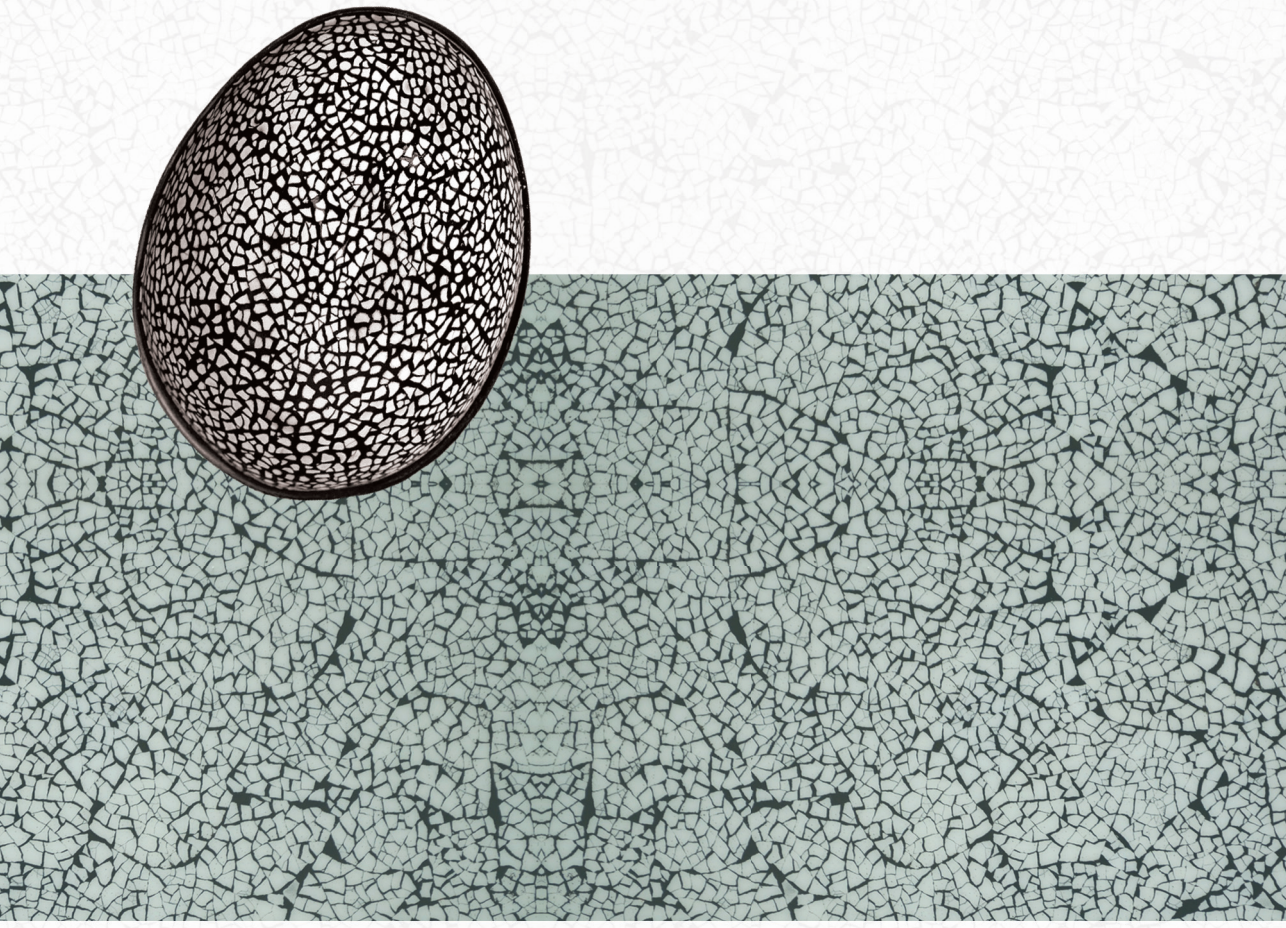
Clomiphene Citrate in PCOS



Nienke S. Weiss

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Nienke Weiss, Amsterdam, the Netherlands, 2018

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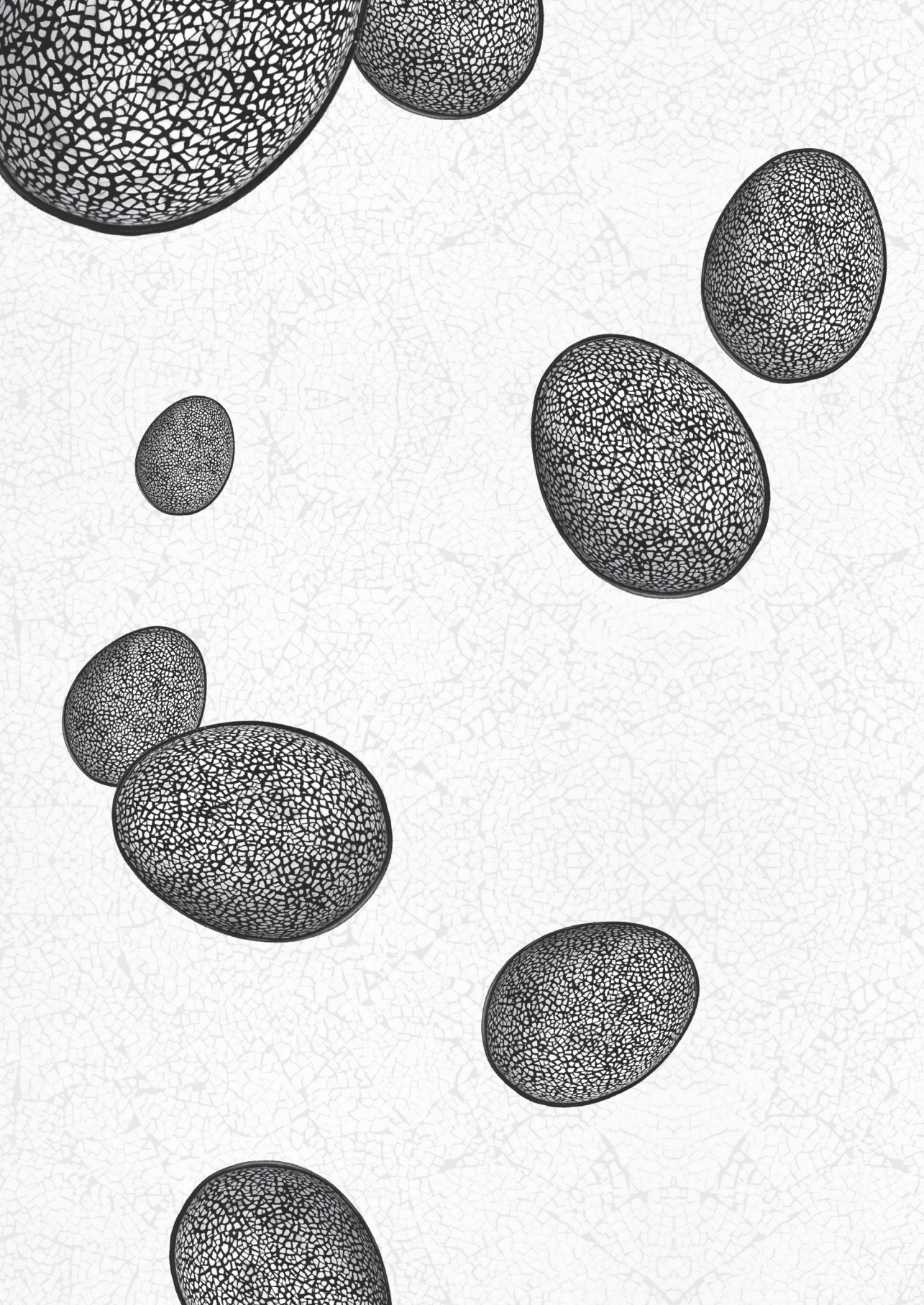

