UNIVERSITY OF AMSTERDAM

# UvA-DARE (Digital Academic Repository)

## Outcome measures in reproductive medicine trials

van Rumste, M.M.E.

**Publication date**
2013
**Document Version**
Final published version

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

# Outcome measures in reproductive medicine trials

Minouche van Rumste

# Outcome measures in reproductive medicine trials

Minouche van Rumste

Outcome measures in reproductive medicine trials
Thesis, University of Amsterdam, the Netherlands
© 2013 Minouche van Rumste

The printing of this thesis was supported by:
Catharina ziekenhuis Eindhoven
Stichting Gynaecologische Endocrinologie en Kunstmatige Humane Voortplanting; Amsterdam

| | |
|---|---|
| Cover | Minouche van Rumste en Chris Bor |
| Lay-out | Chris Bor |
| Printed by | Buijten & Schipperheijn |
| ISBN | 978-90-9027633-5 |

# Outcome measures in reproductive medicine trials

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. D.C. van den Boom
ten overstaan van een door het college voor promoties
ingestelde commissie,
in het openbaar te verdedigen in de Agnietenkapel
op maandag 1 juli 2013, te 16.00 uur

door

Minouche Maria Elisabeth van Rumste

geboren te Terneuzen

## Promotiecommissie

| | |
|---|---|
| Promotores: | Prof. dr. B.W.J. Mol |
| | Prof. dr. J.L.H. Evers |
| Co-promotores: | Prof. dr. F. van der Veen |
| | Dr. M. van Wely |
| Overige leden: | Prof. K.T. Barnhart |
| | Dr. B.J. Cohlen |
| | Prof. dr. F.M. Helmerhorst |
| | Dr. A.H.L.C. van Kaam |
| | Dr. M.H. Mochtar |
| | Prof. dr. S. Repping |

Faculteit der Geneeskunde

Aan mijn vader

# Contents


| | | |
|---|---|---|
| Chapter 1 | General introduction and outline of thesis | 9 |
| Chapter 2 | Measuring outcomes in fertility trials - can we rely on clinical pregnancy rates? *Fertility and Sterility 2010; 94:1647-51* | 19 |
| Chapter 3 | Monitoring of stimulated cycles in assisted reproduction (IVF and ICSI) *The Cochrane Library, Cochrane Database of Systematic Reviews 2008; 2:CD005289* | 31 |
| Chapter 4 | Is controlled ovarian stimulation in intrauterine insemination an acceptable therapy in couples with unexplained non-conception in the perspective of multiple pregnancies? *Human Reproduction 2006; 21:701-4* | 49 |
| Chapter 5 | The influence of the number of follicles on pregnancy rates in intrauterine insemination with ovarian stimulation: a meta-analysis *Human Reproduction Update 2008; 14:563-70* | 61 |
| Chapter 6 | Interventions and multiple pregnancies in reproductive medicine: critical appraisal of the available evidence *submitted* | 79 |
| Chapter 7 | Long-term outcome in couples with unexplained subfertility and an intermediate prognosis initially randomized between expectant management and immediate treatment *Human Reproduction 2011; 27:444-50* | 93 |
| Chapter 8 | IVF with planned single embryo transfer versus IUI with ovarian stimulation in couples with unexplained subfertility, an economic analysis *Reproductive BioMedicine Online; conditionally accepted for publication* | 107 |
| Chapter 9 | Summary and discussion | 121 |
| | Samenvatting en discussie | 131 |
| Appendices | Abbreviations | 143 |
| | List of co-authors and affilliations | 147 |
| | Publications | 151 |
| | Dankwoord | 155 |
| | Curriculum Vitae | 160 |

# Chapter 1

# Introduction

# INTRODUCTION

Subfertile couples undergo fertility treatments with the aim to get at least one healthy baby.[1] An ESHRE consensus report proposed that the primary outcome in fertility trials should be singleton live birth rate.[2] However, fertility trials mostly report on clinical or ongoing pregnancy rates. The side effects or complications, due to these fertility treatments, are poorly described, for the mother as well as for the fetus. How the pregnancy develops and what the obstetrical and neonatal outcome is, is often not mentioned. In 35% of clinical fertility trials, pregnancy loss is not reported and only a minority (7%) do report on serious adverse events, such as premature and very premature birth.[3] If important outcomes are incompletely reported, the value of fertility trials for counselling couples on the risk-benefit ratio of a treatment, for themselves or for their infants, is limited.

Subfertility is defined as the absence of conception in a period of 12 months of aiming for conception through unprotected intercourse.[4] Subfertile couples may undergo diagnostic or prognostic tests, such as assessment of ovulation, tubal patency testing and semen analysis.[5] When a cause for subfertility is found, the couple will receive therapy to either solve or bypass this problem to conceive. If a specific cause cannot be found, the couple is diagnosed with unexplained subfertility.[4]

In couples with unexplained subfertility the idea is to bring more gametes closer together: intrauterine insemination (IUI) with controlled ovarian stimulation (COS) is a common treatment.[4,6,7] In a meta-analysis of couples with unexplained subfertility, ovarian stimulation in combination with IUI has been shown to result in significantly higher pregnancy rates per woman as compared to IUI in the natural cycle.[8] The main driver behind the additional effectiveness of COS to IUI is multifollicular growth.[9] However, in the meta-analysis mentioned above, a comparison with no treatment or expectant management was not made. This is important, since in subfertile couples with a good prognosis for spontaneous conception, expectant management is a valid approach.[10,11] In couples with an intermediate prognosis, between 30 and 40%, the effectiveness of COS-IUI over a period of 6 months is similar to expectant management.[12] In fact, a 30-year old woman with a regular cycle and otherwise unexplained subfertility has 10 years with in total 120 ovulatory cycles ahead, in which she can conceive. It is questionable whether ovarian hyperstimulation for 6 cycles, which theoretically doubles the conception chances per cycle, really adds to the outcome of the 120 cycles that this woman still is going to get in her reproductive life. Evaluation of this additional value is therefore crucial.

In women undergoing ovarian stimulation in IVF, usually the next step in assisted conception if IUI has failed, the ovarian stimulation has serious drawbacks like ovarian hyperstimulation syndrome (OHSS) and the risk of multiple pregnancies.[13] The latter risk is also increased in women undergoing ovarian stimulation in IUI.

OHSS is characterized by the presence of multiple luteinized cysts within the ovaries. hCG causes the ovary to undergo extensive luteinization. In IVF, the use of hCG for final oocyte maturation and/or release, the continued use of hCG for luteal support, and the occurrence of a pregnancy resulting in hCG production, are risk factors for OHSS. When the risk of OHSS in IVF is thought to be high, the dosage of FSH can be changed during ovarian stimulation or hCG medication can be withheld. The incidence of OHSS varies widely, between 0.2% and 5%, of all assisted reproduction cycles.[14] Most cases of OHSS are mild, but it can be life threatening.[15,16] Two-dimensional ultrasound and serum estradiol determination is conventionally used in IVF to monitor the maturation of follicles and to ensure safe practice.

Another complication after IVF and COS-IUI is multiple pregnancy or, more specifically, pregnancy complications that occur as a result of such multiple pregnancies. Multiple pregnancies carry increased medical risks for mother and offspring, such as prematurity, preeclampsia, growth restriction and caesarean section, and increase the likelihood of social and economic problems in families and societies.[17-19] Since assisted reproductive technologies (ART), like COS-IUI and IVF became available, the number of multiple pregnancies has increased. In the United States there was an increase of 75% in twin births between 1980 and 2000. Over the same period the rate of triplet and higher order multiple pregnancies had risen four-fold.[20] Since the number of monozygotic twins has remained relatively constant (0.3-0.4% of all pregnancies), the increase in multiple pregnancies is the result of increasing numbers of dizygotic twins, triplets and higher order multiples. This is influenced by increasing maternal age, but mainly due to the use of agents for ovulation induction in ART.[21]

The incidence of multiple pregnancies after COS-IUI is poorly documented, but it is estimated that the multiple PR is 10-40% per cycle, and that 30-50% of all multiple pregnancies are due to COS-IUI.[20] The ESHRE consensus report on the risks and complications in ART concluded that the primary outcome measure in all fertility studies should ideally be singleton live birth rate and that twin and higher order multiple pregnancies should be considered complications.[22]

Multiple pregnancy rates in IVF can be reduced applying single embryo transfer (IVF-SET), instead of double embryo transfer (IVF-DET). A Cochrane review reported no significant difference in cumulative live birth rates following IVF-SET and one freeze-thaw, compared to one cycle of IVF-DET.[23] In IUI, the number of follicles per stimulated cycle can be lowered by milder ovarian stimulation, possibly resulting in less multiple pregnancies.

Apart from effectiveness and complications also costs should be considered when discussing assisted conception in couples with unexplained infertility. Costs consist of cost of treatment and cost of obstetrical and neonatal complications, as well as the long-term cost related to disabilities in the offspring. In this respect, multiple pregnancies impose a large burden on health care costs.[24-26]

One ART treatment cycle itself can be cheaper as compared to another treatment, but might increase costs due to complications. Moreover, multiple cycles might be necessary to achieve an ongoing pregnancy.[27,28]

# BACKGROUND

In fertility trials it is unusual to describe obstetrical outcomes. Although the endpoint of a treatment in fertility trials is usually an ongoing pregnancy, such a pregnancy does not guarantee the live birth of a baby.[1] This resulted in a change from pregnancy to live birth as the primary outcome in trials. However, this change is not based on clinical data and we hypothesized that pregnancy rates and live birth rates are not that different in subfertility studies.

A complication in ART is the occurrence of OHSS. Although OHSS is a serious complication in IVF, intensive monitoring during ovarian stimulation is inconvenient and expensive. A simplification could be restricting monitoring to ultrasonography.

Another complication is multiple pregnancies. The dilemma in COS-IUI is finding the balance in reducing the number of multiple pregnancies, for a still acceptable pregnancy rate. We wanted to evaluate the role of the number of follicles in COS-IUI in relation to ongoing pregnancy rate and multiple pregnancies in couples treated for unexplained non-conception. Hence we performed a retrospective cohort analysis. Although the rationale for addition of COS to IUI is to increase the pregnancy rate by multifollicular growth, studies reporting on the number of preovulatory follicles in relation to pregnancy rates in ovarian hyperstimulation with IUI showed contradictory results. Whereas the majority of the studies report a positive association between the number of follicles and pregnancy rate, we failed to find such a positive association in previous studies.[12,29-34] To address this contradiction, we performed a systematic review of the literature on the subject.

Furthermore, it remained questionable, whether it is possible to design and conduct high quality pragmatic randomized controlled trials studying the impact of prevention strategies to reduce multiple pregnancies after ART.

Since cost-effectiveness is becoming more important, we wondered whether the recommendation for expectant management in couples with an intermediate prognosis for pregnancy, would hold after three years. An economic evaluation, considering ongoing pregnancies and cumulative costs, was conducted.

Recently, an explorative randomized controlled trial was performed that evaluated whether IVF-eSET would lead to a similar pregnancy rate as three cycles of IUI-COS, but with a lower multiple pregnancy rate. This trial suggested that one cycle of IVF-eSET might be as effective as three cycles of IUI-COS as primary treatment.[35] In view of this finding, costs may play an important role in the decision on one or the other treatment.

# OUTLINE OF THE THESIS

In **chapter 2**, we report the results of a meta-analysis on the estimates of treatment effect in 143 randomized clinical trials in reproductive medicine comparing clinical pregnancies with live birth as outcome measure.

In **chapter 3**, we report the effects of ovarian monitoring by ultrasound only versus ultrasound plus serum estradiol measurement on IVF outcomes in women undergoing stimulated cycles in IVF and intracytoplasmic sperm injection (ICSI) treatment. Two randomized controlled trials were included this review. The clinical pregnancy rates and the occurrence of OHSS were compared.

In **chapter 4**, we report the results of a retrospective cohort study among 300 couples with unexplained subfertility undergoing IUI-COS in a university clinic. An inventory of the relationship between the number of follicles in IUI-COS cycles and the ongoing pregnancy rates and multiple pregnancies was made.

In **chapter 5**, we report a systematic review and meta-analysis to express the relation between the number of follicles and pregnancy rates. Relevant papers reporting follicle numbers in IUI cycles were included.

In **chapter 6**, we report whether studies evaluating strategies to prevent multiple pregnancies have sufficient power to reduce multiple pregnancies. Finally, we report if randomized controlled trials on subfertility, which describe multiple pregnancies, can show a reduction of 50% in the number of multiple pregnancies.

In **chapter 7**, we report the long-term effectiveness of expectant management or treatment with IUI-COS in couples with unexplained subfertility and intermediate prognosis of natural conception. Couples were randomly allocated to 6 months expectant management or immediate start with IUI-COS. We followed couples until 3 years after randomization and registered pregnancies and resources used. We investigated whether the recommendation not to treat during the first 6 months is valid, regarding the long-term effectiveness and cumulative costs. Economic evaluation was performed from the perspective of the health care institution.

In **chapter 8**, we report 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 unexplained or mild male factor subfertility. The costs per included couple and per ongoing pregnancy were calculated and compared.

In **chapter 9** we summarize the results of the studies presented in this thesis.

# REFERENCES


1. Min JK, Breheny SA, MacLachlan V, Healy DL. What is the most relevant standard of success in assisted reproduction? The singleton, term gestation, live birth rate per cycle initiated: the BESST endpoint for assisted reproduction. Hum Reprod 2004; 19:3-7.
2. Land JA, Evers JLH. Risks and complications in assisted reproduction techniques: Report of an ESHRE consensus meeting. Hum Reprod 2003; 18:455-7.
3. Dapuzzo L, Seitz FE, Dodson WC, Stetter C, Kunselman AR, Legro RS. Incomplete and inconsistent reporting of maternal and fetal outcomes in infertility treatment trials. Fertil Steril 2011; 95:2527-30.
4. NVOG-guideline: http://nvog-documenten.nl: Guideline: "Onverklaarde subfertiliteit".
5. NVOG-guideline: http://nvog-documenten.nl: Guideline: "Oriënterend Fertiliteitsonderzoek".
6. NICE-guideline: http://publications.nice.org.uk/fertility-cg11. Guideline Fertility:"Assessment and treatment for people with fertility problems".
7. ASRM-guideline: http://www.asrm.org/Guidelines. Guideline: "Effectiveness and treatment for unexplained infertility".
8. Verhulst SM, Cohlen BJ, Hughes E, Te Velde E, Heineman MJ. Intra-uterine insemination for unexplained subfertility. Cochrane Database Syst Rev 2006 Oct 18;(4):CD001838.
9. 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.
10. Hunault CC, Laven JS, van Rooij IA, Eijkemans MJ, te Velde ER, Habbema JD. Prospective validation of two models predicting pregnancy leading to live birth among untreated subfertile couples. Hum Reprod 2005; 20:1636-41.
11. van der Steeg JW, Steures P, Eijkemans MJ, Habbema JD, Hompes PG, Broekmans FJ, van Dessel HJ, Bossuyt PM, van der Veen F, Mol BW; CECERM study group (Collaborative Effort for Clinical Evaluation in Reproductive Medicine). Pregnancy is predictable: a large-scale prospective external validation of the prediction of spontaneous pregnancy in subfertile couples. Hum Reprod 2007; 22:536-42.
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. Van Voorhis BJ. Outcomes from assisted reproductive technology. Obstet Gynecol 2006; 107:183-200.
14. Delvigne A, Rozenberg S. Epidemiology and prevention of ovarian hyperstimulation syndrome (OHSS): a review. Hum Reprod Update 2002; 8:559-77.
15. 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.
16. Sigterman TA, Monen L, van Rumste MME. Fatale afloop na ovarieel hyperstimulatie syndroom bij in-vitro fertilisatie. NTOG 2012; 125: 393-6.
17. Campbell DM, Templeton A. Maternal complications of twin pregnancy. Int J Gynaecol Obstet 2004; 84:71-3.
18. Pinborg A. IVF/ICSI twin pregnancies: risks and prevention. Hum Reprod Update 2005; 11:575-93.
19. 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.
20. Fauser BC, Devroey P, Macklon NS. Multiple birth resulting from ovarian stimulation for subfertility treatment. Lancet 2005; 365:1807-16.
21. The ESHRE Capri Workshop Group. Multiple gestation pregnancy. Hum Reprod 2000; 15:1856-64.
22. Land JA, Evers JL. Risks and complications in assisted reproduction techniques: Report of an ESHRE consensus meeting. Hum Reprod 2003; 18:455-7.

23. Pandian Z, Bhattacharya S, Ozturk O, Serour G, Templeton A. Number of embryos for transfer following in-vitro fertilisation or intra-cytoplasmic sperm injection. Cochrane Database Syst Rev. 2009 Apr 15;(2):CD003416.

24. Gerris J, De Sutter P, De Neubourg D, Van Royen E, Vander Elst J, Mangelschots K, Vercruyssen M, Kok P, Elseviers M, Annemans L, Pauwels P, Dhont M. A real-life prospective health economic study of elective single embryo transfer versus two-embryo transfer in first IVF/ICSI cycles. Hum Reprod 2004; 19:917-23.

25. Lukassen HG, Schönbeck Y, Adang EM, Braat DD, Zielhuis GA, Kremer JA. Cost analysis of singleton versus twin pregnancies after in vitro fertilization. Fertil Steril 2004; 81:1240-6.

26. Scotland GS, McLernon D, Kurinczuk JJ, McNamee P, Harrild K, Lyall H, Rajkhowa M, Hamilton M, Bhattacharya S. Minimising twins in in vitro fertilisation: a modelling study assessing the costs, consequences and cost-utility of elective single versus double embryo transfer over a 20-year time horizon. BJOG 2011; 118:1073-83.

27. Pashayan N, Lyratzopoulos G, Mathur R. Cost-effectiveness of primary offer of IVF vs. primary offer of IUI followed by IVF (for IUI failures) in couples with unexplained or mild male factor subfertility. BMC Health Serv Res 2006; 6:80.

28. Chambers GM, Sullivan EA, Shanahan M, Ho MT, Priester K, Chapman MG. Is in vitro fertilisation more effective than stimulated intrauterine insemination as a first-line therapy for subfertility? A cohort analysis. Aust N Z J Obstet Gynaecol 2010; 50:280-8.

29. Tomlinson MJ, Amissah-Arthur JB, Thompson KA, Kasraie JL, Bentick B. Prognostic indicators for intrauterine insemination (IUI): statistical model for IUI success. Hum Reprod 1996; 11:1892-6.

30. Nuojua-Huttunen S, Tomas C, Bloigu R, Tuomivaara L, Martikainen H. Intrauterine insemination treatment in subfertility: an analysis of factors affecting outcome. Hum Reprod 1999; 14:698-703.

31. Stone BA, Vargyas JM, Ringler GE, Stein AL, Marrs RP. Determinants of the outcome of intrauterine insemination: analysis of outcomes of 9963 consecutive cycles. Am J Obstet Gynecol 1999; 180:1522-34.

32. Dickey RP, Taylor SN, Lu PY, Sartor BM, Rye PH, Pyrzak R. Effect of diagnosis, age, sperm quality, and number of preovulatory follicles on the outcome of multiple cycles of clomiphene citrate-intrauterine insemination. Fertil Steril 2002; 78:1088-95.

33. Ibérico G, Vioque J, Ariza N, Lozano JM, Roca M, Llácer J, Bernabeu R. Analysis of factors influencing pregnancy rates in homologous intrauterine insemination. Fertil Steril 2004; 81:1308-13.

34. van Rumste MM, den Hartog JE, Dumoulin JC, Evers JL, Land JA. Is controlled ovarian stimulation in intrauterine insemination an acceptable therapy in couples with unexplained non-conception in the perspective of multiple pregnancies? Hum Reprod 2006; 21:701-4.

35. Custers IM, König TE, Broekmans FJ, Hompes PG, Kaaijk E, Oosterhuis J, Mochtar MH, Repping S, van Wely M, Steures P, van der Veen F, Mol BW. Couples with unexplained subfertility and unfavorable prognosis: a randomized pilot trial comparing the effectiveness of in vitro fertilization with elective single embryo transfer versus intrauterine insemination with controlled ovarian stimulation. Fertil Steril 2011; 96:1107-11.

Chapter 2

# Measuring outcomes in fertility trials - can we rely on clinical pregnancy rates?

Jane F. Clarke, Minouche M.E. van Rumste, Cindy M. Farquhar, Neil P. Johnson, Ben W.J. Mol, Peter Herbison

Fertility and Sterility 2010; 94:1647-51

# ABSTRACT

**OBJECTIVE** To assess whether the estimates of treatment effect in randomized clinical trials (RCTs) in reproductive medicine differ when either clinical pregnancy or live birth is used as outcome measure.

**DESIGN** Meta-analysis.

**SETTING** We analyzed RCTs in reproductive medicine found in systematic reviews in the Cochrane Library that reported on both clinical pregnancy and live birth.

**PATIENT(S)** Subfertile couples.

**INTERVENTION(S)** For each individual RCT, data on clinical pregnancy and live birth were extracted.

**MAIN OUTCOME MEASURE(S)** We compared the outcome of each study by calculating a kappa-statistic (statistically significant treatment effective or not) and by comparing the odds ratio by calculating the ratio of the odds ratios (ROR).

**RESULT(S)** 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] .68 - .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).

**CONCLUSION(S)** 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.

# INTRODUCTION

The aim of reproductive medicine is to assist couples with an unfulfilled desire to become parents. Although the endpoint of a treatment for assisted reproduction is usually an ongoing pregnancy, such a pregnancy however does not guarantee the live birth of a baby (1). Recently, it has been proposed that singleton live birth rate should be the primary endpoint in subfertility trials (2). However, in some settings follow-up until live birth is an additional challenge for the investigator. When a third-line fertility treatment results in an ongoing pregnancy, the couple usually returns to a local gynecologist or midwife, thus limiting easy follow-up. In some countries, care for women with low-risk singleton pregnancies is provided in a primary care setting (3). Moreover, many trials are performed within limited budgets, thus hampering an additional follow-up time of 30 weeks, which is needed for a complete report on live birth. Therefore, a majority of subfertility studies report pregnancy instead of live birth as the endpoint.

The potential major drawback of using pregnancies as the endpoint of studies is the known pregnancy losses from the first trimester to live birth (4). First, a report of the absolute number of pregnancy rates would underestimate the number of couples that finally become parents. Second, differences in pregnancy loss rates between couples in two arms of an intervention trial would result in a difference in the estimates of treatment effect, because odds ratios calculated from pregnancy rates would be different from odds ratios calculated from live birth rates. If the latter were the case, odds ratios calculated from pregnancy rates will give false estimates of pregnancy rates.

Pregnancies from assisted reproduction technologies (ARTs) such as IVF and ovulation induction are known to have increased rates of multiple pregnancies. In clinics that do not have a single embryo transfer policy, the expected rates of multiple pregnancies following ART can be as high as 30–40% of pregnancies (5). Multiple pregnancies are associated with an increased risk of pregnancy loss, compared with singleton pregnancies. Therefore, it is of importance that subfertility trials report the birth of healthy children.

Unfortunately, the recent change from pregnancy to live birth as an endpoint is not based on clinical data. We hypothesized that pregnancy rates and live birth rates are not that different in subfertility studies. The aim of this study is to assess whether the use of either clinical pregnancy rates or live birth rates makes a difference in the statistical results and the conclusions of effectiveness of treatment.

# MATERIALS AND METHODS

## Search strategy

The Cochrane MDSG (Menstrual Disorders and Subfertility Group) clinical trial database contains over 4,300 subfertility trials. The integrity of Cochrane reviews is well recognised because they are also based on high-quality randomized controlled trials (RCTs), we decided to use their database for our search. We used the Web-based software that the Cochrane editorial groups use to support their editorial workflows (6). In January 2008, we conducted a search for all Cochrane systematic reviews in reproductive medicine that reported on both live birth and clinical pregnancy. Reviews and RCTs had to report odds ratios (ORs) with 95% confidence intervals (CIs) on both clinical pregnancy and live birth. The definition used for clinical pregnancy was an intrauterine gestational sac of at least 6 weeks' gestation. The definition of live birth was a pregnancy that resulted in the birth of at least one living baby. Two reviewers independently checked whether the reviews and RCTs reported these outcomes. In the case of disagreement, the judgment of a third reviewer was decisive. RCTs that combined ongoing pregnancies and live birth as one single outcome were not included. RCTs that were reported in more than one Cochrane review were included only once.

## Statistical analysis

The systematic reviews were grouped into reviews of assisted reproductive technologies (ART) and non-assisted reproductivetechnologies (non-ART). The definition of ART was treatments and procedures involving the handling of human eggs and sperm or the use of fertility drugs for the purpose of establishing a pregnancy. In contrast, non-ART was defined as interventions that allow future natural conceptions, such as surgery or tubal flushing. Data extraction was done by two reviewers using the Cochrane software Review Manager 5 (Revman 5). We collected data on treatment allocation and on outcome (i.e. clinical pregnancy and live birth). First, we calculated the weighted mean rates of clinical pregnancy and live birth for treatment and control groups. This was done for all studies, as well as for ART and non-ART studies separately. The pooled treatment effect as estimated by studies from clinical pregnancy and live birth was expressed with an OR per study. Differences between estimates on treatment effect based on clinical pregnancy and live birth were expressed by calculating a ratio of the odds ratios (ROR) as previously described by Schulz (7). To calculate the ROR, we used the statistical program of Revman 5. The nearer the ROR is to 1, the smaller the differences in conclusion from studies reporting on clinical pregnancy and studies reporting on live birth as outcome.

Subsequently, the data were plotted in Bland-Altman graphs (8). In these graphs, the mean of the ORs of pregnancy and live birth is plotted on the x-axis, and the difference between the two ORs is plotted on the y-axis (live birth minus pregnancy). Points above the average

line have ORs for live birth that are higher than those for pregnancy. In the conventional Bland-Altman plot, each point has equal weight. We reported plotting symbols that are proportional to the size of the study to illustrate the weight of the included studies.

The presence or absence of concordance between outcomes in RCTs was also reported. RCTs were categorized as no evidence of a significant treatment effect if the 95% CI around the OR included 1, or as evidence of a significant treatment effect if the 95% CI around the OR did not include 1. After categorizing the RCTs in this way, conclusions based on clinical pregnancy and the conclusions based on live birth were compared in a two-by-two table. The agreement beyond chance between these conclusions was reported as a kappa statistic. A kappa value of 0 indicates no agreement beyond chance between the two ORs, whereas a kappa value of 1 indicates perfect agreement. Similarly as for RCTs, the concordance between Cochrane reviews reporting on clinical pregnancy and life birth was reported in the same manner as was done for RCTs—using kappa-statistics.

# RESULTS

## Search

From the Cochrane database, we identified 67 reviews of RCTs in reproductive medicine, of which 42 reported on both clinical pregnancy and live birth as an outcome. These 42 reviews contained a total of 654 RCTs. Four reviews containing 14 RCTs were excluded, because all the included RCTs combined ongoing pregnancy and live birth in one single outcome. Of the remaining 640 RCTs, 160 reported on live birth, of which 143 reported on both pregnancy and live birth outcomes (22%). Of these 143 RCTs, 111 reported on ART and 32 reported on non-ART.

## Data

Table 1 shows the pooled data for clinical pregnancy and live birth as reported for treatment and control groups. For both treatment and control groups, a total of 1,219 pregnancies of the 6,512 clinical pregnancies (19%) were lost between diagnosis of clinical pregnancy and birth. There was a 5.4% difference between clinical pregnancy (30.3%) and live birth rates (24.9%) in the treatment groups, which represented a pregnancy loss rate of 18% (2780/3390). The difference between clinical pregnancy (27.9%) and live birth rates (22.4%) in the control groups was 5.5%, representing a pregnancy loss rate of 19.5% (2513/3122).

The Bland-Altman plots are shown for both ART (Fig. 1) and non-ART (Fig. 2). Both figures show that the majority of the included studies have a good correlation. The smaller studies with high ORs show less correlation between pregnancy and live birth. The mean difference in ORs was 0.1 for ART and –0.01 for non- ART studies. The ROR was 1.01 for

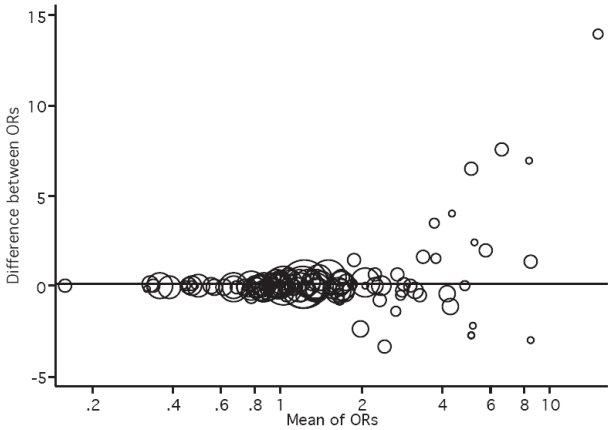



**Figure 1** Bland-Altman plot of agreement between ORs for ART studies. The size of the circle is proportional to the size of the study. Points above the average line have ORs for live birth that are higher than those for pregnancy.

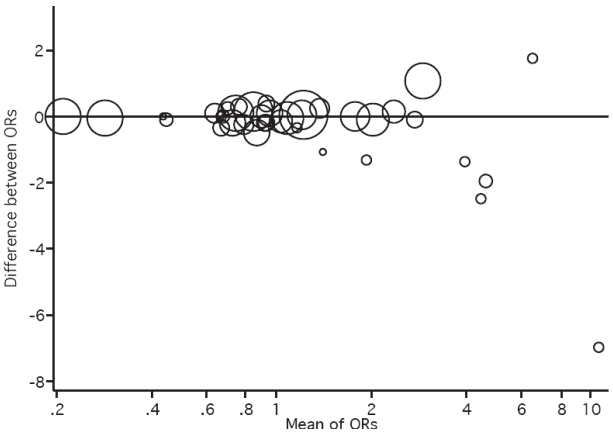



**Figure 2** Bland-Altman plot of agreement between OR for non-ART studies. The size of the circle is proportional to the size of the study. Points above the average line have ORs for live birth that are higher than those for pregnancy.

all studies (95% CI, 0.9–1.12), 0.99 for ART studies only (95% CI, 0.87–1.13), and 1.03 for non-ART studies (95% CI, 0.86–1.23).

Of the 143 RCTs, 114 studies (80%) reported no evidence of significant treatment effect when based on either pregnancy or live birth rates. In 21 studies (15%), evidence of a significant treatment effect was reported. Five studies (3.5%) reported evidence of a significant treatment effect in pregnancy rate, but not in live birth rate. Three studies (2%) showed the opposite and reported evidence of significant treatment effect in live birth rate, but not clinical pregnancy rate. The kappa value indicating the agreement beyond chance was 0.81 (95% CI, 0.68–0.94).

Of the 63 subfertility Cochrane reviews, 41 (65%) reported no evidence of a significant treatment effect for pregnancy rates and live birth rates, and 19 (30%) reported evidence of significant treatment effect in both outcomes. Two reviews (3.2%) reported evidence of a significant treatment effect in pregnancy rate but not live birth rate, whereas one review (1.6%) reported evidence of significant treatmenteffect in live birth rate but not clinical pregnancy rate. The kappa value was 0.89 (95% CI, 0.77–1.00).

**Table I.** Treatment effect size for RCTs categorised as ART and non-ART

| | ART / non-ART | No. of studies | Treatment group N/inclusion (%) | Control group N/inclusion (%) | OR for treatment effect (95% CI) |
|---|---|---|---|---|---|
| Clinical pregnancy rate | ART | 111 | 2608/8277 (31.5%) | 2256/7981 (28.3%) | 1.2 (1.11-1.27) |
| | non-ART | 32 | 782/2894 (27.0%) | 866/3223 (26.9%) | 1.0 (0.89-1.12) |
| | All | 143 | 3390/11171 (30.3%) | 3122/11204 (27.9%) | 1.1 (1.07-1.20) |
| Live birth rate | ART | 111 | 2207/8277 (26.7%) | 1870/7981 (23.4%) | 1.2 (1.13-1.31) |
| | non-ART | 32 | 573/2894 (19.8%) | 643/3223 (20.0%) | 0.98 (0.87-1.12) |
| | All | 143 | 2780/11171 (29.4%) | 2513/11204 (22.4%) | 1.2 (1.08 - 1.23) |
| | | | Difference between clinical pregnancy and live birth (%) | Difference between clinical pregnancy and live birth (%) | Ratio of the odds ratios (95% CI) |
| Difference in proportions for CPR and LBR | ART | 111 | 4.8% | 4.9% | 0.99 (0.87-1.13) |
| | non-ART | 32 | 7.2% | 6.9% | 1.03 (0.86-1,23) |
| | All | 143 | 5.4% | 5.5% | 1.01 (0.9-1.12) |

# DISCUSSION

We found 67 systematic reviews, 42 of which reported on both outcomes. A minority of the RCTs reported both on clinical pregnancy and live birth (22%). Almost all included RCTs showed good correlation between the outcome pregnancy rates and live birth rates.

## Strengths and Weaknesses

We extracted data from the Cochrane reviews and not the original RCTs. In this study, we relied on the authors and reviewers to have included good quality RCTs. However, the quality of RCTs in reproductive medicine has been found to be poor, notably in failing to report allocation concealment and live birth outcomes (9, 10). There is evidence of a progressive improvement in the quality of gynecological RCTs over the years (11). However, not all of the included Cochrane reviews have been updated, and some more recently published studies may have been overlooked. Less than 5% of all the available studies from the Cochrane MDSG register could be included. The definition of clinical pregnancy that we used was a gestational sac of at least 6 weeks' gestation. An outcome that may be a more reliable surrogate for live birth is a viable pregnancy (the presence of a fetal heart) or, even better, ongoing pregnancy (12 weeks' gestation with confirmation of a heartbeat). The definition of live birth was any birth after 20 weeks' gestation in which signs of life were present. A healthy child born at term would be a more preferable definition. We were reliant on the consistent use of definitions by the authors of the reviews.

## Alignment with other findings

Couples undergoing fertility treatments want to know the likelihood of success, meaning at least one healthy, live infant (1). However, it is unusual to describe obstetric outcome in fertility studies. Most RCTs are powered to detect differences in pregnancy rates, but they are not powered to detect a significant difference in live birth rate or multiple pregnancy rates (12, 13). Although there is no debate that a multiple pregnancy increases the risk of many pregnancy complications, it is also important to consider that most multiple pregnancies end in the birth of two healthy babies. Consequently, as the studies are not powered to detect differences in twin rates, therefore they are not capable of detecting any differences in poor outcome relating to complications in pregnancy.

The application of surrogate outcomes in medical research has been previously debated (14). Surrogate outcomes are often used when observation of clinical outcomes requires long follow-up. A guiding principle for using surrogate outcomes is that there must be a valid reason to accept them. Usually, this is not believed to be the case in reproductive medicine, because it is not difficult to report live birth with adequate follow-up. The risk associated with making a link between any target outcome and its surrogate is that it is not valid. In this study, we have documented the extent of the link and reported a 5.4% difference between pregnancy rate and live birth rate. We want to stress that, in interventions that have interaction with miscarriage or pregnancy complications, it is important to consider differences in pregnancy rates and live birth rates carefully. For example, a treatment that increases multiple pregnancy rates, resulting in higher pregnancy risks, or a treatment that reduces pregnancy loss in the treatment group, such as metformin (15), will influence the ultimate outcome.

