated with study drugs are also perceived to relate to efficacy, and to reflect local beliefs that the more uncomfortable a drug makes one feel or the more bitter it tastes then the more efficacious it is.

Perceptions of adverse events relating to hidden sickness and weak blood suggest an inadequate comprehension of adverse drug events during the informed consent process. This needs improved health literacy training for better appreciation of adverse drug events, even outside clinical trials. Additionally, revising informed consent to highlight adverse events will facilitate better recognition of these effects in future trials, both with pregnant women and the general population.

Home visits were interpreted as a showing of love. This is rather optimistic compared to another study where pregnant women noted the burdens of research participation, including inconvenience and time commitments in keeping medication schedules,

among others.²⁴ Time commitment, as a burden in research participation, did not come up in the current study. Rather, the frequency of blood sampling (five) posed levels of anxiety that were comparable with another Ghanaian study.²⁵ Home visits were also conceptualised as a government programme similar to findings in a study on concomitant treatment of HIV and malaria in Tanzania.²⁶ The government link likely emanated from home visits conducted during national immunisation days when community health nurses and trained volunteers conducted home visits to immunise children.

Linking home visits and blood draws to HIV/AIDS is similar to findings from a previous study.²⁶ This link may arise from a development project implemented previously in the study area. This project provided support to people living with HIV/AIDS and included home visits. Although the HIV status of beneficiaries was not disclosed, it is possible that this activity contributed to shaping the association between home visits to particular people and the suspicion that they have HIV/AIDS. HIV/AIDS stigmatisation remains problematic in Ghana.

Contrary to preconceived notions from local beliefs and literature, there were no cultural barriers to blood draws at home.^{27,28} However, there was mistrust regarding the true purpose of the blood samples being taken. In line with local belief systems, some participants and relatives expressed fears that blood samples could be 'spiritually' used to financially enrich the researchers at the risk of harm to participants. Health facility-based draws were preferable as they removed doubts over the intended purpose of the sampling process. Researchers planning studies involving blood sampling in pregnant women should consider using a health facility for the procedure to help increase trust.

Similar interpretations of blood draws, including those devoid of spiritual connotations, have been expressed in other studies, and play a key role in poor understanding of the aims of research.^{27–30} Perceptions about blood draws reflect local orientations and, in some cases, community meetings have been held to discuss concerns raised.²⁷ The current study lacked such an approach as there was a need to preserve confidentiality. None of the women refused blood sampling. This may raise concerns about their genuine autonomy to refuse the procedure, but this was not the case as they were able to express concern over the number of times blood was sampled. Moreover, they understood they could leave the study at any point without repercussions. Blood sampling acceptance likely depended on perceived health benefits.

The current study combines actual experiences and perceptions of trial participants with those of non-trial participants presented with hypothetical situations. The dichotomy between 'what is' and 'what could be' is thus diminished. It has been 8 y since the study was conducted but the findings remain relevant as they contribute relevant and novel knowledge to understanding the sociocultural perspectives pregnant women may bring to bear on the design and conduct of clinical trials. None of the trial participants interviewed suffered a serious adverse event or withdrew from the trial. A random selection of the trial participants for this substudy may have led to inclusion of women with serious adverse events whose interpretations and experiences could have been vastly different. This is acknowledged as a limitation. Nevertheless, the views expressed are valid as they include dissenting opinions on various issues.

Conclusion

Perceptions shaping pregnant women's decisions to partake in clinical trials are relevant for participant recruitment and retention. With more trials involving pregnant women, researchers need to appreciate sociocultural aspects of research from the perspective of pregnant women. Ethics committees must ascertain the cultural appropriateness of clinical research procedures as these may impact upon the research. Further research of this subject is needed in more highly educated women and their male partners to ensure a broader appreciation.

Authors' contributions: This work forms part of JO's doctoral work. JO and HKT conceived the study; JO and ROA designed the study protocols and interview guides, implemented the study and analysed the transcripts; JO wrote the first draft of the manuscript with review by ROA; HKT and PM critically revised the manuscript for intellectual content. All authors read and approved the final manuscript. HKT and PM are guarantors of the paper.

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Data availability: The interview transcripts can be made available upon request to the corresponding author.

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