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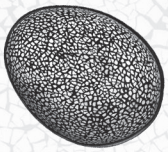
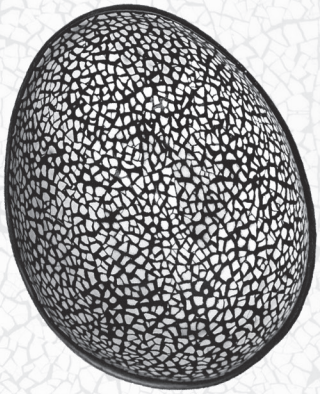
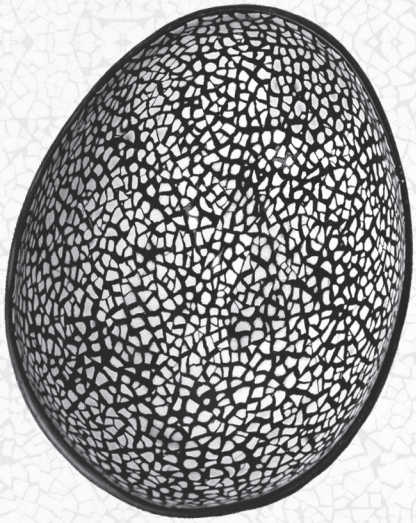
General Introduction and Outline of the thesis







GENERAL INTRODUCTION

10 to 15% of all couples are having difficulties conceiving. Around 20 to 25% of the women of these subfertile couples suffer from anovulation.[1] Ovulation disorders are commonly categorized into three types. World Health Organization (WHO) Type I ovulation disorders are caused by hypothalamic pituitary failure. Typically, these women have primary or secondary amenorrhea, characterized by low gonadotrophins and low estrogens. Approximately 10% of women with anovulation have a group I ovulation disorder. Type II ovulation disorders are defined as dysfunction of the hypothalamic-pituitary-ovarian axis. Around 85% of women with anovulation have a type II ovulation disorder. Most of these women present themselves with irregularities in the pattern of menstrual bleeding. Type III ovulation disorders are caused by ovarian failure and around 5% of women with anovulation have a type III ovulation disorder. Clinical symptoms of these women are an irregular, short menstrual cycle and hot flushes.[2]

This thesis focuses on women with WHO type II anovulation who wish to conceive. Since these women typically have normal serum follicle stimulating hormone (FSH) and estradiol levels, they are commonly referred to as women with normogonadotropic anovulation.[3]

The majority of women with normogonadotropic anovulation are diagnosed with polycystic ovary syndrome (PCOS). In 2003, the European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine consented on the diagnostic criteria of PCOS. The consensus was that the diagnosis must be based on having two out of three of the following symptoms: oligo- or anovulation, clinical and/or biochemical signs of hyperandrogenism and polycystic ovaries.[4] To date, the pathogenesis has not been completely unraveled, but the current understanding is that PCOS is a multifactorial disorder caused by a combination of diverse genetic aspects and environmental factors such as hyperandrogenemia, insulin resistance and obesity.[5] New insights suggest that increased levels of anti-Müllerian hormone play a role by causing increased LH pulsatility and secretion through the activation of GnRH. [6]

Over the years, various treatment options for women with normogonadotropic anovulation and PCOS who wish to conceive have been developed. This thesis aims to contribute to the finetuning of some of the most common treatment regimens for these women, i.e. ovulation induction with clomiphene citrate and gonadotrophins.[2]

Clomiphene citrate is a selective estrogen receptor modulator (SERM) with a non-steroidal compound closely resembling estrogen. It blocks receptors in the hypothalamus and pituitary, interfering with the feedback mechanism of endogenous estrogen. Subsequently, this negative feedback causes a change in the pattern of pulsatile release of GnRH which, in turn, results in a discharge of FSH from the pituitary gland. Finally, this increased level of FSH stimulates folliculogenesis.[7,8] In around 75% of women starting ovulation induction with

CC, ovulation is restored and approximately half of those women will conceive with CC. [9,10] If ovulation induction with CC has not lead to the birth of a child, second line treatment is ovulation induction with parental medication i.e. gonadotrophins. Gonadotrophins were originally extracted from pituitary glands, followed by extraction from the urine of post-menopausal women. [11,12] In 1988, recombinant FSH preparations entered the market.[13] Treatment with exogenous gonadotrophins elicit pregnancy rates of 45%.[10]

Background of the thesis

The research presented in this thesis emerged from a collaboration of the Centers of Reproductive Medicine of the VU Medical Center of Amsterdam and the Academic Medical Center of Amsterdam. Both centers have a longstanding history of translational and clinical research in the field of subfertility and PCOS. Professor Schoemaker pioneered the field in the Netherlands and initiated this successful line of research.