We found the pregnancy loss rate from clinical pregnancy to live birth rate to be almost 19%. A previous report on pregnancy loss after ART shows a total risk of pregnancy loss

**Table 2.** Discordant randomized control trials

| Study | Pregnancy treatment events | Treatment total | Control events | Control total | OR M-H, Fixed (95%CI) |
|---|---|---|---|---|---|
| 2.1 ART | | | | | |
| Gerris 199923 | 21 | 27 | 14 | 26 | 3.00 [0.91-9.87] |
| Levron 200225 | 8 | 46 | 20 | 44 | 0.25 [0.10-0.66] |
| Matorras 199621 | 31 | 47 | 17 | 41 | 2.74 [1.15-6.50] |
| Matorras 200226 | 56 | 255 | 47 | 260 | 1.28 [0.83-1.97] |
| Petersen 200528 | 10 | 40 | 3 | 40 | 4.11 [1.04-16.29] |
| 2.2 NON ART | | | | | |
| Jinno 199722 | 12 | 32 | 3 | 31 | 5.60 [1.40-22.47] |
| Palomba 200427 | 31 | 55 | 39 | 54 | 0.50 [0.22-1.10] |
| Vandermolen 2001 | 6 | 12 | 1 | 15 | 14 [1.37-142.89] |

of 29%, and 58% of all pregnancy losses occurred before 6 weeks' gestation (16). From 6 weeks'gestation onward, the risk of pregnancy loss ranged 10–45%, depending on female age and ART type (16). Pregnancy rates can therefore be used as primary outcome in fertility studies. The 19% pregnancy losses found in this study can be used to extrapolate pregnancy outcomes to live birth and help to counsel patients.

## Disagreement with other findings

Pregnancy losses were greater in non-ART than in ART studies — 26.2% and 16.2%, respectively. This finding is not in agreement with the literature (17) and may be explained by the fact that the number of studies reporting non-ART interventions was limited. Another explanation might be that the embryos that survive the cleavage and blastocyst stages may be already self-selected for survival (18). Furthermore, there is evidence that twin pregnancies from ART result in relatively fewer pregnancy losses, compared with singleton pregnancies, than are usually reported (17, 19, 20).

We found discordant outcomes between pregnancy and live birth in eight studies (21–28), see Table 2. In these studies, the ORs of the treatment and control groups were in agreement with each other, but one of the ORs (treatment or control) was not statistically significant. Remarkably, in one study there was one more live birth than the number of pregnancies reported (28). We suspect that the authors of the review reporting this study did not correctly copy the data or that one twin birth was counted as two live births.

In conclusion, a minority of RCTs in reproductive medicine report on live birth. In RCTs, conclusions on treatment effect based on the endpoints (clinical pregnancy and live birth) are usually comparable, and the comparison between treatment groups will not be compromised. However, pregnancy losses should always be incorporated in clinical decision making, because live birth rate is the only outcome of real interest to the couple.

| Live birth treatment events | Live birth total | Control events | Control total | OR M-H, Fixed (95%CI) |
|---|---|---|---|---|
| | | | | |
| 20 | 27 | 10 | 26 | 4.57 [1.42-14.71] |
| 8 | 46 | 15 | 44 | 0.41 [0.15-1.09] |
| 26 | 47 | 16 | 41 | 1.93 [0.83-4.53] |
| 56 | 255 | 36 | 260 | 1.75 [1.11-2.77] |
| 9 | 40 | 4 | 40 | 2.61 [0.73-9.32] |
| | | | | |
| 9 | 32 | 3 | 31 | 3.65 [0.88-15.08] |
| 20 | 55 | 32 | 54 | 0.39 [0.18-0.85] |
| 4 | 12 | 1 | 15 | 7.00 [0.66-73.93] |

# REFERENCES


1. Min JK, Breheny SA, MacLachlan V, Healy DL. What is the most relevant standard of success in assisted reproduction? The singleton, term gestation, live birth rate per cycle initiated: the BESST endpoint for assisted reproduction. Hum Reprod 2004;19:3-7.
2. Land JA, Evers JLH. Risks and complications in assisted reproduction techniques: Report of an ESHRE consensus meeting. Hum Reprod 2003;18:455-7.
3. Amelink-Verburg MP, Verloove-Vanhorick SP, Hakkenberg RM, Veldhuijzen IM, Bennebroek Gravenhorst J, Buitendijk SE. Evaluation of 280,000 cases in Dutch midwifery practices: a descriptive study. BJOG 2008;115:570-8.
4. Johnson NP. No more surrogate end-points in randomised trials - the PCOSMIC trial protocol for women with polycystic ovary syndrome using metformin for infertility with clomiphene. Aust N Z J Obstet Gynaecol 2006;46:141-5.
5. Human Fertilization and Embryology Authority. http://www.hfea.gov.uk/en/default.html
6. www.archie.cochrane.org
7. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA 1995;273:408-12.
8. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1:307-10.
9. Helmerhorst FM, Belfield T, Kulier R, Maitra N, O'Brien P, Grimes DA. The Cochrane Fertility Regulation Group: synthesizing the best evidence about family planning. Contraception 2006;74:280-6.
10. Dias S, McNamee R, Vail A. Evidence of improving quality of reporting of randomized controlled trials in subfertility. Hum Reprod 2006;21:2617-2627.
11. Selman TJ, Johnson NP, Zamora J, Khan KS. Gynaecologic surgery from uncertainty to science: evolution of randomised controlled trials. Hum Reprod 2008;23:827-31.
12. Vail A, Gardener E. Common statistical errors in the design and analysis of subfertility trials. Hum Reprod 2003;18:1000-4.
13. Myers ER, McCrory DC, Mills AA, Price TM, Swamy GK, Tantibhedhyangkul J, et al. Effectiveness of assisted reproductive technology (ART). Evid Rep Technol Assess 2008;167:1-195.
14. Grimes DA and Schulz KF. Surrogate end points in clinical research: hazardous to your health. Obstet Gynecol 2005;105:1114-8.
15. Thatcher SS, Jackson EM. Pregnancy outcome in infertile patients with polycystic ovary syndrome who were treated with metformin. Fertil Steril 2006;85:1002-9.
16. Farr SL, Schieve LA, Jamieson DJ. Pregnancy loss among pregnancies conceived through assisted reproductive technology, United States, 1999-2002. Am J Epidemiol 2007;165:1380-8.
17. Tummers P, De Sutter P, Dhont M. Risk of spontaneous abortion in singleton and twin pregnancies after IVF/ICSI. Hum Reprod 2003;18:1720-3.
18. Los FJ, Van Opstal D, van den Berg C. The development of cytogenetically normal, abnormal and mosaic embryos: a theoretical model. Hum Reprod Update 2004;10:79-94.
19. La Sala GB, Nucera G, Gallinelli A, Nicoli A, Villani MT, Blickstein I. Lower embryonic loss rates among twin gestations following assisted reproduction. J Assist Reprod Genet 2005;22:181-4.
20. Lambers MJ, Mager E, Goutbeek J, McDonnell J, Homburg R, Schats R, et al. Factors determining early pregnancy loss in singleton and multiple implantations. Hum Reprod 2007;22:275-9.
21. Matorras R, Gorostiaga A, Diez J, Corcostegui B, Pijoan JI, Ramon O, Rodriguez-Escudero FJ. Intrauterine insemination with frozen sperm increases pregnancy rates in donor insemination cycles under gonadotropin stimulation. Fertil Steril 1996;65:620-5.
22. Jinno M, Katsumata Y, Hoshiai T, Nakamura Y, Matsumoto K, Yoshimura Y. A therapeutic role of prolactin supplementation in ovarian stimulation for in vitro fertilization: the bromocriptine-rebound method. J Clin Endocrinol Metab 1997;82:3603-11.

23. Gerris J, Neubourg D, Mangelschots K, Van Royen E, Vande Meerssche M, Valkenburg M. Prevention of twin pregnancy after in-vitro fertilization or intracytoplasmic sperm injection based on strict embryo criteria: a prospective randomized clinical trial. Hum Reprod 1999;14:2581-7.

24. Vandermolen DT, Ratts VS, Evans WS, Stovall DW, Kauma SW, Nestler JE. Metformin increases the ovulatory rate and pregnancy rate from clomiphene citrate in patients with polycystic ovary syndrome who are resistant to clomiphene citrate alone. Fertil Steril 2001;75:310-15.

25. Levron J. Shulman A, Bider D, Seidman D, Levin T, Dor J. A prospective randomized study comparing day 3 with blastocyst-stage embryo transfer. Fertil Steril 2002;77:1300-1.

26. Matorras R, Urquijo E, Mendoza R, Corcostegui B, Exposito A, Rodriguez-Escudero FJ. Ultrasound-guided embryo transfer improves pregnancy rates and increases the frequency of easy transfers. Hum Reprod 2002;17:1762-66.

27. Palomba S, Orio F Jr, Nardo LG, Falbo A, Russo T, Corea D, et al. Metformin administration versus laparoscopic ovarian diathermy in clomiphene citrate-resistant women with polycystic ovary syndrome: a prospective parallel randomized double-blind placebo-controlled trial. J Clin Endocrinol Metab 2004;89:4801-9.

28. Petersen CG, Mauri AL, Baruffi RL, Oliveira JBA, Massaro FC, Elder K, et al. Implantation failures: success of assisted hatching with quarter-laser zona thinning. Reprod Biomed Online 2005;10: 224-9.

Chapter 3

# Monitoring of stimulated cycles in assisted reproduction (IVF and ICSI)

Irene Kwan, Siladitya Bhattacharya, Alex McNeil, Minouche M.E. van Rumste

The Cochrane Library, Cochrane Database of Systematic Reviews 2008; 2:CD005289

# ABSTRACT

**BACKGROUND** Traditional monitoring of ovarian hyperstimulation during in vitro fertilisation (IVF) treatment has included ultrasonography plus serum estradiol concentration to ensure safe practice by reducing the incidence and severity of ovarian hyperstimulation syndrome (OHSS). The need for intensive monitoring during ovarian stimulation in IVF is controversial. It has been suggested that close monitoring is time consuming, expensive and inconvenient for the woman and simplification of IVF therapy by using ultrasound only should be considered. This systematic review assessed the effects of ovarian monitoring by ultrasound only versus ultrasound plus serum estradiol measurement on IVF outcomes and the occurrence of OHSS in women undergoing stimulated cycles in IVF and intracytoplasmic sperm injection (ICSI) treatment.

**OBJECTIVES** To quantify the effect of monitoring controlled ovarian stimulation in IVF and ICSI cycles with ultrasound plus serum estradiol concentration versus ultrasound only in terms of live birth rates, pregnancy rates and the incidence of OHSS.

**SEARCH STRATEGY** We searched the Menstrual Disorders and Subfertility Group Specialised Register of controlled trials, Cochrane Central Register of Controlled Trials (CENTRAL) on the latest issue of The Cochrane Library, MEDLINE (1966 to May 2007), EMBASE (1980 to May 2007), CINAHL (1982 toMay 2007), the National Research Register, and web-based trial databases such as Current Controlled Trials. There was no language restriction. Additionally all references in the identified trials and background papers were checked and authors were contacted to identify relevant published and unpublished data.

**SELECTION CRITERIA** Only randomised controlled trials that compared monitoring with ultrasound plus serum estradiol concentration versus ultrasound only in women undergoing ovarian hyperstimulation for IVF and ICSI treatment were included.

**DATA COLLECTION AND ANALYSIS** Two review authors independently examined the electronic search results for relevant trials, extracted data and assessed trial quality. They resolved disagreements by discussion with two other authors. Outcomes data were pooled when appropriate and summary statistics presented when limited data did not allow meta-analysis.

**MAIN RESULTS** Our search strategy identified 1119 potentially eligible reports, of which two met our inclusion criteria. These involved 411 women who underwent controlled ovarian stimulation monitoring. Our primary outcome 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.

**AUTHORS' CONCLUSIONS** There is no evidence from randomised trials to support cycle monitoring by ultrasound plus serum estradiol as more efficacious than cycle monitoring by ultrasound only on outcomes of live birth and pregnancy rates. A large well-designed randomised controlled trial is needed that reports on live birth rates and pregnancy, with economic evaluation of the costs involved and the views of the women undergoing cycle monitoring. A randomised trial with sufficiently large sample size to test the effects of different monitoring protocols on OHSS, a rare outcome, will pose a great challenge. Until such a trial is considered feasible, cyclemonitoring by transvaginal ultrasound plus serum estradiol may need to be retained as a precautionary good practice point.

# BACKGROUND

A successful outcome from in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI) in assisted reproduction depends on a preliminary phase of controlled ovarian hyperstimulation using exogenous gonadotrophins. The aim is to produce multiple follicles without incurring the risk of ovarian hyperstimulation syndrome (OHSS), which is the most serious iatrogenic complication of ovarian stimulation. OHSS is associated with development of a large number of follicles and is a potentially fatal condition as it can lead to ascites, pleural and pericardial effusion, haemoconcentration and coagulopathy (Schenker 1978 ). The incidence of OHSS is estimated to range from 0.2% to 2.7% of all assisted reproductive cycles, including with intra-uterine insemination (Asch 1991; MacDougall 1992; Nygren 2002; Roest 1996; Smitz 1990).

Controlled ovarian stimulation is traditionally monitored by means of ultrasound (US) in order to gain information on the number and size of developing follicles and to assist in determining the optimal time for human chorionic gonadotrophin (hCG) administration prior to oocyte retrieval. The overall aim is to ensure safe practice by reducing the incidence and severity of OHSS. Some fertility units also measure serum estradiol concentration during the course of stimulation, to provide added information about ovarian response and the potential risk of hyperstimulation. This combination of ultrasonography and serum estradiol concentration has been suggested to be the gold standard for monitoring stimulated cycles in IVF and ICSI procedures (Rizk 1992).

US monitoring alone has been reported to provide more accurate information on follicular number and size than can be obtained by serum estradiol concentration alone, in women with anovulatory infertility undergoing gonadotrophin induction therapy (Haning 1982; Hardiman 1990; Shoham 1991).

A cohort study comparing US only versus US plus hormonal determinations, including serum estradiol concentrations, for ovarian monitoring in women undergoing IVF reported no differences in live birth rate and the incidence of OHSS. There was a significant economic benefit in the US only monitoring protocol (Murad 1998). Another cohort study reported that US alone, performed during ovarian stimulation in IVF and intrauterine insemination, predicted 88% of cycle decisions as compared to 100% of cycle decisions that were predicted using combined monitoring (Confino 1996).

A third non-randomised study reported no differences in IVF outcomes and incidence of OHSS between women whose ovarian response was monitored by US and serum estradiol concentration on the day of human chorionic gonadotrophin (hCG) administration and women who were monitored with US and only had the serum estradiol concentration checked if the risk of OHSS was deemed to be high (Thomas 2002).

The need for intensive monitoring during ovarian stimulation in IVF is controversial. It has been suggested that close monitoring is time consuming, expensive and inconvenient for

the woman (Howard 1988; Rainhorn 1987; Tan 1992). Simplification of IVF therapy by minimal monitoring has been reported to have no adverse effects on treatment outcome and incidence of OHSS (Abdalla 1989; Roest 1995; Tan 1994). Some IVF programs have abandoned the use of hormone assay completely (Kemeter 1989; Tan 1994; Vlaisavljevic 1992).
This systematic review aimed to assess the effect of ovarian monitoring by US only versus US plus serum estradiol measurement on IVF outcomes and the occurrence of OHSS in women undergoing stimulated cycles in IVF and ICSI.



# OBJECTIVES

To quantify the effect of monitoring controlled ovarian stimulation in IVF and ICSI cycles with ultrasound only versus ultrasound plus serum estradiol concentration in terms of live birth rates, pregnancy rates and the incidence of OHSS.

# METHODS

## Criteria for considering studies for this review

### Types of studies

Randomised controlled trials only. Quasi-randomised controlled trials and randomised controlled trials of cross-over design were excluded because data from the precrossover phase could not be isolated.

### Types of participants

All women undergoing ovarian stimulation with gonadotrophins in IVF and ICSI procedures.

### Types of interventions

Monitoring with ultrasound versus monitoring with ultrasound plus serum estradiol concentrations.

### Types of outcome measures

Primary outcomes

- Live birth rate per woman

Secondary outcomes

- Pregnancy rate and multiple pregnancy rate per woman (pregnancy as established by pregnancy test or ideally confirmed by ultrasound)
- Number of oocytes recovered
- Number of cancelled cycles
- Rate of ovarian hyperstimulation syndrome(OHSS) per woman
- Costs of monitoring with ultrasound versus monitoring with ultrasound plus serum estradiol concentrations

## Search methods for identification of studies

We searched the Menstrual Disorders and Subfertility Group Specialised Register of controlled trials, Cochrane Central Register of Controlled Trials (CENTRAL) on the latest issue of The Cochrane Library, MEDLINE (1966 to May 2007), EMBASE (1980 to May 2007), CINAHL (1982 to May 2007), the National Research Register, and web-based trial databases such as Current Controlled Trials. There was no language restriction. Additionally, all references in the identified trials and background papers were checked and authors contacted to identify relevant published and unpublished data. The search strategy was adapted to fit individual databases which use different subject headings. The search strategy for MEDLINE was as follows:

1. randomized controlled trial.pt.
2. double-blind method/
3. random allocation/
4. random$.ti,ab,sh.
5. Randomized Controlled Trials/
6. ((single or double or triple or treble) adj5 (blind$ or mask$)).ti.
7. single-blind method/
8. clinical trial.pt.
9. exp clinical trials/
10. (clin$ adj5 trial$).ti,ab,sh.
11. meta analysis/
12. meta analysis.pt.
13. (metaanaly$ or meta-analy$ or (meta adj analy$)).tw.
14. (systematic$ adj5 (review$ or overview$)).ti.
15. (methodologic$ adj5 review$).tw.
16. (methodologic$ adj5 overview$).tw.
17. ("review" or "review academic" or "review tutorial").pt.
18. (medline or medlars or embase).tw,sh.
19. (scisearch or psychinfo or psycinfo).tw,sh.
20. (psychlit or psyclit).tw,sh.
21. cinahl.tw,sh.
22. ((hand adj2 search$) or (manual$ adj2 search$)).tw,sh.
23. (electronic database$ or bibliographic database$ or computeri? ed database$ or online database$).tw,sh.
24. (pooling or pooled or mantel haenszel).tw,sh.
25. (peto or dersimonian or der simonian or fixed effect).tw,sh.
26. or/1-25
27. Ovulation Induction/
28. Ovarian Hyperstimulation Syndrome/

29. Ovarian Follicle/
30. Follicle Stimulating Hormone/
31. Luteinizing Hormone/
32. Gonadotropins/
33. (ovulat$ adj5 (induct$ or stimulat$)).tw.
34. (ovar$ adj5 (induct$ or stimulat$ or follicle$)).tw.
35. ((ovar$ or ovulat$) adj5 (hyperstimulat$ or hyper stimulat$ or hyper-stimulat$)).tw.
36. gonadotrop?in$.tw.
37. (luteiniz$ adj5 hormone$).tw.
38. (stimulat$ adj5 (cycle$ or hormone$)).tw.
39. or/27-38
40. exp Fertilization in Vitro/
41. (IVF or in vitro fertili?ation or in-vitro fertili?ation or in-vitrofertili?ation).tw.
42. exp Sperm Injections, Intracytoplasmic/
43. ((intracytoplasmic or intra-cytoplasmic) adj5 sperm inject$).tw.
44. or/40-43
45. 39 and 44
46. ultrasonography/
47. (ultrasound or ultrasonograph$ or ultra-sound or ultra-sonograph$).tw.
48. ((ovar$ or ovulat$) adj5 (monitor$ or scan$ or measur$)).tw.
49. ESTRADIOL/an [Analysis]
50. ((oestrad$ or estrad$) adj5 (monitor$ or scan$ or measur$)).tw.
51. (hormon$ adj5 (measure$ or monitor$ or assay$)).tw.
52. or/46-51
53. 26 and 45 and 52
54. animal/ not (human/ or (human/ and animal/))
55. 53 not 54



## Data collection and analysis

*Trial identification*

Two review authors (IK, AMN) independently examined the electronic search results for reports of possibly relevant trials. These reports were retrieved in full. Both authors independently applied the selection criteria to the trial reports and resolved disagreements by discussion with two other review authors (SB, MM).

Quality assessment

Since there is evidence that the quality of allocation concealment particularly affects the results of studies (Schulz 1995), two review authors independently scored this quality as shown.

A: randomised trial deemed to have taken adequate measures to conceal allocation (i.e. central randomisation; serially numbered, opaque, sealed envelopes; or other description that contained elements convincing of concealment).

B: randomised trial in which the authors either did not report an allocation concealment approach at all or did not clarify the process involved as 'sealed envelopes', 'random

number tables', or 'computer-generated numbers'; or have reported an approach that did not fall into one of the other categories.

C: randomised trial in which allocation concealment was inadequate (such as quasi-randomised trials in which allocation was by alternation or reference to case record numbers or to dates of birth). These trials were excluded from this review.

If the method used to conceal allocation was not clearly reported, the author was contacted for clarification. We then compared the scores allocated and resolved differences by discussion. From the published data, the following were assessed independently by two review authors:

- criteria for including participants and assessing outcomes;
- use of intention-to-treat analysis;
- use of valid prospective power calculations;
- numbers lost to follow up;
- blinding of outcome assessment.

*Data extraction*

Two review authors (IK, AMN) independently extracted the data and information on the following: method of allocation concealment, number of randomised patients, types of participants, interventions and outcomes. The review authors were not blinded to the authors or publication journal when doing this. Results were compared and any differences resolved by discussion (SB, MM). We contacted the authors for clarification where there was insufficient information in the published report.

Analysis

Data extracted from the trials were analysed on an intention-to-treat basis (when this was not done in the original report, re-analysis was performed with the implicit assumption of outcome by including patients with missing data in the denominator but not the numerator). The primary analysis included only reported data. When live birth rates were not available, we reported pregnancy rates. The effects of the interventions on the outcome measures were meta-analysed based on clinical judgment as to whether the studies were addressing similar questions. Outcomes which were dichotomous (such as pregnancy rates and OHSS rates) were analysed as relative risks (RR) with 95% confidence intervals (CI) and outcomes which were continuous (such as number of oocytes retrieved) were analysed using weighted mean difference (WMD). We used RevMan software with the Mantel-Haenszel method and a fixed-effect model. Due to the limited number of studies identified, pooling of data was carried out on similar outcomes when such data were available; when these data were not available summary statistics were presented for individual studies.

Details of the studies, including methods, participants, intervention, outcomes, allocation concealment and any other details such as incidence of violation of protocol, were entered into the table 'Characteristics of included studies'. Studies which were excluded from

the review were presented in the table 'Characteristics of excluded studies' with a brief statement of the reason for exclusion, but no further information.
It is the intention of the review authors that the review is updated regularly.

# RESULTS

## Description of studies



See Table 1 and 2 for a summary of the characteristics of respectively the included and excluded studies. Our search strategy identified 1119 potentially eligible reports, of which three appeared to meet the inclusion criteria. We excluded one study (Murad 1998) because it was a non-randomised comparison. We did not identify any quasi-randomised

**Table 1.** Characteristics of included studies

Golan 1994

| | | |
|---|---|---|
| Methods | Randomised controlled trial (method not reported)<br>No report of sample size calculation | |
| Participants | 114 women undergoing IVF/embryo transfer programme<br>(first IVF attempt only) | |
| Interventions | US + serum estradiol concentration (n=57) versus US alone (n=57) | |
| Outcomes | Pregnancy rate/ oocyte retrieval. No of oocytes retrieved<br>No of cases of OHSS | |
| Notes | Intention-to-treat. No of cycles not reported<br>Author contacted: no data details were made available | |
| ***Risk of bias*** | | |
| **Item** | **Authors' judgement** | **Description** |
| Allocation concealment? | Unclear | B Unclear |

Lass 2003

| | | |
|---|---|---|
| Methods | Randomised controlled trial (computer-generated randomisation, assignment code in individual sealed envelopes, sample size calculation carried out before trial) Patient-blinded | |
| Participants | 297 women undergoing IVF treatment (had < 3 previous attempts;<br>ICSI excluded) | |
| Interventions | US + serum estradiol concentration (n=148) versus US alone (n=149)<br>(one cycle only) | |
| Outcomes | Pregnancy rate / woman No of oocytes retrieved No of cases of OHSS | |
| Notes | Nine women (3%) dropped out Not Intention to treat One cycle only Author contacted: no data details were made available | |
| ***Risk of bias*** | | |
| **Item** | **Authors' judgement** | **Description** |
| Allocation concealment? | Unclear | B Unclear |

US ultrasonography
OHSS ovarian hyperstimulation syndrome

**Table 2.** Characteristics of excluded studies

| | |
|---|---|
| Murad 1998 | Not a randomized trial |

or crossover trials. The two papers which met our inclusion criteria (Golan 1994; Lass 2003) involved 411 women who underwent controlled ovarian stimulation monitoring. They were published in 1994 and 2003.

*Golan 1994*

This trial involved 114 women (mean age 30.6 +/4.2 years versus 31 +/4.4 years; mean duration of infertility 5.2 +/3 years versus 4.6 +/3 years, in the two groups respectively). The women were randomly assigned to ultrasound and serum determinations of estradiol, progesterone and luteinizing hormone concentrations versus ultrasound alone. Only women undergoing their first IVF attempt were included. The outcomes measured were number of oocytes retrieved, pregnancy rate per oocyte retrieval, pregnancy rate per embryo transfer and number of OHSS cases. The criteria for ovarian hyperstimulation were not defined. The number of pregnancies and cancelled cycles were not documented. Live birth rates were not provided.

*Lass 2003*

This trial involved 297 women (mean age 33.2 +/3.4 years versus 33.0 +/34 years, in the two groups respectively; mean duration of infertility not reported) randomly assigned to daily ultrasound and serum estrogen E2 level assessments versus daily ultrasound assessment alone. Only one cycle of treatment was given to these women who had no more than three previously failed IVF attempts. Women undergoing ICSI were excluded. The outcomes measured were pregnancies per oocyte pick up, number of oocytes retrieved, pregnancy outcome and OHSS rates. The criteria for ovarian hyperstimulation were not defined. There was no report of the number of cancelled cycles. Live birth rate was not documented.

## Risk of bias in included studies

*Methods of randomisation*

The method of randomisation was not reported in one trial (Golan 1994); the author was not able to provide these methodological details. In the other trial, randomisation was performed using a computer-generated randomisation list and sealed envelopes (Lass 2003).

*Methods of allocation concealment*

The method of allocation concealment was not reported in either trial. Both authors were not able to provide these methodological details. Women were described as blinded in one trial (Lass 2003) but no further information was available.

*Use of a prospective power calculation*

This was not reported in one trial (Golan 1994). In the other study, a power calculation was described and, based on pregnancy as an outcome; about 230 women per group were required in order to have a power of 70% to show a difference of 5%. The final number of women recruited was 148 and 149 in each arm, respectively (Lass 2003).

*Criteria for including participants*

Only women undergoing the first IVF attempt were included in one trial (Golan 1994). In the other study, women with no more than 3 previous unsuccessful IVF were included and given only one single cycle of treatment (Lass 2003). Women undergoing ICSI were excluded in both trials.



*Criteria for assessing outcomes*

In one study, pregnancy rate was presented as pregnancy per oocyte retrieval; the definition of pregnancy was not provided (Golan 1994). In the other trial clinical pregnancy, presented as pregnancy per cycle, was defined as a pregnancy in which a fetal sac (with or without fetal heart activity) was visualised by ultrasound on day 28 to 42 after hCG administration (Lass 2003). The definition of OHSS was not provided in either trial.

*Numbers lost to follow up*

No dropouts were reported in one trial and the number of women at randomisation and in the analyses was the same (Golan 1994). In the other trial, nine patients (3%) dropped out (Lass 2003).

*Use of intention-to-treat analysis*

In one trial, data analysed were based on the same number of women as at randomisation, satisfying the intention-to-treat criteria (Golan 1994). In the other trial, nine patients (3%) dropped out and analysis was not based on the intention-to-treat principle (Lass 2003).

*Blinding of outcome assessment*

There was no report of blinding of assessment in either trial.

**Table 3.** Comparison of US + estradiol versus US only

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Clinical pregnancy per woman | 1 | 297 | Risk Ratio (M-H, Fixed, 95% CI) | 1.07 [0.77, 1.49] |
| 2 Mean number of oocytes retrieved | 2 | 411 | Mean Difference (IV, Fixed 95% CI) | -0.55 [-1.79, 0.69] |
| 3 OHSS rate | 2 | 1233 | Risk Ratio (M-H, Fixed, 95% CI) | 0.74 [0.40, 1.37] |
| 3.1 OHSS rate (all) | 2 | 411 | Risk Ratio (M-H, Fixed, 95% CI) | 0.73 [0.30, 1.78] |
| 3.2 OHSS rate (severe) | 2 | 411 | Risk Ratio (M-H, Fixed, 95% CI) | 0.43 [0.06, 2.89] |
| 3.3 OHSS rate (non-severe) | 2 | 411 | Risk Ratio (M-H, Fixed, 95% CI) | 0.88 [0.32, 2.38] |

## Effects of interventions

### *Summary of comparison*

### *Live birth rate*

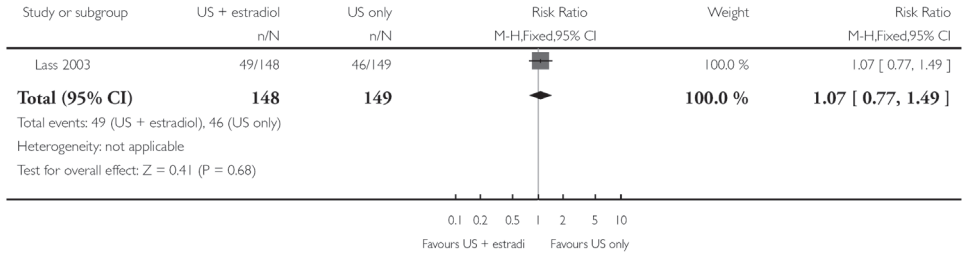
No data were available.

### *Pregnancy rate (Table 4)*

One trial (Golan 1994) reported the clinical pregnancy rate per oocyte retrieval (22% in the ultrasound plus estradiol group versus 25% in the ultrasound only group), the number of pregnancies in each group was not reported. It was not clear if each woman only had one treatment cycle initiated. Although the number of women randomised was known, the number of women who underwent oocyte retrieval was not reported hence the actual number of pregnancies could not be calculated.

In the second trial (Lass 2003), the clinical pregnancy rate was 33% in the ultrasound plus estradiol group versus 31% in the ultrasound only group (RR 1.07, 95% CI 0.77 to 1.49).

**Table 4.** Clinical pregnancy per woman



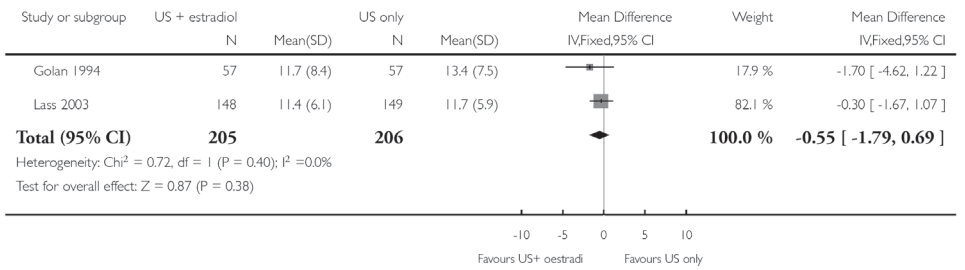

### *Multiple pregnancy rates*

No data were available.

### *Number of oocytes recovered (Table 5)*

The mean number of oocytes retrieved between the two arms was (11.7 +/- 8.4 versus 13.4 +/- 7.5) in one trial (Golan 1994) and (11.4 +/- 6.1 versus 11.7 +/- 5.9) in the other trial (Lass 2003). Combining the data from the two trials, the weighted mean difference

**Table 5.** Mean number of oocytes retrieved



(WMD) for the number of oocytes retrieved was -0.55 (-1.79 to 0.69, I2 = 0%). For this outcome, there was no significant difference between the two treatments.

*Number of cancelled cycles*

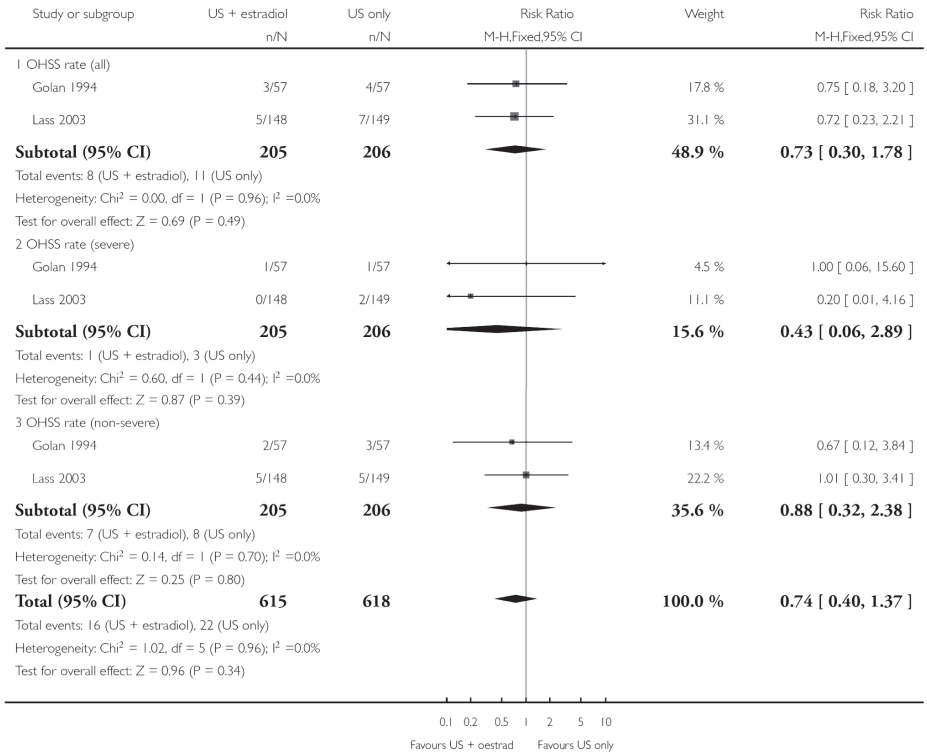
No data were available

*Rate of ovarian hyperstimulation syndrome(OHSS), including severe OHSS (Table 6)*

In one trial (Golan 1994), the incidence of non-severe OHSS was 2/57 in the ultrasound plus estradiol arm compared with 3/57 in the ultrasound only arm (3.5% versus 5.3%; RR 0.67, 95% CI 0.12 to 3.84). The figures in the second trial (Lass 2003) for nonsevere OHSS were 5/148 versus 5/149 (3.4% versus 3.4%; RR 1.01, 95% CI 0.32 to 2.38). Pooling



**Table 6.** OHHS rate




the results of these two trials, the relative risk for non-severe OHSS was 0.88 (95% CI 0.32 to 2.38, I2 = 0%).

Although severe OHSS was not listed as an outcome in the protocol, we considered it clinically important to include as part of the analyses. The incidence of severe OHSS was 1.8% versus 1.8% in one trial (Golan 1994) and 0% versus 1.3% in the other trial (Lass 2003). Pooling the results of these two studies, the relative risk for severe OHSS was 0.43

(95% CI 0.06 to 2.89, I2 = 0%). Available data from the two trials favoured combined monitoring with ultrasound plus estradiol but with wide confidence intervals.

*Costs of monitoring with ultrasound versus monitoring with ultrasound plus serum estradiol concentration*

No data available

# Discussion

## Principal findings

The pooled data from the two trials did not show any significant differences between the monitoring procedures and confidence intervals were wide for all the identified outcomes with reported data. Therefore, the evidence is insufficient to determine the comparative effectiveness of cycle monitoring by transvaginal ultrasound plus serum estradiol estimation and transvaginal ultrasound alone in women undergoing IVF.

