Embedding trials in evidence-based clinical practice
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CHAPTER 5

PREGNANT WOMEN’S CONCERNS WHEN INVITED TO A RANDOMIZED TRIAL

Katrien Oude Rengerink, Sabine L.M. Logtenberg, Lotty Hooft, Patrick M.M. Bossuyt, Ben Willem J. Mol
Chapter 5 | Pregnant women’s concerns when invited to a randomized trial

ABSTRACT

Introduction Although pregnant women were until the 1990’s excluded from clinical trials, the Food and Drug Administration nowadays allows - and even encourages - responsible inclusion of pregnant women in trials with adequate safety monitoring. Still, randomized trials in pregnant women may face specific enrolment challenges.

Methods We performed a qualitative case control study. Women who had been recently invited to one of eight clinical trials during pregnancy or shortly after giving birth were invited for a face-to-face interview, to identify their motives for participation. We selected both participants and non-participants, in a 1:1 ratio. We started the interview in an open fashion, asking for the women’s main motive for participation or non-participation. When no new information emerged we continued with a semi-structured interview, guided by a topics list. Transcripts of the interviews were analysed using a constant-comparative approach. Two researchers identified barriers and facilitators for participation, conjoined into main themes.

Results Of 28 participants invited to this study, 21 consented to be interviewed. Contribution to scientific research was for 5 of 12 participants the main motive for participation in the trial, while 5 mentioned to have participated because the intervention was not available outside the trial. Key motives for non-participation (n=9) were a negative association or dislike of the intervention, either because it might do harm (n=6) or for practical reasons (n=3). Combining the open and topic-list guided interviews led to 47 sub-codes, which we conjoined into seven main themes: external influence, research and healthcare, perception own situation, study design, intervention, information and counselling, and uncertainty.

Conclusion We identified seven main themes that seem to influence their decision about participation. We noted that uncertainty about scientific research and/or the intervention was reported to be of considerable importance. New studies should look into methods to further reduce the feeling of uncertainty around trial participation decisions by pregnant women.
INTRODUCTION

Up to the 1990s, pregnant women were often excluded from clinical trials, for their own protection.\textsuperscript{1} However, pregnancy does in general not prevent or cure a woman from (acquiring) a disease. The efforts to protect the foetus from research-related risks, by excluding pregnant women from research, places worldwide women and their foetuses at risk from unstudied interventions.\textsuperscript{2,3}

In the United States about 2 in 3 of pregnant women are given a (off-label) prescription medication during pregnancy, often based on limited evidence on safety or effectiveness.\textsuperscript{2} Effectiveness research is needed to inform evidence-based healthcare decisions, and results of studies in non-pregnant women may not always apply to pregnant women. The Food and Drug Administration nowadays allows – and even encourages – responsible inclusion of pregnant women in drug trials with adequate safety monitoring.\textsuperscript{4}

Randomized trials in pregnant women may still face specific enrolment challenges. Enrolment problems are not limited to studies in pregnant women, but studies including pregnant women are unique, since two patients are involved: the mother and her unborn foetus. A woman may refuse treatment for herself if she feels this could harm her baby, or she may feel bound to accept interventions that might benefit the foetus. Additionally, the father’s feelings may also influence decision-making about participation in a trial.\textsuperscript{5}

Tooher and colleagues performed a narrative review on factors influencing recruitment for maternal and perinatal trials.\textsuperscript{6} They identified four participant factors that influence recruitment: understanding of risk, recruitment process and procedures, participants understanding of the research process and methodological issues, and patient characteristics. Their conclusions were based on a limited number of studies on maternal trials, and several of these were performed because recruitment was problematic. It is uncertain to what extent these results also apply to other studies. Moreover, trial participation considerations may have changed over time and could differ between countries. We performed a qualitative study to identify main barriers and motivators for enrolment in obstetrical trials in the Netherlands.
Chapter 5 | Pregnant women’s concerns when invited to a randomized trial

METHODS

DESIGN

We performed a qualitative case-control study. Women recently invited to clinical trials during or shortly after pregnancy were invited for a face-to-face interview about their main motives to accept or decline the invitation to participate in a RCT. This study is part of the IMPACT study, in which enrolment of patients in trials is studied at different levels. Our study did not require formal approval of an ethics committee or internal review board, according to Dutch law, as confirmed by the ethics committee of the Academic Medical Centre and the Onze Lieve Vrouwe Gasthuis.

SELECTION OF TRIALS AND INVITATION OF INTERVIEWEES

We identified women invited less than 3 months ago to enrol in a clinical trial in obstetrics and sampled, in a 1:1 ratio, stratifying for whether they had accepted or had declined enrolment. These women were selected from eight multicentre studies that had been actively recruiting patients between February and June 2010, all running in the Consortium for Women’s health and Reproductivity studies: Allo, Apostel I, Apostel II, Chips, WOMB, Ppromexil, Hypitat2, and ProTwin trial. A short description of these trials is shown in Table 1; more information about these studies can be found at www.studies-obsgyn.nl.

