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Reasons for accepting or declining participation in the ASPRE trial: A qualitative study with women at high-risk of preterm pre-eclampsia

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What is already known about this topic?

- Motives for participation in medicated clinical trials in pregnancy include the potential health benefit of the trial participation, satisfaction with the received information, safety of the trial procedure and altruism;
- Less is known about reasons for declining, in particular amongst those at high-risk; avoidance of harm and practical barriers appear to play a role. Concerns about the placebo and negation of high-risk status have also been suggested as possible reasons.

What does this study add?

- A deeper understanding of reasons that facilitate, and hinder, women's participation in medicated clinical trials in pregnancy, especially in those identified as high-risk;
- A proposal to integrate psychological theories in an attempt to understand why women, when presented with the same risk status information, chose different behavioural pathways (ie taking part or declining participation in a clinical trial) to manage the threat posed by their high-risk status.

Abstract

Objective: To identify factors that affected the decision of pregnant women at high-risk for preeclampsia (PE) in accepting or declining participation in a medicated clinical trial (ASPRE) for the prevention of preterm-PE.

Method: This was a qualitative, cross-sectional study. A purposive sample of 14 participants and 13 decliners of the ASPRE trial were interviewed using semi-structured interviews. Data were analysed using template analysis.

Results: For participants, their high-risk status seem to have motivated them to take part in the trial. This was enabled by their perception that the trial drug aspirin was commonly used, the safety of the procedure, and the belief that they will be in receipt of extra monitoring in pregnancy. Decliners expressed discomfort about taking medications in pregnancy, and about the presence of the placebo arm; they seemed to be motivated by desire to reduce harm. Satisfaction with the information provided by the medical professionals was also influential in women's decision making, and so were the views of their partners and other trusted individuals.

Conclusion: Pregnant women's motivation to take part or to decline participation in a medicated trail can be understood as an attempt to cope with the threat posed by their high-risk status.

Key words: *ASPRE, preeclampsia, randomised controlled trials participation, qualitative research.*

Introduction

Due to concerns over maternal and fetal safety, pregnant women were excluded from clinical trials before 1993[1]. Since then, there has been a growing recognition of the importance of involving pregnant women in clinical trials in order to develop knowledge regarding the safety and effectiveness of medical interventions in this population. Currently, responsible inclusion of pregnant women in medicated trials with adequate monitoring is not only recommended but also encouraged[2].

Recruitment rates for pregnancy trials are low with only about 30% of eligible women choosing to participate[3,4]. Little is known about factors that influence participation in clinical trials during pregnancy and in particular in medicated clinical trials[5,6]. The most commonly given reasons for participation include potential health benefits to the mother and/or the baby[7-9], potential for superior care based on trial participation[8,9], satisfaction with the information received[8-12], absence of perceived harm of the research[9,11], and altruism[9,10]. There have only been three studies, to date, that have examined pregnant women's reasons for declining participation in medicated trials[7,11,12] . Understanding reasons for not taking part is of crucial importance as success of a trial depends on satisfactory recruitment. The reasons suggested so far include: risk limitation to the pregnancy, presence of the placebo arm, lack of satisfaction with the information about the trial and practical barriers[7,11,12]. In a study involving decliners at high-risk (for preterm labour), some women rejected participation based on their negation of their high-risk status[12]. Although it has been suggested that recruitment is influenced by the perceived trial relevance[13], it is not clear to what extent the health risk status of the pregnant women or their perception of their health risk plays a role in women's decision-making.

Psychological theories[14], such as for example the self-regulation theory[15]suggest that, when faced with a new health threat (e.g. an illness or an abnormal screening result),

individuals will form their own representations of that threat. Behavioural changes to ameliorate the threat will be dependent on the extent to which an individual perceives the risk as significant and personal, as well as the extent to which they believe that a change in their behaviour could impact the risk status and the outcome[16,17]. The relevance of psychological theories that consider these processes has not been explored thus far with 'at-risk' participants and decliners of medicated trials in pregnancy.

Studies regarding participation in medicated clinical trials, with rare exceptions[11], have been limited by the significant time lapse, extending to several years, between the actual decision-making regarding participation in the trial and the recounting of the experience. Such methodological limitations very likely introduced numerous possible biases (e.g. memory bias, bias influenced by the outcome of the pregnancy or the effectiveness of the trial drug) relating to the recall of the relevant information. Additionally, the majority of studies only sampled either those who participated, or only those who declined, offering in such a way a limited understanding of the factors influencing participation in medicated trials in pregnancy.

