

ORIGINAL ARTICLE

Participating in a trial in a critical situation: a qualitative study in pregnancy

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Background: Randomised controlled trials of interventions in critical situations are necessary to establish safety and evaluate outcomes. Pregnant women have been identified as a potentially vulnerable population.

Objective: To explore women's experiences of being recruited to ORACLE, a randomised controlled trial of antibiotics in pre-term labour.

Methods: Twenty qualitative interviews were conducted with women who had participated in ORACLE. Analysis was based on the constant comparative method.

Results: Women gave prominence to the socioemotional aspects of their interactions with healthcare professionals in making decisions on trial participation. Comments on the quality of written and spoken information were generally favourable, but women's accounts suggest that the stressful nature of the situation affected their ability to absorb the information. Women generally had poor understanding of trial design and practices. The main motivation for trial participation was the possibility of an improved outcome for the baby. The second and less prominent motivation was the opportunity to help others, but this was conditional on there being no risks associated with trial participation. In judging the risks of participation, women seemed to draw on "common sense" understandings including a perception that antibiotics were risk free.

Discussion: Recruitment to trials in critical situations raises important questions. Future studies should explore how rigorous governance arrangements for trials, particularly in critical situations, can protect participants rather than relying on ideals of informed consent that may be impossible to achieve. Future research should include a focus on interactions between research candidates and professionals involved in recruitment.

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Randomised controlled trials of interventions in critical situations are necessary to establish safety and provide evidence about outcomes. Pregnant women have traditionally been identified as a potentially vulnerable population,^{1,2} and it is therefore particularly important that their experiences and perspectives, especially in critical situations, be understood.^{3,4} A small but increasing body of work has demonstrated the potential of studies using qualitative research methods to access the perspectives of trial participants. This has explored, for example, the difficulties experienced by participants in relation to the concepts and design of clinical trials.⁵⁻⁷ The particular problems experienced by people approached to take part in trials during stressful critical situations, such as those that prevail in neonatology, have been identified.⁸ However, research on trial participation during pregnancy to date has largely focused on general attitudes to trials and on reasons for participation and non-participation, and there has been a lack of qualitative research in this area.^{9,10}

In this paper we report an investigation into women's experiences of being recruited to ORACLE, a randomised controlled trial of antibiotics in pre-term labour. ORACLE was designed to test the hypothesis that treatment with broad spectrum antibiotics prolongs labour and improves neonatal mortality and morbidity in women who are less than 37 weeks pregnant and experiencing either pre-term labour or pre-labour rupture of the membranes.

METHODS

This qualitative study was conducted with the approval of the North West Multicentre research ethics committee and focused on women who had participated in ORACLE.^{11,12}

ORACLE, funded by the UK Medical Research Council, used a 2×2 factorial design with four treatment possibilities: Augmentin 375 mg; erythromycin 250 mg; both antibiotics; either antibiotic with placebo, or both placebos. The trial medicines were intended to be taken four times daily for 10 days or until delivery. During the period of the trial (July 1994 to May 2000) 11 154 women were randomised to ORACLE from 161 maternity units worldwide including 135 units in the UK. The trial showed that, for women in spontaneous pre-term labour, antibiotics do not prolong pregnancy or improve the health and survival of babies. By contrast, for women with pre-term pre-labour rupture of the fetal membranes, erythromycin prolonged pregnancy and was associated with babies having fewer infections and less respiratory support as well as fewer abnormal cerebral ultrasound scans on discharge from hospital (a marker for later development problems). Augmentin was associated with a higher incidence in babies of the very rare but potentially serious condition of necrotising enterocolitis, a gastrointestinal disease that causes destruction of the bowel.

The trial followed best practice at the time regarding obtaining informed consent. Midwives involved in the trial underwent intensive training regarding the trial and the importance of informed consent was emphasised throughout. The National Childbirth Trust (a consumer group in maternity care) was closely involved in the development of the information leaflet given to parents.

All ORACLE participants in the UK were asked if they would like to receive a copy of the trial results. Participants in the Trent region of the UK who had requested the results of the trial were asked to either complete a questionnaire or opt for a face to face interview. Those who agreed were

interviewed at home by KW, who obtained written consent from participants and maintained a reflexive diary to record contextual details and her reflections on the research process.