Women were eligible if they were still pregnant or their baby was born alive and they were able to speak the Dutch language well enough to participate in the interview, without an interpreter. For practical reasons, only patients from three different geographical areas were contacted: Amsterdam (Academic Medical Centre; St Lucas Andreas Hospital; Onze Lieve Vrouwe Gasthuis), Enschede (Medisch Spectrum Twente) and Veldhoven (Maxima Medical Center). We started our invitations with the women most recently invited to the trials. One of the interviewers worked as a clinical midwife, and as such was also responsible for recruitment of patients in the Onze Lieve Vrouwe Gasthuis. Excluded were women who had a professional relation with the interviewer. Interviewees were initially contacted via a letter, sent on behalf of both their gynaecologist or the local trial coordinator, and the interviewers. After about a week the patients were contacted by phone, and invited for an interview.

THE INTERVIEW

The interview was run face-to-face, unless the respondent explicitly requested a telephone call.
interview, or when the travel time to visit the patient was 2 hours or more. The interview took place at the patient’s home, or in the hospital, whichever was preferred by the interviewee.

We started the interview in an open fashion, by asking the women for their main reason for participation, or non-participation, in the trial. When this open part did not produce any new information, we continued with a semi-structured interview. This section was guided by a topic list, to cover all aspects that might have contributed to the decision making process. This topic list, available in Appendix 1 (Dutch), targeted potential barriers and facilitators for (non)participation. It was developed based on a literature review and with input from experienced gynaecologists and midwives. The topic list included factors related to personal benefit, altruism, knowledge and information about the trial and the trial process, distrust, attitude, organisation aspects and influence of the social environment. If new topics emerged during the interview, they were added to the topic list. 

The total number of interviews was not set, but depended on data saturation. We estimated that an interview with 5 to 10 women in both groups would be needed to reach saturation. We planned to perform two additional interviews when data saturation was reached. We also collected maternal ethnicity, age, parity, educational level, height and weight before pregnancy.

ANALYSIS
All interviews were recorded with a voice-recorder and transcribed; explicit non-verbal communication was noted. The transcribed interview was sent to the interviewee, and we asked her to confirm its correctness and completeness (member-check). Transcripts of the interviews were analysed using Microsoft Excel. The aim of the analysis was to conceptualize the content of the interviews in main themes. Analysis was performed according to the taxonomy of Strauss and Corbin (‘create theory out of data’), where one starts with line-by-line open coding of all relevant phrases of barriers or motivators for participation (open coding), using a constant comparison method: newly gathered data are continually compared with previously collected data and their coding in order to refine the development of theoretical categories.

After this open coding, the codes were grouped into subcategories (axial coding), and conjoined into themes (selective coding). All transcripts were reread and recoded, using the improved coding structure to ensure no codes were missing. If a fragment fitted more
Two researchers (SL and KOR) independently marked barriers and facilitators for participation for the first seven interviews. Thereafter one researcher marked barriers and facilitators, checked by a second researcher, and dissolved by consensus if needed. These phrases of barriers and facilitators were classified into categories and conjoined into themes.

RESULTS

INTERVIEWEES

We sent 28 women an invitation by mail. When we called the women thereafter, to answer any remaining questions and be informed about their decision on participation, 4 women could not be reached after four or more attempts. Two women declined the invitation for an interview (reason not noted); one woman who initially consented to an interview was admitted to the hospital for emergency care and her interview was cancelled. In total 21 interviews were performed; 12 with trial participants and 9 with women who declined participation. Of these, 17 were face-to-face interviews and 4 interviews were by phone (in 3 cases because this was requested by the interviewee and in one case because of the distance).

The interview took on average about half an hour. After transcription of the recorded interview, 20 of 21 interviewees approved its content, 1 woman did not respond. Characteristics of the interviewees are shown in Table 2. Although our inclusion criteria were designed to select only patients invited to enroll in a trial no longer than three months ago because of potential recall bias, five women were invited for this study more than three months ago after their RCT invitation. This was mostly due to the registration of non-participants in a trial, which was not always complete. All respondents stated they remembered the situation to be discussed in the interview very well, which we could confirm during the interviews.
### Table 1: Overview of trials from which patients were selected for an interview.