## Strengths and weaknesses of the review

This study is the first comprehensive systematic review to assess the effects of cycle monitoring with ultrasound plus estradiol estimation versus ultrasound only. As a Cochrane review it will be updated regularly.

The methodological quality of the trials was variable (see section under 'Methodological quality of included studies'). The small number of trials identified and the lack of detail provided in each trial, despite requests to the authors, limited our ability to aggregate data meaningfully, especially in terms of pregnancy rates per cycle. There was a possibility that some of the randomised women may not have reached oocyte recovery due to cycles cancelled for inappropriate ovarian stimulation (either an under or over response). This is important in a trial where ovarian response may be affected by the monitoring regimen. The studies reviewed were limited by their small sample sizes. As the definition of OHSS was not presented in the two trials, it was uncertain if the reported cases of severe OHSS were similar in nature. The criteria for inclusion in the two trials also varied. Only first IVF attempts were included in one study and the number of cycles of treatment given was not reported (Golan 1994). In the other study, women with no more than three previous unsuccessful IVF treatments were included and they were given only one single cycle of treatment ( Lass 2003). These population characteristics could influence the success of the IVF treatment.

### Implications of extra monitoring tests

Cycle monitoring with both ultrasound and estradiol measurement is likely to involve higher costs (to cover technicians and laboratory costs, outpatient attendance) when compared with ultrasound alone. Unnecessary monitoring may cause women anxiety, though it is unclear if women will be more satisfied because of a placebo effect of being monitored.

The trials reviewed were not designed to test the cost effectiveness of the two interventions. However, it was suggested in one trial (Golan 1994) that avoiding serum hormone determination might save over US$150 (at early 1990 prices) in each cycle and compensate for the cost of the gonadotropin releasing hormone analogues (GnRHa).

Based on the results of this review, there is no evidence from randomised trials to support cycle monitoring by ultrasound plus serum estradiol as more efficacious than cycle monitoring by ultrasound only, relating to live birth and pregnancy rate outcomes.

To find a difference in rare outcome such as OHSS, a large randomised study requiring the recruitment of about 5000 women is needed, which would pose a great challenge. The interpretation of ultrasound involves some degree of inter-observer variability and, at present, a cycle monitoring protocol including both ultrasound and serum estradiol may need to be retained as a precautionary good clinical practice point.



## AUTHOR'S CONCLUSIONS

### Implications for practice

There is no evidence from randomised trials available to determine if cycle monitoring by transvaginal ultrasound plus serum estradiol concentrations is more effective than by transvaginal ultrasound alone in women undergoing IVF, relating to live birth and pregnancy rates. There is unlikely to be a trial sufficiently large to prove or disprove conclusively if either intervention can reduce OHSS rates, an important but rare outcome of ovarian stimulation. Until such a trial is considered feasible, cycle monitoring by transvaginal ultrasound plus serum estradiol may need to be retained as a good practice point.

### Implications for research

A large well-designed randomised controlled trial that reports on live birth and pregnancy rates as outcomes and provides an economic evaluation of the costs involved and the views of the women undergoing cycle monitoring is needed to show if both monitoring protocols are equivalent. A randomised trial with sufficiently large sample size to test the effect of different cycle monitoring protocols on OHSS will pose a great challenge.

## Acknowledgements

We are grateful thank the author for responding to our queries. We also thank Debbie Pledge for her help in updating the search strategy.

# REFERENCES

## References to studies included in this review


Golan 1994 {published data only} Golan A, Herman A, Soffer Y, Bukovsky I, Ron-El R. Ultrasonic control without hormone determination for ovulation induction in in-vitro fertilization/embryo transfer with gonadotrophin-releasing hormone analogue and human menopausal gonadotrophin. Human Reproduction 1994;9(9):1631–3.

Lass 2003 {published data only} Lass A, UK Timing of hCG Group. Monitoring of in vitro fertilization-embryo transfer cycles by ultrasound versus by ultrasound and hormonal levels: a prospective, multicenter, randomized study. Fertility and Sterility 2003;80(1):80–5.


## References to studies excluded from this review


Murad 1998 {published data only} Murad NM. Ultrasound or ultrasound and hormonal determinations for in vitro fertilization monitoring. International Journal of Gynaecology and Obstetrics 1998;63(3):271–6.


## Additional references


Abdalla 1989 Abdalla HI, Baber RJ, Leonard T, Kirkland A, Mitchell A, Power M, et al.Timed oocyte collection in an assisted conception programme using GnRH analogue. Human Reproduction 1989;4(8):927–30.

Asch 1991 Asch RH, Li HP, Balmaceda JP, Weckstein LN, Stone SC. Severe ovarian hyperstimulation syndrome in assisted reproductive technology: definition of high risk groups. Human Reproduction 1991;6(10):1395–9.

Confino 1996 Confino E, Binor Z, Molo MW, Rawlins R, Balos R, Mullaney K, et al.Sonographically monitored ovarian stimulation for assisted reproduction: a prospective, blind study. Journal of Reproductive Medicine 1996;41(1):7–10.

Haning 1982 Haning RV Jr, Austin CW, Kuzma DL, Shapiro SS, Zweibel WJ. Ultrasound evaluation of estrogen monitoring for induction of ovulation with menotropins. Fertility and Sterility 1982;37(5):627–32.

Hardiman 1990 Hardiman P, Thomas M, Osgood V, Vlassopoulou V, Ginsburg J. Are estrogen assays essential for monitoring gonadotropin stimulant therapy?. Gynecological Endocrinology 1990;4(4):261–9.

Howard 1988 Howard WF, Chihal HJ, Strain CA, Smith M. Programmed follicular stimulation reduces cycle cost and stress with no compromise in cycle quality: use of a modified programmed protocol. Journal of In Vitro Fertilisation and Embryo Transfer 1988; 5(6):343–6.

Kemeter 1989 Kemeter P, Feichtinger W. Experience with a new fixed-stimulation protocol without hormone determinations for programmed oocyte retrieval for in-vitro fertilization. Human Reproduction 1989;4 Suppl(8):53–8.

MacDougall 1992 MacDougall MJ, Tan SL, Jacobs HS. In-vitro fertilization and the ovarian hyperstimulation syndrome. Human Reproduction 1992;7 (5):597–600.

Murad 1998 Murad NM. Ultrasound or ultrasound and hormonal determinations for in vitro fertilization monitoring. International Journal of Gynaecology and Obstetrics 1998;63(3):271–6.

Nygren 2002 Nygren KG, Andersen AN. Assisted reproductive technology in Europe, 1999. Results generated from European registers by ESHRE. Human Reproduction 2002;17(12):3260–74.

Rainhorn 1987 Rainhorn JD, Forman RG, Belaisch-Allart J, Hazout A, Fries N, Testart J, et al.One year's experience with programmed oocyte retrieval for IVF. Human Reproduction 1987;2(6):491–4.

Rizk 1992 Rizk B, Smitz J. Ovarian hyperstimulation syndrome after superovulation using GnRH agonists for IVF and related procedures. Human Reproduction 1992;7(3):320–7.

Roest 1995 Roest J, Verhoeff A, van Heusden AM, Zeilmaker GH. Minimal monitoring of ovarian hyperstimulation: a useful simplification of the clinical phase of in vitro fertilization treatment. Fertility and Sterility 1995;64(3):552–6.

Roest 1996 Roest J, Mous HV, Zeilmaker GH, Verhoeff A. The incidence of major clinical complications in a Dutch transport IVF programme. Human Reproduction Update 1996;2(4):345–53.

Schenker 1978 Schenker JG, Weinstein D. Ovarian hyperstimulation syndrome: a current survey. Fertility Sterility 1978;30(3):255–68.

Schulz 1995 Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA 1995;273 (5):408–412.

Shoham 1991 Shoham Z, Di Carlo C, Patel A, Conway GS, Jacobs HS. Is it possible to run a successful ovulation induction program based solely on ultrasound monitoring?The importance of endometrial measurements. Fertility and Sterility 1991;56(5):836–41.

Smitz 1990 Smitz J, Camus M, Devroey P, Erard P, Wisanto A, Van Steirteghem AC. Incidence of severe ovarian hyperstimulation syndrome after GnRH agonist/HMG superovulation for in-vitro fertilization. Human Reproduction 1990;5(8):933–7.

Tan 1992 Tan SL, Balen A, el Hussein E, Mills C, Campbell S, Yovich J, et al.A prospective randomized study of the optimum timing of human chorionic gonadotropin administration after pituitary desensitization in in vitro fertilization. Fertility and Sterility 1992; 57(6):1259–64.

Tan 1994 Tan SL. Simplifying in-vitro fertilization therapy. Current Opinion in Obstetrics and Gynecology 1994;6(2):111–4.

Thomas 2002 Thomas K, Searle T, Quinn A, Wood S, Lewis-Jones I, Kingsland C. The value of routine estradiol monitoring in assisted conception cycle. Acta Obstetricia et Gynecologica Scandinavica 2002;81(6): 551–4.

Vlaisavljevic 1992 Vlaisavljevic V, Kovacic B, Gavric V. In vitro fertilization program based on programmed cycles monitored by ultrasound only. Journal of the International Federation of Gynaecology and Obstetrics 1992;39 (3):227–31.

Chapter 4

# Is controlled ovarian stimulation in intrauterine insemination an acceptable therapy in couples with unexplained non-conception in the perspective of multiple pregnancies?

Minouche M.E. van Rumste, Janneke E. den Hartog, John C.M. Dumoulin, Johannes L.H. Evers, Jolande A. Land

Human Reproduction 2006; 21:701-4

# ABSTRACT

**BACKGROUND** Controlled ovarian stimulation (COS) with intrauterine insemination (IUI) is a common treatment in couples with unexplained non-conception. Induction of multifollicular growth is considered to improve pregnancy outcome, but it contains an increased risk of multiple pregnancies and ovarian hyperstimulation syndrome. In this study the impact of the number of follicles (>14 mm) on the ongoing pregnancy rate (PR) and multiple PR was evaluated in the first four treatment cycles.

**METHODS** A retrospective cohort study was performed in all couples with unexplained non-conception undergoing COS-IUI in the Academic Hospital of Maastricht. The main outcome measure was ongoing PR. Secondary outcomes were ongoing multiple PR, number of follicles of ≥14 mm, and order of treatment cycle.

**RESULTS** Three hundred couples were included. No significant difference was found in ongoing PR between women with one, two, three or four follicles respectively (P = 0.54), but in women with two or more follicles 12/73 pregnancies were multiples. Ongoing PR was highest in the first treatment cycle and declined significantly with increasing cycle order (P = 0.006), while multiple PR did not change.

**CONCLUSIONS** In COS-IUI for unexplained non-conception, induction of more than one follicle did not improve the ongoing PR, but increased the risk of multiple pregnancies. Multiple PR remained high in the first four cycles with multifollicular stimulation. Therefore, in order to reduce the number of multiple pregnancies, in all IUI cycles for unexplained non-conception monofollicular growth should be aimed at.

# INTRODUCTION

Intrauterine insemination (IUI) with controlled ovarian stimulation (COS) is a common treatment in couples with unexplained non-conception. In a randomized controlled trial in couples with unexplained non-conception, COS in combination with IUI has been shown to result in significantly higher cumulative pregnancy rates (PR) per couple (33%) as compared to unstimulated intracervical insemination (10%), COS alone (19%) or IUI alone (18%) (Guzick *et al.*, 1999). The main benefit of the addition of COS to IUI is considered to be due to the induction of multifollicular growth (Cohlen, 1998). However, stimulating excess follicles has serious drawbacks considering the risk of ovarian hyperstimulation syndrome (OHSS) and multiple pregnancies. Multiple pregnancies carry medical risks for mother and offspring, and increase the likelihood of social and economic problems in families and societies.



Since assisted reproductive technologies, i.e. IUI and IVF, have become available, the number of multiple pregnancies has increased. In the USA there was an increase of 75% in twin births between 1980 and 2000. Over the same period the rate of triplet and higher order multiple pregnancies has risen 4-fold in the USA (Fauser *et al.*, 2005). Since the number of monozygotic twins has remained relatively constant (0.3–0.4% of all pregnancies) (ESHRE Capri Workshop Group, 2000), the increase in multiple pregnancies is the result of increasing numbers of dizygotic twins, triplets and higher order multiples. This is influenced by increasing maternal age, but mainly due to the use of agents for ovulation induction in assisted reproduction treatment (ESHRE Capri Workshop Group, 2000).The incidence of multiple pregnancies after COS-IUI is poorly documented, but it is estimated that the multiple PR is 10–40% per cycle, and that 30–50% of all multiples are due to COS-IUI (Fauser *et al.*, 2005). So far few studies (Nuojua-Huttunen *et al.*, 1999; Gleicher *et al.*, 2000) have investigated the relationship between multiple PR and number of follicles induced in COS-IUI.

The aim of this study was to evaluate the role of the number of follicles in COS-IUI in relation to ongoing PR and complications (multiple pregnancies) in couples treated for unexplained non-conception. Furthermore, we investigated whether increasing cycle order or patient variables influenced the outcome.

# MATERIALS AND METHODS

## Patients

A retrospective cohort study was performed in all couples with unexplained non-conception that had been treated with COS-IUI in the Academic Hospital of Maastricht, The Netherlands, in the period August 1993 till April 2004.

According to the local protocol, couples were offered a maximum of four cycles of COS-IUI. For IUI either fresh partners' sperm or cryopreserved donor sperm was used. All couples with unexplained non-conception had tried to conceive for ≥24 months. Couples using donor sperm had had ≥12 cycles of intracervical insemination. All had normal findings in their fertility work-up. This work-up consisted of confirmation of an ovulatory cycle by ultrasound, semen analysis, post-coital testing and evaluation of tubal function by hysterosalpingography and/or laparoscopy. Tubal status was considered to be normal if there were no adhesions and at least one tube was patent at pertubation during hysterosalpingography or laparoscopy. Minimal endometriosis was considered compatible with the definition of unexplained non-conception. For each couple, female age and duration of non-conception until start of treatment was registered, and whether unexplained non-conception was primary or secondary. Furthermore, we recorded the number of follicles measuring ≥14 mm at the time of HCG injection, the number of positive pregnancy tests and the number of ongoing singleton and multiple pregnancies. Only cycles in which HCG was given were included.

## Ovarian stimulation and insemination protocol

The aim of COS was to achieve two or three dominant follicles, i.e. follicles with diameters of ≥18 mm. The preparation used for ovarian stimulation was Humegon (Organon, Oss, The Netherlands), Menogon (Ferring, Hoofddorp, The Netherlands) or Menopur (Ferring, Hoofddorp, The Netherlands). Stimulation was started on day 3 of the cycle with a fixed dose of 150 IU of HMG s.c. per day. The ovarian response was monitored by serial vaginal ultrasonographic follicular measurements. If there was no response, or if more than four follicles were recruited, the starting dose of HMG was adjusted accordingly in the next cycle. Ovulation was triggered with the injection of 5000 IU of HCG s.c. (Pregnyl; Organon, Oss, The Netherlands) when at least one dominant follicle was detected.

The administration of HCG was withheld, and IUI was cancelled in stimulation cycles with more than four follicles with a diameter of ≥14 mm, or more than three dominant follicles. IUI was performed only once, 40–48 h after administering HCG, using fresh or cryopreserved sperm samples. The suspension of processed sperm was introduced into the uterine cavity with an IUI canula (Lettix, Apeldoorn, The Netherlands). The luteal phase was supported with 200 mg intravaginal progesterone three times a day for a period of 14 days after insemination (Progestan, Organon, Oss, The Netherlands) or a total of three injections of 1500 IU HCG s.c. (Pregnyl) on day 3, 6 and 9 after insemination respectively. A pregnancy test was performed in urine 12–14 days after IUI and was considered positive when HCG level was >25 mIU/ml. An ultrasound scan was performed between 9 and 12 weeks of gestation and the number of gestational sacs with fetal cardiac activity was established. An ongoing pregnancy was defined as cardiac activity at 9–12 weeks of gestation.

### Semen preparation

Either fresh partner's semen was used, produced ~4 h before IUI, or cryopreserved donor semen, which had been frozen in human sperm preservation medium with glycerol as a cryoprotectant (Mahadevan and Trounson, 1983). Before IUI, all fresh and thawed semen samples were subjected to a discontinuous density gradient centrifugation using PureSperm (Nidacon, Gothenburg, Sweden) (Laursen *et al.*, 2003). After centrifugation at 800 g for 15 min, the sperm pellet was washed twice with fresh medium by centrifugation for 10 min at 200 g, and finally resuspended in a total volume of 0.5 ml. Semen was evaluated before processing for volume, total number, motility and progressive motility, and this was combined into the progressively motile sperm density (PMSD). In our laboratory a PMSD of >3×106/ml is considered to reflect normozoospermia (Enginsu *et al.*, 1992).

### Statistical analysis

For the comparison of baseline patient characteristics and outcome, a Wilcoxon test and a $\chi^2$-test were used where appropriate. For the comparison of ongoing PR and multiple PR, a $\chi^2$-test for linear trend was used. $P < 0.05$ was considered to reflect statistical significance. Other characteristics that potentially are associated with the occurrence of pregnancy might bias our findings by confounding. Potential confounders are previous pregnancies, female age, duration of non-conception, non-conception being primary or secondary, cycle order and semen quality. In order to control for these potential confounders, we performed a multivariable logistic regression analysis, in which pregnancy was the dependent variable, and both follicle number as well as the potential confounders were independent variables.



## RESULTS

Overall, 300 couples were included, with a total of 879 cycles of COS-IUI. Cryopreserved semen was used for 34 couples in 92 cycles. There were 82 couples who had secondary unexplained non-conception. Since patient characteristics and treatment outcomes did not differ between couples using fresh semen and cryopreserved semen, these two groups have been combined for further analyses. The baseline characteristics of couples included are shown in Table I. The mean semen volume was 3.3 ml (range 0.2–9.7) and mean sperm concentration 66.3×106/ml (range 2.2–264). All couples with <24 months of unexplained non-conception had secondary non-conception, and were offered COS-IUI treatment without delay, based on findings at examination and treatment in the past.

The PR per cycle was 10.9%. The cumulative PR in four cycles was 32.0% per couple. Twenty-three couples had a miscarriage (2.6% per cycle) and one couple had an ectopic pregnancy (0.1% per cycle). The cumulative ongoing PR in four cycles was 23.0% per couple. The ongoing multiple PR in four cycles was 16.4%, of which 12.3% were twins

and 4.1% were triplets. The multiple PR per positive test was 12.5%. The odds ratio of the number of follicles for the occurrence of pregnancy was 1.0 (95% CI 0.75–1.3). This did not change in the multivariable analysis.

In Table II the ongoing and multiple PR according to the number of pre-ovulatory follicles of ≥14 mm is given. No statistically significant difference in ongoing PR was found between patients who had one or more than one follicle respectively (ongoing PR 7.9%, 95% CI 5.0–11.7 and 8.5%, 95% CI 6.4–11.0 respectively). In patients who had one follicle, no multiple pregnancies were found, whereas in patients with more than one follicle, 12/73 ongoing pregnancies were multiples.

Although COS was applied in all couples, 36.0% of the couples had only one follicle of ≥14 mm in the first cycle. In the next cycle the dose of HMG was adjusted, and none of the couples had repeated cycles with one follicle. Table III gives the outcome according to order of treatment cycle. Ongoing PR was the highest in the first treatment cycle (11.7%)

**Table I.** Baseline characteristics of couples with unexplained non-conception undergoing controlled ovarian stimulation with intrauterine insemination

| | |
|---|---|
| No. of couples | 300 |
| Female age (years) | 33 (20-41) |
| Duration of non-conception (months) | 39.6 (1-137) |
| Primary non-conception (%) | 70.7 |
| PMSD (x106/ml) | 16.4 (0.1-120) |
| PMSD = progressively motile sperm density. | |

**Table II.** Ongoing and multiple pregnancy rates (PR) in couples with unexplained non-conception undergoing controlled ovarian stimulation with intrauterine insemination according to the number of pre-ovulatory follicles of ≥14 mm at the time of HCG administration.

| Follicle number | Cycles | Ongoing (%) PR[a] | Singletons | Multiples | Multiple PR (%) |
|---|---|---|---|---|---|
| 1 | 279 | 22 (7.9) | 22 | - | - |
| 2 | 358 | 27 (7.5) | 22 | 5 | 18.5 |
| 3 | 210 | 22 (10.5) | 16 | 6 | 27.3 |
| 4 | 30 | 2 (-) | 1 | 1 | 50 |
| 5 | 2 | - | | | |

[a] $\chi^2$-Test for linear trend: $P = 0.54$.

**Table III.** Ongoing and multiple pregnancy rates (PR) per cycle in couples with unexplained non-conception undergoing controlled ovarian stimulation with intrauterine insemination in four cycles.

| Cycle number | Couples | Ongoing (%) PR[a] | Singletons | Twins | Triplets | Multiple PR[b] (%) |
|---|---|---|---|---|---|---|
| 1 | 300 | 35 (11.7) | 31 | 4 | - | 11.4 |
| 2 | 242 | 19 (7.9) | 16 | - | 3 | 15.8 |
| 3 | 187 | 12 (6.4) | 9 | 3 | - | 25.0 |
| 4 | 150 | 7 (4.7) | 5 | 2 | - | 28.5 |

[a] $\chi^2$-Test for linear trend: P = 0.006.
[b] $\chi^2$-Test for linear trend: $P = 0.16$.

and declined significantly with increasing cycle order (7.9% in the second cycle, 6.4% in the third and 4.7% in the fourth cycle) (P = 0.006). No statistically significant trend was noted in the multiple PR, which was 11.4% in the first, 15.8% in the second, 25.0% in the third and 28.5% in the fourth treatment cycle.

## DISCUSSION

In couples with unexplained non-conception, COS-IUI is a widely used and effective treatment before resorting to IVF. In our study 32% of the couples conceived in four treatment cycles of COS-IUI, which is within the range of 20–33% reported by others (Guzick *et al.*, 1999; Ibérico *et al.*, 2004). The PR per cycle in our study was 10.9%. In the literature, PR per cycle has been reported to vary from 9 to 20% (Crosignani *et al.*, 1991; Nulsen *et al.*, 1993; Zikopoulos *et al.*, 1993; Guzick *et al.*, 1999; Dickey *et al.*, 2002; Ibérico *et al.*, 2004). Several studies have been performed to search for plausible causes for these differences in PR, and for determinants of success concerning COS-IUI therapy. It has been shown that an increasing maternal age, a longer duration of non-conception and a poor semen quality have a negative impact on the PR in couples receiving COS-IUI (Dickey *et al.*, 2002; Duran *et al.*, 2002; Ibérico *et al.*, 2004), whereas couples with unexplained or cervical factor non-conception have a more favourable outcome (Steures and van der Steeg, 2004). It has been assumed that the number of pre-ovulatory follicles and order of the treatment cycle affect the outcome of COS-IUI as well.

In our study, couples with unexplained non-conception that had one follicle at the time of HCG administration had an ongoing PR of 7.9%, and couples who had multifollicular growth had an ongoing PR of 8.5%. The difference in PR found between these two groups is not statistically significant (OR 1.1, 95% CI 0.6–2.0). A sample size of >10,000 cycles would be needed to detect a difference in PR of ≥1 percentage point over a control rate of 7.9%, with a power of 80% at a significance level of 0.05, so the difference in PR found in our study is not clinically relevant. Moreover, the absolute increase in PR of 0.6% in multifollicular cycles indicates that the number needed to treat is 166, i.e. 166 multifollicular (as opposed to monofollicular) cycles are needed for one additional pregnancy, which would result in at least 28 multiple pregnancies. Therefore, in IUI for unexplained non-conception, monofollicular stimulation is equally effective as compared to multifollicular stimulation, it is less costly and has fewer adverse effects in terms of multiple pregnancies.

In the literature, however, there is controversy concerning the number of pre-ovulatory follicles in COS-IUI and subsequent PR. Some studies show an increase in PR when follicle numbers rise (Tomlinson *et al.*, 1996; Nuojua-Huttunen *et al.*, 1999; Stone *et al.*, 1999; Dickey *et al.*, 2002; Ibérico *et al.*, 2004), whereas others found that two follicles at the

time of IUI did not increase the ongoing PR as compared to one follicle (Steures *et al.*, 2004). One of the possible causes for this heterogeneity in results reported may be due to the inclusion of couples with different causes of non-conception and different prognosis, like male factor non-conception, tubal factor nonconception and anovulation. Furthermore, in some studies clomiphene citrate was used for ovulation induction, while in others gonadotrophins were administered. Although there is still insufficient evidence for a statistically significant difference in PR (Althaullah *et al.*, 2002), gonadotrophins seem to be superior to clomiphene citrate.

Although induction of multifollicular growth is considered to improve pregnancy outcome in COS-IUI, it contains the risk of multiple pregnancies. In unexplained non-conception a multiple PR of 9–36% per couple has been reported (Zikopoulos *et al.*, 1993; Guzick *et al.*, 1999; Nuojua-Huttunen *et al.*, 1999; Ibérico *et al.*, 2004). Guzick *et al.* (1999) did not report on the number of follicles, but had 17 sets of twins (7.4% per couple), four triplets (1.7% per couple) and three quadruplets (1.3% per couple). In the study by Zikopoulos *et al.* (1993) the mean follicle number was 3.8 per cycle, and the multiple PR was 36%. Nuojua-Huttunen et al. (1999) reported a multiple PR of 13.7%, but found no correlation between the number of large follicles and the multiple PR. In our study the aim of COS was to achieve two or three dominant follicles, and in 68.3% of the treatment cycles multifollicular growth was obtained. In these multifollicular cycles nine twins and three triplets occurred, and the multiple PR in multifollicular cycles was 17.1%.

In COS-IUI cycles one decides either to administer HCG or to cancel the cycle, by estimating the risk for multiple pregnancies and OHSS by the number of pre-ovulatory follicles. Pregnancies are considered to originate from dominant follicles, but smaller follicles have been shown to have a substantial contribution as well (Navot *et al.*, 1991; Valbuena *et al.*, 1996; Richmond *et al.*, 2005). In order to prevent multiple pregnancies in COS-IUI the total number of pre-ovulatory follicles >14 mm at the time of HCG injection should be taken into consideration.

In our study, a statistically significant decrease in ongoing PR was found with increasing order of treatment cycle in COS-IUI in couples with unexplained non-conception. This is confirmed by Aboulghar *et al.* (2001), who reported a cumulative PR of 39.2% in the first three cycles and a PR of only 9.3% in the next three cycles. In the study by Nuojua-Huttunen *et al.* (1999) 97% of pregnancies occurred within the first four treatment cycles, and Ibérico *et al.* (2004) reported that 74.2% of pregnancies occurred within the first two treatment cycles. These studies indicate that there appears to be an upper limit to the number of successful treatment cycles, beyond which additional pregnancies are less likely to occur. Although the overall PR was found to decrease significantly with increasing cycle order, in our study the multiple PR was not influenced by the order of treatment cycle, since multiples were present in every rank number. No studies were identified in the literature that examined the occurrence of multiple pregnancies in relation to the rank of the treatment cycle.

In conclusion, in COS-IUI for unexplained non-conception, induction of more than one dominant follicle did not improve the ongoing PR significantly, but increased the risk of multiple pregnancies. In subsequent cycles with multifollicular growth, multiple PR remained high. Therefore, in order to reduce the number of multiple pregnancies, in all IUI cycles for unexplained non-conception, monofollicular growth should be aimed at. It remains to be established whether the cumulative PR levels off after four treatment cycles in monofollicular IUI, as it seems to do in multifollicular COS-IUI.

# REFERENCES


Aboulghar M, Mansour R, Serour G, Abdrazek A, Amin Y and Rhodes C (2001) Controlled ovarian hyperstimulation and intrauterine insemination for treatment of unexplained infertility should be limited to a maximum of three trials. Fertil Steril 75,88–91.

Althaullah N, Proctor M and Johnson NP (2002) Oral versus injectable ovulation agents for unexplained subfertility. Cochrane Database Syst Rev (3) CD003052.

Cohlen BJ (1998) Intrauterine insemination and controlled ovarian hyperstimulation. In Templeton AA, Cooke I and O'Brien PMS (eds) Evidence-based Fertility Treatment. RCOG Press, London, pp 205–216.

Crosignani PG, Walters DE and Soliani A (1991) The ESHRE multicentre trial on the treatment of unexplained infertility: a preliminary report. Hum Reprod 6,953–958.

Dickey RP, Taylor SN, Lu PY, Sartor BM, Rye PH and Pyrzak R (2002) Effect of diagnosis, age, sperm quality, and number of preovulatory follicles on the outcome of multiple cycles of clomiphene citrate–intrauterine insemination. Fertil Steril 78,1088–1095.

Duran HE, Morshedi M, Kruger T and Oehninger S (2002) Intrauterine insemination: a systematic review on determinants of success. Hum Reprod Update 8,373–384.

Enginsu ME, Pieters MHEC, Dumoulin JCM, Evers JLH and Geraedts JPM (1992) Male factor as determinant of in-vitro fertilization outcome. Hum Reprod 7,1136–1140.

ESHRE Capri Workshop Group (2000) Multiple gestation pregnancy. Hum Reprod 15,1856–1864.

Fauser BCJM, Devroey P and Macklon NS (2005) Multiple birth resulting from ovarian stimulation for subfertility treatment. Lancet 365,1807–1816. Gleicher N, Oleske DM, Tur-Kaspa I, Vidali A and Karande V (2000) Reducing the risk of high-order multiple pregnancy after ovarian stimulation with gonadotrophins. New Engl J Med 343,2–7.

Guzick DS, Carson SA, Coutifaris C, Overstreet JW, Factor-Litvak P, Steinkampf MP, Hill JA, Mastroianni L, Buster JE, Nakajima ST et al (1999) Efficacy of superovulation and intrauterine insemination in the treatment of infertility. National Cooperative Reproductive Medicine Network. New Engl J Med 340,177–183.

Ibérico G, Vioque J, Ariza N, Lozano JM, Roca M, Llacer J and Bernabeu R (2004) Analysis of factors influencing pregnancy rates in homologous intrauterine insemination. Fertil Steril 81,1308–1313.

Laursen SB, Andersen CY, Hindkjaer J and Erb K (2003) A clinical study comparing PureSperm and SpermFilter for density gradient separation of human spermatozoa in assisted reproduction. Acta Obstet Gynecol Scand 82,929–935.

Mahadevan M and Trounson AO (1983) Effect of cryoprotective media and dilution methods on the preservation of human spermatozoa. Andrologia 15,355–366.

Navot D, Goldstein N, Mor-Josef S, Simon A, Relou A and Birkenfeld A (1991) Multiple pregnancies: risk factors and prognostic variables during induction of ovulation with human menopausal gonadotrophins. Hum Reprod 6,1152–1155.

Nulsen JC, Walsh S, Dumez S and Metzger DA (1993) A randomized and longitudal study of human menopausal gonadotropin with intrauterine insemination in the treatment of infertility. Obstet Gynecol 82,780–786.

Nuojua-Huttunen S, Tomas C, Bloigu R, Tuomivaara L and Martikainen H (1999) Intrauterine insemination treatment in subfertility: an analysis of factors affecting outcome. Hum Reprod 14,698–703.

Richmond JR, Deshpande N, Lyall H, Yates RWS and Fleming R (2005) Follicular diameters in conception cycles with and without multiple pregnancy after stimulated ovulation induction. Hum Reprod 20,756–760.

Steures P and van der Steeg JW for CECERM (2004) Prediction of an ongoing pregnancy after intrauterine insemination. Fertil Steril 82,45–51.

Steures P, van der Steeg JW, Verhoeve HR, van Dop PA, Hompes PGA, Bossuyt PMM, van der Veen F, Habbema JDF, Eijkemans MJC and Mol BWJ (2004) Does ovarian hyperstimulation in intrauterine insemination for cervical factor subfertility improve pregnancy rates? Hum Reprod 19,2263–2266.

Stone BA, Vargyas JM, Ringler GE, Stein AL and Marrs RP (1999) Determinants of the outcome of intrauterine insemination: analysis of outcomes of 9963 consecutive cycles. Am J Obstet Gynecol 180,1522–1534.

Tomlinson MJ, Amissah-Arthur JB, Thompson KA, Kasraie JL and Bentick B (1996) Prognostic indicators for intrauterine insemination (IUI): statistical model for IUI success. Hum Reprod 11,1892–1896.

Valbuena D, Simon C, Romero JL, Remohi J and Pellicer A (1996) Factors responsible for multiple pregnancies after ovarian stimulation and intrauterine insemination with gonadotropins. J Assist Reprod Genet 13,663–668.

Zikopoulos K, West CP, Thong PW, Kacser EM, Morrison J and Wu FC (1993) Homologous intra-uterine insemination has no advantage over timed natural intercourse when used in combination with ovulation induction for the treatment of unexplained infertility. Hum Reprod 8,563–567.

Chapter 5

# The influence of the number of follicles on pregnancy rates in intrauterine insemination with ovarian stimulation: a meta-analysis

Minouche M.E. van Rumste, Inge M. Custers, Fulco van der Veen, Madelon van Wely, Johannes L.H. Evers, Ben Willem J. Mol

Human Reproduction Update 2008; 14:563-70

# ABSTRACT

**BACKGROUND** The influence of multifollicular growth on pregnancy rates in subfertile couples undergoing intrauterine insemination (IUI) with controlled ovarian hyperstimulation (COH) remained unclear.

**METHODS** Relevant papers were identified by searching MEDLINE, EMBASE and the Cochrane Library. A meta-analysis was performed and Mantel–Haenszel pooled odd ratios (ORs) and risk differences with 99% confidence intervals (CIs) were calculated to express the relation between the number of follicles and pregnancy rates.

**RESULTS** 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 OR for pregnancy after two follicles as compared with monofollicular growth was 1.6 (99% CI 1.3 – 2.0), whereas for three and four follicles, this was 2.0 and 2.0, respectively. Compared with monofollicular growth, pregnancy rates increased by 5, 8 and 8% when stimulating two, three and four follicles. The pooled OR for multiple pregnancies after two follicles was 1.7 (99% CI 0.8 – 3.6), whereas for three and four follicles this 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.

**CONCLUSIONS** Multifollicular growth is associated with increased pregnancy rates in IUI with COH. Since in cycles with three or four follicles the multiple pregnancy rate increased without substantial gain in overall pregnancy rate, IUI with COH should not aim for more than two follicles. One stimulated follicle should be the goal if safety is the primary concern, whereas two follicles may be accepted after careful patient counselling.

# INTRODUCTION

Controlled ovarian hyperstimulation (COH) with intrauterine insemination (IUI) is frequently used in couples that suffer from unexplained subfertility. In a meta-analysis on couples with unexplained subfertility, ovarian stimulation in combination with IUI was shown to result in significantly higher pregnancy rates per woman as compared with IUI in the natural cycle (OR 2.3, 95% confidence interval (95% CI) 1.5 – 3.7) (Verhulst *et al.*, 2006).

The drawback of multifollicular growth in IUI and COH is the risk of multiple pregnancies. Although there is debate whether a multiple pregnancy should be seen as a complication of assisted reproductive techniques, there is consensus that a multiple pregnancy carries increased risks on pregnancy complications, such as preterm delivery, growth retardation and preecclampsia (Land and Evers, 2003; van Wely et al., 2006). In view of this dilemma, the balance between a decrease of the number of follicles in women undergoing IUI with COH for a still acceptable pregnancy rate is extremely important.