The aim of the current qualitative study was to elucidate the decision-making of pregnant women invited to take part in a medicated trial, i.e. the ASPRE trial, which examined whether daily use of a low-dose aspirin would reduce the incidence of preterm-preeclampsia (PE) in high-risk women. High-risk women were identified by the first trimester screening combined test and then randomly assigned to either 150 mg aspirin per day, or placebo, from 11 to 14 weeks until 36 weeks' gestation. Out of 2641 women eligible for inclusion in the ASPRE trial across the participating centres in six different European countries, 33% declined to participate and a further 8.5% withdrew consent after randomisation[18]. Our study examined the views of eligible UK-based women.

By understanding reasons for women's decision to take part or to decline participation in the ASPRE trial, our study aims to offer insights that could inform recruitment into future medicated perinatal trials. Furthermore, some of the concerns expressed by the decliners could potentially be relevant to medical professionals offering therapeutic prophylaxis to women at high-risk of preterm PE. The strength of the adopted design was in that this study was nested within the ongoing ASPRE trial, and the use of qualitative methodology enabled in-depth exploration of women's explanations of participation and non-participation.

Methods

Study Design and Sample

A qualitative approach was adopted using semi-structured interviews (topic guide is given in Table 1) that allowed in depth exploration of the influences on women's decision of whether or not to participate in the trial. The schedule was flexible enough to allow participants to introduce new issues of relevance. A purposive sample[19] of both participants (n = 14) and decliners (n = 13) of the ASPRE trial, all identified to be at high-risk for preterm-PE, were recruited from two London hospitals that participated in the ASPRE trial. The mean gestational age at time of interview was 21^{+5} weeks' gestation for participants (SD = 4.19), and 26^{+3} weeks for decliners (SD = 6.41)

Procedure

Pregnant women attending their 11-14 weeks' ultrasound appointment at two London hospitals were offered the opportunity to be screened for preterm-PE risk status. Women who took part were identified as either screen negative, i.e. low-risk for developing preterm-PE, or screen positive, i.e. high-risk for developing preterm-PE. Study inclusion criteria and procedure of the ASPRE trial have been published previously[18].

Women at high-risk of PE who had either accepted or declined participation in the ASPRE trial were mailed information about the current study together with a reply form and

a pre-paid envelope. They were informed that the research team was carrying out an independent evaluation of the impact of PE screening, risk status and trial participation on women's experience of pregnancy (data for the current study constitute a sub-section of the data collected for this larger project). In this way, we clearly positioned ourselves 'outside' of the medical research team involved with the recruitment into the trial, in order to facilitate engagement and disclosure of personal views. The reply form allowed women to give details of how and when they would like to be contacted; they were given the choice of the setting for the interview, either at their home or at the hospital. If neither was accepted, a telephone interview was offered. Two reminder letters were mailed to those who did not respond. Of those who consented, in each group, consecutive women were contacted until the target number of interviews was reached. Taking into consideration previous published research[5-10, 12], it was estimated that an interview with 10-12 women in each group would be needed to reach data saturation.

The interview was conducted by the second author (ZD, a PhD student, female, with previous training and experience in conducting interviews). The interviews were conducted face-to-face, at the woman's home (participants: n = 6; decliners: n = 2) or the hospital (participants: n = 7; decliners: n = 6), unless the woman explicitly requested a telephone interview (participants: n = 1; decliners = 5). Where the interviews took place face-to-face, the researcher obtained written informed consent; verbal informed consent was obtained during telephone interviews. All participants were aware that they had the right to decline answering questions if they were uncomfortable and terminate the interview without giving reasons and without subsequent influence on their antenatal care. The interviews lasted on average 30 minutes; they were audio-recorded. The local National Health Service research ethics committee granted ethics approval for this study (ref: 14/LO/1238).

Data analysis

Data for the current study constitute a sub-section of the interview data collected to evaluate the impact of PE screening and trial participation on pregnant women. The interview transcripts were analysed using template analysis, a method for thematic analysis and organisation of data[20], previously utilised in healthcare research[21,22] . Template analysis was chosen because it allows for development of *a-priori* themes, i.e. themes that are significant to the research question, to be developed before data analysis begins.