<table>
<thead>
<tr>
<th>Trial acronym*</th>
<th>Research question</th>
<th>Treatment arms</th>
<th>Eligible women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allo</td>
<td>Does antenatal allopurinol administration reduce hypoxic-ischaemic encephalopathy in neonates exposed to intra-uterine asphyxia?</td>
<td>Allopurinol or placebo, antenatal administered to the mother</td>
<td>Women at term in whom the foetus is suspected of intra-uterine asphyxia</td>
</tr>
<tr>
<td>Apostel I</td>
<td>Is testing for fibronectin a cost-effective strategy that prevents unnecessary treatment in women with threatened preterm labour?</td>
<td>Tocolytics (nifedipine) or placebo</td>
<td>Patients with symptoms of preterm labour, and a negative fibronectin test and a cervical length between 10-30 mm</td>
</tr>
<tr>
<td>Apostel II</td>
<td>Does sustained tocolysis in women with threatened preterm labour reduce neonatal morbidity?</td>
<td>Nifedipine or placebo for 12 days</td>
<td>Women between 24 to 31() weeks pregnant who have been treated with tocolysis and steroids for preterm birth for 48 hours</td>
</tr>
<tr>
<td>CHIPS</td>
<td>Is there a difference on pregnancy loss or NICU admission between less tight and tight control of blood pressure in women with non-severe non-proteinuric pre-existing hypertension or gestational hypertension remote from term?</td>
<td>‘less tight’ dBP control or ‘tight’ dBP control</td>
<td>Women with non-severe non-proteinuric pre-existing hypertension or gestational hypertension remote from term</td>
</tr>
<tr>
<td>Hypitat II</td>
<td>What is the effectiveness and efficiency of induction of labour in women with pregnancy induced hypertension or mild preeclampsia with a gestational age of 34-37 weeks of pregnancy, as compared to expectant management under regular monitoring?</td>
<td>Induction of labor or expectant management under regular monitoring</td>
<td>Women with pregnancy induced hypertension or mild preeclampsia with a gestational age of 34 - 37 weeks of gestation</td>
</tr>
<tr>
<td>Ppromexil</td>
<td>What is the effectiveness and cost-effectiveness of induction of labor after PPROM between 34 and 37 weeks gestation compared to expectant monitoring?</td>
<td>Induction of labor or expectant monitoring</td>
<td>Pregnant women with preterm premature rupture of membranes between 34 + 0/7 weeks to 37 weeks of gestation</td>
</tr>
<tr>
<td>ProTWIN</td>
<td>Is prophylactic use of a cervical pessary effective in the prevention of preterm delivery and the neonatal mortality and morbidity resulting from preterm delivery in multiple pregnancy?</td>
<td>Pessary or no treatment.</td>
<td>All women presenting with a multiple pregnancy between 12-20 weeks of gestation</td>
</tr>
<tr>
<td>WOMB</td>
<td>What is the effect of RBC transfusion on health related quality of life?</td>
<td>RBC transfusion or no intervention</td>
<td>Women with PPH or a decrease in Hb, 12 to 24 hours after delivery or caesarean section</td>
</tr>
</tbody>
</table>

*More information about these studies can be found at: www.studies-obsgyn.nl
Table 2: Characteristics of the women included

<table>
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<th>Code</th>
<th>Ethnicity</th>
<th>Level of education</th>
<th>Age</th>
<th>Study</th>
<th>Parity*</th>
<th>Place</th>
<th>Hospital</th>
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<td>MMC</td>
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*Parity was registered at the time of the interview.

MAIN MOTIVE FOR TRIAL PARTICIPATION OR NON-PARTICIPATION

Contribution to scientific research was for 5 of the 12 participants the main motive for participation in the trial, as responded to the first open question:

Mw J “I think research projects are actually never bad, and this is not a type of research where they do real experiments, so it is always good to learn from this someone else”

Mw L “In our first pregnancy our daughter was in fetal distress, and then it became a caesarean section. Then maybe this had been an option as well, because it is associated with fetal distress, and then administer this. And for my husband it was actually by asking further: does it have disadvantages for the child? No? Then we participate, because the study is also necessary. .... Also my medical background, I also worked on the labor wards. You are working in medicine, so you are open for innovation and technique.”
Mw T “There are two issues: in my first pregnancy I had preeclampsia, so I was very well aware what the consequences would be for me, and then also for the child. ... For me, I supported the aim of the study, so deliver the baby from 34 weeks, because the maternal and fetal risks do not outweigh, so to say. Second, I am in an academic hospital, already for years, also for other treatments, and I believe very much in academic. I believe in development and trying things. Well, and research is part of that, because if you do not do any studies, you can never do something new.”

Mw U “Well at first I was invited to participate in a study about the pessary, to participate in a twin study. Well, I thought, seems good, I have a little twin sister and I got pregnant with ICSI, so for me there were also people who participated in such a study, because of which I am pregnant now.”

Mw Z “Well, first, It was very much applicable, and it was the choice between taking blood or iron, and otherwise it would anyway be iron, so I thought let’s see what happens. And I was in the blood group, in retrospect I was very happy with it. And, what I just said, I do studies myself often, yes, than you better see the importance of it, that you need to recruit people, so eh, that is the only motivation.”

