UNIVERSITY OF AMSTERDAM

UvA-DARE (Digital Academic Repository)

Outcome measures in reproductive medicine trials

van Rumste, M.M.E.

Publication date
2013

Link to publication

Citation for published version (APA):
van Rumste, M. M. E. (2013). *Outcome measures in reproductive medicine trials*. [Thesis, fully internal, Universiteit van Amsterdam].

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: https://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, P.O. Box 19185, 1000 GD Amsterdam, The Netherlands. You will be contacted as soon as possible.

UvA-DARE is a service provided by the library of the University of Amsterdam (https://dare.uva.nl)

Download date:18 Nov 2026

Chapter 9

Summary and discussion

SUMMARY

A substantial number of couples with childwish are affected by subfertility. Although they have trouble to achieve a pregnancy, they are not truly infertile.[1] In the Netherlands one in six couples is confronted with either subfertility or infertility.[1] The aim of reproductive medicine is to provide help to such couples.
Diagnostic tests in such couples sometimes find the specific cause for the fertility problem, for example occluded Fallopian tubes or azoospermia. However, even after extensive investigation a proportion of subfertility cases remains unexplained. These couples are diagnosed with unexplained subfertility.

The aim of assisted reproductive technologies (ART) in couples with unexplained subfertility is to bring more gametes closer together. Intrauterine insemination (IUI) with controlled ovarian stimulation (COS) is usually the first treatment.[2-4] The main factor enhancing chances of pregnancy in COS-IUI is ovarian stimulation.[5] If COS-IUI does not result in a pregnancy, in vitro fertilisation (IVF) is offered as the next treatment. Stimulation of the ovaries to induce multifollicular growth is also part of the IVF treatment. The ovarian stimulation in COS-IUI and IVF induces the risk of ovarian hyperstimulation syndrome (OHSS) and multiple pregnancies.[6] These risks are not to be taken lightly. Most cases of OHSS are mild, but the syndrome can be life threatening.[7,8]

Multiple pregnancies give rise to higher medical risks for mother and offspring, such as preeclampsia, caesarean section, prematurity, growth restriction and higher health care costs.[9-11] The most effective way to prevent these ART-induced risk is to stop offering fertility treatments involving ovarian stimulation, or at least multiple follicle development. This will bring multiple pregnancy rates back to the levels found in nature. Reducing the multiple pregnancy rates should always be balanced against the potential decrease in the overall chances of conception.

This thesis addresses the prevention of OHSS and multiple pregnancies, and the economic burden of treatment modalities in couples with unexplained subfertility.

Chapter 1 *gives an outline and describes the objectives of this thesis.*

Chapter 2 *presents a meta-analysis on the estimates of treatment effect in randomized clinical trials in reproductive medicine comparing clinical pregnancies with live birth as the outcome measure.*
We compared the outcome measure clinical pregnancy with live birth in fertility studies and assessed whether the outcome differs between studies. We analyzed randomized

controlled trials in reproductive medicine that were found in systematic reviews as published in the Cochrane Library, provided they reported on both clinical pregnancy and live birth. For each individual RCT, data on clinical pregnancy and live birth were extracted. We compared the outcome of each study by calculating a kappa-statistic (agreement beyond chance of effectiveness of either treatment) and by comparing the odds ratio by calculating the ratio of the odds ratios (ROR). We found 67 systematic reviews, of which 42 reported on pregnancy and live birth. These 42 reviews included 654 RCTs, of which 143 (22%) reported both on pregnancy and live birth. The pregnancy loss rates in the treatment and control groups were comparable. Of the 143 RCTs, the conclusion based on pregnancy rate and live birth rate was comparable (kappa value of 0.81; 95% confidence interval [CI], 0.68–0.94). The odds ratios estimating treatment effect from pregnancy and live birth were also comparable (ROR, 1.01, 95% CI 0.9 to 1.12). In conclusion, only a minority of randomized clinical trials in reproductive medicine report on live birth. Conclusions on the effectiveness of a treatment based on either clinical pregnancy or live birth as endpoints are comparable. Clinical pregnancy is a proxy of live birth as endpoint.