The research team consisting of two experienced academic psychologists (AN and JP) and a PhD student (ZD) developed an initial template, that drew on previous literature[5-10, 12] and pilot data derived from five participants and three decliners of the ASPRE trial to define our codes. Interview data were then mapped onto the initial template during the series of weekly meetings. Working collaboratively, we discussed and agreed to discard a priori themes and codes if they did not prove to be useful in capturing the key meanings present in the data which led to the modifications of the template; where material emerged which did not appear adequately covered by an existing code, the template was further modified. Previously coded transcripts were then re-coded to the modified template in an iterative process. The research team agreed that after about 8 interviews in each participant group, the template appeared stable and ZD proceeded to work through the remaining interview transcripts individually (the final coding template is available from the corresponding author on request).

Main themes and subthemes, where relevant, are illustrated by the verbatim extracts from interviews with both participants and decliners of the ASPRE trial. Whilst main themes represent principal findings regarding reasons for women's participation or non-participation in the ASPRE trial, the subthemes (where identified) offer additional discrimination; although

all encompassed by the main theme, the subthemes are distinct from each other that is they are internally homogenous and externally heterogenous[23].

Results

Of the 255 ASPRE trial participants approached, 178 (69.8%) did not respond; 63 (24.7%) responded but declined and 14 (5.5%) agreed to take part in the study. Of the 211 women ASPRE trial decliners contacted, 183 (86.7%) did not respond, 15 (7.1%) responded and declined and 13 (6.2%) agreed to take part in the current study. Amongst those who responded but declined participation in the interview study, the most commonly cited reason for declining participation was lack of time. We could not identify any systematic differences between women who agreed to take part in the study and those who declined. Characteristics of the women, both participants and decliners of the ASPRE trial who constituted our study sample, are presented in Table 2.

The context of decision-making: Knowledge and understanding of the ASPRE trial aims and procedures

Two themes, one indicating *good understanding* and the other indicating *absence of clear understanding of the ASPRE trial aims and procedural requirements* were identified. The majority of women (24/27), at an average of 10 weeks since the entry into the trial, were able to recall and report at least some of the key details regarding the aims, procedure and requirements of the trial.

> *"Taking the tablets, they explained everything, the tablets some would be aspirin some would be like dummy, they wouldn't know, we wouldn't know and to take them every day and they gave me the diary and explained if I have any symptoms or anything just to write it down."* (Participant 1).

In contrast, a limited understanding of the trial's aims and procedures were shown by three women (one participant and two decliners) who could not recall accurately the key aspects of the trial.

"They said to me that I would need to go in each week for an ECG I think it was and then I would just need to take these tablets and then they would see if they would work on like me and the other people that were taking part." (Decliner 11).

Factors influencing participation

Five main themes were identified as reasons for participation in the ASPRE trial: *positive attitudes towards the trial drug aspirin, personal benefit from trial participation, altruism, satisfaction with the information received* and *views of significant others and trusted professionals*. Some women expressed more than one theme as their reasons for participation in the trial. For the theme *positive attitudes towards aspirin*, two sub-themes were established: *little risk posed by participating in the trial* and *preference for taking the active tablet.*

Theme 1: Positive attitudes towards aspirin

Positive attitudes towards aspirin were identified as the key reason for the women's acceptance of trial participation; these were endorsed by the majority of participants (n = 13). There was a sense of reassurance that aspirin was being used in the trial, because it was a medicine they were familiar with and they were aware of its use for various conditions.

"I think if it was something other than aspirin…it would've been a harder decision but because it's aspirin or nothing it didn't really…just see it as safe, a lot of people take aspirin every day for various different things." (Participant 14).

In their explanations of their decisions to take part in the trial, the women highlighted their familiarity with aspirin and simultaneously acknowledged that the alternative was 'nothing' (ie. placebo) which meant that the trial posed little risk. This is captured by the subtheme:

Little risk posed by participating in the trial. This sub-theme refers to the women's perception (n = 8) that the trial procedure was appraised as low in risk as it involved either taking aspirin (ie a safe drug) or nothing (that is a placebo), which facilitated their participation:

> *"I knew its aspirin or placebo, if it would have been a weird drug that I hadn't known about that it would be completely different, because I knew its either aspirin or not than I thought it's fine"* (Participant 2)

Due to these reasons, the decision to take part in the trial was not too difficult for most participants. Some women expressed that the reassurance provided by the doctor about the safety of aspirin had informed their view that indeed the trial posed little risk to themselves and the baby, and taking part was thus preferable to not taking part, given their high-risk status.