Five participants mentioned to have participated because the intervention was not available outside the trial:

Mw M “Most of influence is of course that the consequences of shortage of oxygen are pretty fierce, if you could reduce that somehow by taking a certain substance, I would choose that. Yes, yes, well and because the substance was already in use for other purposes, yes, it is not fully tested for shortage of oxygen, that it should not be harmful, than its your assumption that it therefore would only have advantages. And then I think something like, I want to participate in that study.”

Mw P “Okay, well, it was mainly because the fact that there was a chance that my labor would be induced, otherwise I would have to wait till 37 weeks anyway .... Of course also the reason to contribute to research, that was also a good objective, but that was not the most important thing. ‘I thought: I want to go for immediate induction’. I could not imagine that I had to stay in the hospital for five days, because I was not allowed to do anything, and I thought like: “bring it on...”
Mw Q: “At a first glance: I do not imagine myself lying here for another 5 weeks, and pretty soon thereafter the idea that you are already open from down there, and a risk of infection for yourself and for the baby, and yes, in Enschede the doctors also said: the baby was viable enough, so that was a reason to participate for us.”

Mw V: “That if the baby would be born, that my high blood pressure would be gone, that’s what I thought, that was about it. But on the other side, I was a bit scared, shall I get it earlier, that was at 36 weeks, so it was a bit the consideration what would be best. Then she explained me, the earlier the child would be out, the better it could be for mother and child, so that was actually the reason that I said: I participate.”

Mw W: “That was because I hoped it would be better for the child, although I had an uneasy feeling all the time. That was because nobody could tell you what the potential negative consequences were, yes, I had an uneasy feeling all the time.”

One women thought an extra test could only be positive, a kind of ‘there is no harm in trying’:

Mw N “And I had something like, in my case it can only be positive, because I mean, the test would indicate whether the chance was very high that you would deliver very soon, or that it could take a while. So, I really felt like, I felt that I ran little risk, because if the test would show that you would fall into the test group, than you would get either a placebo or tocolytics”.

For one women the reason was not very clear, she probably meant to be better informed about her medical condition:

Mw Y “Than you know how and what”.

Key motives for the 9 non-participants were a negative association or dislike of one of the interventions, either because it might do harm (n=6):

Mw C “Well there were multiple reasons. When your colleague started about it, when I had an appointment about it, I thought ‘Oh my God, no, not a pessary. Because I had a friend who was admitted to the hospital because the pessary [not in pregnancy] had caused many bleedings, so that’s what I told her, that was a life threatening situation, so I had a feeling like, if I think now about pregnancy and a pessary, I do not get very happy.”
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Mw D: “For me it was pretty clear actually, when I was here, I thought something like ‘let mother nature just do the work. I am pretty religious (Muslim), but there might be a reason why the children are born early, I believe in God you know, I have something like: destiny determines, actually, if the children want to be born early, then that is the case, if not it is not. That was my consideration. I was also scared, if I participate and something happens with me, a bit or a lot blood loss, or something with the babies.”

Mw E: “She (baby) was 4 weeks too early and the blood pressure kept rising, they did not get it down. I was lying there for a month, and I had enough of it, you want something to change. Then they asked me: do you want to participate in the study? At a certain moment the doctors said, we don’t know it anymore. Then I thought: if they don’t know, who does, I had to choose myself. ….. And then I thought, actually: ‘I can better prolong it for a while, look how long it will take. Because if I had decided to participle, will you be induced or not, that is also an uncertainty. So, then the disappointment is still big. Then I decided not to do it, let’s have a look how long we can prolong it.”

Mw G: “I had a very tough pregnancy, with a lot of bleeding, and actually the nine months were completely uncertain. … I got lung maturation injections and I got tocolysis and then I did not feel my baby any longer. … When they asked if I would receive more tocolysis, I associated it with that, and I wanted to feel my baby again as soon as possible, to get the certainty back a bit, that everything was alright. So that was for me the most important reason.”

Mw I: “At first, I tended to participate, because in my environment many people said: imagine it works, your babies will stay in longer. But I had the feeling that the pregnancy goes very well, that it all, yes I react quite strong on things, jewels or a piercing or something, then I think, if something is brought into my body, maybe it might react strangely. If nothing is wrong and you do that, that’s a bit scary. And that you could not choose which group you will get in, that pretty logical in a study, but that’s why I finally decided not to.”

Mw K: “Well, it’s not without a reason that they tell you that from 37 weeks you are officially allowed to deliver, so, yes, I thought it was a risk to be induced at 34 weeks. Because the doctors do not say without a reason, from 37 weeks doctors will automatically induce you, and they are doing a study, and I did not want to be a guinea pig. If then something goes wrong...”
Or for practical reasons associated with the intervention (n=3):

Mw A “I wanted to participate if I could choose for iron tablets, but that choice was not there. You have to participate blindly and then determines I don’t know who, I don’t know how that works, but then determines someone else for you which of the two you are going to do. What is also complicated, I did not want a blood transfusion. I was lying there on a drip and I had a catheter and then I thought that with iron tablets I could go home and otherwise I would have stayed somewhat longer.”