Interviews focused on women's reactions to the results leaflet (reported elsewhere¹³) and on their experiences of joining and participating in the trial. Because the study took place after the trial results had been published, interviews occurred some considerable time after trial participation and after women had received a summary of the results of the trial. An interview prompt guide, developed following literature review and discussions within the project team, was used as a framework for the interviews although it was used flexibly and in response to the directions in which participants wished to take interviews. Interviews were transcribed verbatim. A systematic and iterative method of analysis based on the constant comparative method was employed.¹⁴ Initially "open codes" were generated, representing the significance of sections of text. Open codes were then incrementally grouped into organising categories or themes. These categories were modified and checked constantly in order to develop a coding frame. This consisted of thematic categories with explicit specifications that described what types of data should be assigned to what kinds of categories. The coding frame was programmed into QSR N5 software and was used by CJ to process the dataset systematically. Assignment of data to categories was independently validated by MDW.

RESULTS

Twenty two women opted for a face to face interview and 20 of these were interviewed. Their accounts suggested that they were between 22 and 33 weeks pregnant at the time they were recruited into the ORACLE trial. Women were mostly white (n = 19); 18 were married; 11 were in employment; and none had been educated to university level. Most (n = 13) had at least one child before the ORACLE trial and seven had had a previous premature delivery. Accounts from 10 women suggested that they had ruptured membranes at the time of the trial; the others were in pre-term labour. Although participants had been drawn from a single UK region, they had been recruited to the trial at multiple trial centres.

Being asked to participate

Although nine participants mentioned being provided with the trial information sheet at the time of recruitment, the sheet appeared not to play a prominent role in the decision to participate in the trial. For most women the decision to participate was primarily based on their exchanges with the healthcare professionals who made the recruitment approach, and appeared to involve a response to socio-emotional aspects of those exchanges rather than their informational content.

"Yeah, but she was lovely, she took her time with me and said, you know, anything that I wanted to do, she came back in an hour to see, you know, if I'd made me mind up or I could, you know, let her know whenever. But I'd made me mind up straight away and she was, you know, took her time with me over everything." (Participant 1)

Those mentioning the amount of information provided about the trial (n = 7) were satisfied. Comments on the quality of the information given were generally favourable, although women's accounts suggested that their ability to absorb information was compromised by the stressful nature of the situation.

"... they were very, very sympathetic and receptive to anything and spent time explaining. But there's only, to be fair, when everything else was going on around you – there was only so much I took in and, I don't know, I can't say that's a complaint because that's just what's

happened, I don't know how much I understood at the time because I was more worried about everything else." (Participant 8)

Information women recalled being given included information on the placebo, the potential for antibiotics to prevent premature delivery, the safety of the antibiotics, and the potential for the trial to assess the usefulness of antibiotics in threatened premature delivery.

Knowledge of trial practices

Accounts from more than half the participants suggested that they understood that the aim of the trial was to examine the usefulness of antibiotics in preventing pre-term labour, but there was little mention of other trial outcomes including infant mortality and morbidity. Trial practices including use of placebos, randomisation, and blinding appeared to be poorly understood. Although all but one account mentioned the use of a placebo or "dummy" tablet and recognised that trial participants (and usually the healthcare professional) would be blinded to the treatment arm, the reasons for these practices remained obscure for women.

"... you don't know, at all. That's the information that you get, you will not know what drug, whether you are on the drug or not, because all the tablets are the same, even the staffing people don't know. So nobody knows except the people that are hundreds of miles away, do you know what I mean? You think, 'Well thanks, just hold my life in the balance'." (laughs) (Participant 4)

Some indication of why a placebo might be useful was demonstrated in just five accounts.

"That's right, yes, because you've got to have a comparison haven't you? Otherwise there's no point doing the trial, so yeah." (Participant 20)

Two women believed that their part in the research was less valuable if they took the placebo and one thought that if she was taking the placebo she was not in the trial. Three expressly stated that a placebo was unnecessary. Many felt that taking the placebo would involve additional risks, mostly because it would involve not taking the active treatment.