Chapter 3 *evaluates the effect of measurement of serum estradiol in addition to ultrasound as compared to ultrasound alone on IVF outcomes in women undergoing stimulated cycles in IVF and ICSI treatment.*

We performed a meta-analysis. Randomised controlled trials that compared monitoring with ultrasound plus serum estradiol concentration versus ultrasound alone in women undergoing ovarian hyperstimulation for IVF and ICSI treatment were included. Our search strategy identified 1,119 potentially eligible reports, but most of them did not study the requested comparison. Only two RCTs met our inclusion criteria. These involved 411 women who underwent controlled ovarian stimulation monitoring. Our primary outcome measure of live birth rate was not reported in either study. One trial reported clinical pregnancy rate per woman (33% versus 31%; RR 1.07, 95% CI 0.77 to 1.49). The second trial reported clinical pregnancy rate per oocyte retrieval (22% versus 25%). There was no significant difference between the ultrasound plus estradiol group and the ultrasound alone group in the mean number of oocytes retrieved (WMD -0.55, 95%CI -1.79 to 0.69) and the incidence of ovarian hyperstimulation (RR 0.73, 95% CI 0.30 to 1.78) for the two studies. Therefore, we concluded that there is no evidence to support cycle monitoring by ultrasound plus serum estradiol as more (or less) efficacious than cycle monitoring by ultrasound alone on outcomes of pregnancy rates and OHSS.

Chapter 4 *describes the relationship between the number of follicles in COS-IUI cycles and the ongoing pregancy rates and multiple pregnancies.*

We performed a retrospective cohort study in all couples with unexplained subfertility undergoing IUI-COS in the Academic Hospital of Maastricht. Three hundred couples in the period August 1993 till April 2004 were included. No significant difference was

found in ongoing pregnancy rates between women with one, two, three or four follicles respectively (P = 0.54), but in women with two or more follicles 12 out of 73 pregnancies were multiple pregnancies. In conclusion, in IUI-COS for unexplained subfertility, induction of more than one follicle did not improve the ongoing pregnancy rate, but increased the risk of multiple pregnancies. Multiple pregnancies remained high in the first four cycles with multifollicular stimulation. We concluded in this chapter that, in order to reduce the number of multiple pregnancies, monofollicular growth should be the target in IUI cycles for unexplained subfertility.

Chapter 5 *presents the results of a systematic review and meta-analysis on the relation between the number of follicles and pregnancy rates is presented.*
We included relevant papers reporting follicle numbers in IUI cycles. Mantel–Haenszel pooled odd ratios and risk differences with 99% confidence intervals (CI) were calculated for pregnancy rates and multiple pregnancy rates. We included 14 studies reporting on 11,599 cycles. The absolute pregnancy rate was 8.4% for monofollicular and 15% for multifollicular growth. The pooled odds ratio for pregnancy after two follicles as compared with monofollicular growth was 1.6 (99% CI 1.3 to 2.0), whereas for three and four follicles, the pooled odds ratio was 2.0 and 2.0, respectively. Compared with monofollicular growth, pregnancy rates increased by 5%, 8% and 8% when stimulation resulted in two, three and four follicles. The pooled odds ratio for multiple pregnancies after two follicles was 1.7 (99% CI 0.8 to 3.6), whereas for three and four follicles the pooled odds ratio was 2.8 and 2.3, respectively. The risk of multiple pregnancies after two, three and four follicles increased by 6, 14 and 10%. The absolute rate of multiple pregnancies was 0.3% after monofollicular and 2.8% after multifollicular growth. We conclude that multifollicular growth is associated with increased pregnancy rates in IUI-COS. Since in cycles with three or four follicles the multiple pregnancy rates increased without substantial gain in overall pregnancy rate, IUI-COS should not aim for more than two follicles. This meta-analysis contradicts the conclusion from our retrospective study (chapter 4). One stimulated follicle should be the goal if safety is the primary concern, whereas two follicles may be accepted after careful patient counselling regarding the reproductive and obstetrical risks of twins.

