Chapter 5

Difficulties in recruitment for a randomized controlled trial involving hysterosalpingography

Denise AM Perquin1, Anton JM de Craen2 and Frans M Helmerhorst3

1 Department of Obstetrics and Gynecology, Medical Center Haaglanden, The Hague, The Netherlands,

2 Department of Gerontology and Geriatrics, Leiden University Medical Center, Leiden, The Netherlands

3 Department of Gynecology, Division of Reproductive Medicine, Leiden University Medical Center, Leiden, The Netherlands

Reprod Health 2006 Jun 13; 3 : 5
Abstract

Background: The usefulness of hysterosalpingography (HSG) as routine investigation in the fertility work-up prior to laparoscopy and dye had been assessed in a randomized controlled trial. Recruiting subjects to the study was more difficult than anticipated. The objective of this study was to explore possible reasons for non-participation in the trial.

Methods: All newly referred subfertile women admitted to the Reproductive Medicine Clinic of Leiden University Medical Center between 1 April 1997 and 31 December 1999, were eligible for the study. The reasons for non-participation were evaluated by scrutinizing the medical records.

Results: Out of 759 women, a total of 127 (17%) agreed to participate in the trial. The most important reason for non-participation was because of exclusion criteria (73%). Other reasons were inattentive clinicians (3%) and patient-associated reasons (24%). Patient refusal and indecisiveness to enroll in the study were the most common patient-associated reasons. The most frequently stated reason for trial refusal was reluctance to undergo laparoscopy and dye mainly due to issues related to anesthesia and scheduling of procedure.

Conclusion: Almost three-quarters of recruitment difficulties in this study were due to unavoidable reasons. To overcome the remaining avoidable reasons for non-participation, attention should be paid to appropriate instruction of the study protocol to the participating doctors and to provide adequate information, in layman’s terms, to the patients. Reminding patients by notes or telephone calls for attending the clinic are helpful. It may be contingent upon tracing the reasons of clinicians and patients for non-participation to improve enrollment during a trial.
**Background**

Between April 1997 and April 2002 we performed a pragmatic\(^1\) multicenter randomized controlled trial comparing two different diagnostic strategies in the routine fertility work-up\(^2\). The hysterosalpingography (HSG) group underwent HSG first. If HSG showed normal uterine cavity, patent tubes and no tubal pathology, laparoscopy and dye followed after six months. In case of suspected tubal pathology, laparoscopy was performed within one or two months after HSG. The laparoscopy group did not receive HSG but underwent laparoscopy and dye directly after randomisation.

The power of the trial was based on randomisation of 750 subfertile women. Recruitment of patients into the trial was more difficult than expected. We estimated the highest recruitment rate from Leiden University Medical Center (LUMC). However, about halfway through the trial, we had only recruited 177 women instead of an estimated 375. To understand this low recruitment rate, we initiated the current study to find strategies to avoid the major reasons for non-participation which could be implemented during the second half of the study or later in other studies in reproductive medicine. This study identified potential eligible participants visiting one of the three participating hospitals (Leiden University Medical Center) during the first half of the recruitment period.

**Methods**

All women in our study participated in a multicenter randomized controlled trial with or without the performance of HSG to assess the usefulness of hysterosalpingography as routine investigation in the fertility work-up prior to laparoscopy and dye. Recruitment strategy, description of subjects, and main results of the trial have been published elsewhere\(^2\). In short, the trial was performed in one university hospital (Leiden University Medical Center, Leiden) and two non-university teaching hospitals (Medical Center Haaglanden, The Hague and Groene Hart Hospital, Gouda). All newly referred subfertile women who visited one of the three hospitals between April 1997 and April 2002 were eligible for inclusion in the trial. Exclusion criteria were a) subfertility less than 1 year, b) woman older than 37 years at time of first visit, c) anovulation in spite of clomifene citrate or bromocriptin use, d) abnormal semen analysis according to WHO criteria\(^3\), or e) testing of tubal patency performed in the past. Women were asked to participate in the trial by their treating gynecologist at the time that HSG would normally be planned and informed consent was obtained. If the women refused to participate in the trial, the reason for non-
participation was recorded. A computer-based 1:1 ratio randomisation procedure was used to allocate the women into two groups; the HSG group or the laparoscopy group. Informed consent was obtained from all women. The Institutional Review Boards of each of the three hospitals approved all stages of the trial.