Although the rationale for addition of COH with IUI is to increase the pregnancy rate by multifollicular growth (Cohlen, 1998), studies reporting on the number of preovulatory follicles in relation to pregnancy rates in ovarian stimulation with IUI show contradictory results. Whereas the majority of the studies report a positive association between the number of follicles and pregnancy rate (Tomlinson *et al.*, 1996; Nuojua-Huttunen *et al.*, 1999; Stone et al., 1999; Dickey et al., 2002; Ibérico et al., 2004), we failed to find such a positive association in previous studies (van Rumste *et al.*, 2006; Steures *et al.*, 2006). Moreover, two studies reported high ongoing pregnancy rates of 16.6 and 10.4% even though 60% of the cycles were monofollicular (Ragni *et al.*, 2004; Crosignani and Somigliana, 2007).

This contradiction raised the question whether multifollicular growth does increase pregnancy rates over that attributed to monofollicular growth in couples undergoing COH and IUI. To address this issue, we performed a systematic review of the literature on the subject.



# MATERIAL AND METHODS

## Search strategy

The meta-analysis was performed according to the MOOSE criteria (Stroup et al., 2000). We performed a computerized search in MEDLINE (1966 – July 2007), EMBASE (1988 – July 2007) and the Cochrane Library (2006: 2) to identify articles reporting on the number of follicles and pregnancy rates in couples undergoing treatment with IUI and COH. Keywords used were follicle number, controlled ovarian stimulation, hyperstimulation, IUI, clomiphene citrate, follicle stimulating hormone, human menopausal gonadotrophin,

subfertility and fertility, with a limitation to humans and 'not IVF'. No restriction on language was used. References detected with the related articles function in Pubmed were also checked to identify cited articles not captured by electronic searches. The reference lists of all identified articles and eligible primary studies were examined for identification of additional articles. Studies were included if they reported on the number of preovulatory follicles and subsequent pregnancy rates in couples undergoing IUI with COH. All couples undergoing IUI with COH, irrespective of their diagnosis of subfertility, were included.
The number and size of follicles during the ovarian stimulation were detected by ultrasound. The size of a follicle was measured in millimetres. All follicles above a certain cut-off diameter at time of human chorionic gonadotrophin (hCG) administration were recorded. The cut-off diameter varied per study. We defined monofollicular growth as one follicle on the day of hCG administration. Multifollicular growth was defined as more than one follicle counted, irrespective of their diameter. Pregnancy was defined as a positive urine or serum hCG test. Clinical pregnancy was defined as a pregnancy confirmed by ultrasound at 6 weeks of gestation. Ongoing pregnancy was defined as a pregnancy with fetal cardiac activity seen at ultrasound at 12 weeks of gestation.
All studies were scored on methodological quality. We assessed whether the study was prospective, whether it was a randomized controlled trial (RCT), a cohort study or a case – control study, whether the study was blinded and whether the assessment of the number of follicles, as well as the outcome, was defined. Assessment of methodological quality and data extraction was done by two reviewers independently (MvR, IC). In case of disagreement, the judgement of a third reviewer (BWM) was decisive.

## Statistical analysis

For each study, we constructed tables comparing the number of follicles counted in relation to the pregnancy rate. To do so, several categories of multifollicular growth (two follicles, three follicles or four follicles or more) were classified against monofollicular growth, which was the reference strategy.
The analysis was then stratified for different levels of multifollicular growth. First, we assessed pregnancy rates in cycles with two follicles compared with cycles with monofollicular growth, then we assessed all studies in which pregnancy rates in cycles with three follicles were compared with cycles with monofollicular growth. We performed the same analysis comparing four or five follicles to monofollicular growth.
Homogeneity was tested by means of the Breslow–Day test. P-values less than 0.05 were considered to indicate statistical significance. If homogeneity could not be rejected, i.e. if the P-value of the Breslow-Day test was .0.05, a pooled odd ratios (ORs) with a 99% CI was calculated for each exposure by means of a fixed effect model (Mantel – Haenszel method), thus pooling the ORs of the evaluated studies. If homogeneity had to be rejected, the range of point estimates of individual studies was reported. A similar analysis

was done for multiple pregnancies. The analysis on multiple pregnancies was limited to those cycles in which a pregnancy had occurred. The risk differences (RDs) with 99% CI were calculated for pregnancy and multiple pregnancy for the various cut-off values for multifollicular growth as compared to monofollicular cycles.

Post hoc subgroup analyses were performed, in which we pooled studies that used comparable cut-off values for follicle diameter. In a sensitivity analysis, we repeated the main analysis while excluding studies that used donor semen and studies that did not specify the exact number of follicles.

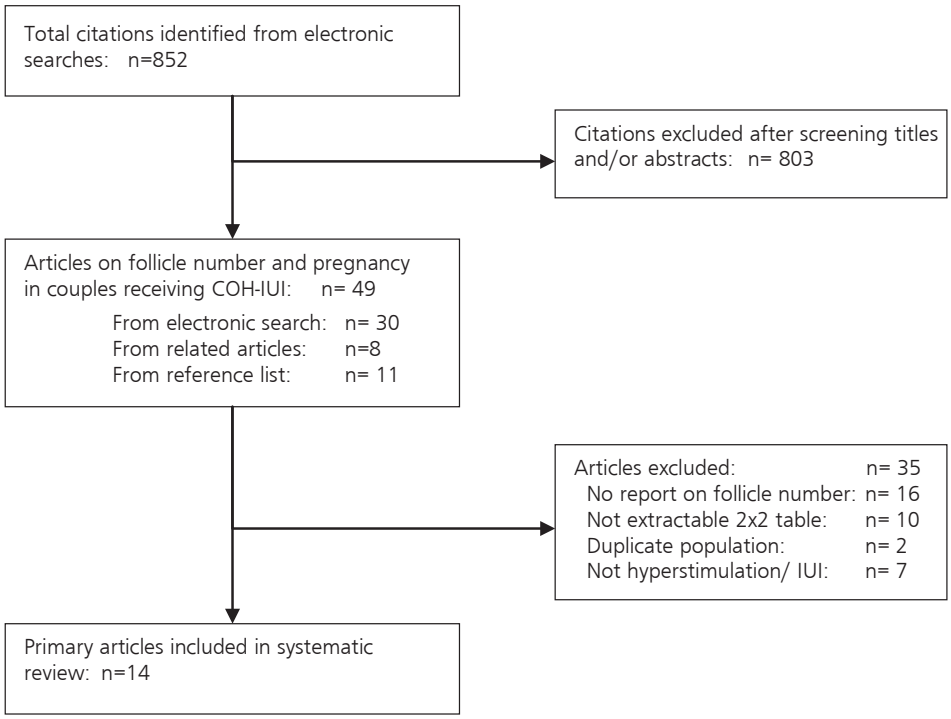



**Figure 1.** Study selection process for systematic review of relation between follicle number and pregnancy rates in IUI with COH.



# RESULTS

## Literature identification and study characteristics

The process of literature identification and selection is summarized in Fig. 1. Of the 49 detected articles, 14 studies met the inclusion criteria. The included studies and their characteristics are listed in Table I. The studies reported on a total of 11 599 cycles in

**Table I.** Study characteristics of included studies.

| Study (year) | Quality | Patient characteristics | Number of patients | Number of cycles |
|---|---|---|---|---|
| Dodson and Haney (1991) | Retrospective cohort | All types of subfertility | 371 | 720 |
| Tomlinson et al. (1996) | Retrospective cohort | All types of subfertility | 134 | 260 |
| Vollenhoven et al. (1996) | Retrospective cohort | All types of subfertility | 107 | 237 |
| Nuojua-Huttunen et al. (1999) | Retrospective cohort | All types of subfertility | n.s. | 811 |
| Dickey et al. (2001) | Prospective cohort | All types of subfertility | 4000 | 2728 |
| Khalil et al. (2001a) | Retrospective cohort | Unexplained, mild male factor, anovulation | 893 | 2466 |
| Khalil et al. (2001b) | Retrospective cohort | Donor semen | 351 | 1118 |
| Özcakir et al. (2002) | Retrospective cohort | Not stated, excluded male or unilateral tube factor | 180 | 180 |
| Ibérico et al. (2004) | Retrospective cohort | Unexplained | 470 | 1010 |
| Steures et al. (2004) | Retrospective cohort | Cervical factor | 181 | 213 |
| Goverde et al. (2005) | Randomized controlled trial | Unexplained, mild male factor | 85 | 334 |
| Sikandar et al. (2005) | Retrospective cohort | Unexplained, mild male factor | 290 | 290 |
| van Rumste et al. (2006) | Retrospective cohort | Unexplained | 300 | 879 |
| Steures et al. (2006) | Randomized controlled trial | Unexplained | 127 | 353 |

CC, clomiphene citrate; FSH, follicle stimulating hormone; hCG, humane chorionic gonadotrophin; hMG, human menopausal gonadotrophin; n.s., not stated; US, ultrasound

7489 couples. Eleven studies were retrospective cohort studies, one was a prospective cohort study (Dickey *et al.*, 2001) and two were RCTs (Goverde *et al.*, 2005; Steures *et al.*, 2006). In the first RCT, pregnancy outcome of IUI in natural cycles and IUI in stimulated cycles were compared in couples with unexplained subfertility and mild male subfertility (Goverde et al., 2005). In the second RCT, couples with unexplained subfertility were randomly assigned to IUI with COH or to expectant management (Steures *et al.*, 2006). Only the subset of couples receiving IUI in stimulated cycles were included in this review. The excluded studies are summarized in Table II.

| Medication | Follicle size at count (mm) | On hCG day: at least one follicle of length (mm) | Cancellation criteria | Cycles with multifollicular growth | Pregnancy test | PR per cycle |
|---|---|---|---|---|---|---|
| hMG | 17 | 17 | n.s. | 635 | serum hCG | 15% |
| FSH, hMG | 18 | 18 | >3 follicles >18 mm | 153 | n.s. | 21% |
| hMG | 14 | 18 | E2>2500 pg/ml | 218 | US at 6 weeks | 9.3% |
| Combination of CC and hMG | 16 | 16 | n.s | 634 | US at 12 weeks | 13% |
| hMG, CC and both in the same cycle | 12 | 16 (hMG) 18 (cc/ hMG) or LH surge | n.s | 2319 | serum hCG and US at 6 and 12 weeks | 15% |
| Combination of CC and hMG | 14 | 18 | >5 follicles >15 mm | 1942 | US at 6 weeks | 12% |
| Combination of CC and hMG | 16 | 16 | >4 follicles >16 mm | 777 | US at 6 weeks | 22% |
| FSH, hMG | 18 | 18 | n.s. | 103 | US at 5.5 weeks | 18% |
| hMG | 16 | 18 | >5 follicles >15 mm | 564 | Urine test | 9.2% |
| CC and FSH | 14 | 16 | >4>14 mm or >3>16 mm | 113 | US at 12 weeks | 13% |
| FSH | 14 | 18 | >6>14 mm or >3>18 mm | 239 | US at 12 weeks | 9.9% |
| hMG, CC and both in the same cycle | 16 | 16 | n.s. | 113 | serum hCG | 10% |
| hMG | 14 | 18 | >4 follicles >14 mm | 600 | US at 12 weeks | 8.3% |
| FSH, hMG | 11 | 16 | >5>12 mm or >3>16 mm | 247 | US at 12 weeks | 4.5% |



In all studies, couples with primary and secondary subfertility were included. All couples had undergone a fertility work-up, including confirmation of ovulation by ultrasound, semen analysis and evaluation of tubal function by hysterosalpingography and/or laparoscopy, before treatment with IUI and COH was started. The mean female age varied from 31 to 34 years. Patients received gonadotrophins and/or clomiphene citrate. All patients received hCG to induce ovulation. Definitions of multifollicular growth varied greatly between studies with the minimal diameter of a follicle ranging from 11 to 18 mm. Two studies used multiple cut-off points for follicle diameters (Dickey *et al.*, 2001; Steures *et al.*, 2006). One of the included studies reported a specific definition of multifollicular

**Table II.** Excluded studies.

| Study (year) | Reason for exclusion |
|---|---|
| Schenker *et al.* (1981) | Not hyperstimulation/IUI |
| Stone *et al.* (1987) | Not extractable 2x2 table |
| Deaton *et al.* (1990) | No report per follicle number |
| Dickey *et al.* (1991) | Not hyperstimulation/IUI |
| Martinez *et al.* (1991) | No report per follicle number |
| Silverberg *et al.* (1991) | Not hyperstimulation/IUI |
| Dickey *et al.* (1992) | Not hyperstimulation/IUI |
| Ben-Nun *et al.* (1993) | No report per follicle number |
| Chang *et al.* (1993) | Not extractable 2x2 table |
| Plosker *et al.* (1994) | Not hyperstimulation/ IUI |
| Pittrof *et al.* (1996) | No report per follicle number |
| Valbuena *et al.* (1996) | Not extractable 2x2 table |
| Goldfarb *et al.* (1997) | No report per follicle number |
| Hughes (1997) | No report per follicle number |
| Cohlen *et al.* (1998) | No report per follicle number |
| Hughes *et al.* (1998) | No report per follicle number |
| Pasqualotto *et al.* (1999) | Not extractable 2x2 table |
| Stone *et al.* (1999) | Not hyperstimulation/ IUI |
| Gleicher *et al.* (2000) | Not extractable 2x2 table |
| Tsai *et al.* (2000) | No report per follicle number |
| Dickey *et al.* (2002) | Duplicate population |
| Go¨ker *et al.* (2002) | Not extractable 2x2 table |
| Kaplan *et al.* (2002a) | Not extractable 2x2 table |
| Kaplan *et al.* (2002b) | Not extractable 2x2 table |
| Filicori *et al.* (2003) | No report per follicle number |
| Makkar *et al.* (2003) | Not extractable 2x2 table |
| Cantineau *et al.* (2004) | No report per follicle number |
| Deng and Clark (2004) | No report per follicle number |
| Papageorgiou *et al.* (2004) | No report per follicle number |
| Wang *et al.* (2004) | No report per follicle number |
| Dickey *et al.* (2005) | Duplicate population |
| Filicori *et al.* (2005) | Not hyperstimulation/IUI |
| Richmond *et al.* (2005) | Not extractable 2x2 table |
| Al-Inany *et al.* (2006) | No report per follicle number |
| Park *et al.* (2007) | No report per follicle number |

growth, i.e. the growth of more than one follicle with a diameter of ≥14 mm on the day of hCG administration (Goverde *et al.*, 2005).

In four studies, the end-point was a clinical pregnancy and in six studies, ongoing pregnancy. Two studies proved pregnancy by rising levels of hCG in blood serum (Dodson and Haney, 1991; Sikandar *et al.*, 2005), one study used a urine pregnancy test (Ibérico *et al.*, 2004) and another study did not state the method of pregnancy test (Tomlinson *et al.*, 1996). Seven studies did report on live birth, but none of these studies reported on live birth per number of preovulatory follicles (Dodson and Haney, 1991; Nuojua-Huttunen *et al.*, 1999; Dickey *et al.*, 2001; Khalil *et al.*, 2001a,b; Goverde *et al.*, 2005; Steures *et al.*, 2006).

## Data on pregnancy rates

The overall mean pregnancy rate of all included cycles was 13.3% per cycle. In 8657 cycles, multifollicular growth was achieved (74.6%), ranging from 39 to 85% per study. Data on pregnancy rates in cycles with two follicles versus cycles with monofollicular growth are shown in Fig. 2A. Homogeneity was not rejected ($\chi^2$ = 14.7, P = 0.33). The pooled OR for pregnancy after two follicles as compared with monofollicular growth was 1.6 (99% CI 1.3 – 1.9). The RD was 0.05 (99% CI 0.03 – 0.06), meaning an increase in pregnancy rate of 5% when two follicles were stimulated as compared with monofollicular growth. Two studies compared multifollicular growth to monofollicular growth without specifying the number of follicles. One study compared the pregnancy rate in cycles with two till six follicles with the pregnancy rate in cycles with monofollicular growth, whereas another study compared the pregnancy rate in cycles with two and three follicles with the pregnancy rate in cycles with monofollicular growth (Goverde *et al.*, 2005; Steures *et al.*, 2006). These studies were only included in the analysis of two follicles versus one follicle and left out in the subsequent analyses of three and four follicles.

Twelve studies reported on three follicles versus cycles with monofollicular growth. Data on pregnancy rates of these cycles are shown in Fig. 2B. Homogeneity was not rejected ($\chi^2$ = 18.4, P = 0.07). The pooled OR for the pregnancy rate after three follicles as compared with monofollicular growth was 2.0 (99% CI 1.6 – 2.5). The chance on a pregnancy increased by 8% (RD 0.08, 99% CI 0.05 – 0.10).

Data on pregnancy rates in cycles with four follicles versus cycles with monofollicular growth are shown in Fig. 2C. Eleven studies reported on this item. Again, homogeneity could not be rejected ($\chi^2$ = 7.5, P = 0.67). The pooled OR for the pregnancy rate after four follicles as compared with monofollicular growth was 2.0 (95% CI 1.5 – 2.7). The chance on a pregnancy increased by 8% (RD 0.08, 99% CI 0.04 – 0.11).

Six studies reported on pregnancy rates in cycles with five follicles versus cycles with monofollicular growth. Again, homogeneity was not rejected ($\chi^2$ = 0.88, P = 0.97). The pooled OR for the pregnancy rate after five follicles as compared with monofollicular growth was 2.8 (95% CI 2.1 – 3.8).

The number of studies that reported on pregnancy rates after six follicles or more, as well as the number of patients in these categories, was limited, making meta-analysis not

useful. Overall, the absolute pregnancy rate in these 14 studies increased from 8.4 to 15% when multifollicular growth was achieved as compared to monofollicular stimulation.
In subgroup analyses, we calculated the odd ratios for pregnancy after two follicles versus one follicle from studies that reported on cut-off values for follicle diameter of 11 – 12, 13 – 14, 15 – 16 and 17 – 18 mm, respectively. We found that pooled odd ratios at these cut-off values were 2.4 for 11 – 12 mm [99% CI 1.5 – 4.0 (Dickey *et al.*, 2001; Steures *et al.*, 2006)], 1.4 for 13 – 14 mm [99% CI 0.9 – 2.0 (Vollenhoven et al., 1996; Khalil *et al.*, 2001a; Steures *et al.*, 2004; Goverde *et al.*, 2005; van Rumste *et al.*, 2006)], 1.6 for 15 – 16 mm [99% CI 1.3 – 2.1 (Nuojua Huttunen *et al.*, 1999; Dickey *et al.*, 2001; Khalil *et al.*, 2001b; Ibérico *et al.*, 2004; Sikandar *et al.*, 2005; Steures *et al.*, 2006)] and 1.8 for 17 – 18 mm [99% CI 1.3 – 2.4 (Dodson and Haney, 1991; Tomlinson et al., 1996; Dickey et al., 2001; Özcakir *et al.*, 2002)]. Leaving out the study that used donorsperm (Khalil *et al.*, 2001b) and the studies that did not specify the exact number of follicles (Goverde et al., 2005; Steures *et al.*, 2006) did not alter the outcome of the analysis (OR of 1.6 with a 99% CI 1.3 – 2.0).

## Data on multiple pregnancy rates

In 12 of the 14 studies multiple pregnancies were reported. Of the 1481 pregnancies found in these 12 studies, there were 274 multiple pregnancies (18.5%). In nine studies with 1286 pregnancies, the number of twin pregnancies was specified. Of these pregnancies, 181 were twins (79.7% of the multiple pregnancies).

Data on multiple pregnancy rates after two follicles versus monofollicular growth of the five studies that reported on this topic are shown in Fig. 3. Homogeneity was not rejected ($\chi^2 = 5.9$, P = 0.21). The pooled OR for multiple pregnancies per conceived cycle after two follicles as compared with monofollicular growth was 1.7 (99% CI 0.8 – 3.6). The risk of multiple pregnancies for two follicles as compared with monofollicular growth increased by 6% (RD 0.06, 99% CI 20.02 to 0.15).
The absolute pregnancy rate in these five studies was 7.4% after monofollicular growth versus 13.4% after multifollicular growth. The absolute rate of multiple pregnancies was 0.3% after monofollicular growth versus 2.8% after multifollicular growth. Consequently, the multiple pregnancy rate in case of pregnancy was 3.7% after monofollicular growth and 17% after multifollicular growth.
The three studies that reported on multiple pregnancy rates per conceived cycle after growth of three follicles versus monofollicular growth showed an OR of 2.8 (99% CI 1.2 – 6.4, $\chi^2$ for homogeneity 2.8, P = 0.25) and an increased risk of a multiple pregnancy of 14% (RD 0.14, 99% CI 0.03 – 0.24). Three studies reported on multiple pregnancy rates per conceived cycle after four or more follicles as compared with monofollicular growth.

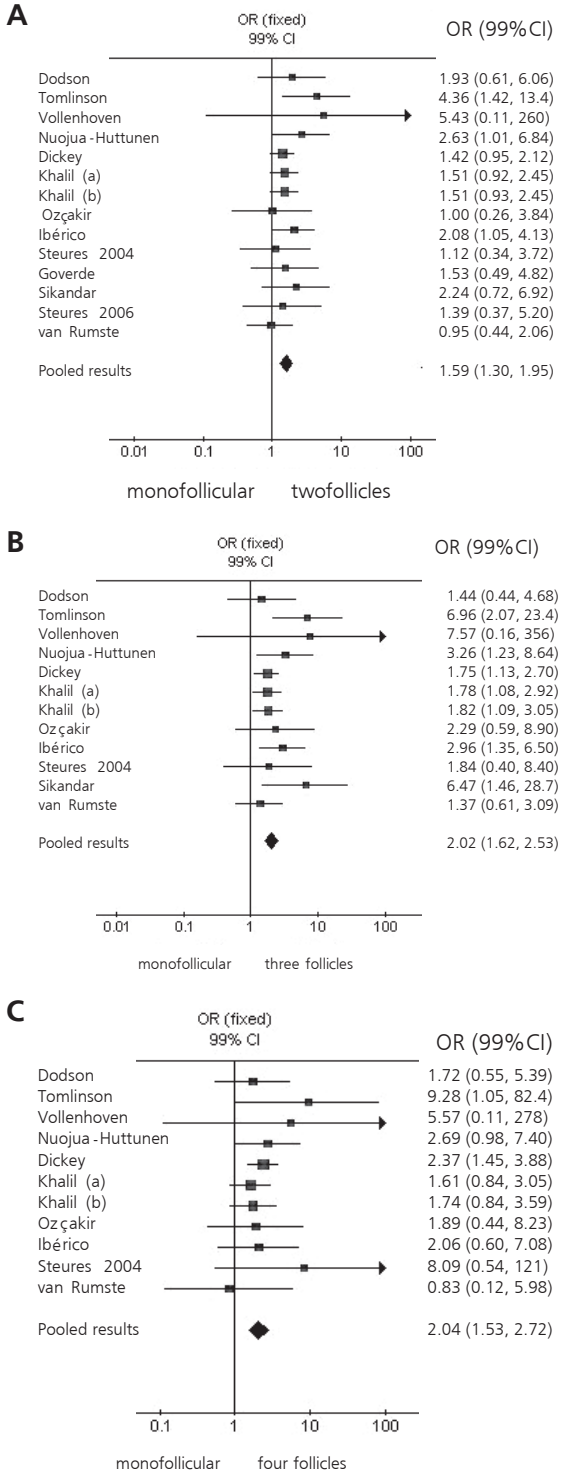



**Figure 2:** (A) Odd ratios (95% CI) on pregnancy rates, two follicles versus monofollicular growth. Reported on the x-axis is the OR for pregnancy rate, where one means no difference between multifollicular growth and monofollicular growth, less than one favours monofollicular growth and more than one favours multifollicular growth. (B) Odd ratios (95% CI) on pregnancy rates, three follicles versus monofollicular growth. (C) Odd ratios (95% CI) on pregnancy rates, four follicles versus monofollicular growth.

The pooled OR for the pregnancy rate was 2.3 (99% CI 0.9 – 5.9, $\chi^2$ for homogeneity 2.9, P = 0.24). The risk of a multiple pregnancy was 10% (RD 0.10, 99% CI 20.03 to 0.24).

# DISCUSSION

In this review, we included 14 studies reporting on 11 599 cycles of IUI with COH in 7489 couples. The pooled OR for pregnancy after two follicles as compared with monofollicular growth was 1.6 (99% CI 1.3 – 2.0), whereas for three and four follicles as compared with monofollicular growth this was 2.0 (99% CI 1.6 – 2.5) and 2.0 (99% CI 1.5 – 2.7), respectively. The chance of a pregnancy was 5% higher when two follicles were stimulated as compared with monofollicular growth (RD of 0.05, 99% CI 0.03 – 0.06) and 8% higher when three or four follicles were present (RD of 0.08, 99% CI 0.05 – 0.10 and RD of 0.08, 99% CI 0.04 – 0.11, respectively). Pregnancy rates increased from 8.4% to 15% per cycle when multifollicular growth was achieved as compared with monofollicular stimulation. The pooled OR for multiple pregnancies after two follicles as compared with monofollicular growth was 1.7 (99% CI 0.8 – 3.6), whereas for three and four follicles as compared with monofollicular growth this was 2.8 (99% CI 1.2 – 6.4) and 2.3 (99% CI 0.9 – 5.9). The risk of multiple pregnancies in case of pregnancy was 6% higher when two follicles were present as compared with monofollicular growth (RD of 0.06, 99% CI 0.00 – 0.13). Multiple pregnancy rates increased from 3.7% to 17% per conceived cycle when multifollicular growth was achieved as compared with monofollicular stimulation. To achieve one additional pregnancy, 16 cycles of multifollicular growth instead of monofollicular growth are necessary (number needed to treat = 16) at the cost of two additional multiple pregnancies (number needed to harm = 8).

The validity of a meta-analysis depends on the quality of the individual studies included. When combining observational studies heterogeneity among groups is to be expected (Stroup *et al.*, 2000). In this analysis, 12 cohort studies and two RCTs were included, using

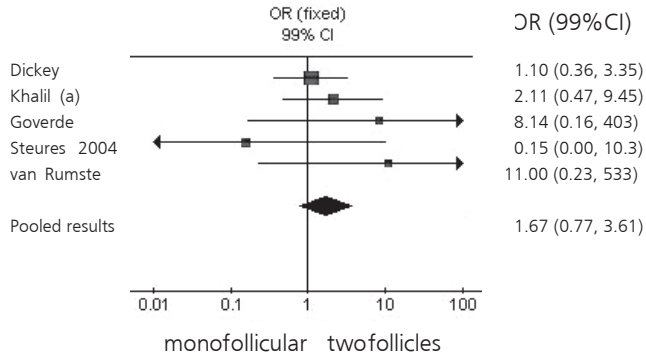



**Figure 3:** Odd ratios (95% CI) on multiple pregnancy rates, two follicles versus monofollicular growth. Analysis was limited to cycles in which women conceived.

the data of the IUI with COH arm of the RCTs. We noticed heterogeneity between studies regarding inclusion criteria for couples involved, use of ovarian stimulation medication, follicle size at count and use of pregnancy test. Seven studies included various kinds of subfertility (Dodson and Haney, 1991; Tomlinson *et al.*, 1996; Vollenhoven *et al.*, 1996; Nuojua-Huttunen *et al.*, 1999; Dickey *et al.*, 2001; Khalil *et al.*, 2001a; Özcakir et al., 2002), whereas five studies only included couples with unexplained subfertility (Ibérico *et al.*, 2004; Goverde *et al.*, 2005; Sikandar *et al.*, 2005; van Rumste *et al.*, 2006; Steures *et al.*, 2006). One study included only couples with donor insemination (Khalil et al., 2001b). In that study, the male partners had azoospermia, severe oligozoospermia or severe genetic disorders. Donor sperm was used and at least two million motile spermatozoa were inseminated during IUI. Women underwent hormonal screening for confirmation of a spontaneous ovulation and tubal patency was established. Since the male factor was overcome by using donor sperm and the women were ovulatory with patent tubes, we classified those couples as having 'unexplained subfertility'. These women did receive ovarian stimulation and IUI and we therefore decided to include these cycles in our review. The odd ratios were comparable to the other studies. Another difference in the studies was the definition of a pregnancy. Although nowadays live birth is by many preferred as the primary outcome in subfertility studies, data on this outcome could not be extracted from the studies. However, 10 out of 14 studies in this review report on viable pregnancy. It is known that 95% of these pregnancies will end in the birth of a healthy child. The included studies also showed heterogeneity in the cut-off value for follicle counting at time of hCG administration. Cut-off values varied between 11 and 18 mm. Pregnancies can occur in cycles with follicles of <15 mm (Richmond et al., 2005). Two studies used multiple cut-off values for follicle diameter (Dickey *et al.*, 2001; Steures *et al.*, 2006). Dickey *et al.* (2001) reported that in monofollicular cycles pregnancy rates were 7.1 and 11.9% at cut-off values of 12 and 18 mm, respectively, whereas in multifollicular cycles pregnancy rates were 16.4 and 18.4%. Steures *et al.* (2006) reported, in a much smaller study, a similar trend. Apparently, larger follicles will provide more often a viable oocyte, thus resulting in higher pregnancy rates.

The cut-off value for follicle size is also important in the light of occurrence of multiple pregnancies. Whereas only the large follicles are considered in clinical management, the accompanying smaller follicles may well lead to an increased risk of a multiple pregnancy. In more than half of the studies included in this review only follicles larger than 15 mm were counted at the time of hCG administration. These are mainly the older studies in which the stimulation protocol was usually more aggressive and cut-off values for follicle size were higher. Therefore, multiple pregnancies could be found in supposedly monofollicular cycles. It may be due to the increased awareness to prevent multiple pregnancies that methods of IUI and cancellation criteria are more clearly described nowadays (Land and Evers, 2003). Five of the included studies in this review did not state their cancellation criteria. Nearly all these studies were older than 5 years. The other studies did all describe

cancellation criteria, but none of them used the same criteria (Table I). In studies published before 2003, the multiple pregnancy rate in monofollicular cycles was 5.6% (Dickey *et al.*, 2001; Khalil *et al.*, 2001a), while 0.4% monozygotic twins would be expected (The ESHRE Capri workshop group, 2000). We found no multiple pregnancies in monofollicular cycles (out of 37 pregnancies) in studies published in the last 5 years (Goverde *et al.*, 2005; van Rumste *et al.*, 2006; Steures *et al.*, 2006).

We are also aware that the previous treatment cycles might be of influence on subsequent treatment cycles. Some women will only achieve one dominant follicle during the treatment with IUI and COH. Part of the hyperstimulation cycles producing only one follicle may reflect decreased ovarian reserve and hence impaired oocyte quality. Since none of the studies included restricted their outcomes to the first treatment cycle of IUI with COH, women were included who only achieved monofollicular growth in second and third cycles as well, resulting in more monofollicular cycles with lower pregnancy rates. Nowadays, cancellation criteria are defined more precisely. Two studies reported a very high percentage of monofollicular cycles of 60% due to strict cancellation criteria of two follicles >14 mm and two follicles >15 mm, respectively (Ragni et al., 2004; Crosignani and Somigliana, 2007). In the first study, no multiple pregnancies occurred whereas in the second study the multiple pregnancy rate was 8.3%. In spite of the high percentage of monofollicular growth, the ongoing pregnancy rate was 16.6 and 10.4%, respectively.

In conclusion, multifollicular growth is associated with increased pregnancy rates in IUI with COH. Since in cycles with three or four follicles, the multiple pregnancy rate increased without substantial gain in overall pregnancy rate, ovarian stimulation in IUI should not aim for more than two follicles. One stimulated follicle should be the goal if safety is the primary concern, whereas two follicles may be accepted after careful counselling of the patient.

# REFERENCES


Al-Inany HG, Abou-Setta AM, Aboulghar M. Gonadotrophin-releasing hormone antagonists for assisted conception. Cochrane Database. Syst Rev 2006;3:CD001750.

Ben-Nun I, Cohen E, Shulman A, Fejgin M, Goldberg S, Beyth Y. The inability of preovulatory ovarian scans to predict multifetal pregnancy occurrence in a follow-up of induction of ovulation with menotropins. Fertil Steril 1993;60:781 – 785.

Cantineau AEP, Cohlen BJ, Al-Inany H, Heineman MJ. Intrauterine insemination versus fallopian tube sperm perfusion for non tubal infertility. Cochrane Database Syst Rev 2004;3:CD001502.

Chang MY, Huang HY, Lee CL, Lai YM, Chang SY, Soong YK. Treatment of infertility using controlled ovarian hyperstimulation with intrauterine insemination: the experience of 343 cases. J Formos Med Assoc 1993;92:341 – 348.

Cohlen BJ. Intrauterine insemination and controlled ovarian hyperstimulation. In: Templeton AA, Cooke I, O'Brien PMS (eds). Evidence-based Fertility Treatment. London: RCOG Press, 1998,205 – 216.

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 – 1558.

Crosignani PG, Somigliana E, Intrauterine Insemination Study Group. Effect of GnRH antagonists in FSH mildly stimulated intrauterine insemination cycles: a multicentre randomized trial. Hum Reprod 2007;22:500 – 505.

Deaton JL, Gibson M, Blackmer KM, Nakajima ST, Badger G, Brumsted JR. A randomized, controlled trial of clomiphene citrate and intrauterine insemination in couples with unexplained infertility or surgically corrected endometriosis. Fertil Steril 1990;54:1083 – 1088.

Deng CY, Clark S. Superovulation and intrauterine insemination in treatment of idiopathic infertility in 202 cycles. Zhongguo Yi Xue Ke Xue Yuan Xue Bao 2004;26:178 – 181.

Dickey RP, Olar TT, Taylor SN, Curole DN, Rye PH, Matulich EM. Relationship of follicle number, serum estradiol, and other factors to birth rate and multiparity in human menopausal gonadotropin-induced intrauterine insemination cycles. Fertil Steril 1991;56:89 – 92.

Dickey RP, Olar TT, Taylor SN, Curole DN, Rye PH. Relationship of follicle number and other factors to fecundability and multiple pregnancy in clomiphene citrate-induced intrauterine insemination cycles. Fertil Steril 1992;57:613 – 619.

Dickey RP, Taylor SN, Lu PY, Sartor BM, Rye PH, Pyrzak R. Relationship of follicle numbers and estradiol levels to multiple implantation in 3,608 intrauterine insemination cycles. Fertil Steril 2001;75:69 – 78.

Dickey RP, Taylor SN, Lu PY, Sartor BM, Rye PH, Pyrzak R. Effect of diagnosis, age, sperm quality, and number of preovulatory follicles on the outcome of multiple cycles of clomiphene citrate-intrauterine insemination. Fertil Steril 2002;78:1088 – 1095.

Dickey RP, Taylor SN, Lu PY, Sartor BM, Rye PH, Pyrzak R. Risk factors for high-order multiple pregnancy and multiple birth after controlled ovarian hyperstimulation: results of 4,062 intrauterine insemination cycles. Fertil Steril 2005;83:671 – 683.

Dodson WC, Haney AF. Controlled ovarian hyperstimulation and intrauterine insemination for treatment of infertility. Fertil Steril 1991;55:457 – 467.

Filicori M, Cognigni GE, Pocognoli P, Tabarelli C, Ferlini F, Perri T, Parmegiani L. Comparison of controlled ovarian stimulation with human menopausal gonadotropin or recombinant follicle-stimulating hormone. Fertil Steril 2003;80:390 – 397.

Filicori M, Cognigni GE, Gamberini E, Parmegiani L, Troilo E, Roset B. Efficacy of low-dose human chorionic gonadotropin alone to complete controlled ovarian stimulation. Fertil Steril 2005;84:394 – 401.

Gleicher N, Oleske DM, Tur-Kaspa I, Vidali A, Karande V. Reducing the risk of high-order multiple pregnancy after ovarian stimulation with gonadotropins. N Engl J Med 2000;343:2 – 7.

Göker EN, Özcakir HT, Terek MC, Levi R, Adakan S, Tavmergen E. Controlled ovarian hyperstimulation and intrauterine insemination for infertility associated with endometriosis: a retrospective analysis. Arch Gynecol Obstet 2002;266:21 – 24.