Mw B “I was in the AMC, that is an academic hospital, and there they do a lot of research. I had to come extra, it was for example about a pessary for prevention of preterm birth, I had to come extra to measure it and for an ultrasound. I did seriously consider it, but the extra visits, for example if I would have pain or if it would not fit well. And, I just heard I was pregnant of a twin with 1 amnion, that is a very exceptional situation, a lot of information is coming to you”.

Mw O [unplanned pregnancy]: “……Yes, and everything went very fast, then I had really something like, well I do not have to induced tomorrow. That… the chance was 50% and I did not want it. No, that’s all too soon. Because you are.. no… you are after three weeks that I was attending the hospital I was admitted. I had never been admitted in a hospital. I was homesick, yes. But, I did not have something like, get him tomorrow. That was too soon. I could not process that”.

Women also mentioned it played a role that it was their first pregnancy, or she was already in an exceptional situation given a mono-amniotic twin pregnancy.

THEMES IDENTIFIED AS RELATED TO THE DECISION ON TRIAL PARTICIPATION

During the phase of open coding 47 subcategories were identified, based on phrases relating to barriers and facilitators. These subcategories were aggregated into 13 main categories, and further classified into seven main themes: (1) external influence, (2) research and healthcare, (3) perception own situation, (4) study design, (5) intervention, (6) information and counseling, and (7) uncertainty. These main themes, with corresponding sub codes, are summarized in Table 3. Each of the themes is discussed separately below.
A. External influence
Women indicated that they discussed the invitation for enrollment in a trial with their partner, where the partner’s opinion influenced the choice on participation. In all but two cases this was a unanimous decision, in the two cases the woman and her partner disagreed. Women indicated that opinions of persons other than their partner were not very influential.

“I discussed it with my husband. I thought, like, if it would have been only my decision, I would have agreed to participate. My answer depended on my husband’s opinion. He thought it was a good decision, so we unanimously agreed on participation. Interviewer: “What if you partner had disagreed? ”Participant: “Then I would not have participated in the trial.”” (Allo trial participant)

Women indicated they had decided on participation without consulting their gynecologist, however when the gynecologist was contacted, his or her opinion was mostly influential. All respondents felt free to make their own decision, without feeling pressure from anyone to participate.

B. (Contribution to) research and healthcare
Women indicated as a reason for participation their contribution to scientific research, as they were convinced about its importance.

“I reasoned also, like, these are studies for the future, and I have a daughter, and you never know... I am prepared to participate for others, so things will be better in the future than how they are now. I am benefiting from what others have done before me.” (Hypitat II trial participant)

Interviewees who had declined participation also judged scientific research important – either mentioned in the open question or during the semi-structured part of the interview. In their case other themes, like uncertainty, the intervention, the trial design and their personal situation, outweighed this importance.
Chapter 5 | Pregnant women’s concerns when invited to a randomized trial

Table 3: Main themes that influence trial participation

<table>
<thead>
<tr>
<th>Theme</th>
<th>Sub codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>External influence</td>
<td>▪ Concern from social environment</td>
</tr>
<tr>
<td></td>
<td>▪ Trust in the health professional</td>
</tr>
<tr>
<td></td>
<td>▪ Feeling of disappointing the health professional</td>
</tr>
<tr>
<td>Research and healthcare</td>
<td>▪ Familiarity with scientific research</td>
</tr>
<tr>
<td></td>
<td>▪ Willingness to contribute to research</td>
</tr>
<tr>
<td></td>
<td>▪ Feeling of participating in an experiment</td>
</tr>
<tr>
<td>Perception one’s own situation</td>
<td>▪ Perception own situation and medical history</td>
</tr>
<tr>
<td></td>
<td>▪ Feeling very eligible or very ineligible for scientific research</td>
</tr>
<tr>
<td>Trial design</td>
<td>▪ Randomization</td>
</tr>
<tr>
<td></td>
<td>▪ Blinding</td>
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<tr>
<td></td>
<td>▪ Placebo</td>
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<tr>
<td></td>
<td>▪ Additional efforts</td>
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<tr>
<td></td>
<td>▪ Insurance of medical research</td>
</tr>
<tr>
<td>Intervention</td>
<td>▪ Intervention</td>
</tr>
<tr>
<td></td>
<td>▪ Natural course</td>
</tr>
<tr>
<td>Information and counseling</td>
<td>▪ Written information</td>
</tr>
<tr>
<td></td>
<td>▪ Counseling: information and timing, atmosphere</td>
</tr>
<tr>
<td></td>
<td>▪ Time for consideration on participation</td>
</tr>
<tr>
<td>Uncertainty</td>
<td>▪ Fear</td>
</tr>
<tr>
<td></td>
<td>▪ Stress</td>
</tr>
<tr>
<td></td>
<td>▪ Doubt</td>
</tr>
<tr>
<td></td>
<td>▪ Physician does not know what is best</td>
</tr>
</tbody>
</table>