First, in 1987, luteinizing hormone-releasing hormone (LHRH) was evaluated as a possible treatment for women with PCOS. Ovulation induction with clomiphene citrate and gonadotrophins had been introduced almost three decades earlier, but multiple pregnancies and ovarian hyperstimulation syndrome following these treatments were serious issues. By administering pulsatile LHRH to women with PCOS, successful singleton pregnancies were accomplished. Therefore, LHRH was suggested as a safe alternative treatment.[14]

In 1992, another road was taken by studying the safety of ovulation induction with pulsatile gonadotrophin-releasing hormone (GnRH) regarding multiple pregnancies in women with hypothalamic amenorrhea. By studying anovulatory women who were administered different doses of pulsatile GnRH, it was found that GnRH resulted in a high number of multiple pregnancies, especially when higher pulse doses were given and when women conceived during their first treatment cycle.[15] In view of these complications, it was investigated whether pulsatile gonadotrophin-releasing hormone agonists (GnRH-a) would contribute to the treatment of women with PCOS. The mechanism of GnRH-a treatment was studied and clarified as GnRH-a seemed to enhance multifollicular growth by its influence on the FSH level and FSH threshold during follicular growth.[16] In 2000, this research topic was extended by trying to finetune follicular growth in PCOS. It was hypothesized that, if the FSH threshold for an individual woman could be determined accurately, the optimal gonadotropin dose would only marginally have to exceed this threshold, resulting in fewer complications. Indeed, by comparing ovulation induction with gonadotrophins with and without GnRH-a in low-dose step-up treatment, the FSH threshold in women with PCOS was shown to determine the number of growing follicles. The clinical corollary was the introduction of a low-dose step-up treatment regimen with gonadotrophins.[17] To date, this low-dose step-up regimen is widely used as a successful and safe treatment modality. For pulsatile GnRH and their agonists the curtain fell after a systematic review showed that data

were too limited to either prove or discard the value of pulsatile GnRH treatment in women with PCOS. [18]

Alongside the research on medical ovulation induction, surgical treatment of PCOS was the second line of research. First, in 1998, five surgical techniques, i.e. laparoscopic ovarian biopsy, unilateral oophorectomy, ovarian electrocautery, and laparoscopic and transvaginal laser treatment of the ovaries, were compared in women with clomiphene resistant PCOS. Results were promising: around 70% of women became ovulatory after treatment with ovarian biopsy, electrocautery and laparoscopic laser treatment. Unilateral oophorectomy was also effective, but in view of its invasiveness and radical nature could only be considered if other options had failed. Transvaginal interstitial laser treatment did not seem an effective option.[19] In 2004, the question whether gonadotrophins or electrocautery should be the first treatment of choice in patients with clomiphene citrate resistant polycystic ovary syndrome was addressed. A randomized trial proved that laparoscopic electrocautery of the ovaries and ovulation induction with gonadotrophins are equivalent in terms of pregnancy rates in women with clomiphene resistant PCOS. In the same year, a systematic review showed that recombinant FSH is probably not more effective than urinary FSH for this indication.[18,20] In 2015, the long term follow up of the RCT comparing electrocautery of the ovaries with gonadotrophins was studied. Compared to ovulation induction with gonadotrophins, laparoscopic electrocautery of the ovaries seemed to increase the chance for a second child and reduced the need for artificial reproductive treatment later in life. The thesis containing these results also presented the study protocol and initiated the study of chapter 5 of the current thesis.[21]

A possible role for metformin was explored around the same period. A randomized clinical trial showed that metformin is not an effective addition to clomiphene in the induction of ovulation in therapy naïve women, while a meta-analysis on women with clomiphene resistant PCOS showed that the combination of clomiphene with metformin is the preferred treatment option as second line treatment, i.e. before starting with surgical treatment or gonadotrophins.[22]

Meanwhile, other studies were ongoing to gain more knowledge on the pathogenesis and endocrinology of PCOS. First, in 2000, the prognosis of menstrual cycle disorders during adolescence was studied in a prospective cohort study of women of 15-18 years old. After a follow up period of three years it was concluded that the menstrual cycle pattern in the first year after menarche is a better predictor for ovulatory dysfunction in adulthood than androgen- or LH levels, and that oligomenorrhea later in life can be predicted by irregular menstrual cycles and polycystic ovaries in puberty.[23] Other studies investigated the influence of ovarian ageing in PCOS. Data of women with PCOS of 30 years and older, obtained by interviews, showed that ageing women gain regular menstrual cycles, probably due to the decline in the size of their follicle cohort. After comparing serum endocrine levels and

ultrasound measurements in women with different cycle patterns and different follicle counts, it was demonstrated that women who achieved regular menstrual cycles had a smaller follicle count compared with younger, still irregularly menstruating women with PCOS.[24]
In 2010, the relationship between microvascular function and insulin resistance in women with PCOS was explored. The response of vasodilatation on insulin in lean and obese women with and without PCOS was measured. These measurements demonstrated that both lean and obese women are characterized by impaired insulin-induced capillary recruitment.[25] In 2014, analysis of the neuroendocrine regulation suggested LH as an additional diagnostic test for PCOS. Also, the endocrine changes caused by laparoscopic ovarian laser treatment were examined: Laser evaporation resulted in a sustained decrease of testosterone, androstenedione and anti-Mullerian Hormone and prevented an increase of inhibin B in the first hours after surgery.[26] Finally, in 2017, a twin study showed that the pathogenesis of PCOS can mostly be explained by genetic factors with a smaller share of environmental factors. It was also found that the birth weight and age of menarche are both unrelated to the development of PCOS later in life.[27]