Recruitment of subjects into the trial was lower than expected. We elucidated this current study to explore the determinants of non-participation during the first half of the recruitment period among all potentially suitable subjects of Leiden University Medical Center to find strategies to avoid the major reasons for non-participation. We reviewed the medical records from all newly referred subfertile women who visited the Reproductive Medicine Clinic of Leiden University Medical Center from 1 April 1997 to 31 December 1999. The medical record of each subfertile couple contained either a sticker indicating that the woman participated in the study or documented the reasons for non-participation.

Results

From 1 April 1997 to 31 December 1999, 759 newly referred subfertile women visited the Reproductive Medicine clinic of Leiden University Medical Center. A total of 127 women (17%) met the inclusion criteria and agreed to participate in the trial, the remaining 632 did not. The unavoidable reasons (467 women; 73%) and avoidable reasons (165 women; 27%) for non-participation are summarized in table 1. Almost three-quarters of the women did not participate due to exclusion criteria (73%), 3% due to inattentive doctors and the remaining 153 women (24%) due to patient-associated reasons. From these 153 women, 72 of them refused and 19 women were indecisive to enroll in the study. Fifty women never showed up for randomisation after the initial visit. Personal circumstances such as leaving the area and relationship problems were also reported (n = 7).

Table 2 shows reasons for trial refusal among the 72 women. The most frequent stated reason was reluctance to laparoscopy and dye (35 women; 49%). Twenty-seven women (37%) did not state a reason for non-participation.
Difficulties in recruitment for a randomized controlled trial involving hysterosalpingography

Table 1. Unavoidable and avoidable reasons for non-participation

| Unavoidable reasons                        | N = 467 | %  |
|--------------------------------------------|---------|----|
| Exclusion criteria                         | 460     | 73 |
| Androgenic factor                          | 173     |    |
| Tubal testing performed in the past        | 114     |    |
| Pregnant before randomisation              | 91      |    |
| Women older than 37 years at first visit   | 55      |    |
| Anovulation                                | 27      |    |
| Patient’s reason                           | 7       | 1  |
| Personal circumstances                     | 7       |    |

| Avoidable reasons                         | N = 165 | %  |
|-------------------------------------------|---------|----|
| Doctor’s reason                           | 19      | 3  |
| Eligible, but not approached              | 19      |    |
| Patient’s reason                          | 146     | 23 |
| Refused to participate                    | 72\(^1\) |    |
| No show-up after initial visit            | 50      |    |
| Indecisiveness                            | 19      |    |
| Language barrier                          | 5       |    |

\(^1\)see Table 2

Table 2: Patient’s reasons for trial refusal

| Reasons                                      | N = 72 | %  |
|----------------------------------------------|--------|----|
| Reluctance to laparoscopy and dye:           | 35     | 49 |
| General anesthesia                          | 20     |    |
| The timing of the laparoscopy is too soon   | 15     |    |
| Reluctance to hysterosalpingography:         | 3      | 4  |
| Fear for pain                               | 3      |    |
| Don’t want to be involved in a research project | 7    | 10 |
| Reasons not documented                      | 27     | 37 |
Discussion

In retrospect, it seems clear that we had too optimistic recruitment targets. Main unavoidable reasons for nonparticipation in the trial were not meeting the inclusion criteria and personal circumstances. In 19 of 165 avoidable reasons for nonparticipation, it appeared that doctors were inattentive to approach their eligible patients for the trial. More details of their negligence were not documented, except that in general these doctors appeared to be willingly participating in the trial. Attention should be paid to appropriately instruct participating doctors in order to increase the recruitment of eligible patients. We have no evidence that physicians’ preferences influenced the outcome of the randomized trial4. However, discussing the clinical relevance of the question as well as practical issues in the period that the protocol of the trial was designed appeared to be essential in the prevention of barriers in clinical recruitment5.