A participant of the Ppromexil trial suggested to improve publicity on clinical trials and research in pregnancy:

“Maybe one should increase the awareness about the existence of studies one can participate in in case of pregnancy. Maybe, somehow, more people should be informed once pregnant, so they know about trial participation. Myself, I did not think about it - I have not experienced this before. I think receiving a folder with ‘scientific research for pregnant women’ in advance would decrease the level of stress. If you had read it, you would know it might be coming up. So one can already think about research.”

C. Perception of one’s own situation

The personal perception of one’s own situation appeared influential in the decision on participation: women considered themselves either very eligible or not at all eligible for scientific research, sometimes taking into account their current complicated pregnancy, medical history or their own nature.
“There are people who participate in trials; that is very special and good, but I am not such a person, all that twiddling to my body. Maybe I would if it had been a singleton pregnancy, but now, with twins, it is already scary: and all the twiddling to your body. I prefer nature”. (ProTwin trial non-participant)

Intuitional or emotional aspects seemed to be influential. This became apparent in citations and also when explicitly asked whether their decision was a rational decision, women answered they trusted their feelings or they were inclined to participate but it did not feel good.

D. Trial design
Randomization was perceived as negative by women, which resulted in uncertainty. Women could not explain (in any way) why randomization was used, or could be used, however this lack of knowledge was not necessarily a barrier for participation.

“If I had decided to participate, there would be uncertainty about induction. So the disappointment can be huge. No, with the uncertainty you don’t know if you take a left or a right. If you decide yourself, you know where you go. You now: I go right”. (HYPITAT II trial non-participant)

E. Intervention
Participants mentioned potentially receiving the intervention as a reason for participation, either because of the potential therapeutic benefit, or since they preferred an intervention over expectant monitoring or no intervention.

“Well, if in this case, if they stay in longer, that’s an advantage for me as well. That was actually the only reason to participate. But I needed to be convinced that there were no disadvantages, that it was not detrimental if they stayed in shorter, because of that”. (ProTwin trial participant)

Other women disliked an interventional (“active”) strategy, and rather preferred the natural course, or were more focused on potential (unknown) negative effects. As an explanation for this, women mentioned that the risk of the natural course is one you do not choose for, but which is already present, contrary to the eventual risk of an intervention or trial participation, which feels as the women’s choice and therefore more as their responsibility. All non-participants stated that a negative association with the
intervention or a direct or more indirect negative effect of intervention, as discussed under the main motivations.

“They were uncertain about side-effects for the baby, so then I decided not to take any risk. To me it was already pretty clear: during my time here, I wanted to let mother nature take its course. I am not going to mess with it. If nature decided it to be this way, I let it be, you know”. (ProTwin trial non-participant)

F. Information and counseling

Women considered the information adequate. However, respondents remarked that the counseling was very hastily. A no rush atmosphere, often where counseling was done by a research nurse or midwife, with sufficient time to discuss patients questions was viewed as positive.

“Thinking back, I realized it matters a great deal who comes to inform you about the study. Imagine a research midwife is standing at my bed, taking the time, versus a doctor is sitting at the windowsill, just not looking at her watch, saying “I have 5 minutes, so you have to decide now, otherwise it will be too late.” That makes a difference, and influences the outcome of the decision.” (Apostel II participant)

One women mentioned to have received unclear and incomplete written information, but that did not withhold her from participation.

“I only understood later that these were the same tocolytics as you would receive usually, there is nothing different about. It is not a new medication, that’s what I understood later. That was unclear at the time I had to decide, it seemed if it was a new medication, with a new method to look at whether the baby would stay in longer with premature rupture of membranes and what the harmful effects for the child or the mother would be. If they had explained it better, had told me what the potential adverse effects were - that is of course the point of the trial - than it would have been easier to participate. If they had only said something like “the only potential harmful effect is that you baby may be a bit smaller, or bigger, or more left, or right” but it’s quite difficult if you don’t know. It’s an ethical dilemma.” (Apostel II trial participant)

All but one women judged the time to consider participation adequate, or they understood why the time to consider participation was short (as in the Allo trial). Women
declined participation because there was a too overwhelming amount of new information, or the timing was not very well.

G. Uncertainty

The theme “uncertainty” emerged both in women who accepted and in women who had declined the invitation to participate. Non-participants explicitly mentioned to have declined participation because the feelings of uncertainty, even before they had reached the stage explicitly weighing advantages and disadvantages on participation. Women who declined participation indicated this uncertainty prevailed over other factors that could have led to participation.