Chapter 6 *addresses the question whether studies evaluating strategies to prevent multiple pregnancies have sufficient power to demonstrate any reduction in multiple pregnancies.*
We searched the Cochrane Menstrual Disorders and Subfertility Group (MDSG) database for randomized controlled trials that report on multiple pregnancies. Data on sample size, power calculation, multiple pregnancies and multiple live births were extracted. For each study, we calculated the required sample size to detect a reduction of 50% in the number of multiple pregnancies with 80% power at the 95% confidence level to detect this minimally important clinical difference. We found 83 reviews summarizing and appraising 904 randomized controlled trials reporting on pregnancy after fertility

treatment. Ten reviews with 95 randomized controlled trials evaluated interventions that aimed to prevent multiple pregnancies. Of these 95 randomized controlled trials, 9 had enough power to detect a difference in multiple pregnancy rates (9.5%). The remaining 73 reviews included 809 randomized controlled trials with multiple pregnancies as secondary outcome, of which 176 reported numbers of multiple pregnancies (22%). Only 15 of these 176 randomized controlled trials had adequate power to detect the imputed minimally important difference for multiple pregnancies (8.5%). We therefore conclude that in reproductive medicine, the overwhelming majority of published clinical studies reporting on interventions aimed at preventing multiple pregnancies lack adequate power. The shift in practice towards strategies aimed at reducing multiple pregnancies is based on common sense and clinical intuition rather than on robust data.

Chapter 7 *presents the long-term effectiveness and the economic evaluation of a randomized controlled trial comparing immediate treatment with IUI-COS with six months of expectant management.*
Previously, this trial had reported that immediate treatment with IUI-COS did not increase ongoing pregnancy rates compared with six months of expectant management in couples with unexplained subfertility and intermediate prognosis of natural conception.[12] The couples were then treated according to local protocol, usually IUI-COS followed by IVF.
We followed couples until 3 years after randomization and registered pregnancies and resources used. Primary outcome was time to ongoing pregnancy. Secondary outcome was treatment costs. Analysis was by intention-to-treat. Economic evaluation was performed from the perspective of the health care institution. Time to ongoing pregnancy did not differ between groups (log-rank test P= 0.98). The median time to pregnancy was 13 months (95% CI: 8–18) in the expectant management group versus 14 months (95% CI: 10–18) in the immediate treatment group. Cumulative ongoing pregnancy rates were 72–73% for expectant management and IUI-COS groups, respectively (relative risk 0.99, 95% CI 0.85 to 1.1). Estimated mean costs per couple were € 3,424 (95% CI € 880 to € 5,968) in the expectant management group and € 6040 (95% CI € 4,055 to € 8,125) in the IUI-COS group resulting in an estimated saving of € 2,616 per couple (95% CI € 385 to € 4,847) in favour of expectant management. In conclusion, in couples with unexplained subfertility and an intermediate prognosis of natural conception, initial expectant management for 6 months results in a considerable cost-saving with no delay in achieving pregnancy or jeopardizing the chance of pregnancy.

Chapter 8 *describes the economic analysis of an explorative randomized controlled trial comparing one cycle of in vitro fertilization (IVF) with elective single embryo transfer (eSET) versus three cycles of IUI-COS in couples with a poor prognosis for natural conception.*
Couples with unexplained or mild male factor subfertility were included. One cycle of IVF-eSET plus frozen-thawed cycles versus three cycles of IUI-COS were compared in a four

months time frame. In IVF-eSET one top-quality embryo is transferred, but if no top-quality embryo is present, double embryo transfer is performed. The outcome measures were ongoing pregnancy rates and costs. We randomly assigned 58 couples to IVF-eSET and 58 couples to IUI-COS. The ongoing pregnancy rates were 24% (14 out 58 couples) in the IVF-eSET group, versus 21% (12 out 58 couples) in the IUI-COS group with 2 and 3 multiple pregnancies, respectively. In 25% of the IVF cycles two embryo's were transferred. The mean cost per included couple was significantly different, € 2,781 in the IVF-eSET group and € 1,876 in the IUI-COS group. The difference in costs per ongoing pregnancy was € 2,456 in favour of IUI-COS. In conclusion, in couples with unexplained subfertility, one cycle of IVF-eSET resulted in an additional € 900 per couple compared to three cycles of IUI-COS, for no increase in ongoing pregnancy rates or decrease in multiple pregnancies. Considering a 24% ongoing pregnancy rate following COS-IUI, IVF-eSET would be the dominant treatment at a 38% ongoing pregnancy rate.

CLINICAL IMPLICATIONS

When diagnosed with unexplained subfertility after the basic fertility workup, women younger than 38 years still have good prospects of becoming pregnant.[12,13] Some clinicians and couples believe that immediately start of ART shortens the time to pregnancy. ART however bears the risk for OHSS as well as multiple pregnancies. Couples could try to conceive naturally, without the risks of ART, but this may take more time.