This longstanding research line has contributed to our insight into the pathogenesis and endocrinology of PCOS, but also into the effectiveness and safety of treatment of therapy naïve women and women with clomiphene resistance. This thesis follows up on this by addressing two important knowledge gaps in the treatment of women with PCOS.
The first is how to treat effectively and safely women that ovulate regularly with clomiphene but fail to conceive after six to nine cycles. These women are defined as having clomiphene failure**.** International guidelines do not provide well founded recommendations.[2,28,29]
The second gap is the value of IUI in anovulatory women. IUI was originally designed to increase pregnancy chances in couples with male subfertility.[30] Subsequently, IUI was also introduced to couples with unexplained subfertility and subfertility based on a 'cervical factor', also referred to as cervical 'hostility'.[2,31] Whether IUI ameliorates the pregnancy rates for women with anovulation is unknown. There are several studies that have shown that clomiphene may have a negative effect on the cervical mucus and thus may induce cervical factor-subfertility, thereby suggesting that IUI may help women to conceive during their clomiphene treatment.[32-34]
Finally, next to the effectiveness, treatment costs and patient preference play a significant role in clinical decision making, which had not been studied so far. [35,36]

OUTLINE OF THE THESIS

Chapter 2 systematically reviews the literature on women with PCOS who were treated with gonadotrophins. With this study we updated the evidence on the effectiveness and safety of all types of gonadotrophins i.e. urinary and recombinant, for ovulation induction. We included randomized controlled trials that compared these types of gonadotrophins and as primary outcome measure we chose live birth.

Chapter 3 presents a prospective follow up study which was performed to assess the prognostic value for pregnancy of the postcoital test in women with WHO type II anovulation. A postcoital test was performed in one of the first three ovulatory cycles in women treated with clomiphene. Ovulation induction with clomiphene was continued for at least six cycles and pregnancy rate and time to conception were compared.

Chapter 4 presents the results of a retrospective cohort study of 114 women with WHO type II anovulation who did not conceive within their first six ovulatory cycles with clomiphene and who were continuously treated with clomiphene. Follow up ended at a total of 12 treatment cycles with clomiphene and primary outcome measure was the cumulative incidence rate of an ongoing pregnancy.

Chapter 5 shows the outcomes of a multicenter randomized trial comparing gonadotrophins with clomiphene both with or without IUI in 666 women with clomiphene failure. The main outcome measure was the birth of live child conceived within eight months after randomization.

Chapter 6 reports on the results of a cost-effectiveness analysis of the randomized controlled trial presented in chapter 3. For each of the treatment strategies that we compared, we calculated the mean costs and effectiveness and calculated the incremental cost-effectiveness ratios.

Chapter 7 provides the results of a patient preference study of 145 normogonadotropic anovulatory treatment naive women wishing to conceive. We performed a Discrete Choice Experiment in five fertility clinics in the Netherlands. Participating women filled out questionnaires containing several treatment characteristics of interest concerning ovulation induction with clomiphene citrate, gonadotrophins as well as intercourse and IUI. We used a multinominal logit model and performed a latent class analysis to determine women's treatment preferences considering clomiphene citrate, gonadotrophins and IUI.

Chapter 8 summarizes this thesis, provides implications for clinical practice and provides suggestions for future research.

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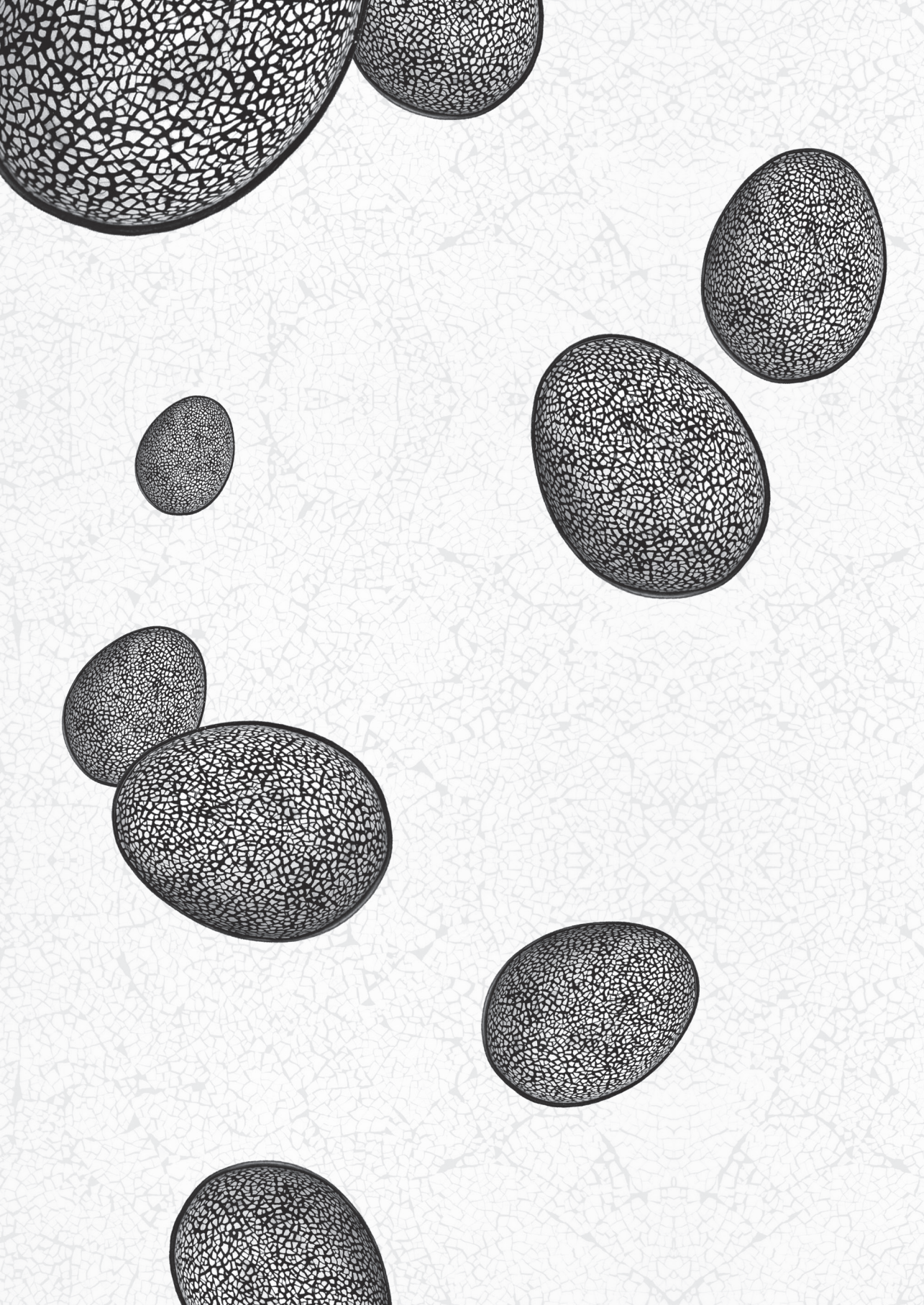