“No, I did not consider that, I did not think about it. For me the safety of the baby was most important. No, I did not see an advantage. No, that ‘advantages aspect’, they did not talk about it. And I did not ask for it.” (Promexil trial non-participant)

Both participants and non-participants indicated that the invitation to participate in scientific research was stressful. Being confronted with an (unexpected) choice about trial participation was a decision that needed thorough consideration.

“Whether it is really stress, I am not sure, we have talked about it a lot, both my husband and I, and also with a friend of mine who lives in Rotterdam. It was also on my mind quite a lot, but whether it has caused me physical stress, I am not sure. Yes, I have thought a lot about it, as one never seems to make the right decision. If he had been born, and something had been wrong, while I had not participated, I would have wished I had. On the other hand: if I had participated in the trial and something had gone wrong, I would have wished not to have participated in the trial.” (Apostel II trial participant)

Some of the women were really surprised when confronted with the fact that ‘2010 state of the art health professionals’ do not know what is best.

“They said “We think it is silly to say - and may sound very strange to you - but we have to be honest: we don’t know”. And I was lying there and thinking all the time “I’ll see what happens” until that moment. Then I thought “I feel left to my fate”. I thought it was very honest, but also very hard. You are there for a reason, and they are supposed to know, they have studied for this. I assumed they could tell me in what direction to go, but that, they could not. That is really tough. They could only provide me with certain facts, that neither actually, and the research was there for a reason.” (HYPITAT II trial non-participant)
DISCUSSION

Contribution to scientific research was for many participants their main motive for participation in the trial, while others mentioned to have participated because the specific intervention was not available outside the trial. Key motives for non-participation were a negative association or dislike of the intervention, either because it might do harm or for practical reasons. We identified seven themes that influenced trial participation. We noted that uncertainty about scientific research and/or the intervention was reported to be of considerable importance.

This study has looked at a variety of trials, not selected on their recruitment performance, but we selected from running at the time of our study within the Dutch consortium for obstetric studies. We have sampled patients from multiple centers, invited for enrollment by diverse health professionals, in three different geographical areas in the Netherlands. This way we aimed at having a detailed picture of reasons for (non)enrollment in clinical trials.

Fortunately, most of the invited took part in the interview, only two of eleven non-participants invited by phone declined to be interviewed, and one interview had to be cancelled because of medical reasons. We expected that patients who had declined enrollment in the trial would also be more tended to decline an interview, and thereby excluding general reasons for non-participation in health research, unrelated to the specific trial.

A number of potential limitations of our analysis may invite discussion. In general, qualitative research may be seen as vulnerable, since interpretation is an inevitable part of the analysis of the transcripts. This could lead to difference in interpretations between researchers. To reduce this risk, two researchers examined the transcripts. Discrepancies were discussed until agreement was reached.

Five of the 21 respondents were interviewed more than three months after the invitation enroll in a clinical trial. It is possible that they could recall all factors that influenced the decision, or that their memories differed from their thoughts in the decision making process. All interviewees stated, to our surprise, that the counseling and the decision making process were very well remembered. During the interview only incidental a respondent said not to remember well if a specific topic had been discussed.

The seven themes we identified in this study have been mentioned before in the literature.
Kenyon et al. performed interviews with women who had participated in the ORACLE trial, a randomized trial investigating the value of administration of antibiotics during premature labor.\textsuperscript{18}

They concluded that women gave prominence to the socio-emotional aspects of their interactions with healthcare professionals in making decisions on trial participation. The interviews suggested that the stressful nature of the situation affected their ability to absorb the information. The main motivation for trial participation was the possibility of an improved outcome for the baby. The second motivation was an opportunity to help others, but this was conditional on there being no risks associated with trial participation. McCann and colleagues introduced the term ‘conditional altruism’ based on non-participant observation of recruitment consultations and in-depth interviews with people invited to participate in the UK REFLUX trial. It describes that the willingness to help others that may initially incline people to participate in a trial, but that is unlikely to actually lead to trial participation unless people also recognize that participation will benefit them personally.\textsuperscript{19}

Uncertainty due to unfamiliarity with research or research methods was also identified as a theme related to trial participation in pregnant women by Mohanna et al,\textsuperscript{5} and in a systematic review by Ross et al, not restricted to pregnant women.\textsuperscript{20} Women reported that they would let mother Nature do her work, and were reluctant to actively choose an intervention in what until then was perceived as an uncomplicated pregnancy. Lyerly et al report that risks associated with undertaking medical interventions during pregnancy were focused on, not taking into account the demonstrable risk to both woman and fetus of failing to intervene.\textsuperscript{21}