> "*I suppose because if I wasn't part of the trial I wouldn't be taking anything anyway. It's not really, I am kind of, I am not losing out*" (Participant 8)

Preference for taking the active tablet (i.e. aspirin). This sub-theme refers to the expressed desire of three women who stated that they would have liked to know that they were in the active arm of the trial and therefore taking the aspirin tablet rather than a placebo. These women's answers revealed that knowing that they were screened as high-risk of preterm-PE created a sense of discomfort and a desire to minimise this risk through taking aspirin.

> *"I would have liked the confirmation that what I am taking is aspirin…if I've got a risk I want to try the thing that is going to lower that risk."* (Participant 3).

However, at the same time, the women recognised the experimental nature of the project and the need for randomisation and were happy to comply with the trial requirements.

Theme 2: Personal benefit from trial participation

This theme reflects women's beliefs that by participating in the trial they would personally benefit by obtaining superior antenatal care i.e. having additional scans and monitoring; this was expressed by 11 out of 14 women. In view of their high-risk status, this additional care was seen as a source of comfort and reassurance, preferential to not participating in the trial:

> *"I felt more like I was going to get more help. I was going to get more care. For me, that was really nice…this time I've had extra scans and I have been monitored and my blood pressure has been checked more. I think the care has been nice for me."* (Participant 4).

Theme 3: Altruism

This theme refers to the altruistic attitudes expressed by 12 participants of the trial. As illustrated by the quote below, the majority of women who agreed to participate in the ASPRE trial believed that in doing so they would contribute to the medical knowledge regarding PE treatment.

> *"…probably just to assist with the research to be honest. I know it's really difficult to recruit and I am quite happy to kind of be part of the trial that might make it better in the future, which sounds quite altruistic"* (Participant 5).

Theme 4: Satisfaction with the information received

Satisfaction with the information received by the medical team had a positive impact on women's decision to participate in the ASPRE trial. Eight participants reported feeling reassured by the provided information, the way medical professionals answered their questions and by the provision of contact details in case of any problems, which facilitated their participation in the trial, as illustrated by the quote below:

"They were really good to me. Really good. They have been listening to my heart and checking how things are going….they gave me enough information to make me want to do the trial. It's helped". (Participant 4)

Theme 5: Views of significant others and trusted professionals

All but one woman reported discussing the trial with their significant others, be it their partner, other family members, or professionals they trusted (e.g. midwife):

"My husband and I had a bit of a discussion what we would lose if we did or didn't do it, so kind of together we decided there was nothing to lose by going through" (Participant 10)

The input from others was seen as important, but most women expressed the view that the decision was solely theirs or one jointly made with their partner. Some significant others were supportive of them taking aspirin or happy to go with whatever decision the woman felt comfortable with. One woman reported that her partner did not wish for her to take part but she decided to participate regardless of his view.

Factors influencing non-participation

Four themes, amongst reasons cited by the decliners of the ASPRE trial were identified: *negative attitudes towards medications, placebo arm, insufficient information about the trial* and *views of significant others and trusted professionals*. Some women endorsed more than one of these themes as their reasons for declining participation.

Theme 1: Negative attitudes towards medications intake in pregnancy

The most commonly given reason for declining participation, which was discussed by twelve women, was negative attitudes towards taking medication during pregnancy. The women's responses highlighted a general unease regarding intake of any medication whilst pregnant:

"I wouldn't have been interested, because I don't want to take anything, any sort of medication. Me personally, it's just how I am… I didn't want to be in that position where I have to take medication, because I don't have to, basically" (Decliner 8).

Although the women acknowledged their high-risk status for preterm-PE, this information did not motivate them to take action. The representation of this threat was weighed against the 'intrusiveness' of the preventative trial intervention which was then rejected.

"..the idea of taking a drug every single day when you are pregnant, even though it's known to be safe ...I would have more kind of acceptable intervention...would be more regular blood pressure monitoring or more regular urine samples or something like that, rather than taking a drug every day, just because I think you have it so drummed into you that you have to be careful what you put in your mouth when you are pregnant. The thought of taking a drug every day seems like quite a major thing to do and also quite a medical thing to do" (Decliner 1).