Apprehensiveness towards one of the diagnostic procedures in this trial (laparoscopy) was mentioned by the women as the most prominent and avoidable reason for nonparticipation in the trial. General anesthesia prior to laparoscopy appeared to be a main obstacle for enrolment in the trial. Providing more adequate information on the actual procedure and using layman’s terms may improve the rate of participation in such a trial. Although well educated and employed persons were more likely to refuse randomisation because of preference4, we think that providing more information focused on problems that may emerge from questionnaires disseminated among potential participants in the development of the trial, may optimize recruitment. Some patients did not wish to be involved in a research project. Once patients have made up their mind and once they have prepared a distinct preference, it is nearly impossible to persuade them for enrolment6.

One shortcoming of our paper is that we studied the major reasons of non-participation of potentially eligible participants visiting only one hospital. Unavoidable reasons of non-recruitment accounted for three quarters of the non-participation. The exclusion factor might be higher in an academic center due to specific criteria for referrals. The referred subfertile couples could have been older, with severe androgenic pathology or proven tubal pathology needing specialized assisted reproductive treatments. Another objective of this study was to find strategies to avoid the major reasons for non-participation which could be implemented during the second half of the study or later in other studies focusing on reproductive medicine. We assume that the major avoidable reasons of non-participation (like trial refusal) would be equally divided among all participating hospitals.

Planning for recruitment should be an important issue in the preparation period when a trial is designed3,8. Attention can also be paid to logistic problems that patients
Difficulties in recruitment for a randomized controlled trial involving hysterosalpingography

may encounter. To minimize the no-show, reminder notes and telephone calls may remind patients to attend the clinic. A member of the research team, who can provide the information on a low profile with a high level of communication skills and understanding, can support the investigators. This person can deal with practical problems, such as patient’s concerns or language barriers. This may contribute to solving the problem of women being less likely to participate in clinical trials9.

Conclusion

In conclusion, this study showed that almost three-quarters of our recruitment failures were due to unavoidable reasons. To overcome the remaining avoidable reasons for non-participation and to increase external validity of a trial, it may be contingent upon tracing reasons of clinicians and patients for non-participation as well as by anticipating practical problems that clinicians and patients may encounter during a trial. In the set up of the trial and during the recruitment, communication and information are the key words.

Competing interests

The author(s) declare that they have no competing interests.

Authors’ contributions

DAMP participated in the design of the study, collected and analyzed the data and wrote the first draft. AJMC performed statistical analyses and took part in the further preparation of the paper. FMH initiated the study, participated in the design of the study, took part in the further preparation of the paper and finalized the manuscript.

Acknowledgements

The authors wish to thank Kim Urgel for her help with collecting the data.
Chapter 5

References

1. Haynes B: Can it work? Does it work? Is it worth it? The testing of healthcare interventions is evolving. BMJ 1999, 319:652-653.

2. Perquin DAM, Dorr PJ, de Craen AJM, Helmerhorst FM: Routine use of hysterosalpingography prior to laparoscopy in the fertility workup: a multicenter randomized controlled trial. Hum Reprod 2006, 21:1227-1231.

3. World Health Organization: WHO laboratory manual for the examination of human semen and semen-cervical mucus interaction 4th edition. Cambridge, Cambridge University Press; 1999:60-61.

4. King M, Nazareth I, Lampe F, Bower P, Chandler M, Morou M, Sibbald B, Lai R: Impact of participant and physician intervention preferences on randomized trials: a systematic review. JAMA 2005, 293:1089-1099.

5. Ross S, Grant A, Counsell C, Gillespie W, Russell I, Prescott R: Barriers to participation in randomised controlled trials: a systematic review. J Clin Epidemiol 1999, 52:1143-1156.

6. Mills N, Donovan JL, Smith M, Jacoby A, Neal DE, Hamdy FC: Perceptions of equipoise are crucial to trial participation: a qualitative study of men in the ProtecT study. Control Clin Trials 2003, 24:272-282.

7. Hunninghake DB, Darby CA, Probstfield JL: Recruitment experience in clinical trials: literature summary and annotated bibliography. Control Clin Trials 1987, 8(Suppl 4):6-30.

8. Collins JF, Bingham SF, Weiss DG, Willford WO, Kuhn RM: Some adaptive strategies for inadequate sample acquisition in veterans administration cooperative clinical trials. Control Clin Trials 1980, 1:227-248.

9. Recruitment of women to clinical trials. Lancet 2002, 358:853.