"... knowing that perhaps I could be taking something that would be of no use whatsoever was a little bit sort of worrying that I was trying to do, trying to stop going into premature labour but the, you know, obviously taking these tablets would make no difference whatsoever." (Participant 3)

Blinding was a particular concern for the participants, with most wishing to be unblinded. Women offered different explanations as to why blinding might be necessary, with only three accounts suggesting it was necessary to ensure any effect was a real effect. Four women believed it was necessary to prevent the trial being blamed for an adverse outcome, including distress to women who did have a pre-term delivery.

"There could be a lot of blame and then a lot of anger and it's a horrendous thought anyway to go thinking that you're going to lose your baby, so to, if you'd actually lost one and you're on the placebo, oh wow, the bitterness you could actually feel, in fact I've gone cold thinking about it cos it just, it's just, you've got to blame somebody haven't you?" (Participant 12)

Motivations for taking part

Two motivations for taking part were prominent in women's accounts. The first, given by half the participants, was to help other women and their babies in a similar position.

"I was, I mean, I was all for it because anything that helps future generations, if they'd have found out that antibiotics did help then it's helping thousands of women after isn't it?" (Participant 7)

These women believed that research was desirable and indicated a strong sense of solidarity with other women. Willingness to help, however, was conditional on there being no risk.

"I mean no, I mean what they would be doing for me was either beneficial or not working at all so it wouldn't have caused any adverse effects for me, but all I could think was it's not gonna harm me or the baby. If it does help anybody else in the future, these trials do result in something being learned, I'm glad to help." (Participant 15)

The second and, for women, much more important motivation for trial participation was the possibility of an improved outcome for their pregnancy. Fear of giving birth prematurely was a prominent feature of many accounts. All but two of the women believed that, by agreeing to take part in the trial, labour might be delayed, making a successful outcome to the pregnancy more likely. Faced with the possibility of giving birth prematurely and seeing the ORACLE trial as a way in which this might be prevented, the decision to take part appeared straightforward.

"At 32 weeks with [baby's name] and I was just kind of laying on the bed and the doctors came in and asked me if I wanted to take part in the trial and we just agreed straight away. Yeah, because we both felt that if, well we just felt it was too early for him to be born and so if there was a chance to stop it we wanted to take it." (Participant 13)

Patients were very clear that they did not feel pressurised by staff to take part in the ORACLE trial. However, the situation they found themselves in exerted considerable pressure.

"I mean, like me at the time, if they'd have told me that if they chopped me leg off it would have stopped the baby coming, do you know what I mean? It were just so scary. The doctors kept saying, you know: 'If it comes now [...] it could have brain damage and this' and everything were just so scary, and then they said: 'We're doing this trial to see, you know, this is ORACLE and this is what it's all about.' And I were just like: 'Yeah, yeah, just ...' you know, you just sort of say: 'Yeah, do it.'" (Participant 6)

Risks associated with participation

Although at the time of interview women had received the leaflet summarising the results of the trial, including the finding that one arm of the trial was associated with an increased risk of necrotising enterocolitis and that antibiotics are effective only for women with pre-term rupture of the membranes, women's accounts showed little recognition of these findings. Most women (n = 15) believed at the time of recruitment—and continued to believe—that there was no risk associated with taking part in the trial or that the main risk in the trial was being allocated to the "wrong" arm of the trial and receiving the placebo rather than the antibiotics. Many women reported being told by healthcare professionals that there was no risk associated with the trial. The perception that there were no risks intensified the feeling that there was "no choice" about whether to participate.

"When the nurse said: 'We've got this trial. There's no harm to the baby that it can cause but it can, if you are in premature labour it can halt things or, you know, carry you further forward.' So for me there was just no choice, you know, that's why I went on. I thought, well if there's no detrimental effect with them then obviously it may make a difference, it may not but the chances, yeah, so that's why." (Participant 3)

Some women drew on "common sense" knowledge about the benign nature of antibiotics to conclude that that the interventions were harmless. Others (n = 7) relied on the credentials of the hospital, the health professionals, or the research process, trusting that they would not expose women or their babies to anything hazardous.