This thesis shows that in couples with unexplained subfertility and an intermediate prognosis, i.e. 30 to 40% chance of a natural conception in the next 12 months, initial expectant management for 6 months results in a considerable cost-saving without delay in achieving pregnancy. If conceiving naturally, the risk for multiple pregnancies is extremely low.[14] We also found that one cycle of IVF-eSET compared to three cycles of COS-IUI, did not result in an increase in ongoing pregnancy rates. When couples with unexplained subfertility will start ART, COS-IUI should be advised over IVF-eSET for now.
Starting with expectant management instead of immediate treatment, or starting with COS-IUI instead of IVF-eSET, in selected subfertile couples, results in potential additional savings. These savings can be used for couples really in need of ART.
When the decision has been made to start ART with COS-IUI treatment, two follicles should be aimed at after ovarian stimulation, to increase the chance for a pregnancy, with an acceptable risk of a twin. In trying to avoid multiple pregnancies, one should take into account that most couples still prefer twin pregnancies. Even in awareness of the risks of a multiple pregnancy, couples treated with IVF prefer the transfer of two embryo's over one

embryo.[15,16] The most challenging task for the doctor in dealing with subfertile couples, is therefore counselling, with respect to the time frame, on the benefits and risks from ART.

IMPLICATIONS FOR FUTURE RESEARCH

We found that using standard meta-analytic techniques, questions about outcomes comparing different treatments of ART could not always be answered, because definitions on pregnancy differed and the outcome measure 'multiple pregnancy' was poorly reported. The evidence for the shift in practice towards strategies aimed at reducing multiple pregnancies seems to be lacking. When trying to compare fertility treatments, concerning multiple pregnancies, a network meta-analysis might be able to combine all the available evidence and should be considered as an option.[17] A network meta-analysis compares multiple treatments using both direct comparisons of interventions within randomised controlled trials and indirect comparisons across trials based on a common comparator.

One should also consider that randomised controlled trials are not initially designed to test the safety of a treatment, just their effectiveness. The concerns about safety might be better addressed in large cohort studies or case-control studies.

With increasing demands on health care and limited resources, it is important for clinicians to consider the economic impact of their interventions. Economic evaluation is the comparative analysis of alternative interventions in terms of both their costs and consequences.[18] Cost-minimisation analysis compares costs when interventions are equivalent. Since it is rather difficult to show this equivalence, cost-minimisation analysis is no longer recommended. Cost-effectiveness analysis combines costs with potential benefits, i.e. clinical outcomes, in comparing interventions. Economic evaluations of health care interventions are said to be challenging to report.[19] In reproductive medicine economic analyses, published in the past 15 years, the methodological standards are seldom implemented.[20] Cost-effectiveness analyses can be improved by more clear and transparent reporting of the design, especially in terms of perspective and study horizon, as well as transparency in values used for costs, probabilities and outcomes. Furthermore, sensitivity analysis are required to address the uncertainly and robustness of the findings.[20,21] Economic studies should follow standards for economic evaluation to optimise the reporting of health economic evaluations, such standards have been recently published.[19,21]

There is no evidence in current literature to prefer one intervention to the other, when multiple pregnancies and cost-effectiveness are taken into account. The INeS study in unexplained subfertile couples, compares COS-IUI, IVF with eSET and IVF in a modified natural cycle.[22] Hopefully, this study will answer the question which intervention is more cost-effective.

Since chances to conceive naturally might remain higher then expected over time, we advice investigation of cost-effectiveness of fertility treatments compared to expectant management, to confirm or reject superiority of a treatment over natural conception.[12,13]