Some women further explained the particular reasons as to why they had a negative attitude towards the trial medication including concerns about the safety of aspirin specifically and/or their medical history and these are explored in the sub-themes below:

Concerns about the safety of taking aspirin. This sub-theme refers to the concerns about the side effects of aspirin intake, which were expressed by five women. Although the women had been informed that adverse effects of aspirin were unlikely and that aspirin was not harmful, they stated that they simply did not wish to take any risk.

"My question was is aspirin dangerous for your unborn child. They were like no, no, 100% no danger. I was a bit surprised about that, because I am sure in the literature I read…you weren't supposed to take it, weren't supposed to take anything other than paracetamol….I kind of decided, I'd minimised what I had been taking in terms of drugs and paracetamol

and stuff. I wasn't going to likely start taking aspirin in case there were any side effects." (Decliner 2).

Medical complications, past and present. Past or existing medical complications and conditions also influenced three women who declined participation in the trial. These women expressed that adding aspirin to their regime of medications for (pre) existing conditions was seen as undesirable, as illustrated below:

"I've got sickle cell disease, there's other medications I take and I didn't want to be taking so much even though he said that the test you will, you might be on a placebo, you might be on a low dose aspirin, I just thought I'm already taking a lot I didn't really want to add another one." (Decliner 13)

Theme 2: Placebo arm

The focus of this theme which we termed 'the placebo arm' is on the feelings of discomfort and uncertainty that six of the decliners expressed regarding the allocation to the placebo arm of the trial or with not knowing in which arm of the trial they would be placed. These two sets of concerns are reflected in the two subthemes below *wanting a guarantee of taking aspirin* and *"you don't know what you are taking":*

Wanting a guarantee of taking aspirin. Four decliners specifically stated that if aspirin were effective in reducing the likelihood of developing preterm-PE, they would want the guarantee of taking it, rather than the possibility of taking the placebo.

"If they had just have said to me that it was just aspirin I probably would have done it. No, it was the fact that well possibly I could be taking nothing for how many months and what good is that going to do for me" (Decliner 12).

Two women were speaking hypothetically, whilst two others declined participation and took aspirin outside of the trial. For the latter two women, the decision to take aspirin was made because of the pressure by family members.

"You don't know what you are taking". Two women expressed that not knowing whether they were taking, aspirin or placebo, would have been confusing to explain to other medical professionals should the need for that arise:

> *"I know I could have gotten the placebo but em, and I think that as well because also not knowing, cos when you're going for your appointment with your midwife or anything had happen and I'd gone in the hospital and they say are you taking any medication, to say well I could be but I don't know, that again is also quite difficult"* (Decliner 5).

Theme 3: Insufficient information about the trial

Three women stated that lack of sufficient information about the trial was a minor contributing factor for their non-participation:

> *"She couldn't answer all of my questions, she probably wasn't expecting me to ask those kind of questions, and I think it would have been quite nice if she could have pointed me to something. I could have read more to give more details*" (Decliner 5)

Theme 4: Views of significant others and trusted professionals

Similarly to the participants of the trial, nine women decliners reported discussing their decision with family members and one woman reported talking to her midwife. Six women reported that their family members' negative attitudes towards medication intake in pregnancy reaffirmed their decision to decline participation:

> *"I brought my mom cos I always bring someone to my hospital appointment…and they told me about the research and even I said no ..she said yeah you made the right choice even I would have said no as well ."* (Decliner 6)

Discussion

Women at high-risk of developing preterm-PE were invited to take part in a RCT, the ASPRE trial, to examine whether aspirin can prevent the occurrence of this condition. Our study findings demonstrated that the majority of both participants and decliners, at approximately three months since being invited into the ASPRE trial, had a good level of understanding and recall of the trial's aims and procedural requirements.

Self-regulation of health and illness theory [15,16] suggests that the motivational impact of high-risk information depends on the representation of that risk which will influence individual's cognitive and behavioural attempts to minimise health threat and associated emotional reactions. Recently, Harris and colleagues[24] used the self-regulation theory to understand the psychological impact of high-risk PE status on pregnant women. In line with other studies which suggest that an individual's perception of risk may not always align with professionals' views[25,26], Harris and colleagues suggested that women found to be at high-risk for PE did not perceive themselves to be at risk for the condition. In managing the threat posed by the positive screening result some women named by the researchers 'danger managers' focused on the consequences of this result on themselves and chose behavioural pathways to manage threat via information seeking, positive behavioural changes and cognitive reappraisals, as their preferred coping strategies. In contrast, women named 'fear managers' focussed on the fetal consequences of PE and they chose avoidance and threat minimisation to cope with the positive PE screening result.