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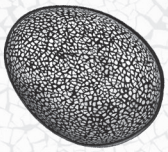
Gonadotrophins for ovulation induction in women with polycystic ovarian syndrome



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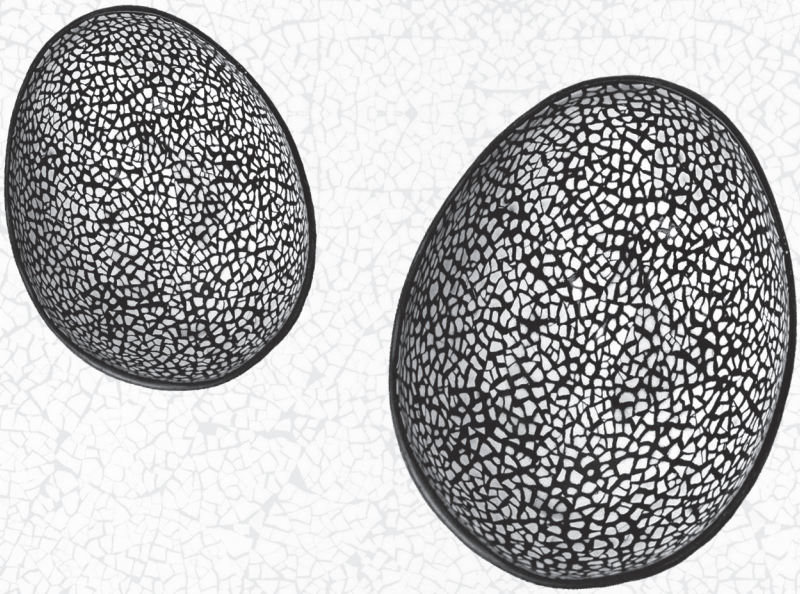


Cochrane Database of Systematic Reviews. 2015 Sept

ABSTRACT

Background: Ovulation induction with follicle stimulating hormone (FSH) is the second-line treatment in women with polycystic ovary syndrome (PCOS) who do not ovulate or conceive on clomiphene citrate (CC).

Objectives: To compare the effectiveness and safety of gonadotrophins as a second-line treatment for ovulation induction in women with CC-resistant PCOS.

Search methods: We searched the Menstrual Disorders & Subfertility Group's Specialist Register of controlled trials, the Cochrane Central Register of Controlled Trials, MEDLINE (1966 to October 2014), EMBASE (1980 to October 2014), CINAHL (1982 to October 2014), National Research Register and web-based trials databases such as Current Controlled Trials. There was no language restriction.

Selection criteria: All randomised controlled trials reporting data on comparing clinical outcomes in women with PCOS who did not ovulate or conceive on CC, and undergoing ovulation induction with urinary FSH (uFSH: FSH-P or FSH-HP), HMG/HP-HMG or recombinant FSH. We included trials reporting on ovulation induction followed by intercourse or intrauterine insemination. We excluded studies that used co-treatment with CC, metformin, LH or letrozole.

Data collection and analysis: Three review authors (NW, MN and MvW) independently selected studies for inclusion, assessed study quality and extracted study data. Primary outcomes were live birth rate per woman (effectiveness outcome) and incidence of ovarian hyperstimulation syndrome (OHSS) per woman (safety outcome). Secondary outcomes were clinical pregnancy, miscarriage, multiple pregnancy, total gonadotrophin dose and total duration of stimulation per woman. We combined data using a fixed-effect model to calculate the odds ratio (OR). We summarised the overall quality of evidence for the main outcomes using GRADE criteria.

Main results: The review includes 14 trials with 1726 women. Ten trials compared rFSH versus urinary-derived gonadotrophins (three rFSH versus HMG and seven rFSH versus FSH-HP), four trials compared FSH-P with HMG. We found no trials that compared FSH-HP with FSH-P.

We found no evidence of a difference in live birth for rFSH versus urinary-derived gonadotrophins (OR 1.26, 95% CI 0.80 to 1.99, 5 trials, 505 women, $I^2 = 0\%$, low-quality evidence) or clinical pregnancy rate (OR 1.08, 95% CI 0.83 to 1.39, 8 trials, 1330 women,

I^2 = 0, low-quality evidence). This suggests that for the observed average live birth per woman with urinary-derived FSH of 16%, the chance of live birth following rFSH is between 13% and 26%.
For the comparison HMG or HP-HMG versus FSH-P there was also no difference in the evidence on live birth rate (OR 1.36, 95% CI 0.58 to 3.18, 3 trials, 138 women, I^2 = 0%, low-quality evidence). This suggests that for a woman with a live birth rate of 18% with HMG or HP-HMG, the chance of live birth following uFSH is between 9% and 37%.
Trial authors used various definitions for OHSS. Pooling the data, we found no evidence of a difference for rFSH versus urinary-derived gonadotrophins (OR 1.52, 95% CI 0.81 to 2.84, 10 trials, 1565 women, I^2 = 0%, very low-quality evidence) and for HMG or HP-HMG versus FSH-P (OR 9.95, 95% CI 0.47 to 210.19, 2 trials, 53 women, I^2 = 0%, very low-quality evidence).

Authors' conclusions: In women with PCOS and CC resistance or CC failure, we found no evidence of a difference in live birth and OHSS rates between urinary-derived gonadotrophins and rFSH or HMG/HP-HMG. Evidence for all outcomes was of low or very low quality. We suggest weighing costs and convenience in the decision to use one or the other.

BACKGROUND

Description of the condition

Subfertility occurs in one in 10 couples world-wide. In about one-third of couples this is based on polycystic ovarian syndrome (PCOS). PCOS is characterised by oligo-anovulation, clinical or biochemical hyperandrogenism and polycystic ovaries[1,2]. The syndrome affects approximately 6% to 10% of women of childbearing age.