Goldfarb JM, Peskin B, Austin C, Lisbona H. Evaluation of predicative factors for multiple pregnancies during gondadotropin/IUI treatment. J Assist Reprod Genet 1997;14:88 – 91.

Goverde AJ, Lambalk CB, McDonnell J, Schats R, Homburg R, Vermeiden JP. Further considerations on natural or mild hyperstimulation cycles for intrauterine insemination treatment: effects on pregnancy and multiple pregnancy rates. Hum Reprod 2005;20:3141 – 3146.

Hughes EG. The effectiveness of ovulation induction and intrauterine insemination in the treatment of persistent infertility: a meta-analysis. Human Reprod 1997;9:1865 – 1872.

Hughes EG, Collins JA, Gunby J. A randomized controlled trial of three low-dose gonadotrophin protocols for unexplained infertility. Hum Reprod 1998;13:1527 – 1531.

Ibérico G, Vioque J, Ariza N, Lozano JM, Roca M, Llacer J, Bernabeu R. Analysis of factors influencing pregnancy rates in homologous intrauterine insemination. Fertil Steril 2004;81:1308 – 1313.

Kaplan PF, Patel M, Austin DJ, Freund R. Assessing the risk of multiple gestation in gonadotropin intrauterine insemination cycles. Am J Obstet Gynecol 2002a;186:1244 – 1247.

Kaplan PF, Katz SL, Thompson AK, Freund RD. Cycle fecundity in controlled ovarian hyperstimulation and intrauterine insemination. Influence of the number of mature follicles at hCG administration. J Reprod Med 2002b;47:535 – 539.

Khalil MR, Rasmussen PE, Erb K, Laursen SB, Rex S, Westergaard LG. Homologous intrauterine insemination. An evaluation of prognostic factors based on a review of 2473 cycles. Acta Obstet Gynecol Scand 2001a;80:74 – 81.

Khalil MR, Rasmussen PE, Erb K, Laursen SB, Rex S, Westergaard LG. Intrauterine insemination with donor semen. An evaluation of prognostic factors based on a review of 1131 cycles. Acta Obstet Gynecol Scand 2001b;80:342 – 348.

Land JA, Evers JLH. Risks and complications in assisted reproduction techniques: report of an ESHRE consensus meeting. Hum Reprod 2003;18:455 – 457.

Makkar G, Ng EH, Yeung WS, Ho PC. Prognostic factors for successful outcome in patients undergoing controlled ovarian stimulation and intrauterine insemination. Hong Kong Med J 2003;9:341 – 345.

Martinez AR, Bernardus RE, Voorhorst FJ, Vermeiden JPW, Schoenmaker J. Pregnancy rates after timed intercourse or intrauterine insemination after human menopausal gonadotropin stimulation of normal ovulatory cycles: a controlled study. Fertil Steril 1991;55:258 – 265.

Nuojua-Huttunen S, Tomas C, Bloigu R, Tuomivaara L, Martikainen H. Intrauterine insemination treatment in subfertility: an analysis of factors affecting outcome. Hum Reprod 1999;14:698 – 703.

Özcakir HT, Goker EN, Terek MC, Adakan S, Ulukus M, Levi R, Tavmergen E. Relationship of follicle number, serum estradiol level, and other factors to clinical pregnancy rate in gonadotropin-induced intrauterine insemination cycles. Arch Gynecol Obstet 2002;266:18 – 20.

Papageorgiou TC, Guibert J, Savale M, Goffinet F, Fournier C, Merlet F, Janssens Y, Zorn JR. Low dose recombinant FSH treatment may reduce multiple gestations caused by controlled ovarian hyperstimulation and intrauterine insemination. BJOG 2004;111:1277 – 1282.

Park SJ, Alvarez JR, Weiss G, Von Hagen S, Smith D, McGovern PG. Ovulatory status and follicular response predict success of clomiphene citrate-intrauterine insemination. Fertil Steril 2007;87:1102 – 1107.

Pasqualotto EB, Falcone T, Goldberg JM, Petrauskis C, Nelson DR, Agarwal A. Risk factors for multiple gestation in women undergoing intrauterine insemination with ovarian stimulation. Fertil Steril 1999;72:613 – 618.

Pittrof RU, Shaker A, Dean N, Bekir JS, Campbell S, Tan SL. Success of intrauterine insemination using cryopreserved donor sperm is related to the age of the woman and the number of preovulatory follicles. J Assist Reprod Genet 1996;13:310 – 314.

Plosker SM, Jacobson W, Amato P. Predicting and optimizing success in an intra-uterine insemination programme. Hum Reprod 1994;9:2014 – 2021.

Ragni G, Alagna F, Brigante C, Riccaboni A, Colombo M, Somigliana E, Crosignani PG. GnRH antagonists and mild ovarian stimulation for intrauterine insemination: a randomized study comparing different gonadotrophin dosages. Hum Reprod 2004;19:54 – 58.

Richmond JR, Deshpande N, Lyall H, Yates RW, Fleming R. Follicular diameters in conception

cycles with and without multiple pregnancy after stimulated ovulation induction. Hum Reprod 2005;20:756 – 760.

van Rumste MM, den Hartog JE, Dumoulin JC, Evers JL, Land JA. Is controlled ovarian hyperstimulation in intrauterine insemination an acceptable therapy in couples with unexplained nonconception in the perspective of multiple pregnancies? Hum Reprod 2006;21:701 – 704.

Schenker JG, Yarkoni S, Granat M. Multiple pregnancies following induction of ovulation. Fertil Steril 1981;35:105 – 123.

Sikandar R, Virk S, Lakhani S, Sahab H, Rizvi J. Intrauterine insemination with controlled ovarian hyperstimulation in the treatment of subfertility. J Coll Physicians Surg Pak 2005;15:782 – 785.

Silverberg KM, Olive DL, Burns WN, Johnson JV, Groff TR, Schenken RS. Follicular size at the time of human chorionic gonadotropin administration predicts ovulation outcome in human menopausal gonadotropin-stimulated cycles. Fertil Steril 1991;56:296 – 300.

Steures P, van der Steeg JW, Verhoeve HR, van Dop PA, Hompes PGA, Bossuyt PMM, van der Veen F, Habbema JDF, Eijkemans MJC, Mol BWJ. Does ovarian hyperstimulation in intrauterine insemination for cervical factor subfertility improve pregnancy rates? Hum Reprod 2004;19:2263 – 2266.

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 – 221.

Stone SC, Schimberni M, Schuster PA, Werlin LB, Weathersbee P. Incidence of multiple gestations in the presence of two or more mature follicles in the conception cycle. Fertil Steril 1987;48:503 – 504.

Stone BA, Vargyas JM, Ringler GE, Stein AL, Marrs RP. Determinants of the outcome of intrauterine insemination: Analysis of outcomes of 9963 consecutive cycles. Am J Obstet Gynecol 1999;180:1522 – 1534.

Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283:2008 – 2012.

The ESHRE Capri Workshop Group. Multiple gestation pregnancy. Hum Reprod 2000;15:1856 – 1864.

Tomlinson MJ, Amissah-Arthur JB, Thompson KA, Kasraie JL, Bentick B. Prognostic indicators for intrauterine insemination (IUI): statistical model for IUI success. Hum Reprod 1996;11:1892 – 1896.

Tsai HD, Chang CC, Hsieh YY, Lee CC, Lo HY. Artificial insemination. Role of endometrial thickness and pattern, of vascular impedance of the spiral and uterine arteries, and of the dominant follicle. J Reprod Med 2000;45:195 – 200.

Valbuena D, Simon C, Romero JL, Remohi J, Pellicer A. Factors responsible for multiple pregnancies after ovarian stimulation and intrauterine insemination with gonadotropins. J Assist Reprod Genet 1996;13:663 – 668.

Verhulst SM, Cohlen BJ, Hughes E, Te Velde E, Heineman MJ. Intra-uterine insemination for unexplained subfertility. Cochrane Database Syst Rev 2006;18:CD001838.

Vollenhoven B, Selub M, Davidson O, Lefkow H, Henault M, Serpa N, Hung TT. Treating infertility. Controlled ovarian hyperstimulation using human menopausal gonadotropin in combination with intrauterine insemination.

J Reprod Med 1996;41:658 – 664. Wang B, Hu Y, Sun H, Zhang N, Xu Z. Investigation of correlative factors affecting successful intrauterine insemination. Zhonghua Nan Ke Xue 2004;10:526 – 529.

van Wely M, Twisk M, Mol BW, van der Veen F. Is twin pregnancy necessarily an adverse outcome of assisted reproductive technologies? Hum Reprod 2006;21:2736 – 2738.

Chapter 6

# Interventions and multiple pregnancies in reproductive medicine: critical appraisal of the available evidence

Minouche M.E. van Rumste, Neil P. Johnson, Jan Bosteels, Siladitya Bhattacharya, Madelon van Wely, Fulco van der Veen, Ben Willem J. Mol

Submitted

# ABSTRACT

**OBJECTIVE** To assess whether studies evaluating strategies to reduce multiple pregnancies associated with assisted reproductive technologies have sufficient power to detect a clinically meaningful magnitude of effect.

**DESIGN** Review.

**SETTING** Randomised controlled trials (RCTs) from the Cochrane Menstrual Disorders and Subfertility Group which have reported on multiple pregnancies.

**POPULATION** Subfertile couples.

**METHODS** Data on sample size, power calculation and multiple pregnancies were extracted. For each study, we calculated the sample size required to detect a 50% reduction in the number of multiple pregnancies with 80% power at the 95% confidence level.

**MAIN OUTCOME MEASURES** Data on multiple pregnancies.

**RESULTS** We found 83 reviews based on 904 RCTs reporting on pregnancy after fertility treatment. Ten reviews, including 95 RCTs evaluated interventions that aimed to prevent multiple pregnancies. Of these, 9 (9.5%) had sufficient power to detect a minimally important difference in multiple pregnancy rates. Of the remaining 73 reviews, including 809 RCTs with multiple pregnancy as secondary outcome, 176 reported on the numbers of multiple pregnancies (22%). Only 15 (8.5%) of these 176 RCTs had adequate power to detect the imputed minimally important difference for multiple pregnancies.

**CONCLUSIONS** 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 intuition rather than robust evaluative data.

# INTRODUCTION

Multiple pregnancies are associated with increased risks for both mother and offspring. Women carrying a multiple pregnancy are more susceptible to ante- or postpartum complications, such as anaemia (27%), pre-eclampsia (12%), or labour complications requiring caesarean section. Children born from multiple pregnancies have a more than 50% chance of growth restriction or prematurity (The ESHRE Capri Workshop Group, 2000; Campbell and Templeton, 2004).

Nowadays, more than half of all multiple pregnancies are the result of assisted reproduction techniques (ART), mainly due to ovarian hyperstimulation and transfer of multiple embryos in in-vitro fertilization (IVF) (Fauser *et al.*, 2005). An ESHRE consensus report on the risks and complications in ART concluded that the primary outcome measure in all fertility studies should ideally be singleton live birth rate and that twin and higher order multiple pregnancies should be considered complications (Land and Evers, 2003). In view of this, the European and American Societies for Reproductive Medicine (ESHRE and ASRM) have asked their members to design studies to prevent iatrogenic multiple pregnancies.

It is questionable, however, whether it is at all possible to design and conduct high quality pragmatic RCTs to evaluate the impact of prevention strategies to reduce multiple pregnancies after ART with singleton live birth rate as a primary outcome, as approximately 50% of all multiple pregnancies deliver at or close to term and neonatal survival of prematurely born neonates has improved significantly in recent decades. Detection of differences in health outcomes of multiples versus singletons is becoming increasingly more difficult because of small effect sizes, which require very large numbers of randomised women and a substantially longer follow-up period, which imposes considerable logistical and financial demands on trials. In absence of such RCTs or other comparative studies, the current move towards reduction of multiples runs the risk of being based on intuition rather than on evidence. Obviously, the most effective way to prevent multiple pregnancies caused by ART is to stop offering fertility treatment involving ovarian stimulation, thus bringing multiple pregnancy rates back to the levels experienced in nature. Consequently, reducing the multiple pregnancy rates should always be balanced against a potential decrease in the overall chances of conception.

We asked ourselves whether published fertility studies reporting data on multiple pregnancies had sufficient power to detect a minimally important clinical reduction of 50% in the multiple pregnancy rate. We studied Cochrane Reviews from the Menstrual Disorders and Subfertility Group, which represent the most robust aggregation of trials in reproductive medicine (Windsor *et al.*, 2012). We also scrutinized definitions and analysed data, which presented multiple pregnancy as an outcome.

# MATERIALS AND METHODS

The database of the Cochrane Menstrual Disorders and Subfertility Group (MDSG) was searched from inception until September 2012 for the retrieval of reviews of RCTs designed to prevent multiple pregnancies. The reviews were separated into the following treatment categories: ovulation induction (OI), intra-uterine insemination (IUI) with and without ovarian stimulation, in vitro fertilisation (IVF) (including IVF-ICSI) and non-ART. The number of randomised controlled trials (RCTs) reporting on multiple pregnancies within these reviews was listed.

Data from the original publications of the retrieved RCTs were extracted. When the original publication could not be obtained, data were extracted from the Cochrane Review. It was examined whether the RCTs had adequate power to detect a significant difference in multiple pregnancy rates by calculating odds ratios and 95% confidence intervals.

Secondly, all remaining reviews with RCTs on fertility studies (ART or non-ART) within the MDSG were included. These reviews were also categorized as stated above. The number of randomised controlled trials (RCTs) within these reviews mentioning multiple pregnancies was reported. If an RCT was referred to in more than one review, it was only included once. The original publications of the retrieved RCTs were carefully read, and data on the number of multiple pregnancies were extracted. We noted whether a power analysis was performed for multiple pregnancies, and calculated what the required sample-size would have been for a study to have 80% power at the 95% confidence level to detect a 50% reduction in multiple pregnancy rates in the intervention group, which we considered to be the minimally important clinical difference. For each study, we compared the required sample size to the reported sample size. In fertility trials involving comparison of two treatments we were guided by the Cochrane reviews in terms of describing a therapy as an 'intervention' or 'control'.

Subsequently, stratification of the studies on year of publication, i.e. before or after 2003, was performed to determine whether the method of reporting on multiple pregnancies changed after the ESHRE consensus report.

# RESULTS

The MDSG contained 178 Cochrane Reviews, of which 16 had been withdrawn (figure 1). Among the 162 active reviews, 83 summarized and appraised topics in the field of reproductive medicine while the other 79 reviews reported on gynaecological topics.

Ten reviews specifically targeted the issue of prevention of multiple pregnancies (figure 1). In two of those reviews no RCTs were included. The other eight reviews included 95 RCTs. In 44 RCTs (46.3%) multiple pregnancies were an outcome measure.

We found 73 reviews on fertility, including RCTs that were not specifically designed to prevent multiple pregnancies, but had multiple pregnancy as a secondary outcome. In 4 of those reviews no RCTs were included. The other 69 reviews included 809 RCTs. In 176 (22%) of these RCTs multiple pregnancies were reported (figure 1).

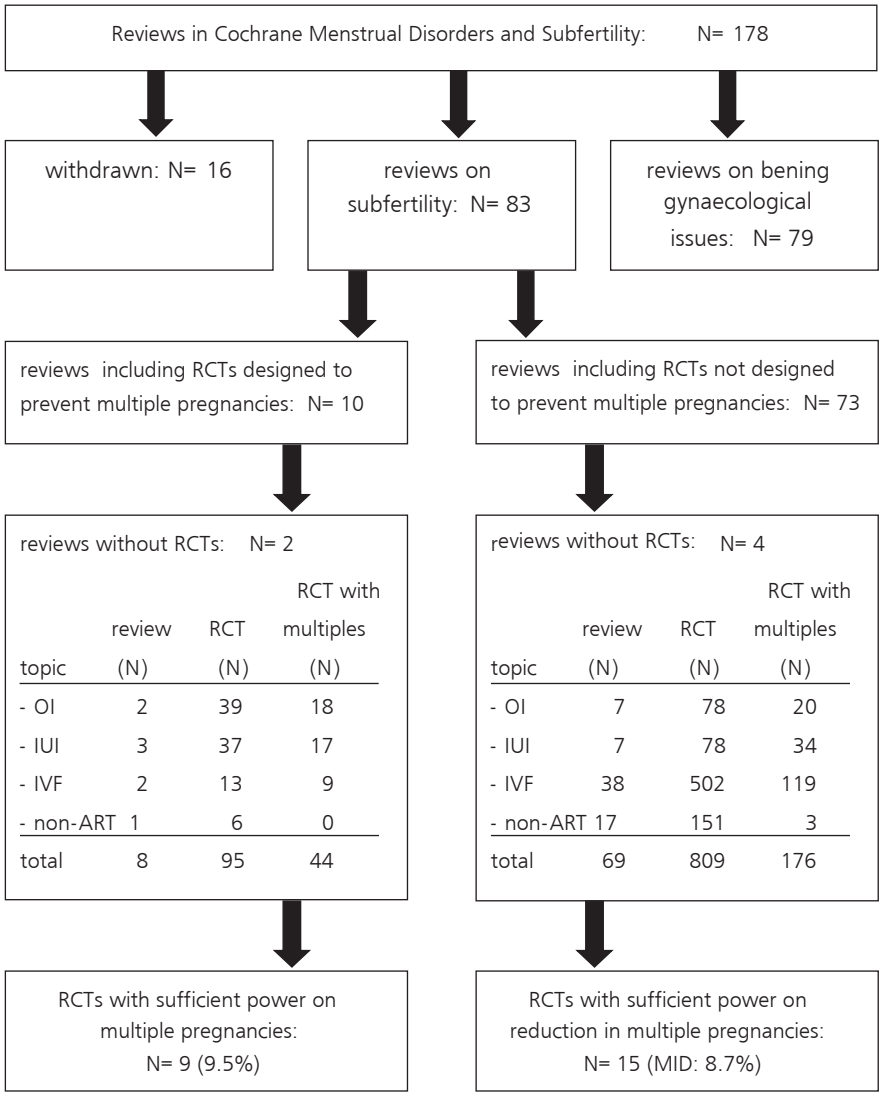



**Figure 1.** Flow chart of included studies

## RCTs intending to prevent multiple pregnancies

The RCTs from the 10 reviews, which studied interventions aimed at preventing multiple pregnancies are categorised in Table 1. None of the included RCTs performed a power analysis on multiple pregnancies to determine the sample size of the study.
Thirty-nine studies on OI were included. In 18 RCTs multiple pregnancies were described. Only one study showed a significant difference in multiple pregnancies between the compared strategies (i.e. the 95% confidence interval did not include 1) (Bayram *et al*., 2004).

**Table 1.** Randomised controlled trials testing strategies to prevent multiple pregnancies.

| treatment strategie review | included RCTs (N) | RCTs including multiple pregnancies (N) | RCTs with significant difference in MPR (N) |
|---|---|---|---|
| **Ovulation Induction** | | | |
| Gonadotrophin therapy for ovulation induction in subfertility associated with polycycstic ovary syndrome | 14 | 6 | 0 |
| Laparoscopic drilling by diathermy or laser for ovulation induction in anovulatory polycystic ovary syndrome | 25 | 12 | 1 |
| **Intra Uterine Insemination** | | | |
| Intra-uterine insemination for male subfertility | 17 | 7 | 2 |
| Intra-uterine insemination for unexplained subfertility | 14 | 9 | 2 |
| Intra-uterine insemination versus timed intercourse or expectant management for cervical hostility in subfertile couples | 6 | 1 | 0 |
| **In Vitro Fertilisation** | | | |
| In vitro fertilisation for unexplained subfertility | 6 | 2 | 0 |
| Number of embryos for transfer following in-vitro fertilisation or intra-cytoplasmic sperm injection | 7 | 7 | 4 |
| In vitro fertilisation versus tubal reanastomosis (sterilisation reversal) for subfertility after tubal sterilization | 0 | - | - |
| Surgery for tubal infertility | 0 | - | - |
| **Non-ART** | | | |
| Lifestyle changes in women with polycystic ovary syndrome | 6 | 0 | 0 |

MPR: multiple pregnancy rate
RCTs: randomised controlled trials

Out of 37 studies on IUI, 17 mentioned multiple pregnancies, of which four (11%) showed significant differences for multiple pregnancies between the treatment strategies.
We found that 9 out of 13 studies on IVF included multiple pregnancy as an outcome. In one review, titled "Number of embryos for transfer following in-vitro fertilisation or

intra-cytoplasmic sperm injection", all included RCTs reported on multiple pregnancies (N=7). Four of the RCTs from this review showed statistically significant differences on multiple pregnancies (31%).
None of the 6 RCTs on non-ART topics mentioned multiple pregnancies. In total, nine of the 95 RCTs showed a significant difference in the multiple pregnancy rate per pregnancy (9.5%).

## RCTs where the primary intention was not to test interventions for the prevention of multiple pregnancies

The 809 RCTs on fertility topics that included multiple pregnancies as secondary outcome are described below per category, OI, IUI, IVF and non-ART, respectively. The minimally important clinical difference was calculated per category and is shown in figures.
Seventy-eight studies on ovulation induction were included, of which 20 reported on multiple pregnancies. In four studies the actual number of multiple pregnancies was not reported. In five studies the number of multiple pregnancies in the intervention group was zero and therefore a reduction in multiple pregnancies could not be calculated. None of the remaining 11 studies had enough pregnancies within the study to show a 50% reduction in multiple pregnancies in the intervention group (figure 2).

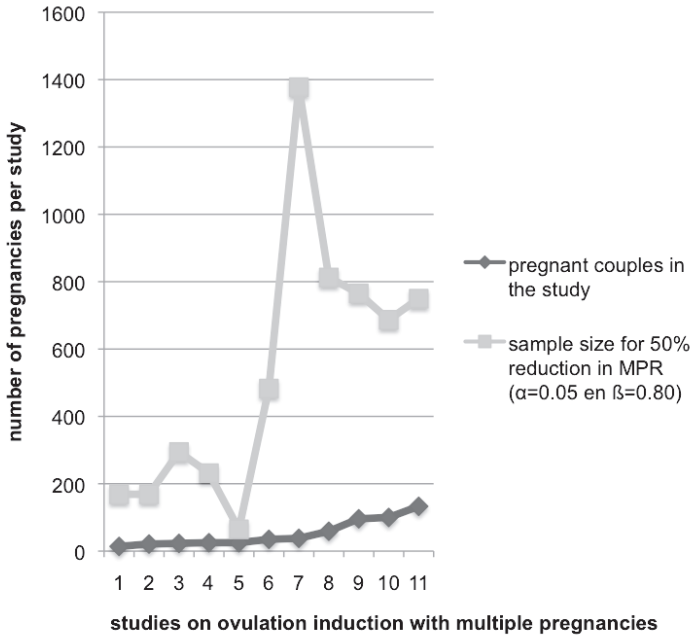



**Figure 2.** Studies on ovulation induction reporting the number of multiple pregnancies and their number of pregnancies needed in the study to show a reduction in multiple pregnancies by half.

We found 78 studies on IUI, of which 34 mentioned multiple pregnancies in their methods section. In two of these studies, the actual number of multiple pregnancies was not reported. In five studies the number of multiple pregnancies in the intervention group was zero and therefore a reduction in multiple pregnancies could not be calculated. The remaining 27 studies did not have enough pregnancies per study to show a 50% reduction in multiple pregnancies in the intervention group (figure 3).

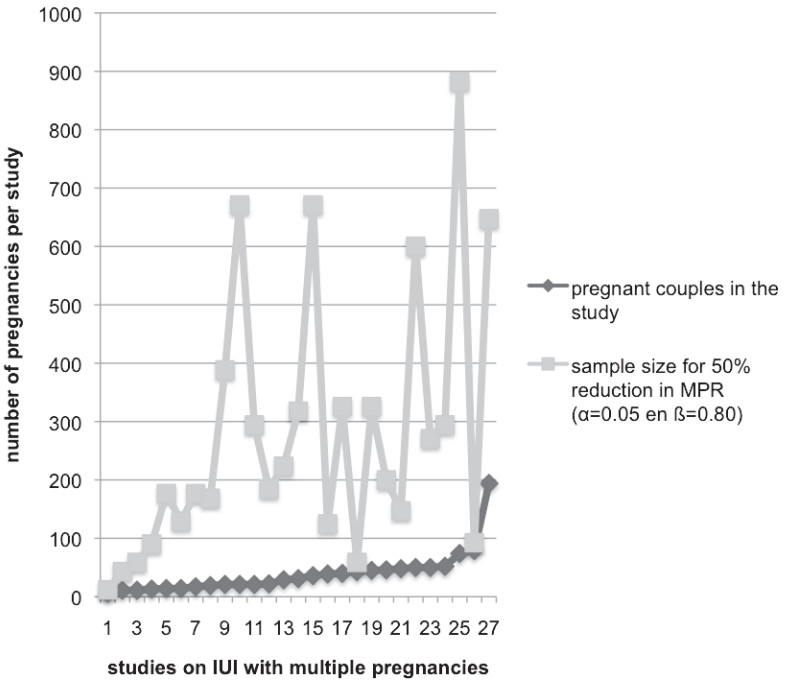



**Figure 3.** Studies on IUI reporting the number of multiple pregnancies and their number of pregnancies needed in the study to show a reduction in multiple pregnancies by half.

Of the 151 studies on IVF, 119 included multiple pregnancy as an outcome. Twenty did not report on the actual number of multiple pregnancies. In four studies the number of multiple pregnancies in the intervention group was zero and therefore a reduction in multiple pregnancies could not be calculated. Of the remaining 95 studies, 15 (16%) had a sample size large enough to show a reduction in multiple pregnancies in the intervention group by half (figure 4). The topics of these 15 IVF studies were stimulation protocol (N= 3), endometrial preparation prior to embryo transfer (N=1), assisted hatching (N=2), culture media (N=2), timing of embryo transfer (N=3), method of embryo transfer (N=2) and luteal phase interventions (N=3). In these studies the average clinical pregnancy rate was 41% (variation from 22% to 68%). The average multiple pregnancy rate was 35% (variation from 11% to 59%).

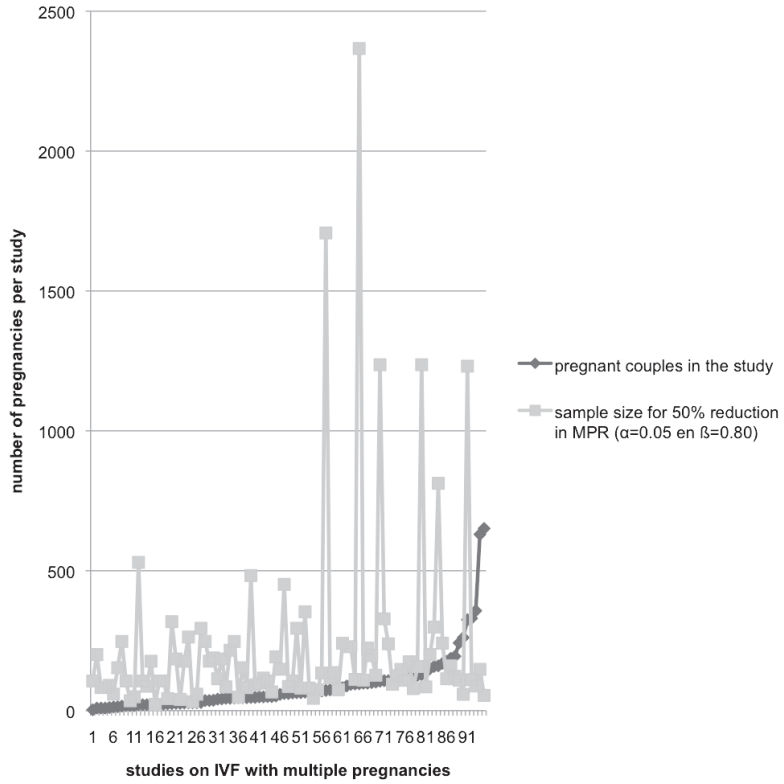



**Figure 4.** Studies on IVF reporting the number of multiple pregnancies and their number of pregnancies needed in the study to show a reduction in multiple pregnancies by half.



Only three studies on non-ART topics mentioned multiple pregnancies. No analysis was performed on these RCTs, as the three could not be grouped together as they addressed different topics (Chinese herbal medicine for polycystic ovarian syndrome; postoperative procedures following pelvic reproductive surgery; tubal flushing for subfertility).

## Minimally important clinical difference

In total, 15 of the 176 (8.5%) analysed RCTs had sufficient power to prove a reduction of 50% in multiple pregnancies.

## Power to detect impact on multiple pregnancy rates

Only one of the 904 included RCTs had multiple pregnancy as the primary outcome and performed a power calculation based on this outcome (Frattarelli *et al.*, 2003). This RCT dealt with cleavage stage versus blastocyst stage embryo transfer and was included in the 'RCTs not designed to prevent multiple pregnancies' section. In this study, it was calculated that the required sample-size needed to be136 patients in order to provide 80% chance

of detecting a 25% difference in multiple pregnancy rates, controlling for the probability of type 1 error at alpha = 0.05. Unfortunately, only 49 patients could be included. The minimally important clinical difference was not reached. A sample size of 32 would be necessary, but only 28 couples in the strategy group were pregnant.

### Publication year and definitions

Of the 904 included RCTs, 524 were published before 2004. One hundred twenty reported multiple pregnancies (23%). Of the remaining 380 RCTs published in the period since 2004, 96 reported on multiple pregnancies (27%). The outcome multiple pregnancy was often descriptive. For example, it was reported that 'one of the miscarriages was a triplet at 10 weeks and the twins delivered' or 'one quintuplet was reduced to twins, both were live births'. Of most multiple pregnancies the actual outcome was not mentioned, like preterm birth or live birth at a given gestation, but they were only reported as an ongoing pregnancy.

## DISCUSSION

### Main findings

We evaluated 83 systematic reviews of RCTs of interventions to prevent multiple pregnancy after fertility treatment or with multiple pregnancy as a secondary outcome. Ten reviews reported on a strategy to prevent multiple pregnancy and included 95 RCTs of which 9 RCTs had sufficient power to show a reduction in multiple pregnancies (9.5%).
Of the remaining 73 reviews, which included 809 RCTs with multiple pregnancy as a secondary outcome, 176 reported on the number of multiple pregnancies (22%) and in 173 The minimally important clinical difference was calculated. Only 15 of the analysed RCTs were able to demonstrate a reduction of 50% in multiple pregnancies in the intervention group (8.7%).

### Strengths and Limitations

This is the first study to critically appraise the reporting of multiple pregnancy rates in ART studies. Since the number of studies reporting data on multiple pregnancies is limited and only a minority of studies have adequate power to detect a clinically important reduction in multiple pregnancies, it is almost impossible to draw a solid evidence- based conclusion on effective preventive strategies.
We realize that the use of Cochrane MDSG reviews to select RCTs constitutes a selection bias. We preferred to use this search strategy because the reviews included in the MDSG contain only good quality RCTs that are updated on a regular basis and have been critically appraised in a consistent manner. We are reasonably confident that the validity of the

results and conclusions of our current review are not compromised by the selection bias (Windsor *et al.*, 2012).

Apart from the issue of power, which is the topic of this paper, there are also additional factors that hamper any attempt at objective comparison of studies. Not only do outcome measures vary from study to study, but the population included might not be representative for the general population. Usually, young women with a relatively good prognosis are included in fertility trials. Studies also vary in terms of treatment strategies, including drugs used, ovarian stimulation protocols, criteria for cancellation or definition of ovarian hyperstimulation. For example, some clinicians will aim for one dominant follicle in subfertile couples, where others will perform an IUI when 3 of 4 dominant follicles are present. This will inevitably influence the chance on a multiple pregnancy. Another example is the SET versus DET trials, which were carried out in good prognosis patients and may therefore not be applicable in the general subfertile population.

## Interpretation

The 15 studies on IVF that were powered to show a 50% reduction in multiple pregnancies evaluated a number of interventions to improve pregnancy rates, such as alternative culture media or stimulation protocols, but were not specifically designed to prevent multiple pregnancies. The average multiple pregnancy rate in these studies was extremely high (35%) compared to generally reported multiple pregnancy rates of 21% after ART in Europe (Ferraretti *et al.*, 2012). Twelve of the 15 studies were published before 2008, including collected data of years before the publication, when multiple pregnancies were less likely to have been considered a complication of ART treatment. It is easier to show a clinically meaningful reduction in multiples where the background rate is high.

There was a small increase in the percentage of trials reporting on multiple pregnancies after the ESHRE consensus report in 2003 (Land and Evers, 2003). An explanation might be that the majority of the trials were published before 2003 and trials published in the years just after the consensus report were carried out without the knowledge of this report. The conduct of a randomised controlled trial, including patient recruitment, data collection, followed by preparation, submission, peer review and publication of a manuscript can take several months. There is also an understandable delay in including new RCTs in Cochrane reviews, since updating the reviews also takes time.

An alternative approach towards evaluation of strategies aimed at preventing multiple pregnancies is to study the non-inferiority of an intervention, which is likely to reduce or even prevent multiple pregnancies, compared to control interventions. Examples of such strategies are tubal reconstructive surgery or IVF with elective Single Embryo Transfer (SET) as alternatives for ovarian hyperstimulation or IVF with two or more embryos (Gomel, 2007, Gerris *et al.*, 2002). We found ten non-inferiority studies, half of them comparing single to double embryo transfer (Gerris *et al.*, 1999; Martikainen *et al.*, 2001; Thurin *et al.*, 2004;

Lukassen *et al.*, 2005; Montfoort *et al.*, 2006). Two other studies were not designed to avoid all (dizygotic) multiple pregnancies, but to reduce the number of multiple pregnancies or the number of high-order multiple pregnancies in IVF (Heijnen *et al.*, 2006 and Vauthier-Brouzes *et al.*, 1994). A further study compared the difference in the embryo-transfer on day 3 or on day 5 on the outcome multiple pregnancy (Frattarelli *et al.*, 2003), whereas yet another study was conducted to assess the number of oocytes retrieved in IVF after pre-treatment with an oral contraception or after standard IVF protocol, but not to show a difference in the number of multiple pregnancies (Huirne *et al.,* 2006). The last of these 10 studies assessed prevention of multiple pregnancies by a low-dose step-up protocol in intra-uterine insemination (Sengoku *et al.*, 1999). Three of the five studies demonstrating the effectiveness of SET in reducing the twin rate in the study population compared to double embryo transfer, had sufficient power to show a reduction in multiple pregnancies. However, it should be noted that the inclusion criteria were limited to couples that all had a good prognosis, as only younger women with good quality embryos could participate in these studies (McLernon *et al.*, 2010). Consequently, the results and conclusions of these non-inferiority studies may therefore not be extrapolated to all women undergoing IVF, but only to those with a good prognosis, i.e. those with good quality embryos who are younger than 36 years.

Multiple pregnancies are generally considered an adverse outcome in ART. Although the contribution of ART to the absolute number of women with a multiple pregnancy is considerable, the consequences for the average individual woman undergoing IVF are less, as the majority of couples either conceive of a singleton pregnancy or do not become pregnant at all. In addition, not every multiple pregnancy ends in a poor outcome, as most multiple pregnancies carry on till term or near term, resulting in the birth of two healthy children (van Wely *et al.*, 2006). Outcomes in twin pregnancies resulting from IVF are comparable to those in spontaneously conceived twins (Vasario *et al.,* 2010).

## CONCLUSION

In conclusion, multiple pregnancy rates are poorly reported in studies on interventions in reproductive medicine and most studies are underpowered to show a difference in multiple pregnancies. Studies designed to show a difference in multiple pregnancies were unable to show convincing differences between alternative strategies due to small numbers of multiple pregnancies in intervention as well as treatment groups. Use of standard meta-analysis techniques are unable to aggregate data on a number of interventions across different populations to reduce multiple pregnancies. Network meta-analysis is able to combine all the available evidence and might be an option. At present, clinical decisions concerning fertility interventions about reduction of multiple pregnancies, are intuitive rather than evidence-based.