Unfamiliarity with randomization was a source of uncertainty; for many patients it remained unclear why randomization is used in scientific research. Robinson and colleagues investigated lay public’s understanding of equipoise and randomization in randomized controlled trials from different perspectives.\textsuperscript{22} The research was not carried out in real healthcare settings. Even participants who could correctly explain the rationale behind random allocation methods, judged it as unacceptable. They doubted the possibility of individual equipoise and saw no scientific benefits of random allocation over doctor/patient choice. Robinson et al. concluded that, given the extent of disparity between the assumptions underlying trial design and the assumptions held by the lay public, the solution is unlikely to be simple. Many women were surprised to learn that the
doctor does not know what is best. This was also reported by Mohanna: ‘Some patients will prefer to assume that [My] doctor knows best [about me and my baby], and not be happy to enter into the discussion of uncertainty that a trial and the issue of informed consent will raise’. Counseling by research staff, instead of the treating physician, seemed to positively influence participation, which has also been also suggested by the review of Tooher and colleagues.

To identify strategies to reduce feelings of uncertainty and stress, further research could elaborate on the work by Junghans and colleagues, where an opt-out versus an opt-in design for low-risk interventions was proposed, as an opt-in system resulted in lower response rates and a biased sample. This could not only increase participation rates, but might also shift the responsibility and difficult decision process from pregnant women to the health professionals. Crombie added the following to this discussion: “Research should be undertaken only when there is a high likelihood of producing valid findings. Ethics requirements which result in invalid research may themselves be unethical.”

Ethical committees should be responsible for determining which trials are eligible to run in this system, with a low or no additional risk to the patient. Patients could be informed about this general policy as soon as they enter the hospital, and are invited to sign a general informed consent about the use of data and efforts to improve quality.

Alternatively, one could think of a classification system of trial risk, where the potential risks of a trial are set out in a uniform label, like energy labels, to make them more transparent for patients.

A class A trial, could for example mean that widely used interventions are compared, without additional risk above usual clinical practice. A class E trial could mean that the new intervention is highly experimental. This classification could be proposed by the principal investigator of the trial, and confirmed by an ethical committee before its use.

In addition, one could imagine that health professionals recommend participants to participate in Class A trials, of low risk, instead of explicitly leaving the choice to the (vulnerable) patient.

Uncertainty could also be reduced, and awareness improved, when pregnant women become more familiar with scientific research in general, and research in pregnancy in specific. A national public campaign, or an information leaflet introducing the goals, methods and necessity of scientific research when entering a midwifery practice or a
hospital could habituate women to scientific research and the methods used. To do so, for example, in 2008 the ‘Get Randomized’ campaign was launched in Scotland, informing the public about the importance of clinical trials using television, radio and newspaper advertising. It showed an improvement in public awareness of clinical trials following the campaign. However, on whether those who recalled the advertising would personally take part in a clinical trials if invited, there was little difference in response following the campaign. In the United States a longer running public service advertising campaign celebrating the ‘everyday medical heroes’ of clinical research has been set up because of the believe that the public has a poor and often negative understanding of clinical research. When patients are aware, or even expecting trials, and regularly ask their health professional whether any trials are running in the department, a clinician might be more inclined to bring up the subject of trial participation, which could have a synergistic effect.

We observed that uncertainty about scientific research and the intervention evaluated was reported to be of considerable importance. A more thorough understanding and knowledge on potential barriers and facilitators may help to improve participation of pregnant women in future trials.
REFERENCES

27. Website: http://www.ciscrp.org/patient/
APPENDIX 1: TOPIC LIST

Openingsvraag: Wat deed u besluiten om wel/niet mee te doen aan het <trial acronym noemen> onderzoek?

TOPICS

- **Persoonlijk voordeel**: therapeutisch voordeel bij deelname, meest recente therapie, voldoening, meer/betere monitoring van ziekte, betere relatie met behandelaar, vrijheid
- **Onbaatzuchtigheid**: bijdrage wetenschap, behandelaar een plezier doen, andere patiënten met deze aandoening helpen
- **Kennis/informatieverstrekking**: precies weten waar je voor kiest, elk moment kunnen stoppen, randomisatie, placebo, geblindeerd onderzoek/dubbel blind onderzoek, doel van de studie, patiëntinformatie
- **Bezorgdheid/wantrouwen**: nadelige gevolgen behandeling, bekende behandeling beter, (extra) injecties/medicatie, bezorgdheid informed consent, angst voor onbekende, verlies controle, inbreuk privacy, studiedesign, stress
- **Organisatorisch**: afspraken, bedenktijd, extra consulten/injecties, reistijd en kosten, werk, kinderopvang, tijd voor “onderzoeks consult”
- **Attitude**: houding ten opzichte van wetenschappelijk onderzoek
- **Sociale omgeving**: invloed partner/omgeving/internet, wie maakte keuze, behandelaar niet enthousiast over studie, verplichting ten opzichte van behandelaar, moment van counseling