Infertility due to chronic anovulation is the most common reason for women with PCOS to seek counselling or treatment. The first line of treatment in these women is ovulation induction with clomiphene citrate (CC), with or without metformin.

About 15% to 20% of women do not ovulate on CC and require alternative or second-line ovulation induction strategies. This failure to ovulate with CC is termed 'clomiphene resistance'. The most common treatment in women with CC-resistant PCOS is ovulation induction with gonadotrophins[3]. A recent review showed that laparoscopic electrocautery of the ovaries is an effective alternative treatment.[4] If women fail to conceive with CC despite regular ovulation, the term 'clomiphene failure' is used. Also in this case, CC treatment is also often changed to second-line ovulation induction with gonadotrophins.

Description of the intervention

The strategy of stimulating follicle development and growth with exogenous gonadotrophins for ovulation induction in women with CC-resistant PCOS is well established.

FSH is found in the pituitary gland and in the circulation in different molecular forms. This molecular heterogeneity is due to the variation in the structures of the carbohydrate moieties, in particular of sialic acid. It is the configuration of these carbohydrate moieties that determines the FSH isoform. The configuration depends on which glycosylation enzymes are available in the cell during synthesis.[5] Each molecular glycoform has a different molecular weight, net charge, circulating half-life and metabolic clearance.[6-9] Gonadotrophins were originally extracted from pituitary gland and later extracted from the urine of post-menopausal women.[10,11]

Over the last five decades, various urinary-derived follicle stimulating hormone (FSH) products, or urofollitropins, have been developed. Menotropin (human menopausal gonadotrophin (HMG)) has been available since the early 1960s and contains FSH, luteinising hormone (LH) and large quantities of potentially allergenic urinary proteins. Purified urofollitropin (FSH-P) has been available since the mid-1980s. FSH-P is devoid of LH but still contains urinary proteins. Highly purified urofollitropin (FSH-HP) has been available since the mid-1990s and contains very small amounts of urinary proteins. The absence of urinary proteins diminishes rare adverse reactions such as local allergy or hypersensitivity.[12,13] The

most recent development in urinary gonadotrophins is highly purified menotropin (HP-HMG), containing equal amounts of FSH and LH activity.

To obtain even higher purity, gonadotrophins were developed using recombinant DNA technology (recombinant FSH (rFSH)) in 1988.[14,15] The production of rFSH is independent of urine collection, thus guaranteeing a high availability of a biochemical pure FSH preparation that is free from LH and urinary protein contaminants. The production process also yields FSH with high specific bioactivity (roughly 100 times higher than for urine-derived FSH products), minimal batch-to-batch discrepancies and low immunogenicity.[16] There is evidence that rFSH has a higher bioactivity than urinary products.[17]

At present two preparations of rFSH are available: follitropin alpha and follitropin beta. Both preparations are similar to pituitary and urinary FSH, although they show minor differences in the structure of the carbohydrate side chains and contain more basic and fewer acidic isohormones than the urinary-derived gonadotrophin preparations.[18-20]

How the intervention might work

In the follicular phase of a normal menstrual cycle, between 10 and 20 antral follicles develop. Of this cohort, one follicle will obtain dominance over the others and will continue to grow until ovulation takes place. In women with PCOS this dominance does not occur. The aim in ovulation induction is to induce growth of up to three follicles. This is accomplished by ovarian stimulation with FSH containing gonadotrophins. Too forceful a regimen will result in overstimulation and hence in an increased risk of multiple pregnancy and ovarian hyperstimulation syndrome (OHSS); a stimulation regimen with too low a dosage of FSH will not result in a dominant follicle and thereby will not lead to ovulation.

Why it is important to do this review

Gonadotrophins are the standard drugs in medical ovulation induction in women with CC-resistant PCOS. The present review is an update and extension of two previous Cochrane reviews.[21,22] Bayram 2001 had compared rFSH with FSH-P and FSH-HP; Nugent 2000 had compared HMG with purified FSH. No Cochrane review has yet compared HMG with rFSH in CC-resistant women. Summarising the evidence on the effectiveness and safety of the various gonadotrophins will help gynaecologists and women to make informed decisions on their use for ovulation induction.

OBJECTIVES

To compare the effectiveness and safety of gonadotrophins as a second-line treatment for ovulation induction in women with CC-resistant PCOS.

METHODS

Criteria for considering studies for this review

Types of studies

We have included randomised controlled trials. We excluded quasi-randomised controlled trials in which allocation was, for example, by alternation, reference to case record numbers or to dates of birth. We also excluded cross-over trials, which are not appropriate in this context.[23]

Types of participants

1. Subfertile women with CC-resistant PCOS undergoing ovulation induction. We define CC resistance as a failure to ovulate with CC doses of at least 100 mg/day for at least five days.
2. Subfertile women with PCOS and CC failure undergoing ovulation induction. We define CC failure as a failure to conceive after three cycles of ovulation induction with CC.
3. Women treated in the past by metformin with or without CC.
4. Women with prior treatment with electrocautery of the ovaries.

Types of interventions

1. Ovulation induction with rFSH versus any other urinary gonadotrophin (HMG, FSH-P, FSH-HP)
2. Ovulation induction with FSH-HP versus FSH-P
3. Ovulation induction with HMG or HP-HMG versus FSH-P or FSH-HP

For all interventions, ovulation induction could include intrauterine insemination. We excluded trials involving co-treatment with CC, metformin, LH or letrozole.

Types of outcome measures

Primary outcomes

1. Live birth rate per woman
2. Incidence of ovarian hyperstimulation syndrome (OHSS) per woman (safety outcome)

Secondary outcomes

3. Clinical pregnancy rate (per woman)
4. Miscarriage rate (per woman)
5. Incidence of multiple pregnancy (per woman and per clinical pregnancy)
6. Total gonadotrophin dose per woman (IU)
7. Total duration of stimulation per woman

Search methods for identification of studies

This review has drawn on the search strategy developed for the Cochrane Menstrual Disorders and Subfertility Group (MDSG) as a whole.

Electronic searches

Marian Showell (Trials Search Co-ordinator of the MDSG) developed the search strategies. See Appendix 1, Appendix 2, Appendix 3, Appendix 4, Appendix 5, Appendix 6 (all available online).