# REFERENCES


The ESHRE Capri Workshop Group. Multiple gestation pregnancy. *Hum Reprod* 2000;**15**: 1856- 64.

Campbell DM, Templeton A. Maternal complications of twin pregnancy. *Int J Gynaecol Obstet* 2004;**84**: 71-3.

Fauser BC, Devroey P, Macklon NS. Multiple birth resulting from ovarian stimulation for subfertility treatment. *Lancet* 2005;**365**: 1807-16.

Land JA, Evers JL. Risks and complications in assisted reproduction techniques: Report of an ESHRE consensus meeting. *Hum Reprod* 2003;**18**: 455-7.

http://www.nice.org.uk/nicemedia/pdf/CG011niceguideline.pdf

Windsor B, Popovich I, Jordan V, Showell M, Shea B, Farquhar C. Methodological quality of systematic reviews in subfertility: a comparison of Cochrane and non-Cochrane systematic reviews in assisted reproductive technologies. Hum Reprod. 2012;27: 3460-6.

Bayram N, van Wely M, Kaaijk EM, Bossuyt PMM, van der Veen F. Using an electrocautery strategy or recombinant follicle stimulating hormone to induce ovulation in polycystic ovary syndrome: randomised controlled trial. *BMJ*. 2004;**328**: 192.

Frattarelli JL, Leondires MP, McKeeby JL, Miller BT, Segars JH. Blastocyst transfer decreases multiple pregnancy rates in vitro fertilization cycles: a randomized controlled trial. *Fertil Steril* 2003;**79**: 228-30.

Ferraretti AP, Goossens V, de Mouzon J, Bhattacharya S, Castilla JA, Korsak V, et al.; European IVF-monitoring (EIM); Consortium for European Society of Human Reproduction and Embryology (ESHRE). Assisted reproductive technology in Europe, 2008: results generated from European registers by ESHRE. *Hum Reprod* 2012;**27**: 2571-84

Gomel V. Reversal of tubal sterilization versus IVF in the era of assisted reproductive technology: a clinical dilemma. *Reprod Biomed Online* 2007;**15**: 403-7.

Gerris J, De Neubourg D, Mangelschots K, Van Royen E, Vercruyssen M, Barudy-Vasquez J, et al. Elective single day 3 embryo transfer halves the twinning rate without decrease in the ongoing pregnancy rate of an IVF/ICSI programme. *Hum Reprod* 2002;**17**: 2626-31.

Gerris J, De Neubourg D, Mangelschots K, Van Royen E, Van de Meerssche M, Valkenburg M. Prevention of twin pregnancy after in-vitro fertilization or intracytoplasmic sperm injection based on strict embryo criteria: a prospective randomized clinical trial. *Hum Reprod* 1999;**14**: 2581-7.

Martikainen H, Tiitinen A, Tomás C, Tapanainen J, Orava M, Tuomivaara L, et al.; Finnish ET Study Group. One versus two embryo transfer after IVF and ICSI: a randomized study. *Hum Reprod* 2001;**16**: 1900-3.

Thurin A, Hausken J, Hillensjö T, Jablonowska B, Pinborg A, Strandell A, et al. Elective single-embryo transfer versus double-embryo transfer in in vitro fertilization. *N Engl J Med* 2004;**351**: 2392-402.

Lukassen HG, Braat DD, Wetzels AM, Zielhuis GA, Adang EM, Scheenjes E, et al. Two cycles with single embryo transfer versus one cycle with double embryo trransfer: a randomized controlled trial. *Hum Reprod* 2005;**20**: 702-8.

van Montfoort AP, Fiddelers AA, Janssen JM, Derhaag JG, Dirksen CD, Dunselman GA, et al. In unselected patients, elective single embryo transfer prevents all multiples, but results in significantly lower pregnancy rates compared with double embryo transfer: a randomized controlled trial. *Hum Reprod* 2006;**21**: 338-3.

Heijnen EM, Klinkert ER, Schmoutziguer AP, Eijkemans MJ, te Velde ER, Broekmans FJ. Prevention of multiple pregnancies after IVF in women 38 and older: a randomized study. *Reprod BioMed Online* 2006;**13**: 386-393.

Vauthier-Brouzes D, Lefebvre G, Lesourd S, Gonzales J, Darbois Y. How many embryos should be transferred in in vitro fertilization? A prospective randomized study. *Fertil Steril* 1994;**62**: 339-42.

Huirne JA, Hugues JN, Pirard C, Fischl F, Sage JC, Pouly JL, et al. Cetrorelix in an oral contraceptive-pretreated stimulation cycle compared with buserelin in IVF/ICSI patients treated with r-hFSH: a randomized, multicentre, phase IIIb study. *Hum Reprod* 2006;**21**: 1408-15.

Sengoku K, Tamate K, Takaoka Y, Horikawa M, Goishi K, Komori H, et al. The clinical efficacy of low-dose step-up follicle stimulating hormone administration for treatment of unexplained inferility. *Hum Reprod* 1999;**14**: 349-53.

McLernon DJ, Harrild K, Bergh C, Davies MJ, de Neubourg D, Dumoulin JC, et al. Clinical effectiveness of elective single versus double embryo transfer: meta-analysis of individual patient data from randomised trials. *BMJ* 2010;**21**: 341:c6945.

van Wely M, Twisk M, Mol BW, van der Veen F. Is twin pregnancy necessarily an adverse outcome of assisted reproductive technologies? *Hum Reprod* 2006;**21**: 2736-8.

Vasario E, Borgarello V, Bossotti C, Libanori E, Biolcati M, Arduino S, et al. IVF twins have similar obstetric and neonatal outcome as spontaneously conceived twins: a prospective follow-up study. *Reprod Biomed Online* 2010;**21**: 422-8.

Chapter 7

# Long-term outcome in couples with unexplained subfertility and an intermediate prognosis initially randomized between expectant management and immediate treatment

Inge M Custers and Minouche ME van Rumste, Jan Willem van der Steeg, Madelon van Wely, Peter GA Hompes, Patrick Bossuyt, Frank J Broekmans, Cees NM Renckens, Marinus JC Eijkemans, Thierry JHM van Dessel, Fulco van der Veen, Ben WJ Mol, Pieternel Steures for CECERM

Human Reproduction 2011; 27:444-50

# ABSTRACT

**BACKGROUND** We recently reported that treatment with intrauterine insemination and controlled ovarian stimulation (IUI-COS) did not increase ongoing pregnancy rates compared with expectant management (EM) in couples with unexplained subfertility and intermediate prognosis of natural conception. Long-term cost-effectiveness of a policy of initial EM is unknown. We investigated whether the recommendation not to treat during the first 6 months is valid, regarding the long-term effectiveness and cumulative costs.

**METHODS** Couples with unexplained subfertility and intermediate prognosis of natural conception (n=253, at 26 public clinics, the Netherlands) were randomly allocated to 6 months EM or immediate start with IUI-COS. 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.

**RESULTS** Time to ongoing pregnancy did not differ between groups (log-rank test P=0.98). Cumulative ongoing pregnancy rates were 72–73% for EM and IUI-COS groups, respectively (relative risk 0.99; 95% confidence interval (CI) 0.85–1.1). Estimated mean costs per couple were €3424 (95% CI €880–€5968) in the EM group and €6040 (95% CI €4055–€8125) in the IUI-COS group resulting in an estimated saving of v2616 per couple (95% CI €385–€4847) in favour of EM.

**CONCLUSIONS** In couples with unexplained subfertility and an intermediate prognosis of natural conception, initial EM for 6 months results in a considerable cost-saving with no delay in achieving pregnancy or jeopardizing the chance of pregnancy. Further comparisons between aggressive and milder forms of ovarian stimulation should be performed.

# INTRODUCTION

Intrauterine insemination with controlled ovarian stimulation (IUI-COS) is commonly used as first-line treatment for couples with unexplained subfertility. Evidence for the effectiveness of this treatment has been lacking, which is worrisome in view of the increased risk of multiple pregnancies in this treatment as a result of ovarian stimulation.[1,2] In couples with a chance of a treatment-independent pregnancy between 30 and 40%, we therefore assessed the effectiveness of IUI-COS compared with expectant management (EM) and found that IUI-COS was not more effective than EM over a period of 6 months.[3] We concluded that in these couples EM should be advocated.

The recommendation not to treat during the first 6 months only holds if the long-term effectiveness is comparable with that of immediate treatment, while the cumulative long-term costs of EM remain lower. Therefore, we followed all couples until 3 years after randomization and registered pregnancies, initiated treatments and costs.

# MATERIALS AND METHODS

## Patients

We report the 3-year follow-up of the couples who had previously been assigned randomly to IUI-COS (immediate treatment group, 127 couples) or EM (EM group, 126 couples) for a period of 6 months.[3] This RCT was performed between June 2002 and July 2005 in 26 fertility centres in the Netherlands. Couples were eligible for the trial in case of unexplained subfertility for at least 1 year, a female partner younger than 39 years with a regular cycle and an intermediate prognosis for an ongoing pregnancy. This prognosis was calculated by the validated prediction model of Hunault and colleagues, which predicts the chance for a spontaneous pregnancy in the next 12 months resulting in a live birth.[4,5] An intermediate prognosis was defined as a probability of a treatment-independent ongoing pregnancy between 30 and 40%.

## Procedures

The original sample size for the RCT had been based on a non-inferiority design to exclude a difference larger than 13% from the assumed ongoing pregnancy rate in the EM group of 22% ($\alpha$=5%, $\beta$=80%). With a sample size of 126 women in each group, we would have a power of 80% to detect a relative risk (RR) of 1.21 or larger for the long-term live birth rate, using a 5% significance level and two-sided testing and assuming a live birth rate of 70% in the control group.

After the initial study period of 6 months, couples who had been unsuccessful in getting pregnant were usually treated according to the guidelines of the Dutch Society of

Obstetrics and Gynaecology.[6] According to these guidelines, primary treatment is six cycles of IUI-COS followed by IVF for three cycles. Couples who were initially allocated to IUI-COS usually continued with three cycles of IVF.

The procedure for IUI-COS was performed according to hospital-specific protocols. The study protocol recommended the use of recombinant FSH (rFSH) for COS. The women started daily s.c. injections of rFSH [Gonal F (Serono Benelux, The Hague, Netherlands) or Puregon (Organon, Oss, Netherlands)] or hMG [Menopur (Ferring, Hoofddorp, Netherlands)] in mean doses of 75 IU, ranging from 37 to 150 IU, until transvaginal sonography showed at least one follicle of at least 16 mm diameter. In some hospitals, clomiphene citrate was used for ovarian stimulation in a dose of 100 mg from Day 3 until Day 7. Ovulation was induced with 5,000 or 10,000 IU of hCG [Pregnyl (Organon)] and women were inseminated 36–40 h later. We withheld hCG and IUI if there were more than three follicles of at least 16 mm diameter, or five of at least 12 mm diameter. We did not give luteal support. We processed semen samples within 1 h of ejaculation by density-gradient centrifugation followed by washing with culture medium. The volume of semen that was inseminated varied between 0.2 and 1.0 ml. We performed the insemination irrespective of the total motile sperm count after preparation on the scheduled day.

Treatment with IVF was also performed according to local protocol. Patients undergoing IVF received COS after down-regulation with a GnRH agonist in a long protocol with a midluteal start. COS was started with 150 U rFSH. Treatment was continued until at least three follicles >18 mm had developed. Ovulation was induced by 10,000 IU hCG (Pregnyl®, Organon, Oss, The Netherlands) and cumulus–oocyte complexes were recovered by transvaginal ultrasound-guided retrieval 36 h thereafter. On Day 3 the embryo transfer took place. According to the number of available embryos and patient preferences, one or two embryos were transferred. Non-transferred good quality embryos were cryo-preserved. When necessary, the frozen embryos were thawed and transferred.

Couples were followed for 3 years after randomization or until an ongoing pregnancy occurred. Primary outcome was time to ongoing pregnancy within 3 years after randomization. Ongoing pregnancy was defined as the presence of fetal cardiac activity during transvaginal ultrasonography at 12 weeks gestation. Secondary end-points were clinical pregnancy, miscarriage and ectopic pregnancy. Clinical pregnancy was diagnosed if there was evidence of a pregnancy by clinical or ultrasound parameters. Miscarriage was defined as a non-viable pregnancy during ultrasonography or pregnancy loss before 12 weeks gestation. Ectopic pregnancy was defined as a pregnancy located outside the uterus that required medical or surgical treatment. After a miscarriage or an ectopic pregnancy, follow-up was further continued until a viable pregnancy occurred. Multiple pregnancy rates were calculated per ongoing pregnancy.

The number of IUI and IVF cycles in both groups were registered.

## Analysis

Analysis was performed according to intention-to-treat, i.e. all pregnancies that occurred in the 3 years following randomization were accounted for per randomized group, whether they occurred spontaneously, after IUI-COS or after IVF.

Kaplan–Meier curves were plotted to illustrate the difference in time to pregnancy between the two groups and the curves were compared with a log-rank test. We performed a Cox regression analysis with age as covariable, where age was stratified into three groups: <32, 32–35 and >35 years. The young age group (<32 years) functioned as a reference group. Ongoing pregnancies, after natural conception or after treatment, in both groups were expressed as a RR with a 95% confidence interval (CI). In all analyses a P-value of 0.05 was considered to indicate statistical significance. Calculations were performed with the Statistical Package for the Social Sciences version 16® (SPSS Inc., Chicago, IL, USA).

## Economic evaluation

The economic evaluation was performed from the perspective of the health care institution. Indirect costs, such as travel expenses or productivity loss, and external costs borne by society were not included. All the participating hospitals were public hospitals and costs were covered by health care insurance. In case of comparable ongoing pregnancy rates in the immediate treatment group and the EM group a cost-minimization study would be performed with focus on the cost-difference between the two strategies within a time horizon of 3 years. In case of a difference in ongoing pregnancy rate, a cost-effectiveness analysis would be performed. We followed the EURONHEED sub-checklist as a guideline for our economic evaluation.[7]

We recorded the number of IUI-COS and IVF treatments and we used data from an inventory study of mean costs of each treatment cycle in The Netherlands in 2005.[8,9] All cycles of therapy were included, including those started in the waiting period. We assumed that the costs for couples who received no treatment were equal to zero, since no additional visits to the clinic were made. The average total dose of gonadotrophins used for the ovarian stimulation in IUI was estimated and was set at 800 IU of FSH per cycle.[8,9] To reflect the concept of time preference, meaning that an amount of money spent or saved in the future is worth less than the same amount today, costs were calculated using a discount rate of 5%, as is consistent with conventional practice.[10,11] The unit costs for one cycle of IVF and one cycle of IUI-COS were estimated at €2139 and €773, respectively. The costs for the hospital component, specialist fee and medication for IUI-COS and IVF are specified in Table 1. The mean costs and the confidence boundaries were estimated by non-parametric bootstrapping to account for the expected skewing of the data owing to the relatively high proportion of patients with no, or very low, costs.[12]

The costs for one ongoing pregnancy per randomized group were calculated by dividing the mean total costs made by the number of ongoing pregnancies per randomized group.

**Table 1.** Costs per resource unit for IUI-COS and IVF

| Resource unit | IUI-COS | IVF |
|---|---|---|
| Hospital component | € 340 | € 984 |
| Specialist fee | € 99 | € 230 |
| Medication | € 334 | € 925 |
| Total | € 773 | € 2.139 |

In IUI-COS cycles, clomiphene citrate can replace FSH.[13] Clomiphene citrate use is low in cost, whereas FSH is expensive. To explore the effect of plausible variations in FSH use, we calculated the total costs for the case where clomiphene citrate would have been used and in the case where a high dose of 1000 IU FSH per cycle had been used.

# RESULTS

In the initial study, 126 couples were assigned to EM and 127 couples to IUI-COS for 6 months. Baseline characteristics at the time of randomization were comparable between the two groups, and have been published in the original article.[3] Mean female age was 33 years, mean duration of subfertility was 2 years, 77% of the couples had primary subfertility and the mean prognosis of the couples was a 35% ongoing pregnancy rate without additional treatment in 12 months. In 47 (11%) cycles of the initial trial, clomiphene citrate was used for COS, resulting in three ongoing pregnancies (6.4% per started cycle). Overall, of the 444 started cycles in the immediate treatment group, 63 cycles (14%) were cancelled because of the risk of high-order multiple pregnancies. Multifollicular growth, defined as more than one follicle with a diameter >15 mm, was achieved in 42% of the inseminated cycles. If follicles >10 mm were included, 70% of the inseminated cycles were multifollicular. In the immediate treatment group, one twin and one triplet pregnancy occurred, and both of these pregnancies resulted from multifollicular cycles in which only one follicle >15 mm was present.

After the initial 6 months, 34 couples (27%) had an ongoing pregnancy in the EM group and 29 couples (23%) in the immediate treatment group. Time to pregnancy showed no significant difference between the two groups. The remaining couples (92 and 98 couples, in the EM group and immediate treatment group, respectively) were followed until they achieved an ongoing pregnancy or for a maximum of 2.5 years. Twelve couples in the EM group (10%) and nine couples in the immediate treatment group (7%) were lost to follow-up, mainly because they had moved to untraceable locations.

Both in the EM group and in the immediate treatment group eight couples (16 couples overall) refrained from further treatment. In the EM group, 82 couples started IUI-COS and two couples immediately started IVF. Of the 52 couples who did not conceive after IUI-COS 42 couples continued with IVF.

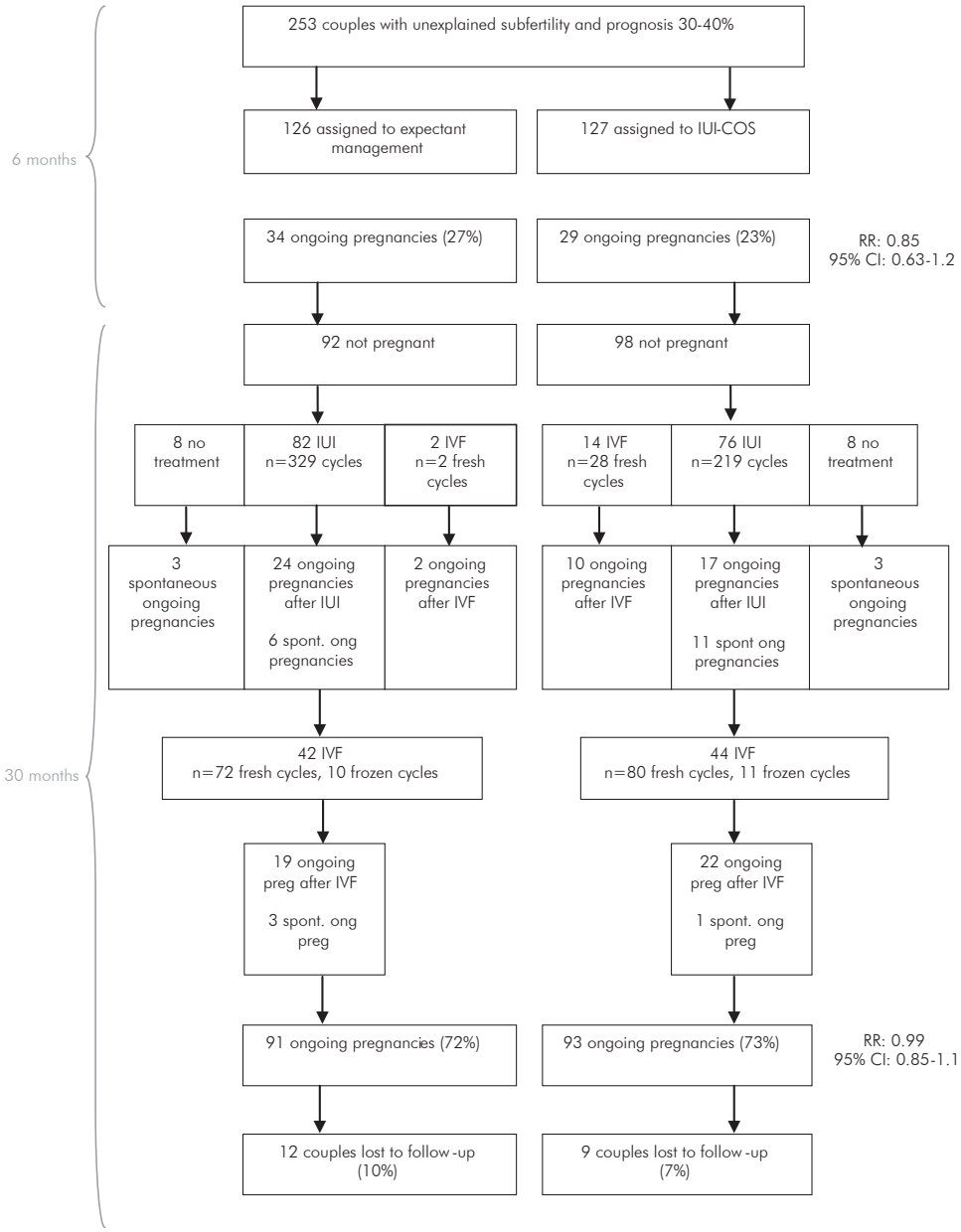



**Figure 1** Flow chart of treatment and pregnancy outcome over 3 years for couples with unexplained subfertility and an intermediate prognosis, initially randomized between EM and immediate treatment IUI-COS, intrauterine insemination and controlled ovarian stimulation; RR, relative risk; CI, confidence interval.

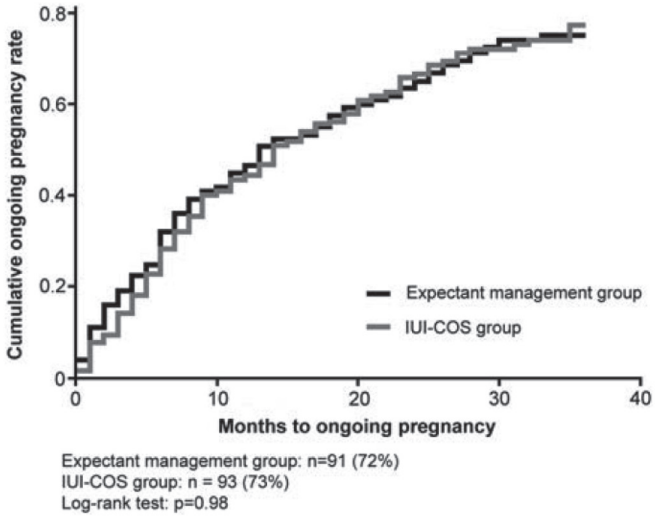



**Figure 2** Time to ongoing pregnancy in couples who were initially randomized between EM and immediate treatment.

In the immediate treatment group, 76 couples continued IUI-COS and 14 couples started IVF. Of the 51 couples who did not conceive after IUI-COS, 44 couples continued with IVF (Fig. 1).

At 3 years, the total number of pregnancies was 109 in the EM group and 125 in the immediate treatment group. The number of ongoing pregnancies was 91 (72%) in the EM group and 93 (73%) in the immediate treatment group, resulting in an RR of 0.99 (95% CI: 0.85–1.1) (Fig. 1).The median time to pregnancy was 13 months (95% CI: 8–18) in the EM group versus 14 months (95% CI: 10–18) in the immediate treatment group. Time to pregnancy showed no significant difference, log-rank test P=0.98, RR 0.99 (95% CI: 0.85–1.1) (Fig. 2). Age was not significantly associated with time to pregnancy in the two treatment groups, the hazard rate (HR) for the 32–35 years group versus <32 years group was 1.2 (P=0.41) the HR for the >35 versus <32 years group was 1.1 (P=0.59).

In the EM group 45 of the 91 ongoing pregnancies occurred after either IUI or IVF treatment, three pregnancies occurred spontaneously in couples refraining from further treatment and nine between treatment cycles, whereas 34 ongoing pregnancies already had occurred in the first 6 months. In the immediate treatment group 49 of the 93 ongoing pregnancies were the result of IUI or IVF treatment and 15 occurred spontaneously, of which 12 occurred between treatment cycles, whereas 29 ongoing pregnancies already occurred in the first 6 months (Fig. 1).

The total number of miscarriages was 17 in the EM group (13% per couple) versus 31 in the immediate treatment group (24% per couple) (RR 0.54, 95% CI: 0.32–0.92). In each group one ectopic pregnancy occurred. In the EM group, there were nine twin pregnancies (multiple pregnancy rate 10% per ongoing pregnancy) with one spontaneously conceived, three after IUI-COS and five after IVF, versus seven twins and one triplet in the immediate

**Table 2.** Pregnancy outcome after three years in couples with unexplained subfertility and an intermediate prognosis initially randomized between EM and immediate treatment.

| | Expectant management group (n=126) | Immediate treatment group (n=127) | RR (95%CI) |
|---|---|---|---|
| All pregnancies | 109 | 125 | 0.88 (0.82-0.94) |
| Ongoing pregnancies, n (%) | 91 (72) | 93 (73) | 0.99 (0.85-1.1) |
| Miscarriages, n (%) | 17 (13) | 31 (24) | 0.54 (0.32-0.92) |
| Ectopic pregnancies, n (%) | 1 (0.8) | 1 (0.8) | 1.0 (0.06-15.9) |
| Multiple pregnancies, n (%) | 9 (8) | 8 (6) | 1.1 (0.45-2.8) |

RR, relative risk; CI, confidence interval.

**Table 3.** Ongoing pregnancies per group and per treatment cycle (IUI and IVF).

| | Expectant management group (n=126) | Immediate treatment group (n=127) | RR (95% CI) |
|---|---|---|---|
| Spontaneous ongoing pregnancies, n (%) | 46 (37) | 26 (20) | 1.8 (1.2-2.7) |
| Number of IUI cycles | 364 | 661 | |
| Ongoing pregnancies after IUI, n (%) | 24 (19) | 35 (28) | 0.7 (0.4-1.1) |
| % ongoing pregnancy per IUI cycle | 6.6 | 5.3 | 1.2 (0.8-2.1) |
| Number of IVF cycles | 75 | 108 | |
| Ongoing pregnancies after IVF, n (%) | 21 (17) | 32 (25) | 0.7 (0.4-1.1) |
| % ongoing pregnancy per IVF cycle | 28 | 30 | 0.9 (0.6-1.5) |

treatment group (multiple pregnancy rate 9% per ongoing pregnancy), with three twins and one triplet after IUI-COS (IUI-COS group) and four twins after IVF (Table 2).
In the EM group 364 IUI cycles were started which resulted in 24 ongoing pregnancies (6.6% per started cycle). In the immediate treatment group 661 IUI cycles were started, resulting in 35 ongoing pregnancies (5.3% per started cycle).
In the EM group 75 IVF cycles were started resulting in 21 ongoing pregnancies (28% per started IVF cycle) versus 108 IVF cycles in the immediate treatment group resulting in 32 ongoing pregnancies (30% per started cycle) (Table 3).



## Economic evaluation

Given the comparable ongoing pregnancy rates in the two groups, we did a cost-minimization and focused on the cost-difference. The costs for one cycle of IUI-COS and one cycle of IVF in the Netherlands were calculated at €773 and €2139, respectively (Table I). In the EM group, 364 IUI cycles and 75 IVF cycles resulted in total costs of €442k. In the immediate treatment group, 661 IUI cycles and 108 IVF cycles resulted in total costs of €742k, suggesting a potential saving of €300k in favour of the EM group. The mean estimated costs per couple

in the EM group were €3424 (95% CI €880–€5968) and in the immediate treatment group €6040 (95% CI €4055–€8125), resulting in an estimated saving of €2616 per couple (95% CI €385–€4847). The estimated costs expressed per ongoing pregnancy were €4741 (SD 545) and €8248 (SD 578) for the EM and immediate treatment group, respectively.
To explore the effect of plausible variations in stimulation medication, sensitivity analyses were performed. First, we evaluated the consequence of the use of clomiphene citrate instead of gonadotrophins. This resulted in IUI-COS costs of €445 per cycle instead of the €773 with FSH. With clomiphene citrate use, the saving in the EM group in comparison with the immediate treatment group was still €203k. Subsequently, we evaluated the effect of the use of a high quantity of 1000 IU FSH per IUI cycle. Medication costs for FSH will rise from €334 to €417 per cycle for 800 and 1000 IU, respectively. This resulted in IUI-COS costs of €856 per cycle. If a high quantity of FSH had been used, potential savings for EM would have been higher, up to €325k.

## DISCUSSION

We compared the long-term consequences of EM for 6 months versus immediate start of treatment with IUI-COS in couples with unexplained subfertility and an intermediate prognosis of a natural conception. Three years after randomization, the time to ongoing pregnancy and cumulative ongoing pregnancy rates were comparable in the two groups but initial EM, followed by IUI-COS and IVF in case of no pregnancy, resulted in an average potential saving of more than €2500 per couple.
If female age is under 39 years, as in our study, and the chance of conception without treatment is between 30 and 40%, a certain delay in treatment is thus extremely cost-effective. Our results are in line with a recent publication that found EM to be more cost-effective in patients with unexplained subfertility compared with a first-line treatment of unstimulated IUI cycles or stimulated clomiphene citrate cycles without IUI.[14]
The recently published FASST trial (a randomized clinical trial to evaluate optimal treatment for unexplained infertility: the fast track and standard treatment trial[15]) studied more aggressive treatment protocols in similar patients as our study. The FASTT trial compared three cycles of IUI/clomiphene citrate and three cycles IUI/FSH followed by three IVF cycles versus the short track i.e. three cycles of IUI/clomiphene citrate immediately followed by IVF. It is intriguing to see that women in both studies had a mean age of 33 years and that other baseline characteristics were comparable between both trials. However, the FASTT trial included 18% patients with diagnoses other than unexplained subfertility (hypo-gonadotrophic/hypo-estrogenic or polycystic ovary syndrome) and the overall prognoses for treatment-independent pregnancy were not reported. Despite the differences in aggressiveness of treatment, nearly 75% of all couples undergoing

comprehensive treatment in both studies had a viable pregnancy. Indeed, median time to pregnancy was shorter in the FASST trial. However, in view of the fact that final viable pregnancy rates were comparable and that assisted reproduction technology (ART) has rarely been evaluated against EM, and also in view of the known and unknown side effects of ART, we feel that more comparisons between aggressive forms of ART and milder forms should be made. Until then, subfertile couples should be informed that ART might reduce time to pregnancy but does not increase the overall pregnancy rates. Also, side effects of ART should be discussed with those couples.

The prognostic model of Hunault *et al.* (2004)[4] has not been validated for women over 39 years old and therefore our data may not be generalized to older women. Usually, older women are offered ART earlier, although evidence on the superiority of such a strategy is lacking.

The number of multiple pregnancies was low in our study and equally divided over both treatment groups. We therefore did not include the extra costs of multiple pregnancies in our analysis. The calculated costs were based on health care cost in the Netherlands. As we implemented all items, except the costs of side effects (multiple pregnancies), of the guideline of EURONHEED[7] we believe our outcomes are transferable to other countries.

A strong point of our study is that we followed a strict treatment protocol with intention-to-treat analysis without the influence of commercial interests. Owing to the long period of follow up (3 years), couples were able to complete six cycles of IUI-COS followed by three cycles of IVF, if necessary. Therefore, we feel that this study reflects daily practice and the results should be applicable to all couples with unexplained subfertility and an intermediate prognosis of natural conception.

Our study can be criticized because of the low pregnancy rates in the cycles with IUI-COS. European registers report higher results for IUI-COS but the outcome is clinical pregnancy rate, not ongoing pregnancy rate.[16] However, within the context of clinical trials, other groups also do not report pregnancy rates over 10% per cycle.[1] The European Society of Human Reproduction and Embryology Capri Workshop Group on IUI[17] reported pregnancy rates of 7% with clomiphene citrate-stimulated IUI and 12% with FSH-stimulated IUI. In the same ESHRE report, it is indicated that pregnancy rates per cycle are high enough to merit clomphine citrate-stimulated IUI in couples with unexplained subfertility in lieu of more costly and complex FSH-stimulated IUI, with the risk of multiple pregnancies. In our study, the explanation of the lower pregnancy rates cannot be found in the medication used for ovarian stimulation, because clomiphene citrate was used in only ~11% of the IUI cycles. In the Netherlands only mild stimulation is common: usually IUI is only performed when one or two follicles are present. This 'dose-finding' may lead to cancellation of cycles, mainly in the first two cycles. However, performing IUI with only one or two follicles is in line with the recommendation of a previous report from van Rumste *et al.* (2008)[18] who found that COS resulting in more than two follicles only enhanced multiple pregnancy rates without an actual gain in number of pregnancies. Despite the low pregnancy rates per cycle after

IUI-COS, we found that >70% of the couples in this population eventually achieved an ongoing pregnancy within 3 years, which is, in counselling for EM, very encouraging for the couple.

One limitation of our study is that unfortunately the original data set did not provide us with a complete breakdown of the number of stimulated cycles for which there was only 1 follicle ≥16, 2 follicles ≥16, 3 follicles ≥16 and >3 follicles ≥16 mm. This information would improve our understanding of the low pregnancy rate for stimulated cycles and also of the circumstances which may help to keep the multiple pregnancy rate low.

Our study, in which we limited IUI-COS to couples with intermediate prospects for spontaneous pregnancies, was a multicentre study in 26 centres in The Netherlands, with a representative spectrum of the quality of care in the country. It is important to stress here that we observed more miscarriages in the early treatment group, which either might be a biological phenomenon or a consequence of the more intensive monitoring of treatment cycles, resulting in a higher detection rate.

As far as the economic evaluation is concerned, one could debate whether it is rational to perform a sensitivity analysis comparing the use of clomiphene citrate to the use of FSH in IUI treatment when a difference is found in pregnancy rates. We are convinced that it is very reasonable, since a large meta-analysis found that the difference in pregnancy rates with FSH or clomiphene citrate stimulation was not statistically significant.[19]

By following the strategy of initial EM in couples with unexplained subfertility and an intermediate prognosis, money can be saved and spent more economically. The savings in the EM group in health care costs of €2616 per couple could be made available to the 28% of the couples who did not conceive after 3 years: each of these couples could spend almost an extra €10 000 on additional treatment, which is equivalent to 12 additional cycles of IUI-COS or four cycles of IVF.

In conclusion, in couples with unexplained subfertility and an intermediate prognosis of natural conception, initial EM for 6 months results in a considerable cost-saving without jeopardizing the chances of having a child.