REFERENCES

1. landelijke netwerkrichtlijn subfertiliteit December 2010
2. NVOG-guideline: http://nvog-documenten.nl: Guideline: "Onverklaarde subfertiliteit".
3. NICE-guideline: http://publications.nice.org.uk/fertility-cg11. Guideline Fertility:"Assessment and treatment for people with fertility problems".
4. ASRM-guideline: http://www.asrm.org/Guidelines. Guideline: "Effectiveness and treatment for unexplained infertility".
5. Cohlen BJ, te Velde ER, van Kooij RJ, Looman CW, Habbema JD. Controlled ovarian hyperstimulation and intrauterine insemination for treating male subfertility: a controlled study. Hum Reprod. 1998; 13:1553-8.
6. Van Voorhis BJ. Outcomes from assisted reproductive technology. Obstet Gynecol 2006; 107:183-200.
7. Braat DD, Schutte JM, Bernardus RE, Mooij TM, van Leeuwen FE. Maternal death related to IVF in the Netherlands 1984-2008. Hum Reprod 2010; 25:1782-6.
8. Sigterman TA, Monen L, van Rumste MME. Fatale afloop na ovarieel hyperstimulatie syndroom bij in-vitro fertilisatie. NTOG 2012; 125: 393-6.
9. Campbell DM, Templeton A. Maternal complications of twin pregnancy. Int J Gynaecol Obstet 2004; 84:71-3.
10. Pinborg A. IVF/ICSI twin pregnancies: risks and prevention. Hum Reprod Update 2005; 11:575-93.
11. Ombelet W, Martens G, De Sutter P, Gerris J, Bosmans E, Ruyssinck G, Defoort P, Molenberghs G, Gyselaers W. Perinatal outcome of 12,021 singleton and 3108 twin births after non-IVF-assisted reproduction: a cohort study. Hum Reprod 2006; 21:1025-32.
12. Steures P, van der Steeg JW, Hompes PG, Habbema JD, Eijkemans MJ, Broekmans FJ, Verhoeve HR, Bossuyt PM, van der Veen F, Mol BW; Collaborative Effort on the Clinical Evaluation in Reproductive Medicine. Intrauterine insemination with controlled ovarian hyperstimulation versus expectant management for couples with unexplained subfertility and an intermediate prognosis: a randomised clinical trial. Lancet 2006; 368:216-21.
13. Custers IM and van Rumste MM, van der Steeg JW, van Wely M, Hompes PG, Bossuyt P, Broekmans FJ, Renckens CN, Eijkemans MJ, van Dessel TJ, van der Veen F, Mol BW, Steures P; CECERM. Long-term outcome in couples with unexplained subfertility and an intermediate prognosis initially randomized between expectant management and immediate treatment. Hum Reprod 2012; 27:444-50.
14. The ESHRE Capri Workshop Group. Multiple gestation pregnancy. Hum Reprod 2000; 15:1856-64.
15. Van Peperstraten AM, Kreuwel IA, Hermens RP, Nelen WL, Van Dop PA, Grol RP, Kremer JA. Determinants of the choice for single or double embryo transfer in twin prone couples. Acta Obstet Gynecol Scand 2008; 87:226-31.
16. Stillman RJ. A 47-year-old woman with fertility problems who desires a multiple pregnancy. JAMA 2007; 297:858-67.
17. Li T, Puhan MA, Vedula SS, Singh S, Dickersin K; Ad Hoc Network Meta-analysis Methods Meeting Working Group. Network meta-analysis-highly attractive but more methodological research is needed. BMC Med 2011; 9:79.
18. Higgins AM, Harris AH. Health economic methods: cost-minimization, cost-effectiveness, cost-utility, and cost-benefit evaluations. Crit Care Clin 2012; 28:11-24.
19. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, Augustovski F, Briggs A, Mauskopf J, Loder E. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. BJOG 2013; 120:765-70.
20. Moolenaar LM, Vijgen SM, Hompes P, van der Veen F, Mol BW, Opmeer BC. Economic evaluation studies in reproductive medicine: a systematic review of methodologic quality. Fertil Steril. 2013 Feb 5. pii: S0015-0282(13)00007-1. doi: 10.1016/j.fertnstert.2012.12.045. [Epub ahead of print]
21. Vijgen SM, Opmeer BC, Mol BW. The methodological quality of economic evaluation studies in obstetrics and gynecology: a systematic review. Am J Perinatol. 2013; 30:253-60.
22. Bensdorp AJ, Slappendel E, Koks C, Oosterhuis J, Hoek A, Hompes P, Broekmans F, Verhoeve H, de Bruin JP, van Weert JM, Traas M, Maas J, Beckers N, Repping S, Mol BW, van der Veen F, van Wely M. The INeS study: prevention of multiple pregnancies: a randomised controlled trial comparing IUI COH versus IVF e SET versus MNC IVF in couples with unexplained or mild male subfertility. BMC Womens Health 2009; 9:35.