We searched the following electronic sources to 22 October 2014:

- Cochrane Central Register of Controlled Trials (CENTRAL) (current issue)
- MEDLINE (from 1966 onwards)
- EMBASE (from 1988 onwards)
- Trial registers for ongoing and registered trials - clinicaltrials.gov, a service of the US National Institutes of Health, or the WHO ICTRP (World Health Organization International Trials Registry Platform search portal)
- Reference lists from reviews and trials
- the Cochrane Library for Database of Abstracts of Reviews of Effects (DARE) (reference lists from non-Cochrane reviews on similar topics)
- Handsearching of appropriate journals
- Conference abstracts on the Web of Knowledge
- OpenGrey for unpublished literature from Europe
- LILACS database, a source of trials from the Portuguese- and Spanish-speaking world
- PubMed and Google for any recent trials that have not yet been indexed in MEDLINE

Searching other resources

We searched the following conference abstracts:

- American Society for Reproductive Medicine and Canadian Fertility and Andrology Society (ASRM/CFAS) Conjoint Annual Meeting (2001 to 2014), Abstracts of the Scientific Oral and Poster Sessions, Program Supplement;
- European Society of Human Reproduction and Embryology (ESHRE) Annual Meeting (2001 to 2014), Abstracts of the Scientific Oral and Poster Sessions, Program Supplement.

We hand searched the references cited in all obtained studies.

We asked Serono Benelux BV and Merck, Ferring and IBSA, the manufacturers of gonadotrophins, for ongoing studies and unpublished data.

Data collection and analysis

Selection of studies

Three review authors (NW, MN and MvW) independently examined the electronic search results for reports of possibly relevant trials, and retrieved these reports in full. All review authors independently applied the selection criteria to the trial reports, rechecking trial eligibility and resolving disagreements by discussion with the other authors.

Data extraction and management

Three review authors (NW, MN and MvW) independently extracted the outcome data and information on funding, location, clinical and design details, and participants. We resolved any differences by discussion. We entered details of the studies into the table Characteristics of included studies (available online). We presented studies that appeared to meet the inclusion criteria but were excluded from the review in the table Characteristics of excluded studies (available online), briefly stating the reason for exclusion but giving no further information.

Assessment of risk of bias in included studies

Three review authors (NW, MN and MvW) extracted information regarding the risk of bias (threats to internal validity) under six domains (also see the Cochrane 'Risk of bias' assessment tool in Appendix 7).[24] We resolved any differences by discussion.

1. Sequence generation. Evidence that an unpredictable random process was used.
2. Allocation concealment. Evidence that the allocation list was not available to anyone involved in the recruitment process.
3. Blinding of participants, clinicians and outcome assessors. Evidence that knowledge of allocation was not available to those involved in subsequent treatment decisions or follow-up efforts.
4. Completeness of outcome data. Evidence that any losses to follow-up were low and comparable between groups.
5. Selective outcome reporting. Evidence that major outcomes had been reported in sufficient detail to allow analysis, independently of their apparent statistical significance.
6. Other potential sources. Evidence of miscellaneous errors or circumstances that might influence the internal validity of trial results.

We sought missing details from the authors of the original publications. We present all details in the 'Risk of bias' table following each included study.

Measures of treatment effect

We summarised all binary outcomes using the odds ratio (OR) with a 95% confidence interval (CI).

We treated ordinal scales, such as amount of gonadotrophin used and duration of ovarian stimulation, as continuous outcomes. We abstracted, calculated or requested means and standard deviations.

Unit of analysis issues

We expressed all outcomes per woman randomised.

We also expressed the secondary outcome of multiple pregnancy per clinical pregnancy.

Dealing with missing data

Where there was insufficient information in the published report, we attempted to contact the authors for clarification. If missing data became available, we included them in the analysis. We anticipated that trials conducted over 10 years ago might not have data on live birth rates. We analysed data extracted from the trials on an intention-to-treat basis. Where randomised participants were missing from outcome assessment, we first contacted the authors for additional data. If further data were not available, we assumed that missing participants had failed to achieve pregnancy and had not suffered any of the reported adverse events.

Assessment of heterogeneity

The presence of statistical heterogeneity of treatment effect among trials was determined using the I^2 statistic.[25] We considered whether clinical and methodological characteristics of the included studies were sufficiently similar for meta-analysis to provide a clinically meaningful summary. We assessed statistical heterogeneity by the measure of the I^2 statistic. We took an I^2 measurement greater than 50% to indicate substantial heterogeneity, in which case we tested the effect of using a random-effects model.[24]

Assessment of reporting biases

In view of the difficulty of detecting and correcting for publication bias and other reporting biases, we aimed to minimise their potential impact by ensuring a comprehensive search for eligible studies and by being alert for duplication of data. If we included 10 or more studies in an analysis, we planned to use a funnel plot to explore the possibility of small-study effects (a tendency for estimates of the intervention effect to be more beneficial in smaller studies).

Data synthesis

When multiple studies were available on a similar comparison, we used Review Manager 5 software to perform the meta-analyses, using the Mantel-Haenszel method with a fixed-effect model. For reporting purposes, we translated primary outcomes to absolute risks. We combined results for continuous outcomes using the mean difference.

Subgroup analysis and investigation of heterogeneity

If excessive heterogeneity existed within strata, we planned to explore this informally using the clinical and design details recorded in the table Characteristics of included studies which is found online. Prospectively, we planned to undertake three different stratifications of the primary outcomes: type of urinary gonadotrophin (HMG, FSH-P and FSH-HP); single or multiple cycles; sponsorship (commercial, non-commercial).[26]

Sensitivity analysis

We conducted sensitivity analyses for the primary outcomes to determine whether the conclusions were robust to arbitrary decisions made regarding study eligibility and analysis. These analyses included consideration of whether the review conclusions would have differed if:

- we had used a random-effects model
- we had reported risk ratios rather than odds ratios

Overall quality of the body of evidence: 'Summary of findings' table

We generated 'Summary of findings' tables using GRADEPRO software. These tables evaluate the overall quality of the body of evidence for main review outcomes using GRADE criteria: study limitations (i.e. risk of bias), consistency of effect, imprecision, indirectness and publication bias. We justified judgements about evidence quality (high, moderate or low), documented them, and incorporated them into the reporting of results for each outcome.