# REFERENCES


1. Fauser BC, Devroey P, Macklon NS. Multiple birth resulting from ovarian stimulation for subfertility treatment. Lancet 2005;365:1807-16.
2. Steures P, van der Steeg JW, Hompes PG, van der Veen F, Mol BW. Intrauterine insemination in The Netherlands. Reprod Biomed Online 2007; 14:110-6.
3. Steures P, van der Steeg JW, Hompes PG, Habbema JD, Eijkemans MJ, Broekmans FJ, Verhoeve HR, Bossuyt PM, van der Veen F, Mol BW; for the 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 randomized clinical trial. Lancet 2006; 368:216-21.
4. Hunault CC, Habbema JD, Eijkemans MJ, Collins JA, Evers JL, te Velde ER. Two new prediction rules for spontaneous pregnancy leading to live birth among subfertile couples, based on the synthesis of three previous models. Hum Reprod 2004; 19:2019-26.
5. van der Steeg JW, Steures P, Eijkemans MJ, Habbema JD, Hompes PG, Broekmans FJ, van Dessel HJ, Bossuyt PM, van der Veen F, Mol BW; for the CECERM study group (Collaborative Effort for Clinical Evaluation in Reproductive Medicine). Pregnancy is predictable: a large-scale prospective external validation of the prediction of spontaneous pregnancy in subfertile couples. Hum Reprod 2007; 22:536-42.
6. Dutch Society of Obstetrics and Gynaecology. http://nvog-documenten.nl.
7. Nixon J, Rice S, Drummond M, Boulenger S, Ulmann P, de Pouvourville G. Guidelines for completing the EURONHEED transferability information checklists. Eur J Health Econ 2009; 10:157-65.
8. Merkus JM. Fertility treatments: possibilities for fewer multiple births and lower costs—the 'Umbrella' study. Ned Tijdschr Geneeskd 2006; 150:1162-64.
9. http://ctg.bit-ic.nl/Nzatarieven/top.do.
10. Weinstein MC, Fineberg HV, Elstein AS, Frazier HS, Neuhauser D, Neutra RR, McNei BJ. Clinical Decision Analysis. Philadelphia: WB Saunders; 1980.
11. Drummond MF, Stoddart GL, Torrance GW. Methods for the Economic Evaluation of Health Care Programmes. Oxford, England: Oxford University Press; 1987.
12. Barber JA, Thompson SG. Analysis of cost data in randomized trials: an application of the non-parametric bootstrap. Stat Med 2000; 19:3219-36.
13. Dankert T, Kremer JA, Cohlen BJ, Hamilton CJ, Pasker-de Jong PC, Straatman H, van Dop PA. A randomized clinical trial of clomiphene citrate versus low dose recombinant FSH for ovarian hyperstimulation in intrauterine insemination cycles for unexplained and male subfertility. Hum Reprod 2007; 22:792-7.
14. Wordsworth S, Buchanan J, Mollison J, Harrild K, Robertson L, Tay C, Harrold A, McQueen D, Lyall H, Johnston L, et al. Clomifene citrate and intrauterine insemination as first-line treatments for unexplained infertility: are they cost-effective? Hum Reprod 2011; 26:369-75.
15. Reindollar RH, Regan MM, Neumann PJ, Levine BS, Thornton KL, Alper MM, Goldman MB. A randomized clinical trial to evaluate optimal treatment for unexplained infertility: the fast track and standard treatment (FASTT) trial. Fertil Steril 2010; 94:888-99.
16. Andersen AN, Goossens V, Ferraretti AP, Bhattacharya S, Felberbaum R, de Mouzon J, Nygren KG; European IVF-monitoring (EIM) Consortium; European Society of Human Reproduction and Embryology (ESHRE). Assisted reproductive technology in Europe, 2004: results generated from European registers by ESHRE. Hum Reprod 2008; 23:756-71.
17. ESHRE Capri Workshop Group. Intrauterine insemination. Hum Reprod Update 2009; 15:265-77.
18. van Rumste MM, Custers IM, van der Veen F, van Wely M, Evers JL, Mol BW. The influence of the number of follicles on pregnancy rates in intrauterine insemination with ovarian stimulation: a meta-analysis. Hum Reprod Update 2008; 14:563-70.
19. Cantineau AE, Cohlen BJ, Heineman MJ. Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with sub fertility (Review). Cochrane Database Syst Rev 2007; 18:CD005356.

Chapter 8

# IVF with planned single embryo transfer versus IUI with ovarian stimulation in couples with unexplained subfertility, an economic analysis

Minouche M.E. van Rumste, Inge M. Custers, Madelon van Wely, Carolien A. Koks, Hans G.I. van Weering, Nicole G.M. Beckers, Gabrielle J. Scheffer, Frank J.M. Broekmans, Peter G.A. Hompes, Monique H. Mochtar, Fulco van der Veen, Ben Willem J. Mol

Reproductive BioMedicine Online; conditionally accepted for publication

# ABSTRACT

Couples with unexplained subfertility are often treated with intra-uterine insemination with ovarian stimulation (IUI-COS), which carries the risk of multiple pregnancies. In couples with unexplained subfertility and a poor prognosis for natural conception, an explorative randomized controlled trial was performed comparing one cycle of in vitro fertilization (IVF) with elective single embryo transfer (eSET) versus three cycles of IUI-COS.

The aim of this study was to assess the economic burden of the treatment modalities. Main 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% in the IVF-eSET group, versus 21% in the IUI-COS group with two and three multiple pregnancies, respectively. The mean cost per included couple was significantly different, 2,781 Euro in the IVF-eSET group and 1,876 Euro in the IUI-COS group. The additional costs per ongoing pregnancy were 2,456 Euro for IVF-eSET. In couples with unexplained subfertility, one cycle of IVF-eSET costed an additional 900 Euro per couple compared to three cycles of IUI-COS, for no increase in ongoing pregnancy rates or decrease in multiple pregnancies. When IVF-eSET results in a 38% ongoing pregnancy rate, IVF would be the preferred treatment.

# INTRODUCTION

In many countries, intra-uterine insemination with controlled ovarian stimulation (IUI-COS) is the first line of treatment in couples with unexplained subfertility. As IUI-COS finds her effectiveness in multiple ovulation, an inevitable side effect of ovarian stimulation is the occurrence of multiple pregnancies with a prevalence varying between 10 to 18% (Brandes et al., 2010; van Rumste et al., 2008; Steures et al., 2007;). Multiple pregnancies are associated with an increased risk for poor outcomes of both mother and children compared to singleton pregnancies, demonstrated for example by an increased rate of preeclampsia or preterm birth (Campbell and Templeton, 2004; The ESHRE Capri Workshop Group, 2000; Pinborg et al., 2004). They also impose a large burden on health care costs, due to the cost of obstetrical and neonatal complications, as well as to the cost of disability in the offspring (De Sutter et al., 2002; Gerris et al., 2004; Lukassen et al., 2004).
We recently conducted an explorative randomized controlled trial that evaluated whether IVF-eSET would lead to a similar pregnancy rate as three cycles of IUI-COS, but with a lower multiple pregnancy rate. This trial suggested that one cycle of IVF-eSET might be as effective as three cycles of IUI-COS as primary treatment (Custers et al., 2011). In view of this finding, costs may play an important role in the decision on one or the other treatment. The aim of our study was therefore to compare the costs of one IVF-eSET cycle versus three IUI-COS cycles in couples with unexplained subfertility.

# MATERIALS AND METHODS

The initial study was performed as a multicenter randomized trial between November 2006 and February 2009. Nine clinics in the Netherlands participated, three University hospitals and six teaching hospitals. The institutional review board of the Academic Medical Centre approved the study, after which there was local approval from the boards of the other participating hospitals. The trial was registered in the clinical trial register as ISRCTN86744378.
All couples had undergone a standard fertility work-up, including assessment of ovulation by basal temperature curve or ultrasound, a tubal patency test and sperm analysis. All couples with unexplained or mild male subfertility, female age between 18 and 38 years and poor fertility prospects, defined as a 12 month prognosis of less than 30% for natural conception according to the model of Hunault (Hunault et al., 2004), were included. They were randomly allocated to one cycle of IVF-eSET followed by one cryo cycle, or to three cycles of IUI-COS. Follow-up ended four months after the first treatment cycle started.
In the IVF-eSET group couples underwent controlled ovarian hyperstimulation after down-regulation with a GnRH agonist in a long protocol with a midluteal start. One

top-quality embryo was transferred on day three. If no top-quality embryo was present, double embryo transfer (DET) was performed. Spare embryos were cryo-preserved on the fourth day (conventional slow freezing) when possible. If the thawed embryo was of good quality, again only one embryo was transferred. The results of the freeze-thaw cycles were also included in this study, providing they were within the timeframe of four months after starting the first treatment. Further details, such as scoring of the quality of the embryo, have been previously described (Custers et al., 2011).

Women in the IUI-COS group underwent controlled ovarian hyperstimulation with 50 to 75IU rFSH (Puregon®, MSD, Oss, the Netherlands). When necessary the dose rFSH was increased. One teaching hospital used 100mg clomiphene citrate for 5 days, starting cycle day three. The goal of ovarian hyperstimulation was to achieve the growth of up to a maximum of three dominant follicles (>18mm). The detailed stimulation protocol and other clinical details for IUI-COS have been previously described (Custers et al., 2011).

The primary outcome was an ongoing pregnancy, defined by an intra-uterine pregnancy with positive heart activity seen by ultrasound at 12 weeks' gestation. We also assessed the number of multiple pregnancies, live birth and financial costs. All analyses were done by intention-to-treat and all randomized couples were included.

## Economic analysis

In the Netherlands, an unlimited number of IUI-COS cycles and up to three cycles of IVF (including cryo-preserved cycles) are covered by health care insurance. The economic analysis was therefore performed from the perspective of the health care institution. We followed the EURONHEED sub-checklist as a guideline for our economic evaluation (Nixon et al., 2009).

We used prices set at November 2010 by the Dutch Health Care Authority (NZa), which were nationwide agreed fixed prices for treatments (http://ctg.bit-ic.nl/Nzatarieven/top.do). The costs for IVF-eSET and IUI-COS included hospital costs, such as clinical and laboratory costs, the specialist fee and the costs of medication. These costs are specified in Table 1. Hospital costs like overhead costs were not included but assumed to be equal. The clinical component includes costs regarding the monitoring of the cycle during treatment, diagnostic tests, visits to the outpatient-clinic, medical equipment, and follow-up of the couple after IUI or embryo transfer in case a pregnancy occurred. The laboratory component includes costs regarding the procedures concerning sperm preparation, in vitro fertilization, embryo scoring and embryo transfer. Medication costs comprises of the total units of rFSH or clomiphene citrate were registered per cycle. Multiple imputations were used in case total units of FSH per cycle were missing. Couples were followed until there was an ongoing pregnancy or until the follow-up period ended. Costs generated by a pregnancy developing beyond 12 weeks' gestation and delivery were not taken into account.

We registered the number of cycles with IVF-eSET and IUI-COS, as well as the ongoing pregnancy rates in both groups. The mean costs per couple per randomized group were calculated. The 95% confidence intervals of the mean costs were estimated by non-parametric bootstrapping to account for the expected skewing of the data.
Cost-effectiveness was defined as the ratio of the sum of the total costs per randomized group divided by the number of couples with an ongoing pregnancy. A scenario analysis was done to explore the cost effectiveness of IVF versus IUI at different ongoing pregnancy rates following IVF using bootstrapping.
To explore the effect of plausible variations in stimulation medication, we performed four sensitivity analyses. First, we calculated the total costs assuming that IUI was performed with clomiphene citrate. Second, total costs were calculated assuming that IUI was performed with the highest dosage of FSH. Third, costs were calculated assuming the lowest dosage of FSH was used in the IVF group. Fourth, costs were calculated using the highest dosage of FSH in the IVF group.

**Table 1.** Specified costs per treatment of IVF or IUI-COS

| | IVF-eSET | IUI |
|---|---|---|
| Hospital component | € 1852.20 | € 436.69 |
| Costs without follicle aspiration and ET | € 1131.37 | |
| Specialist fee | € 332.60 | € 66.58 |
| Medication | | |
| 50mg clomiphene citrate | | € 0.454 |
| 1 IU FSH | € 0.409 | € 0.409 |
| 10,000 IU hCG | € 8.68 | € 8.68 |
| 14 days progesterone | € 14 | |

## Funding

An unconditional grant from Organon, Oss, the Netherlands was received for the initial clinical trial. Patients did not receive compensation for treatment, since IVF and IUI were completely reimbursed by health insurance.



# RESULTS

We randomized 116 couples, of which 58 couples were allocated to IVF-eSET and 58 to IUI-COS (Figure 1). Baseline characteristics of both groups were comparable, with a mean female age of 34 years and duration of subfertility of 2.3 years (Custers et al., 2011). The outcomes per randomized group are shown in Table 2. In the couples treated with IVF-eSET there were 14 ongoing pregnancies (24%). Two of those pregnancies were twin

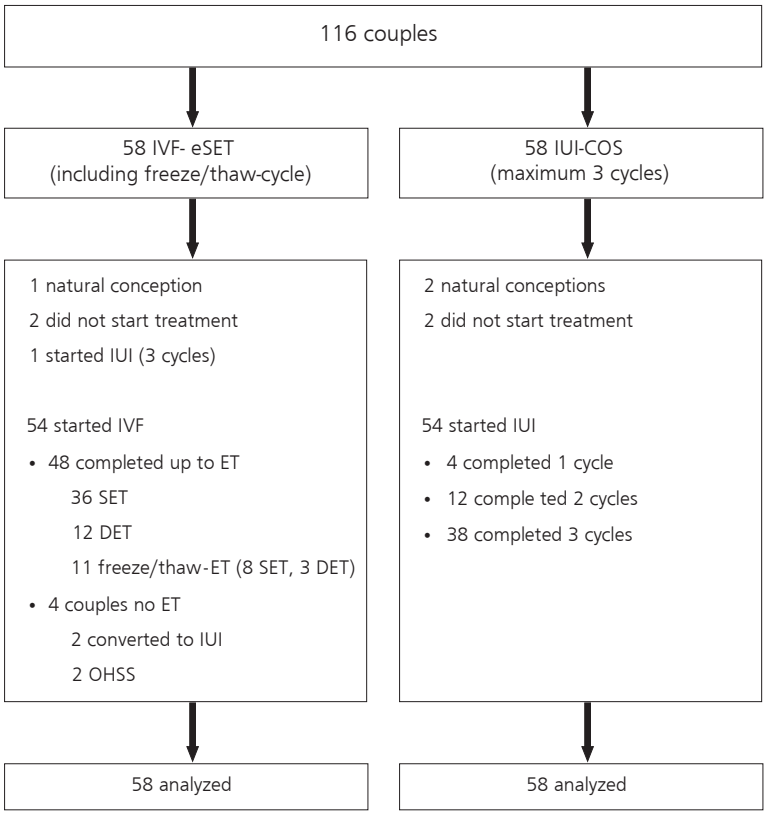



**Figure 1.** Flow chart of randomized couples

pregnancies (multiple pregnancy rate of 14%). Both resulted from transfer of two fresh embryos. In the couples treated with IUI-COS there were 12 ongoing pregnancies (21%), of which two twins and one triplet pregnancy (multiple pregnancy rate of 25%). The triplet pregnancy was reduced to a twin pregnancy and the twins were born at term. All twins were dichorial diamniotic. The pregnancy rates per started treatment cycle were 25.9% for IVF-eSET (54 cycles) and 8.5% for IUI-COS (142 cycles).

As described in the publication on the clinical outcomes of this trial in 74% of all IUI-COS cycles multifollicular growth was achieved. Fourteen IUI-COS cycles were cancelled because of the risk of high order multiple pregnancy (10%). In 116 IUI-COS cycles the number of follicles larger than 15mm was registered. In 59/116 IUI-COS cycles (50.8%) there was more than one follicle larger than 15mm.

## Economic analysis

In 9 couples in the IVF-eSET group and 7 couples in the IUI-COS group the units of FSH used were imputed. In 5 couples receiving IUI-COS treatment, ovarian stimulation was

performed with clomiphene citrate. All of these couples received three cycles of IUI-COS. The number of treatment cycles, amounts of rFSH and clomiphene citrate used and costs per randomization group, are shown in Table 2.

The total costs per randomized group were € 161,327 for the IVF-eSET group and € 108,808 for the IUI-COS group (Table 2), suggesting a potential additional cost of € 52,519 for IVF-eSET. The mean cost per included couple was € 2,781 (95% CI: € 2,293 to € 3,270) in the IVF-eSET group and € 1,876 (95% CI: € 1,462 to € 2,270) in the IUI-COS group ($p<0.01$). The bootstrapped mean difference (95%CI) in costs per couple suggested a cost of € 915 (95% CI 183 to 1,647) for IVF-eSET versus IUI ($p<0.01$). The costs expressed per ongoing pregnancy were € 11,523 and € 9,067, per randomized group respectively. Costs per ongoing pregnancy were € 2,456 higher for IVF-eSET (95% CI 898 to 4,014).

## Sensitivity analysis

In the IVF group the lowest used dosage was 1,050 IU FSH. Applying this low dosage to all couples would have resulted in total costs for the whole randomized group of k€ 141. In this low dose calculation IVF-eSET would still result in € 558 higher cost per couple than IUI-COS.

When assuming the highest used dosage of 3,000 IU FSH for all couples that underwent IVF, the total costs for the whole randomized group would have been k€ 184. In this high dose calculation, the additional costs for IVF-eSET would have been € 1,300 per couple.

Sensitivity analysis showed that if all couples receiving IUI-COS would have received clomiphene citrate, the total costs in the IUI-COS group would have been € 72,617, resulting in a mean cost per included couple of € 1,252. Hence, the potential additional costs per couple would then rise from € 915 to € 1,529 for IVF-eSET.

In the IUI-COS group the highest dosage of FSH was 3,575 IU resulting in a total cost of € 291,703, if this high quantity of FSH would have been used in all IUI-COS cycles. The potential savings per couple after a single IVF-eSET cycle would then be € 2,248. The costs in the two randomized groups would be the same (k€ 155) if a mean dosage of 1,522 IU FSH had been used per IUI-COS cycle by each couple in the IUI-COS group.

## Scenario analysis

We performed a scenario analysis in which we increased the ongoing pregnancy rate in the IVF-eSET group up to 50% (Table 3). IUI-COS was dominant over IVF-eSET at a relative ongoing pregnancy rate of 1.2 or below for IVF-eSET versus IUI-COS. IVF-eSET would be the dominant treatment if the ongoing pregnancy rate would be 1.8 or higher after IVF-eSET versus IUI-COS. In the present study that would relate to a 38% ongoing pregnancy rate after IVF-eSET versus the observed 21% after IUI-COS.

**Table 2.** Outcomes per randomized group

| | IVF-eSET (N=58) | | | | |
|---|---|---|---|---|---|
| | **natural conception** | **IUI** | **IVF** | **cryo-ET** | **total IVF (%)** |
| **clinical outcomes** | | | | | |
| ongoing pregnancies (N) | 1 | 0 | 11 | 2 | 14 (24) |
| multiples (N) | 0 | 0 | 2 | 0 | 2 (14) |
| live birth (N) | 1 | 0 | 11 | 1 | 13 (22) |
| live birth singletons (N) | 1 | 0 | 10 | 1 | 12 (92) |
| live birth twins (N) | 0 | 0 | 1 | 0 | 1 (8) |
| live birth unknown (N) | 0 | 0 | 1 | 0 | 1 (7) |
| **medication** | | | | | |
| cycles rFSH (N) | | 3 | 54 | | 54 |
| total rFSH (IU) | | 1,165 | 98,072 | | 99,237 |
| mean rFSH (IU) | | 388 | 1,816 | | 1,837 |
| cycles CC (N) | | | | | |
| total CC (mg) | | | | | |
| mean CC (mg) | | | | | |
| **costs** | | | | | |
| total costs (€) | | | | | 161,327 |
| mean costs per couple (€) | | | | | 2,781 |
| mean costs per cycle (€) | | | | | 2,933 |
| mean costs per pregnancy (€) | | | | | 11,523 |

**Table 3.** Scenario analysis

| IVF – ongoing pregnancy (%) | IUI – ongoing pregnancy (%) | RR | cost-effectiveness | dominant treatment |
|---|---|---|---|---|
| 24% | 21% | 1.17 | 0.79 | IUI |
| 31% | 21% | 1.5 | 1 | |
| 38% | 21% | 1.83 | 1.24 | IVF |

# DISCUSSION

In couples with unexplained subfertility, we found that IVF-eSET was equally effective as IUI-COS for a similar multiple pregnancy risk, while the mean cost per included couple was € 2,781 (95% CI: € 2,293 to € 3,270) in the IVF-eSET group and € 1,876 (95% CI: € 1,462 to € 2,270) in the IUI-COS group. The additional costs for IVF-eSET per couple were € 915 (95% CI 183 to 1,647) ($p<0.01$) and per ongoing pregnancy € 2,456 (95% CI 898 to 4,014).

| | IUI-COS (N=58) | | | |
|---|---|---|---|---|
| natural conception | IUI1 | IUI2 | IUI3 | total IUI (%) |
| | | | | |
| 2 | 1 | 5 | 4 | 12 (21) |
| 0 | 0 | 2 | 1 | 3 (25) |
| 2 | 1 | 5 | 2 | 10 (17) |
| 2 | 1 | 3 | 1 | 7 (70) |
| 0 | 0 | 2 | 1 | 3 (30) |
| 0 | 0 | 0 | 2 | 2 (17) |
| | | | | |
| | 49 | 45 | 34 | 128 |
| | 30,666 | 34,103 | 23,991 | 88,76 |
| | 626 | 758 | 706 | 963 |
| | 5 | 5 | 5 | 15 |
| | 2,25 | 2,5 | 2,5 | 7,25 |
| | 450 | 500 | 500 | 483 |
| | | | | |
| | | | | 108,808 |
| | | | | 1,876 |
| | | | | 761 |
| | | | | 9,067 |

Our pregnancy rate of 24% in the IVF group was rather low. However, it was comparable to the overall average ongoing pregnancy rate for IVF in the participating clinics (on average 18.7% during the period of this trial for SET and DET). If IVF success rates were higher, like the ones reached in for instance the USA, IVF-eSET would be more cost-effective than IUI-COS. This seems to be feasible, since a cumulative live birth rate, including one freeze-thaw cycle, of 38% was found for IVF-eSET in a systematic review comparing IVF-eSET with IVF-DET (McLernon et al., 2010). Recent developments show that transfer of blastocyst embryos, as compared to day three embryos, will result in a significantly higher live birth rate (Glujovsky et al., 2012). Vitrification of blastocysts results in a significant higher post-thawing survival rate over slow freezing (Kolibianakis et al., 2009). Both modern developments might possibly make IVF the more favourable treatment, but are awaiting assessment through randomized trials.

No pregnancies occurred after IUI-COS with clomiphene citrate, but the number of couples receiving clomiphene citrate in our study was limited to five couples. We feel that they should be included, because of the intention-to-treat analysis and because clomiphene citrate leads to the same pregnancy rates as FSH in IUI-COS (Dankert et al., 2007).

Sensitivity analysis showed that using clomiphene citrate instead of rFSH in all IUI cycles would enlarge the difference in costs for IVF-eSET as compared to IUI-COS. Using 1,522 IU FSH in the IUI-COS group would result in the same costs for IVF-eSET as IUI-COS. The mean use of FSH in IUI cycles found in our study was 580 IU. This is far below the break-even point of 1,522 IU FSH. If all couples included for IUI-COS used FSH, IVF-eSET would still be more costly for the same pregnancy results. Even the lowest dose of medication in IVF-eSET did not alter the fact that IVF-eSET remained more expensive than IUI-COS.

A limitation of our study is the small sample size and the short time horizon of 4 months of the original RCT. We are at present performing a larger study on a similar question (Bensdorp et al., 2009). That study compares similar strategies in two groups of 200 couples over an interval of one year. Moreover, a third arm is added, evaluating IVF treatment in a modified natural cycle (Pelinck et al., 2006), which might lower the costs and therefore might have a better cost-effectiveness.

We realize that health care costs due to multiple pregnancies were not included. However, costs until a gestational age of 12 weeks would be comparable for a multiple pregnancy as compared to a singleton pregnancy. Since the number of multiple pregnancies in both groups was small and comparable, alterations in the results of the economic analysis are not expected. However, we realize that health care for a triplet pregnancy beyond 12 weeks' gestation till weeks after delivery would significantly increase the costs.

In our analysis we did not include the costs made by the couple themselves, which might influence the 'costs per couple'. Since the economic analysis was performed from the perspective of the health care institution, couples included were not asked to keep track of their expenses in so-called cost diaries. These costs include out-of-pocket costs, such as leave of absence, non-prescription drugs and travel expenses (Fiddelers et al., 2009; Reindollar et al., 2010). These costs made outside the health care institution might influence the outcome. In a recent large study cost diaries were included and approximately only 1% of the total costs of couples were due to costs outside the health care institution (Reindollar et al., 2010). Consequently, this would hardly influence the costs per couple as calculated in our study.

Studies on economic analyses on IUI and IVF are scarce. In 2006 a paper was published on the cost-effectiveness of IVF versus IUI followed by IVF (Pashayan et al., 2006). This paper concluded that primary treatment by an IVF cycle would be more cost-effective than first offering IUI followed by IVF. However, this study used pregnancy rates based on previously performed studies or assumptions and used a hypothetical cohort. Also eSET or multiple pregnancies were not taken into account. A second study, the FASST-trial, concluded that IUI with FSH had no additional value to the ART treatment fertility couples received (Reindollar et al., 2010). Although their study seems comparable to ours, their study protocol was different. Both strategies in the FASST-trial included IUI. They compared treatment of IUI with clomiphene citrate followed by IVF (the accelerated arm), with treatment of IUI with clomiphene citrate, followed by IUI with FSH and IVF. The pregnancy rates in FSH-IUI

cycles were comparable to ours (9.8% in the FASST-trial versus 9.6% in our trial), but the women receiving FSH-IUI in the FASST-trial received 150 U FSH per day which is twice as much as in our study. Applying 75 IU FSH would substantially have lowered the costs for FSH stimulated IUI and would result in a more cost-effective therapy. A retrospective cohort study compared one cycle of IVF with two cycles of IUI-COS and concluded that IVF was more effective, but costlier (Chambers et al., 2010). It should be noted that in this study 10% of the included couples with unexplained subfertility tried to conceive for less than 12 months, and thus had a good prognosis for pregnancy. Also, 10% of the couples starting IUI-COS converted to IVF after only one cycle of IUI. These two aspects may have increased healthcare costs. In a randomized controlled trial comparing IUI, IUI-COS, and IVF, for 6 cycles, the cumulative pregnancy rate for IVF was not significantly better than that for IUI (Goverde et al., 2000). IUI was found to be a more cost-effective treatment than IVF. The multiple pregnancy rate in the IVF group was high (21%, including one set of triplets), and does not represent the modern embryo transfer policy of eSET or SET.

We found high multiple pregnancy rates compared to European data published by ESHRE (Ferraretti et al., 2012). Our twin rate after IUI was 25% versus a 10.6% rate (per ongoing pregnancy) in Europe. After IVF-eSET 14% twins were found in our study compared to 20.7% twins after IVF in Europe. If we would implement the European multiple pregnancy rates in our cost-effectiveness analysis, this would result in an even larger difference of cost-effectiveness between IUI-COS and IVF, in favour of IUI. However, using strict SET rather than eSET in IVF, would probably result in a lower multiple pregnancy rate in the IVF arm.

In conclusion, in couples with unexplained subfertility, one cycle of IVF-eSET cost in our setting an additional € 900 per couple compared to three cycles IUI-COS, for no increase in ongoing pregnancy rates or decrease in multiple pregnancies. However, if a clinic has ongoing pregnancy rates of 38% or higher with IVF-eSET, the treatment of choice should be IVF-eSET.

# REFERENCES


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.

Brandes M, Hamilton CJ, Bergevoet KA, de Bruin JP, Nelen WL, Kremer JA. Origin of multiple pregnancies in a subfertile population. Acta Obstet Gynecol Scand 2010;89:1149-54.

Campbell DM, Templeton A. Maternal complications of twin pregnancy. Int J Gynaecol Obstet 2004;84:71-3.

Custers IM, König TE, Broekmans FJ, Hompes PG, Kaaijk E, Oosterhuis J, Mochtar MH, Repping S, van Wely M, Steures P, van der Veen F, Mol BW. Couples with unexplained subfertility and unfavorable prognosis: a randomized pilot trial comparing the effectiveness of in vitro fertilization with elective single embryo transfer versus intrauterine insemination with controlled ovarian stimulation. Fertil Steril 2011;96:1107-11.

De Sutter P, Gerris J, Dhont M. A health-economic decision-analytic model comparing double with single embryo transfer in IVF/ICSI. Hum Reprod 2002;17:2891-6.

The ESHRE Capri Workshop Group. Multiple gestation pregnancy. Hum Reprod 2000;15:1856- 64.

Ferraretti AP, Goossens V, de Mouzon J, Bhattacharya S, Castilla JA, Korsak V, Kupka M, Nygren KG, Nyboe Andersen A; European IVF-monitoring (EIM); Consortium for European Society of Human Reproduction and Embryology (ESHRE). Assisted reproductive technology in Europe, 2008: results generated from European registers by ESHRE. Hum Reprod 2012;27: 2571-84

Fiddelers AA, Dirksen CD, Dumoulin JC, van Montfoort AP, Land JA, Janssen JM, Evers JL, Severens JL. Cost-effectiveness of seven IVF strategies: results of a Markov decision-analytic model. Hum Reprod 2009;24: 1648-55.

Gerris J, De Sutter P, De Neubourg D, Van Royen E, Vander Elst J, Mangelschots K, Vercruyssen M, Kok P, Elseviers M, Annemans L, Pauwels P, Dhont M. A real-life prospective health economic study of elective single embryo transfer versus two-embryo transfer in first IVF/ICSI cycles. Hum Reprod 2004;19:917-23.

http://ctg.bit-ic.nl/Nzatarieven/top.do

Hunault CC, Habbema JD, Eijkemans MJ, Collins JA, Evers JL, te Velde ER. Two new prediction rules for spontaneous pregnancy leading to live birth among subfertile couples, based on the synthesis of three previous models. Hum Reprod 2004;19: 2019-26.

Lukassen HG, Schönbeck Y, Adang EM, Braat DD, Zielhuis GA, Kremer JA. Cost analysis of singleton versus twin pregnancies after in vitro fertilization. Fertil Steril 2004;81:1240-6.

McLernon DJ, Harrild K, Bergh C, Davies MJ, de Neubourg D, Dumoulin JC, Gerris J, Kremer JA, Martikainen H, Mol BW, Norman RJ, Thurin-Kjellberg A, Tiitinen A, van Montfoort AP, van Peperstraten AM, Van Royen E, Bhattacharya S. Clinical effectiveness of elective single versus double embryo transfer: meta-analysis of individual patient data from randomised trials. BMJ 2010;341:c6945. doi: 10.1136/bmj.c6945.

Nixon J, Rice S, Drummond M, Boulenger S, Ulmann P, de Pouvourville G. Guidelines for completing the EURONHEED transferability information checklists. Eur J Health Econ 2009;10: 157-65.

Pashayan N, Lyratzopoulos G, Mathur R. Cost-effectiveness of primary offer of IVF vs. primary offer of IUI followed by IVF (for IUI failures) in couples with unexplained or mild male factor subfertility. BMC Health Serv Res 2006;6: 80.

Pelinck MJ, Vogel NE, Hoek A, Simons AH, Arts EG, Mochtar MH, Beemsterboer S, Hondelink MN, Heineman MJ. Cumulative pregnancy rates after three cycles of minimal stimulation IVF and results according to subfertility diagnosis: a multicentre cohort study. Hum Reprod 2006;21: 2375-83.

Pinborg A, Loft A, Nyboe Andersen A. Neonatal outcome in a Danish national cohort of 8602 children born after in vitro fertilization or intracytoplasmic sperm injection: the role of twin pregnancy. Acta Obstet Gynecol Scand 2004;83:1071-8.

Reindollar RH, Regan MM, Neumann PJ, Levine BS, Thornton KL, Alper MM, Goldman MB. A randomized clinical trial to evaluate optimal treatment for unexplained infertility: the fast track and standard treatment (FASTT) trial. Fertil Steril 2010;94: 888-99.

van Rumste MM, Custers IM, van der Veen F, van Wely M, Evers JL, Mol BW. The influence of the number of follicles on pregnancy rates in intrauterine insemination with ovarian stimulation: a meta-analysis. Hum Reprod Update 2008;14:563-70.

Steures P, van der Steeg JW, Hompes PGA, van der Veen F, Mol BWJ. Intrauterine insemination in The Netherlands. Reprod Biomed Online 2007;14:110-116.

# 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.

Chapter 9

# Samenvatting en discussie

# NEDERLANDSE SAMENVATTING

Bij koppels met een kinderwens bij wie het niet lukt om binnen de periode van een jaar zwanger te worden is sprake van subfertiliteit. In Nederland wordt een op de zes koppels hiermee geconfronteerd.[1] Deze definitie doet dus geen uitspraak over de mogelijkheid of onmogelijkheid alsnog spontaan zwanger te worden. Het doel van voortplantingsgeneeskunde is hulp te bieden aan deze koppels. In eerste instantie ondergaat het koppel onderzoeken om een diagnose te vinden voor hun subfertiliteit. Bij een deel van deze koppels blijft de oorzaak echter onverklaard.

Empirische vruchtbaarheidsbehandelingen die mogelijk hulp bieden bij deze koppels, door (meer) gameten dichter bij elkaar te brengen, zijn ovariële stimulatie met intra-uteriene inseminatie (COS-IUI) of in-vitro fertilisatie (IVF).[2-4] De belangrijkste factor op de zwangerschapskans bij koppels met onverklaarde subfertiliteit is de ovariële stimulatie.[5] Bij ovariële stimulatie worden met behulp van hormonen de eierstokken aangezet tot het uitrijpen van meerdere eicellen. Deze ovariële stimulatie heeft als risico dat er een ovarieel hyperstimulatie syndroom (OHSS) ontstaat of een meerling zwangerschap.[6]
OHSS kan gepaard gaan met een trombo-embolische complicatie en kan zelfs levensbedreigend zijn.[7,8]

Meerling zwangerschappen resulteren in hogere medische risico's van moeder en kinderen, zoals bloedarmoede, preeclampsie, vroeggeboorte, lager geboortegewicht, handicap bij een van de kinderen, en daarmee ook in hogere kosten voor de gezondheidszorg.[9-11] De meest effectieve manier om meerling zwangerschappen ten gevolge van vruchtbaarheidsbehandelingen te voorkomen, is door geen behandeling met ovariële stimulatie toe te passen, of door één eicel te laten uitrijpen, waardoor de kans op een meerling zwangerschap terug wordt gebracht tot het niveau van de natuurlijk ontstane meerling. Anderzijds dient het reduceren van de kans op een meerling altijd te worden afgewogen tegen een mogelijke afname van de kans op zwangerschap.

Dit proefschrift behandelt onderdelen van de preventie van OHSS en meerling zwangerschappen, en de economische analyse van vruchtbaarheidsbehandelingen bij koppels met onverklaarde subfertiliteit.

**Hoofdstuk 1** *beschrijft de inhoud en de doelstellingen van dit proefschrift.*

**Hoofdstuk 2** *presenteert een meta-analyse over het behandeleffect in gerandomiseerde klinische onderzoeken in de voortplantingsgeneeskunde, waarbij klinische zwangerschap als uitkomstmaat vergeleken worden met geboorte van een levend kind.*

Het doel van dit onderzoek was om te vergelijken of de uitkomstmaten klinische zwangerschap en levend geboren kind een verschillend resultaat opleverden voor de behandelgroep en controle groep in het betreffende onderzoek. Gecontroleerde gerandomiseerde onderzoeken (RCTs) in de voortplantingsgeneeskunde, die gevonden werden in systematische reviews zoals gepubliceerd in de Cochrane Library, werden geanalyseerd. Indien het onderzoek zowel klinische zwangerschap als geboorte van een levend kind rapporteerde werd het onderzoek geïncludeerd. Voor elk individuele onderzoek werd de data over klinische zwangerschap en levend geboren kind geëxtraheerd. Voor ieder onderzoek werd de uitkomst vergeleken door de kappa-waarde te berekenen (statistisch significant effect van behandeling of niet) en door het vergelijken de ratio van de odds ratio (ROR). Er werden 67 systematische reviews gevonden. Hiervan rapporteerden er 42 over zwangerschap èn levend geboren kind. Deze 42 reviews bevatte 654 RCTs, waarvan er 143 (22%) zowel zwangerschap als levend geboren kind rapporteerden als uitkomstmaat. De kans op een miskraam was vergelijkbaar in de behandelgroep en de controle groep. In de 143 RCTs bleek de conclusie gebaseerd op zwangerschapskans en kans op een levend geboren kind vergelijkbaar (kappa-waarde van 0,81; 95% betrouwbaarheidsinterval (BI), 0,68 tot 0,94). De odds ratios, voor het inschatten van het behandeleffect van de te bestuderen behandeling, van zwangerschap en levend geboren kind waren eveneens vergelijkbaar (ROR 1,01; 95% BI 0,9 tot 1,12). Concluderend zijn er slechts weinig RCTs in voortplantingsgeneeskunde die levend geboren kind als primaire uitkomstmaat hadden. Conclusies over de effectiviteit van een behandeling veranderen niet wanneer klinische zwangerschap of een levend geboren kind als uitkomstmaat genomen wordt.