All women in our study were aware of their high-risk status for preterm-PE which they recognised to be the reason to have been invited to take part in the ASPRE trial. For participants of the ASPRE trial, their high-risk status represented a threat which seemed to have motivated them towards engagement in action to prevent PE; thus taking part in the trial could be seen as a behavioural pathway to manage threat posed by the high risk test result,

similar to the 'danger managers' active approach to coping with their high-risk status. The familiarity and the perceived safety of the trial drug (aspirin) and the procedure, together with the reassurance provided by the doctors that taking aspirin would cause little or no side effects or risk to themselves or the baby, were important in arriving at the view that the trial posed little threat. Few participants of the trial expressed that knowing that they were high-risk meant that they would have preferred taking aspirin rather than the placebo; however, they were willing to accept the clinical equipoise inherent in the trial and the need for randomisation. A preference for the active drug in medicated clinical trials is often reported[5]. Participants also felt motivated to take part in the trial as they would be in receipt of additional scans and monitoring during pregnancy, which was reassuring given their high-risk status. Apart from personal benefit they also endorsed wishing to contribute to the medical knowledge; altruistic beliefs, but only when self-interests are also endorsed, as appeared to be the case in our sample, have been referred to as 'weak altruism'[27], and have been identified by other studies[6,8].

Contrary to the participants, the majority of decliners expressed negative attitudes towards taking any medications in pregnancy. Similarly to the 'fear managers', these women chose to avoid or decline participation in the trial based on their rejection of the intake of aspirin which they perceived as an excessive request. The women seem to wish to minimise any potential harm or danger that could be caused by medication intake; for most, this was not specifically about aspirin, but more about a desire to minimise any medication intake whilst pregnant. During their decision-making, many decliners seemed to struggle to accommodate apparently discordant messages from the medical professionals: the commonly advocated message of avoiding medicines in pregnancy and the request of taking aspirin through the ASPRE trial participation. Participation in the trial was declined by some women on the grounds that aspirin was not a proven method of PE risk reduction, or that it would be

difficult to explain trial participation to other medical professionals, and hence they did not wish to partake in the trial, again minimising any potential for harm. In contrast, for a few women decliners of the trial, their high-risk status activated beliefs concerning the necessity of action on their part and they declined participation as they wanted the certainty of taking aspirin rather than allowing the possibility of being in the placebo arm of the trial. They subsequently took aspirin outside of the trial. For this subset of women decliners, the threat caused by their high-risk status seem to be so significant that it motivated them to engage in what they saw may be a more certain preventative action against developing preterm PE compared to taking part in the trial where they could be in the placebo arm. This, in a few instances, occurred because of the pressure of significant others.

In line with other studies[7,9,10], views of important and trusted individuals, and women's partners in particular, played a role during women's decision-making regarding participation in the trial. Social support can relieve anxiety in pregnant women[28] and increase the uptake of behaviour change[29]. In our study, the views of significant others seemed to have reinforced women's decision regarding participation. Only in a few cases, the women stated feeling pressured to take the aspirin (outside of the trial) or they decided to take part in the trial against the wishes of their partner.

Some limitations to our study must be noted. First, the study findings reported here are based on in-depth exploration of the reasons regarding participation in the ASPRE trial in a small number of high-risk women in two London hospitals, who were mostly Caucasian, well-educated, and living with their partners. These views might not be generalisable to all women, across the six countries, who accepted or declined participation in the ASPRE trial. Secondly, the response rate to our qualitative study was low, although it was in line with another similar study with high-risk decliners[12]. Thirdly, we suggested that psychological theories and, in particular the self-regulation theory, can be a useful heuristic to understand

women's motivation to take part in the medicated clinical trials. Central to women's coping responses are their representations of threat posed by their risk-status. Whilst we did not specifically examine women's representations of their PE risk-status and related them to their uptake of trial participation, we proposed that this may be a way of understanding why women, presented with the same risk status information, chose different paths to deal with the uncertainty and threat posed by it. We suggest that future research in the area should examine the relevance of the self-regulation theory more specifically in the context of the uptake of participation in clinical trials in women at high-risk. Notwithstanding the above limitations, our study offers insights from both participants and decliners, the latter group often neglected in research, as to what motivated pregnant women to partake or not in a medicated trial for the prevention of preterm-PE.