"Still feel the same. End of day it's only antibiotics which a doctor would give you if you've got a cold, a cough, or whatever so I just felt as if it couldn't do us any harm. It was either gonna work or it wasn't, you know, at end o' day it weren't causing anybody ... it

weren't causing either me or my baby any harm in any way." (Participant 16)

"Yeah, cos I knew they wouldn't, I knew the hospital wouldn't put me at risk, and I did ask a lot of questions at the time." (Participant 7)

Those women who remained concerned about taking drugs during pregnancy (n = 4) balanced the risk of taking the tablets against what they saw as the greater risk associated with premature birth.

"The fear of losing the baby took over which made me decide to try it anyway and then the first couple of tablets I took I was sitting there scared thinking of what was gonna happen to me, you know. But I carried on taking them and I just hoped that they'd help, you know, but ... yeah, I was more frightened of losing the baby. The fear of that took over my fear of tablets." (Participant 10)

DISCUSSION

Research in emergency and critical situations is necessary if evidence about important outcomes, including effectiveness and safety, is to be obtained. This qualitative study has allowed insight into women's decision making about participating in a trial in a critical situation in pregnancy and their beliefs about trial design and concepts. It suggests that, although the trial information sheet was valued,¹⁵ participants attributed their actual decision to participate to features of their interaction with the person who approached them, and relied on a generalised faith that both hospitals and health professionals will act in their interests and only suggest interventions that will be of benefit and carry minimal risks. Although previous work has pointed to the significance of altruism in decisions about trial participation,¹⁶ our study shows that altruism was conditioned by beliefs that participation would increase the likelihood of a positive outcome, particularly for their baby. For most women the most important reason for joining the trial was the perception that there was a possible benefit to their babies. Women did acknowledge the uncertainty as to whether or not the active treatment would work, but perceived that the outcome from the active treatment would be at worst no different from not taking part.

It is unclear where the perception that there was no risk arose; although women reported being told by recruiting staff that there was no risk, we do not have independent verification of this. One possibility, particularly given the passage of time between trial participation and interview, is that women did not recall explanations of risks; another is that participants rationalised risk.¹⁷ Perhaps more salient, however, are accounts of how women appeared to draw on "common sense" understandings in judging the risks of participation. Participants were familiar with taking antibiotics for other conditions and therefore did not perceive significant risks in this situation. In addition, they were confident that the health professionals responsible for their care would not expose them or their baby to anything hazardous.¹⁸ Women were thus drawing on typifications of healthcare and health professionals which, as Schutz¹⁹ describes, function as stocks of knowledge about the world and recipes about how to act in it.

This study has a number of limitations. Interviews were conducted only with women who had decided to participate in the trial, requested the trial results, and responded to the invitation to participate in research about the trial. The interviews did not take place at the time of decision making (which may have been a number of years ago) but, instead, after the trial was complete and participants had received a copy of the trial results. The babies of all the women interviewed had survived and it is likely that reflections on the trial process might have differed had this not been the case. However, this kind of research is difficult to carry out

without encountering problems of this nature, and our findings do provide important insights into people's experiences of trial participation and contribute to an understanding of factors influencing decision making to participate, including the process of consent.

The ORACLE trial generated important evidence about optimal management of pre-term labour. The need to recruit to studies in critical situations, within and outside pregnancy and childhood, remains. How best the rights and interests of participants in these situations can be protected is an important question. One approach is to provide complete and pertinent information with the aim of ensuring autonomy,²⁰ but our findings add to the growing body of evidence that participants' understandings of trials very often differ from those of researchers, even in non-critical situations.^{14–18} There is also evidence that people have difficulties with the consent process outside research situations,²¹ challenging the notion that informed consent is an achievable ideal and raising questions about whether the consent process has been overemphasised as a means of safeguarding the rights and interests of patients. Research ethics committees closely scrutinise patient information sheets, but our study emphasises the fact that such leaflets may play only a limited role in decisions to participate in trials in a critical situation. Instead, participants express a more generalised confidence in the governance and safety of research and report that they respond to the socioemotional qualities of their interactions with individuals who make requests for participation.

Our findings suggest that a much broader view is required of how arrangements for the governance of research can be made robust, rather than relying solely on "informed consent". Future studies should use ethnographic methods to explore the nature of interactions between candidates for research and health professionals involved in recruitment, and evaluate whether combining the roles of "carer" and "researcher" in one professional creates more challenges than it solves.

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Conflict of interest: Sara Kenyon was an investigator on the ORACLE trial.

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