**Hoofdstuk 3** *evalueert of het bepalen van serum oestradiol van toegevoegde waarde is voor de IVF uitkomsten in vergelijking met het alleen echoscopisch vervolgen van de gestimuleerde cycli tijdens IVF en IVF-ICSI behandelingen.*
Er werd een meta-analyse verricht. Gecontroleerde gerandomiseerde onderzoeken (RCTs) bij vrouwen die ovariële stimulatie tijdens een IVF, dan wel IVF-ICSI behandeling ondergingen, waarin echoscopie met bepaling van de serum oestradiol concentraties werden vergeleken met alleen echoscopie, werden in dit onderzoek opgenomen. We vonden 1.119 potentiële onderzoeken, maar de meeste van hen bestudeerden niet de gewenste vergelijking. Slechts twee RCTs voldeden aan de inclusie criteria. Hierin werden 411 vrouwen beschreven, die gecontroleerde ovariële stimulatie ondergingen. De primaire uitkomstmaat levend geboren kind werd in beide onderzoeken niet gerapporteerd. Een onderzoek rapporteerde de klinische zwangerschapskans per vrouw (33% ten opzichte van 31%; relatief risico (RR) 1,07, 95%BI 0,77 tot 1,49). Het tweede onderzoek rapporteerde de klinische zwangerschapskans per verkregen eicel (22% ten opzichte van 25%). In beide onderzoeken was er geen significant verschil tussen de echoscopie met oestradiol groep en de groep met alleen echoscopie, betreffende het gemiddelde aantal verkregen eicellen (gewogen gemiddelde verschil -0,55, 95%BI 1,79 tot 0,69) en het voorkómen van

OHSS (RR 0,73, 95%BI 0,30 tot 1,78). We concluderen dat het niet aantoonbaar is dat het effectiever is (of minder effectief) om echoscopie te combineren met het bepalen van serum oestradiol om de zwangerschapskans of het risico op OHSS te bepalen.

**Hoofdstuk 4** *beschrijft de relatie van het aantal follikels in ovarieel gestimuleerde IUI cycli met de kans op een doorgaande zwangerschap en de kans op een meerlingzwangerschap.* Er werd een retrospectief cohort onderzoek verricht bij alle koppels met onverklaarde subfertiliteit die COS-IUI ondergingen. Driehonderd koppels die in de periode augustus 1993 tot april 2004 in het Academisch ziekenhuis te Maastricht werden behandeld met COS-IUI werden geïncludeerd. Alleen de eerste behandelcyclus werd geanalyseerd voor de vergelijking van het aantal follikels met de bijbehorende zwangerschapskans. Er werd geen significant verschil gevonden in doorgaande zwangerschapskans tussen vrouwen met een, twee, drie of vier follikels (P= 0,54). In de vrouwen met twee of meer follikels bleek er echter sprake te zijn van 12 meerlingzwangerschappen uit 73 zwangerschappen. Wij concludeerden dat bij het stimuleren van meer dan één follikel, in COS-IUI in koppels met onverklaarde subfertiliteit, de zwangerschapskans niet werd vergroot, maar dat wel het risico op een meerlingzwangerschap toenam. In de eerste vier cycli bleef het risico op een meerlingzwangerschap bestaan zolang er sprake was van multifolliculaire stimulatie. De conclusie van dit hoofdstuk is dat, om het aantal meerlingen terug te brengen, monofolliculaire groei beoogd dient te worden in IUI cycli bij koppels met onverklaarde subfertiliteit.

**Hoofdstuk 5** *presenteert een systematisch review en meta-analyse over de relatie tussen het aantal follikels en zwangerschapskansen bij IUI.*
Relevante onderzoeken over IUI behandelingen die het aantal follikels per cyclus rapporteerden werden geïncludeerd. Mantel-Haenszel gecombineerde odds ratios en risico verschillen met 99% betrouwbaarheidsintervallen werden berekend voor zwangerschapskansen en meerling zwangerschapskansen. Veertien onderzoeken werden geïncludeerd. Zij rapporteerden over 11.599 cycli. De zwangerschapskans voor één follikel was 8,4% en voor meerdere follikels 15%. De gecombineerde odds ratio voor zwangerschap na twee follikels, in vergelijking tot één follikel, was 1,6 (99%BI 1,3 tot 2). Voor drie en vier follikels, in vergelijking tot één follikel, was de gecombineerde odds ratio voor beiden 2. De kans op een zwangerschap nam toe met 5%, 8% en 8% wanneer er respectievelijk twee, drie of vier follikels gestimuleerd werden, in vergelijking met één follikel. De gecombineerde odds ratio voor meerlingzwangerschap na twee follikels in vergelijking tot een follikel was 1,7 (99%BI 0,8 tot 3,6). Voor drie en vier follikels, in vergelijking tot één follikel, was de gecombineerde odds ratio voor meerling zwangerschap respectievelijk 2,8 en 2,3. Het risico op een meerlingzwangerschap bij twee, drie of vier follikels nam toe met 6, 14 en 10% ten opzichte van één follikel. Het absolute meerlingpercentage bij een follikel was 0,3% en bij meerdere follikels 2,8%. We concluderen dat IUI met meerdere follikels is

geassocieerd met een toename in de zwangerschapskans. In behandelingen met drie of vier follikels is het risico op een meerlingzwangerschap verhoogd, zonder dat de kans op een zwangerschap substantieel toeneemt. Daarom zou er in COS-IUI behandelingen niet meer dan twee follikels gestimuleerd dienen te worden. Als veiligheid voorop staat zou IUI het best worden toegepast bij één follikel. Twee follikels kunnen echter worden geaccepteerd, zolang het paar goed voorgelicht wordt over de risico's van een tweelingzwangerschap.

**Hoofdstuk 6** *behandelt de vraag of onderzoeken gericht op behandelingen om meerling zwangerschappen te voorkomen, voldoende onderscheidend vermogen hebben om enige afname in het aantal meerling zwangerschappen aan te tonen.*
In de Menstrual Disorders and Subfertility Group database van de Cochrane Library werd gezocht naar gecontroleerde gerandomiseerde onderzoeken (RCTs) die rapporteerden over meerling zwangerschappen. Gegevens over de grootte van de onderzoeksgroep, berekening van de vereiste groepsgrootte, meerling zwangerschappen en levend geboren meerlingen werden verzameld. Voor ieder onderzoek werd berekend hoe groot de onderzoeksgroep diende te zijn, om een reductie van de helft van het aantal meerling zwangerschappen aan te tonen (met een power van 80%, 95%BI). Dit is het minimale belangrijk klinisch verschil (MID). We vonden 83 reviews die 904 RCTs samenvatten en analyseerden, die rapporteerden over zwangerschap na een vruchtbaarheidsbehandeling. Tien reviews met daarin 95 RCTs evalueerden behandelingen die gericht waren op het voorkómen van meerling zwangerschappen. Van deze 95 RCTs waren er 9 voldoende groot om een verschil in de kans op een meerling zwangerschap aan te kunnen tonen (9,5%). De overige 73 reviews includeerden 809 RCTs met meerling zwangerschap als secundaire uitkomstmaat. Hiervan rapporteerden er 176 RCTs over meerling zwangerschappen (22%). Slechts 15 van deze 176 RCTs waren voldoende groot om de MID aan te tonen (8,5%). We kunnen samenvatten dat een zeer groot aantal gepubliceerde klinische onderzoeken in de voortplantingsgeneeskunde niet voldoende onderscheidend vermogen hebben om conclusies te trekken ten aanzien van meerling zwangerschappen. De veranderingen in de dagelijkse praktijk van vruchtbaarheidsbehandelingen die tot doel hebben om meerling zwangerschappen te voorkomen zijn dan ook niet gebaseerd op overtuigende gegevens.

**Hoofdstuk 7** *presenteert de lange termijn uitkomsten en economische evaluatie van een gerandomiseerd klinisch onderzoek dat directe behandeling met COS-IUI vergelijkt met zes maanden afwachtend beleid.*
Een eerder onderzoek, in koppels met onverklaarde subfertiliteit en een matige prognose op een spontane zwangerschap, toonde aan dat direct starten met COS-IUI behandeling niet leidde tot een toename in de kans op een doorgaande zwangerschap in vergelijking met een afwachtend beleid gedurende zes maanden.[12] Na dit onderzoek werden de koppels behandeld volgens locaal protocol, meestal COS-IUI gevolgd door IVF. Tot drie jaar na randomisatie werden koppels gevolgd en werden zwangerschappen en kosten

geregistreerd. De primaire uitkomstmaat was tijd tot doorgaande zwangerschap. Secundaire uitkomstmaat was behandelkosten. Intention-to-treat analyse werd toegepast. De economische analyse werd uitgevoerd vanuit het perspectief van de gezondheidszorg. De tijd tot een doorgaande zwangerschap was niet verschillend tussen de twee groepen (log-rank test P=0,98). De mediane tijd tot een zwangerschap was 13 maanden (95%BI 8 tot 18) in de afwachtende groep en 14 maanden (95%BI 10 tot 18) in de groep met directe behandeling. Cumulatieve doorgaande zwangerschapskansen waren 72% voor de afwachtende groep en 73% voor de groep met directe behandeling (relatief risico 0,99, 95%BI 0,85 tot 1,1). Geschatte gemiddelde kosten per koppel waren € 3.424 (95%BI € 880 tot € 5.968) in de afwachtende groep en € 6.040 (95%BI € 4.055 to € 8.125) in de groep met directe behandeling, resulterend in een geschatte besparing van € 2.616 per koppel (95%BI € 385 to € 4.847) ten behoeve van afwachtende groep. Als conclusie stellen wij, dat bij koppels met onverklaarde subfertiliteit en een matige prognose op een spontane zwangerschap, het starten met 6 maanden afwachtend beleid leidt tot een kostenbesparing zonder dat er een vermindering of vertraging is in de kans op een zwangerschap.

**Hoofdstuk 8** *beschrijft de economische analyse van een gerandomiseerde klinische pilot-onderzoek waarbij een cyclus IVF met het electief terugplaatsen van een embryo (IVF-eSET) wordt vergeleken met drie cycli COS-IUI in koppels met een ongunstige op een spontane zwangerschap.*

Koppels met onverklaarde subfertiliteit of een milde mannelijke factor werden geïncludeerd. Een cyclus IVF-eSET, inclusief cryo-cycli van ingevroren en ontdooide embryo's, versus drie cycli COS-IUI werden vergeleken binnen een periode van vier maanden. Bij IVF-eSET wordt één top-kwaliteit embryo teruggeplaatst, maar in afwezigheid van zo'n top-kwaliteit embryo, worden er twee embryo's teruggeplaatst. De uitkomstmaten waren doorgaande zwangerschapskansen en kosten. Er werden willekeurig 58 koppels toegewezen tot IVF-eSET en 58 koppels tot COS-IUI. De doorgaande zwangerschapskansen waren 24% (14 van de 58 koppels) in de groep met IVF-eSET versus 21% (12 van de 58 koppels) in de groep met COS-IUI. In de IVF-eSET groep traden 2 meerling zwangerschappen op en in de COS-IUI groep 3 meerling zwangerschappen. In 25% van de IVF cycli werd niet één, maar werden twee embryo's terug geplaatst. De gemiddelde kosten per koppel waren significant verschillend, € 2.781 in de IVF-eSET groep en € 1.876 in de COS-IUI groep. Het verschil in kosten per doorgaande zwangerschap was € 2.456 in het voordeel van de COS-IUI groep. Concluderend, in koppels met onverklaarde subfertiliteit, resulteert een cyclus IVF-eSET in bijkomende kosten van € 900 per koppel in vergelijking tot drie cycli COS-IUI zonder een toename in een doorgaande zwangerschapskans of een afname in het aantal meerling zwangerschappen. Wanneer COS-IUI in 24% zou leiden tot een doorgaande zwangerschap, dan zou IVF-eSET bij een doorgaande zwangerschap van 38% de dominante behandeling zijn.

# KLINISCHE IMPLICATIES

Koppels met de diagnose onverklaarde subfertiliteit hebben goede zwangerschapskansen als de vrouw jonger is dan 38 jaar.[12,13] Sommige koppels, maar ook artsen, denken dat de tijd totdat ze zwanger zijn korter wordt wanneer direct gestart wordt met vruchtbaarheidsbehandelingen. Deze behandelingen verhogen echter het risico op OHSS en meerling zwangerschappen. Koppels kunnen proberen spontaan zwanger te worden zonder deze verhoogde risico's, maar het zou meer tijd kunnen kosten totdat ze zwanger zijn.

Dit proefschrift toont aan dat wanneer koppels met een onverklaarde subfertiliteit en een matige kans op een zwangerschap (30 tot 40% kans op een spontane zwangerschap in de komende 12 maanden) in eerste instantie een spontane zwangerschap nastreven gedurende 6 maanden, dit een behoorlijke kostenbesparing oplevert zonder een vertraging in het optreden van de zwangerschap. Bij een spontane zwangerschap is het risico op een meerling zwangerschap extreem laag.[14] Verder vonden we dat een cyclus IVF-eSET in vergelijking met COS-IUI niet leidde tot een toename van de doorgaande zwangerschapskansen. Vooralsnog dienen koppels met onverklaarde subfertiliteit eerst geadviseerd te worden COS-IUI te ondergaan, alvorens te starten met IVF-eSET.
Indien over een langere periode getracht wordt spontaan zwanger te worden, gevolgd door behandelingen met COS-IUI in plaats van direct te starten met IVF-eSET, zal dit mogelijk resulteren in grote besparingen in de gezondheidszorg. Het geld dat deze besparingen oplevert zou dan gebruikt kunnen worden voor de koppels die daadwerkelijk vruchtbaarheidsbehandelingen nodig hebben.
Zodra het besluit genomen wordt om te starten met vruchtbaarheidsbehandelingen in de vorm van COS-IUI, zou gestreefd moeten worden naar het stimuleren van twee follikels om de kans op een zwangerschap te vergroten met een acceptabel risico voor een tweeling. Wanneer men meerling zwangerschappen probeert te vermijden, moet men altijd rekening houden met het feit dat de meeste koppels met subfertiliteit zich niet laten afschrikken door een tweeling zwangerschap. Hoewel ze de risico's kennen die een meerling zwangerschap met zich meebrengt, prefereren koppels die IVF ondergaan de terugplaatsing van twee embryo's boven een embryo.[15,16] De meest uitdagende taak voor de dokter die subfertiele koppels behandelt, ligt dan ook in voorlichting. Voorlichting betreffende de periode tot een zwangerschap, de voordelen (zwangerschapskansen) en de risico's van vruchtbaarheidsbehandelingen.

# TOEKOMSTIG ONDERZOEK

We hebben gevonden dat het gebruik van standaard technieken van meta-analyse niet altijd antwoord kan geven op de uitkomsten van verschillende vruchtbaarheidsbehandelingen. Dit komt doordat definities van zwangerschap verschillend waren of doordat de uitkomstmaat meerling zwangerschap zeer slecht gerapporteerd werd. Het bewijs om vruchtbaarheidsbehandelingen toe- of aan te passen zodat er minder meerling zwangerschappen op zouden treden lijkt vooralsnog te ontbreken. Wanneer getracht wordt om vruchtbaarheidsbehandelingen te vergelijken, betreffende meerling zwangerschappen, zou het mogelijk zijn om met netwerk meta-analyse de beschikbare data te combineren.[17] Een netwerk meta-analyse vergelijkt meerdere behandelingen, waarbij zowel directe vergelijkingen van behandeling in gerandomiseerde klinische onderzoeken als indirecte vergelijkingen tussen onderzoeken worden toegepast, gebaseerd op een zelfde vergelijkingsmaat.

Tevens dient men in gedachten  te houden dat gerandomiseerde klinische onderzoeken in opzet niet ontworpen zijn om de veiligheid van een behandeling te testen. Ze onderzoeken de effectiviteit van de behandeling. De veiligheid van een behandeling zou mogelijk beter in grote cohort onderzoeken of patiënt-controle onderzoeken getoetst worden.

Met toenemende druk op de gezondheidszorg, maar met minder geld en afnemende middelen, is het voor klinisch werkende dokters belangrijk om zicht te hebben op de economische consequenties die hun ingestelde behandelingen hebben. Economische evaluatie is de vergelijkende analyse van alternatieve behandelingen in termen van de kosten en consequenties die deze behandelingen met zich mee brengen.[18] Kosten-minimisatie analyse evalueert de kosten wanneer de interventies gelijke resultaten oplevert. Omdat het moeilijk is om deze gelijkheid aan te tonen wordt de kosten-minimisatie analyse niet langer aanbevolen. De kosten-effectiviteit analyse combineert de kosten met de opbrengsten, de klinische uitkomsten, waarbij de behandelingen vergeleken worden. Economische evaluaties van behandelingen in de gezondheidszorg schijnen moeilijk uit te voeren.[19] In de economische analyses binnen de voortplantingsgeneeskunde zoals gepubliceerd in de laatste 15 jaar, worden de methodologische standaarden zelden geïmplementeerd.[20] Kosten-effectiviteit analyses kunnen worden verbeterd door het helder en transparant weergeven van ontwerp van het onderzoek, speciaal in termen van verwachting en onderzoeksperiode, als door openheid in waarden gebruikt voor kosten, waarschijnlijkheden en uitkomsten. Verder dienen sensitiviteit analyses toegepast te worden om onzekerheden in de gevonden uitkomsten te testen.[20,21] Economische onderzoeken zouden een standaard voor economische evaluatie moeten volgen om het

rapporteren van economische evaluaties in de gezondheidszorg te optimaliseren. Zulke standaarden zijn recent gepubliceerd.[19,21]

In de huidige literatuur is er geen bewijsmateriaal om de ene vruchtbaarheidsbehandeling boven de ander te prefereren, zodra meerling zwangerschappen en kosten-effectiviteit worden meegewogen. De INeS studie, uitgevoerd bij koppels met onverklaarde subfertiliteit, vergelijkt COS-IUI met IVF-eSET en met IVF in de natuurlijke cyclus.[22] Hopelijk geeft dit onderzoek antwoord op de vraag welke vruchtbaarheidsbehandeling kosten-effectiever is.
We adviseren om de kosten-effectiviteit van vruchtbaarheidsbehandelingen te onderzoeken ten opzichte van een afwachtend beleid, omdat de kans op een spontane zwangerschap hoger blijft dan verwacht, ondanks het verstrijken van de tijd. Op deze manier kan getoetst worden of een behandeling daadwerkelijk van toegevoegde waarde is voor het koppel.

# REFERENTIES


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.

# Abbreviations

# ABBREVIATIONS

| | |
|---|---|
| ART | assisted reproductive technologies or assisted reproduction techniques |
| CC | clomiphene citrate |
| CENTRAL | Cochrane Central Register of Controlled Trials |
| CI | confidence interval |
| COS | controlled ovarian stimulation |
| DET | double embryo transfer |
| EM | expectant management |
| eSET | elective single embryo transfer, one top-quality embryo is transferred; if no top-quality embryo is present, double embryo transfer is performed |
| FSH | follicle stimulating hormone |
| hCG | human chorionic gonadotrophin |
| hMG | human menopausal gonadotrophins |
| HR | hazard rate |
| ICSI | intracytoplasmic sperm injection |
| IUI | intra-uterine insemination |
| IVF | in vitro fertilisation |
| MDSG | Menstrual Disorders and Subfertility Group of the Cochrane |
| MID | minimally important difference |
| MPR | multiple pregnancy rate |
| N | number |
| n.s. | not stated |
| OHSS | ovarian hyperstimulation syndrome |
| OI | ovulation induction |
| OR | odds ratio |
| PMSD | progressively motile sperm density |
| PR | pregnancy rate |
| RCT | randomised controlled trial |
| RD | risk differences |
| Revman | Review Manager |
| ROR | ratio of the odds ratios |
| RR | relative risk |
| US | ultrasonography |
| WMD | weighted mean difference |

List of co-authors and their affiliations

# LIST OF CO-AUTHORS AND THEIR AFFILIATIONS

N.G.M. Beckers, Department of Reproductive Medicine, Erasmus Medical Centre, Rotterdam.

Prof. Dr. S. Bhattacharya, Department of Obstetrics and Gynaecology, Aberdeen Maternity Hospital, Aberdeen, UK.

Prof. Dr. P.M. Bossuyt, Departmant of Clinical Epidemiology, Biostatistics and Bio-informatics, Academic Medical Centre, Amsterdam.

J.J.A. Bosteels, Department of Obstetrics and Gynaecology, Imelda Hospital, Bonheiden, Belgium/ CEBAM- the Centre for evidence-based medicine, Belgian Branch of the Cochrane Collaboration, Academic Center for General Practice, Leuven, Belgium.

Prof. Dr. F.J.M. Broekmans, Division of Reproductive Medicine, Department of Obstetrics and Gynaecology, UMC, Utrecht.

J.F. Clarke, Department of Obstetrics and Gynaecology and National Women's Health, University of Auckland, Auckland, New Zealand.

Dr. I.M. Custers, Department of Obstetrics and Gynaecology, Academic Medical Centre, Amsterdam.

Dr. T.J.H.M. van Dessel, Department of Obstetrics and Gynaecology, TweeSteden Ziekenhuis, Tilburg.

Dr. J.C.M. Dumoulin, Center for Reproductive Medicine, Department of Obstetrics and Gynaecology, Maastricht University Medical Centre, Maastricht.

Dr. M.J.C. Eijkemans, Julius Centrum, Universtity Medical Centre Utrecht.

Prof. Dr. J.L.H. Evers, Center for Reproductive Medicine, Department of Obstetrics and Gynaecology, Maastricht University Medical Centre, Maastricht.

Prof. Dr. C.M. Farquhar, Department of Obstetrics and Gynaecology and National Women's Health, University of Auckland, Auckland, New Zealand.

Dr. J.E. den Hartog, Center for Reproductive Medicine, Department of Obstetrics and Gynaecology, Maastricht University Medical Centre, Maastricht.

P. Herbison, Department of Preventive and Social Medicine, Dunedin School of Medicine, Dunedin, New Zealand

Dr. P.G.A. Hompes, Division of Reproductive Medicine, Department of Obstetrics and Gynaecology, Vrije Universiteit Medical Centre, Amsterdam.

Ass.Prof. Dr. N.P. Johnson, Department of Obstetrics and Gynaecology and National Women's Health, University of Auckland, Auckland, New Zealand.

Dr. C.A.M. Koks, Department of Obstetrics and Gynaecology, Máxima Medical Centre, Veldhoven.

I. Kwan, National Collaborating Centre For Women's and Children's Health, Royal College of Obstetricians and Gynaecologists, London, UK.

Prof. Dr. J.A. Land, Department of Obstetrics and Gynaecology, University Medical Centre Groningen, Groningen.

A. McNeil, BMJ Knowledge, BMJ Publishing Group, London, UK.

Dr. M.H. Mochtar, Centre for Reproductive Medicine, Academic Medical Centre, Amsterdam.

Prof. Dr. B.W.J. Mol, Department of Obstetrics and Gynaecology, Academic Medical Centre, Amsterdam/ Máxima Medical Centre, Veldhoven.

Dr. C.N.M. Renckens, Retired, worked at the Department of Obstetrics and Gynaecology, Westfries Gasthuis, Hoorn.

Dr. G.J. Scheffer, Department of Obstetrics and Gynaecology, Gelre Hospital, Apeldoorn.

Dr. J.W. van der Steeg, Department of Obstetrics and Gynaecology, Jeroen Bosch Hospital, Den Bosch.

Dr. P. Steures, Department of Obstetrics and Gynaecology, St. Elisabeth Hospital, Tilburg.

Prof. Dr. F. van der Veen, Centre for Reproductive Medicine, Academic Medical Centre, Amsterdam.

H.G.I. van Weering, Department of Obstetrics and Gynaecology, Rode Kruis Hospital, Beverwijk

Dr. M. van Wely, Centre for Reproductive Medicine, Academic Medical Centre, Amsterdam.

# Publications

# PUBLICATIONS

**van Rumste MM**, Custers IM, van Wely M, Koks CA, van Weering HG, Beckers NG, Scheffer GJ, Mochtar MH, Broekmans FJ, Hompes PG, van der Veen F, Mol BW. IVF with planned single embryo transfer versus IUI with ovarian stimulation in couples with unexplained subfertility, an economic analysis. Conditionally accepted for publication in Reproductive Biomedicine Online.*

Sigterman TA, Monen L and **van Rumste MM**. Fatale afloop na ovarieel hyperstimulatiesyndroom bij in-vitro fertilisatie. NTOG 2012; 125:393-6.

Stegen C, **van Rumste MM**, Mol BW, Koks CA. The value of chromosomal analysis in oligozoospermic men. Fertil Steril 2012; 98:1438-42.

Custers IM and **van Rumste MM**, van der Steeg JW, van Wely M, Hompes PG, Broekmans FJ, Renckens CNM, Eijkemans MJ, van Dessel TJ, van der Veen F, Mol BW, Steures P for 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.*

Penninx JP, Mol BW, Engels R, **van Rumste MM**, Kleijn C, Koks CA, Kruitwagen RF, Bongers MY. Bipolar radiofrequency endometrial ablation compared with hydrothermablation for dysfunctional uterine bleeding: a randomized controlled trial. Obstet Gynecol 2010; 116:819-26.

Clarke JF, **van Rumste MM**, Farquhar CM, Johnson NP, Mol BW, Herbison P. Measuring outcomes in fertility trials: can we rely on clinical pregnancy rates? Fertil Steril 2010; 94:1647-51.*

**van Rumste MM**, Custers IM, van der Veen F, van Wely M, Evers JL, Mol BW. Does the number of follicles influence pregnancy rates in intrauterine insemination with mild ovarian hyperstimulation: a meta-analysis. Hum Reprod Update 2008; 14:563-70.*

Kwan I, Bhattacharya S, McNeil A, **van Rumste MM**. Monitoring of stimulated cycles in assisted reproduction (IVF and ICSI). Cochrane Database Syst Rev 2008 (2): CD005289. Review.*

**van Rumste MM**, den Hartog JE, Dumoulin JC, Evers JL, Land JA. Is controlled ovarian stimulation in intrauterine insemination an acceptable therapy in couples with unexplained non-conception in the perspective of multiple pregnancies?
Hum Reprod 2006; 21:701-4.*

**van Rumste MM**, Evers JL, Farquhar CM. ICSI versus conventional techniques for oocyte insemination during IVF in patients with non-male factor subfertility: a Cochrane review. Hum Reprod 2004; 19:223-7.

**van Rumste MM**, Evers JL, Farquhar CM. Intra-cytoplasmic sperm injection versus conventional techniques for oocyte insemination during in vitro fertilisation in patients with non-male subfertility. Cochrane Database Syst Rev. 2003;(2): CD001301.

**van Rumste MM**, Evers JL, Farquhar CM, Blake DA. Intra-cytoplasmic sperm injection versus partial zona dissection, subzonal insemination and conventional techniques for oocyte insemination during in vitro fertilisation. Cochrane Database Syst Rev. 2000;(2): CD001301.

* presented in this thesis

# Dankwoord

# DANKWOORD

Promoveren is een klus die je niet alleen kunt klaren. Daarom gaat mijn dank uit naar allen die dit met mij mogelijk hebben gemaakt.

Mijn promotoren Prof. Dr. B.W.J. Mol en Prof. Dr. J.L.H. Evers en mijn co-promotoren Prof. Dr. F. van der Veen en Dr. M. van Wely.

**Ben Willem**, hoe kan iemand toekomen met zo weinig slaap? Jij bezit een ongekende gedrevenheid. Mijn tempo ligt duidelijk lager dan dat van jou. Je hebt veel voor me betekend, zowel tijdens onderzoek, de opleiding en voor mijn subspecialisatie. Dank je wel voor je geduld en je vertrouwen. Ik zal nooit vergeten dat 'je niet echt ziek bent, als je niet op de IC ligt'. Anderzijds, zal jij waarschijnlijk nooit vergeten, dat je niet kunt schrijven, 'omdat de zon in je laptop schijnt'.... Ga je het Guinness-book-of-records halen met de meeste promovendi in een jaar? Veel succes "down-under".

**Hans**, de eerste voorzichtige stapjes binnen het onderzoek werden via jou gezet. Het was een geweldige ervaring een Cochrane Review in Nieuw-Zeeland te kunnen schrijven. Daarna volgde de cohort-studie tijdens mijn opleiding. De toon was gezet... Ook jij bedankt voor je vertrouwen in mij.

**Fulco**, F, ontzettend bedankt voor je nauwgezetheid. Na een altijd snelle reactie was een artikel altijd vele malen beter na jouw kritische blik.

**Madelon**, steun en toeverlaat, als het statistiek en analyses betrof. Altijd rustig en behulpzaam, dank je wel.

Leden van de leescommissie, **Professor Barnhart, Dr. Cohlen, Professor Helmerhorst, Dr. van Kaam, Dr. Mochtar** en **Professor Repping**, hartelijk bedankt voor het beoordelen van het proefschrift en het bedenken van interessante vragen.

Alle **patiënten** bedank ik voor hun onbaatzuchtige deelname aan onderzoek. Alleen hierdoor is vooruitgang van het vak mogelijk en kunnen in de toekomst patiënten een evidence based behandeling ondergaan.

Artsen en onderzoekers uit **participerende centra, mede-auteurs**, dank voor jullie medewerking. Bijzondere dank aan mijn mede-onderzoeker, **Inge Custers.** Zonder jouw samenwerking was een groot deel van dit proefschrift er nooit gekomen. De

ESHRE-congressen voelden vertrouwd als wij elkaar weer eens als spreekster afwisselden. Bedankt.

Dear **Cindy, Neil and Jane**, of the Cochrane Menstrual Disorders and Subfertility Group, thank you very much for making me feel so welcome during my stay in Auckland and for all your help in performing the meta-analysis.

Hiernaast zijn er ook enkele die geen directe bijdrage hadden aan dit proefschrift, maar zeker wel indirect. Daarom verdienen ook zij een plaats in dit dankwoord.

**Maatschap gynaecologie** van de **Universiteit Maastricht** en van het **Máxima Medisch Centrum.** Dankzij jullie kreeg ik de geweldige basis om als gynaecoloog aan het werk te gaan. Met mijn **mede-assistenten** werd er gelukkig ook genoeg afleiding gezocht en werden de leukste liedjes bedacht.

Beste **Viviane, Simone, Ingrid, Tom, Ralph, Hans, Dick en Huib**, wat een geweldige maatschap hebben wij. Ieder afzonderlijk heeft meerwaarde voor ons team. Maar van onschatbare waarde is de onvoorwaardelijke steun in moeilijke en mooie tijden! Het voelt goed om in het Catharina te zijn.

**IVF team** van het Catharina ziekenhuis. Ik kwam als 'guppie' om 'de grote man' op te volgen. Verandering is altijd moeilijk, wennen en aftasten. Ik ben er trots op dat we als team bedenken hoe het steeds beter kan!

Mijn paranimfen, Rajaa en Tamara. Lieve **Rajaa**, hoe jij de keuzes in je leven weloverwogen maakt, vind ik fantastisch en inspirerend. Ik hoop dat je deze eigenschap doorgeeft aan jullie kindje! Alweer 6 jaar geleden stond ik naast jou. Ik vind het fijn dat jij nu ook naast mij zal staan.
Lieve **Tamara**, bij zo'n beetje alle life-events was jij nauw betrokken, dus zonder twijfel ook bij deze. Die betrokkenheid is natuurlijk met reden. Jij bent gewoon een geweldig mens! Ik ben super blij met jou als vriendin.

Lieve **vrienden, Nostradames, skiclubje**, wat heerlijk dat ik het bij jullie over andere dingen kan hebben dan over het onderzoek. Ik ben blij dat er weer meer tijd gaat komen om jullie op te zoeken!

Lieve **Marja en Gerard**, bedankt voor al jullie steun, alle oppasmomenten en de laatste noot aan de Nederlandse samenvatting. Jullie zijn geweldige schoonouders! Lieve **Anne-Mieke, Jan, Janne en Roos**. Altijd klaar staan voor een ander, altijd feest!

Mijn broer en zijn gezin. Lieve **Werner, Sabine, Michelle en Robin**. Stille wateren hebben diepe gronden. Meestal aan een half woord genoeg. Wij weten wat we aan elkaar hebben en daar ben ik jullie oneindig dankbaar voor.

Lieve **mam**, wat heb ik een bewondering voor jou! Jij en papa hebben ons altijd gestimuleerd en de ondersteuning gegeven waar nodig. Een betere basis kun je je niet wensen. Ik vind het geweldig hoe lief jij bent geweest voor papa en er voor gezorgd hebt dat zijn laatste wensen uit konden komen. Gelukkig verlies je jezelf ook niet uit het oog. Ik ben trots op je!

**Wout en Loes**, onze eigenwijze, maar ontzettend lieve kinderen. Vanaf nu geen verhaaltjes meer over de circusdirecteur die begint met "Hooggeleerd publiek", maar weer gewoon over Boris Boef. Ik ben trots op jullie!

Mijn allerliefste Lief, **Maarten**. Bedankt voor je eerste hulp bij computerproblemen, voor het lezen van een manuscript, voor de lay-out van de tabellen, maar vooral voor wie je bent. Jij bent slim, oprecht, geïnteresseerd, knap, zorgzaam en lief, maar vooral JOU! Nooit veranderen. Ik hou van je!

Lieve **pap**, hoewel ík het altijd ontkende, bleef jíj volhouden dat ik ooit zou promoveren. Het is eindelijk zover. Wat zou ik je er graag bij hebben gehad vandaag! Je blijft mijn held. Ik mis je.

# CURRICULUM VITAE

Minouche van Rumste werd geboren op 19 november 1973 te Sluiskil. In 1992 behaalde zij haar atheneumdiploma aan het Zeldenrust College te Terneuzen. In juli 2000 behaalde zij haar artsexamen aan de Universiteit Maastricht. Vervolgens vulde zij als ANIOS gynaecologie/obstetrie tweemaal een zwangerschapsverlof in, over een periode van 9 maanden, in het St. Josephziekenhuis te Veldhoven. Hierna startte zij in juli 2001 haar opleiding tot gynaecoloog in het Maastricht Universitair Medisch Centrum (opleiders prof. dr. J.L.H. Evers en prof. dr. G.G. Essed). In januari 2005 keerde zij terug naar Veldhoven, het Máxima Medisch Centrum, om haar opleiding te vervolgen (opleiders prof. dr. S.G. Oei en dr. M.Y. Bongers). Aansluitend volgde zij het traject tot subspecialist in de voortplantingsgeneeskunde, met daarbij tevens aandacht voor de endoscopie, in het Academisch Medisch Centrum (prof. dr. F. van der Veen) en in het Máxima Medisch Centrum (dr. M. Bongers / dr. C.A.M. Koks). Zij startte als chef de clinique gynaecologie/ obstetrie in het Catharina ziekenhuis te Eindhoven. Daar werd zij op 1 mei 2011 aangesteld als staflid gynaecologie en volgde zij dr. Peter van Dop op als hoofd van de IVF afdeling.
Minouche van Rumste is getrouwd met Maarten van Kampen. Zij zijn de trotse ouders van zoon Wout en dochter Loes.