There are a number of implications of our findings. Medicated clinical trials in pregnancy are likely to represent a significant challenge for the recruiters. The ASPRE trial succeeded in achieving high recruitment rates but this may not be the case with less familiar and known medications. As our findings have shown, information regarding safety are of paramount importance to the women invited to participate in a medicated clinical trial. In-person recruitment, that would allow women and their partners an opportunity to address concerns about research safety and procedure, and deal with fear and anxiety concerning medication intake in pregnancy, that are likely to mediate willingness to participate, would be of crucial importance. Such in-person recruitment would also allow delivery of information regarding the importance of participation for altruistic reasons that many women identified as important to them. Apart from recruiters, our study findings also offer useful insights to the clinicians providing counselling to women identified at high-risk of preterm-PE regarding the potential barriers to prophylactic treatment. Including women's partners in counselling regarding medicated treatment in pregnancy, as our findings suggest, would be important so

that the pregnant woman and her partner's concerns are jointly considered. In this way the health professionals will be able to assist the pregnant woman to make informed choices that would enhance her health and pregnancy outcomes.

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Disclosure of interest

None to declare

Contribution to authorship

AN, LP, NO'G and KN designed the study. ZD conducted the interviews, prepared the transcripts and undertook data coding. AN, ZD and JP developed the thematic headings, conducted data analysis and carried out interpretation of the transcripts. AN wrote the paper with the help of other authors. AN will act as guarantor for the paper.

Ethical Approval

NRES Committee London – Surrey Borders ref 14/LO/1238 (date of favorable ethics opinion: 13/08/2014)

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Data availability

Data is available on request to the corresponding author.

References

1. Fracchia GN, Haavisto KH, editors. Clinical trials during pregnancy; rationale and ethical aspects. European Medicines Research: Perspectives in Clinical Trials. Brussels: Medical Research Divisions, European Commission, 1997.
2. Pinnow E, Sharma P, Parekh A, *et al.* Increasing participation of women in early phase clinical trials approved by the FDA. Women's Health Iss 2009; 19: 89-93.
3. Kinnunen TI, Aittasalo M, Koponen P *et al.* Feasibility of a controlled trial aiming to prevent excessive pregnancy-related weight gain in primary health care. BMC Preg Childbirth 2008; 8(1): 37
4. Poston L, Bell R, Croker H. *et al.* effect of a behavioural intervention in obese pregnant women (the UPBEAT study): a multicentre, randomised controlled trial. Lancet Diabetes Endocrinol 2015; 3(10):767-777.
5. Meshaka R, Jeffares S, Sadrudin F, et al. Why do pregnant women participate in research? A Patient Participation Investigation Using Q-Methodology. Health Expect 2016; 20:188-97.
6. Tooher R.L, Middleton PF, Crowther CA. A thematic analysis of factors influencing recruitment to maternal and perinatal trials. BMC Pregnan Childbirth 2008; 8: 36-48.
7. Rengerink, O. K., Logtenber, S., Hooft, L., Bossuyt, P. M. Mol, B. W. (2015) Pregnant Women's Concerns When Invited to a Randomized Trial: A Qualitative Case Control Study, BMC Pregnancy and Childbirth; 15:207-218.
8. Smyth RMD, Jacoby A, Elbourne D. Deciding to join a perinatal randomised controlled trial: experiences and views of pregnant women enrolled in the Magpie trial. Midwifery. 2012; 28, 538 –545.

9. Kenyon S, Dixon-Woods M, Jackson CJ, Windridge K, Pitchforth E. Participating in a trial in a critical situation: A qualitative study in pregnancy. Quality and Safety in Health Care. 2006; 15: 98 –101.
10. Snowdon C, Elbourne, D., Garcia J "It was a snap decision": Parental and professional perspectives on the speed of decisions about participation in perinatal randomised controlled trials. Soc Science & Medicine 2006; 62: 2279-2290.
11. Strömmer S, Lawrence W, Rose T *et al.* Improving recruitment to clinical trials during pregnancy: A mixed methods investigation. Soc Sc Medic 2018; 200: 73-82.
12. Mohanna K, Tunna K. Witholding consent to participate in clinical trials: decisions of pregnant women. Br J Obs & Gynaec 1999; 106:892-897.
13. Frew PM, Saint-Victor DF, Brewinski Isaacs M, *et al.* Recruitment and retention of pregnant women into clinical research trials: An overview of challenges, facilitators, and best practices. Clin Infect Diseases. 2014: 59 (Suppl 7), 400-407.
14. De Wit J, Strobe W. Social cognition models of health behaviour. In A. Kaptein & J Weinman (Eds.) Health Psychology (p.52-83). Oxford: Blackwell.
15. Leventhal H, Benyamini Y, Brownlee S, et al. Illness representations: Theoretical foundations. In KH Petrie & JA Weinman (Eds.) Perception of health and illness (pp,19-46) 1997. Amsterdam: Harwood Academic Publishers.
16. Cameron L, Leventhal, H. (Eds). The self-regulation of health and illness behaviour. 2003; London: Routledge.
17. Marteau TM, Weinman J. Self-regulation and the behavioural response to DNA risk information: A theoretical analysis and framework for future research. Soc Sc Medicine 2006; 62: 1360-1368.
18. Rolnik DL, Wright D, Poon LC, *et al.* Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. NEJM 2017; 377: 613-622.

19. Kuzel AJ. Sampling in qualitative inquiry. In Crabtree BF, Miller WL, (Eds.) Research methods for Primary care. Doing Qualitative Research, 3, Sage Publications, p31-44.
20. King N. 'Doing template analysis', In Symon G, Cassell C, editors. Qualitative organizational research: Core methods and current challenges. London: Sage. 2012. p.426-450.
21. King N, Carroll C, Newton P, Dornan T. "You can't cure it so you have to endure it": The experience of adaptation to diabetic renal disease. Qual Health Research 2002; 12:329-346.
22. McCluskey S, Brooks J, King N, Burton K. The influence of 'significant others' on persistent back pain and work participation: A qualitative exploration of illness perceptions. BMC Musculoskeletal Disorders. 2011; 12: 236-42.
23. Patton MQ. Qualitative evaluation methods. Beverley Hills, 1980, CA:Sage
24. Harris JM, Franck L, Green B, Michie S. The psychological impact of providing women with risk information for pre-eclampsia: A qualitative study. Midwifery; 2014: 30: 1187-1195.
25. Georgsson OS, Grunewald C, Waldenstrom U. Perception of risk in relation to ultrasound screening for Down's syndrome during pregnancy. Midwifery; 2009: 25: 264-276.
26. Marteau T, Kidd J, Cook R et al. Perceived risk not actual risk predicts uptake of amniocentesis. Br J Obstet Gynaecol. 1991; 98: 282-286.
27. Canvin K, Jacoby A. Duty, desire or indifference? A qualitative study of patient decisions about recruitment to an epilepsy treatment trial. Trials 2006; 7: 32-49.
28. Aktan NM. Social support and anxiety in pregnant and postpartum women: a secondary analysis. Clin.Nurs.Res. 2012; 21:183-194.

29. Torkan N, Kazemi A, Paknahad Z, Bahadoran P. Relationship of social cognitive theory concepts to dietary habits of pregnant women. Iranian J Nurs Midwifery Research. 2018; 23: 125-130.

Table 1. Topic guide

In the interviews we explored:
a. Women's knowledge and understanding of the trial's aims and the procedure Example question: Can you remember what you were told about what was the aim of the trial?
b. Women's decision making concerning participation in the trial: how did they make a decision, whether they had enough information to make a decision, their concerns about taking part, and whether they had discussed their decision with anyone? Example question: Did you discuss your decision with anyone, for example your partner or other family members?
c. Factors influencing their decision to take part or to decline participation Example question: What were your main reasons for taking part/declining to take part in the trial?

Table 2. Sample characteristics

	Participants (14)		Decliners (13)	
	N	%	N	%
Ethnicity				
Caucasian	9	64	7	54
Black	4	29	5	38
South Asian	1	7	1	8
Education				
Primary school	0	0	1	8
A levels or equivalent	1	7	3	23
University degree	7	50	5	38
Postgraduate degree	6	43	4	31
Marital Status				
Living with partner	12	86	12	92
In a relationship but not living together	1	7	1	8
Single	1	7	0	0
Pregnancy history				
Previous pregnancy	2	15	4	31
First pregnancy	12	86	9	69
Medical complications				
None	12	86	12	92
Asthma	2	14	0	0
Polycystic ovaries syndrome	0	0	1	8