RESULTS

Description of studies

For details of the studies please see: Characteristics of included studies; Characteristics of excluded studies, both available online.

Results of the search

We identified 18 RCTs, four of which we excluded from analysis. See Figure 1.

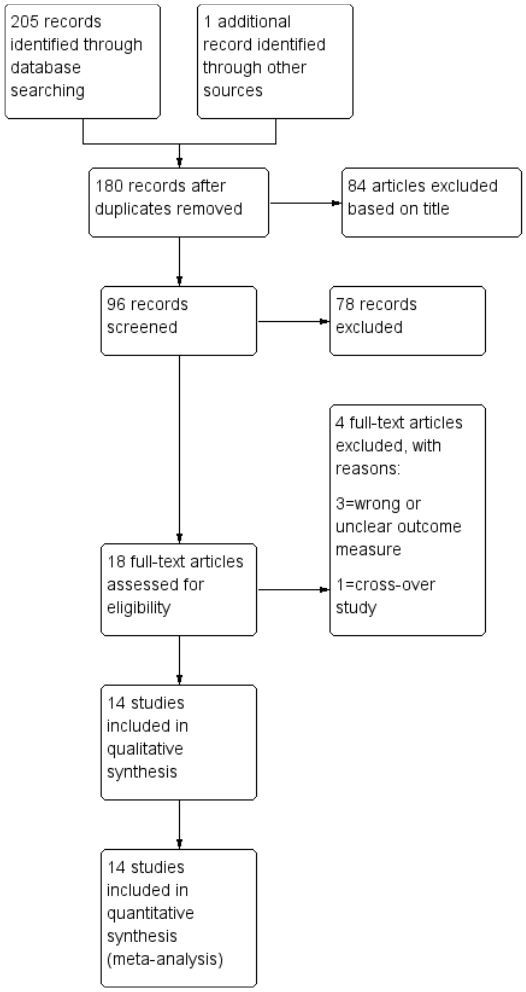


Figure 1. Study flow diagram.

Included studies

We included 14 trials.

1. Ten studies compared the effects of rFSH versus urinary derived gonadotrophins (HMG: Balen 2007; Platteau 2006; Revelli 2006[1-3]; uFSH: Coelingh Bennink 1998; Feigenbaum 2001; Gerli 2004; Loumaye 1996; Szilágyi 2004 [4-8] , Taketani 2010; Yarali 1999).[9,10] Loumaye 1996 was described in a review on human gonadotrophins produced by recombinant DNA technology.[7] The authors of the 2001 Cochrane review (Bayram 2001)[21] collected the data for this trial by personal communication, and we now used them again.

2. There were no studies that compared FSH-HP with FSH-P.
3. Four studies compared FSH-P with HMG (Gadir 1990: McFaul 1990; Sagle 1991; Seibel 1985). Gadir 1990 made an extra comparison with laparoscopic electrocautery of the ovaries. One trial also included normo-ovulatory women with unexplained subfertility (Revelli 2006) For this review, we used only the data of women with PCOS. For Seibel 1985, we included pre-cross-over data.
Seven trials reported data on live birth, and 10 trials (Balen 2007; Coelingh Bennink 1998; Feigenbaum 2001; Gerli 2004; Loumaye 1996; Platteau 2006; Revelli 2006; Szilágyi 2004; Taketani 2010; Yarali 1999) reported the incidence of OHSS. The definition of OHSS varied between trials, as is detailed in the Characteristics of included studies tables (available online). Some studies did not give a definition.
All studies included women who were CC-resistant; six of them also included women with CC failure (Balen 2007; Coelingh Bennink 1998; Gerli 2004; Platteau 2006; Seibel 1985; Yarali 1999). None of the women included in this review had been treated with electrocautery in the past. Nine trials analysed more than one cycle per woman, whereas five trials only analysed one cycle per woman (Balen 2007; Feigenbaum 2001; Platteau 2006; Revelli 2006; Taketani 2010). In three trials intra-uterine insemination (IUI) was performed in some cases (Balen 2007; Gerli 2004; Platteau 2006). All trials used a low-dose step-up protocol, but the protocol used in Loumaye 1996 was unknown. Ten trials reported a commercial sponsor (Balen 2007 , Loumaye 1996 , Coelingh Bennink 1998; Feigenbaum 2001; Platteau 2006; Sagle 1991; Seibel 1985; Szilágyi 2004; Taketani 2010; Yarali 1999).
Only five trials reported a power calculation (Balen 2007; Coelingh Bennink 1998; Loumaye 1996; Platteau 2006; Revelli 2006).

Excluded studies

We excluded four trials: one trial because the outcome measure was the effect of FSH on haemostasis (Ricci 2004)[1]; two studies because the outcome 'pregnancy' was not defined and this outcome was only presented per cycle (Homburg 1990; Jacobs 1987), and one study because it was a cross-over design and it was not possible to extract the pre-cross-over data per woman (Larsen 1990).

Risk of bias in included studies

We summarise the risks of bias in the included studies in Figure 2 and Figure 3.

Allocation

Allocation to the intervention or control group was adequately concealed in three trials (Balen 2007; Loumaye 1996; Platteau 2006). The allocation concealment was inadequate in two trials (Gadir 1990; Gerli 2004) and unclear in the remaining trials.

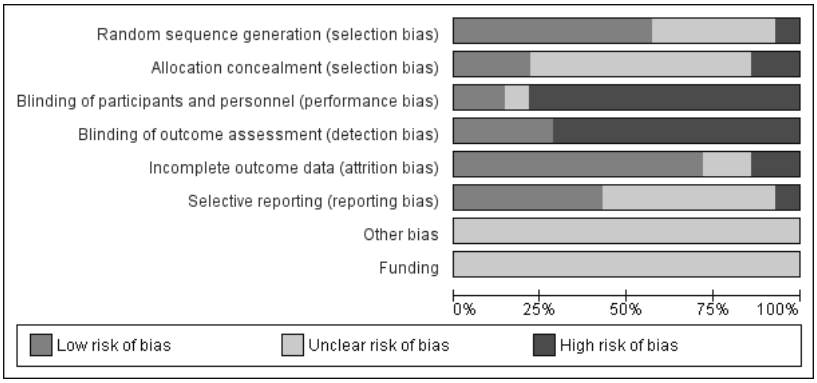


Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

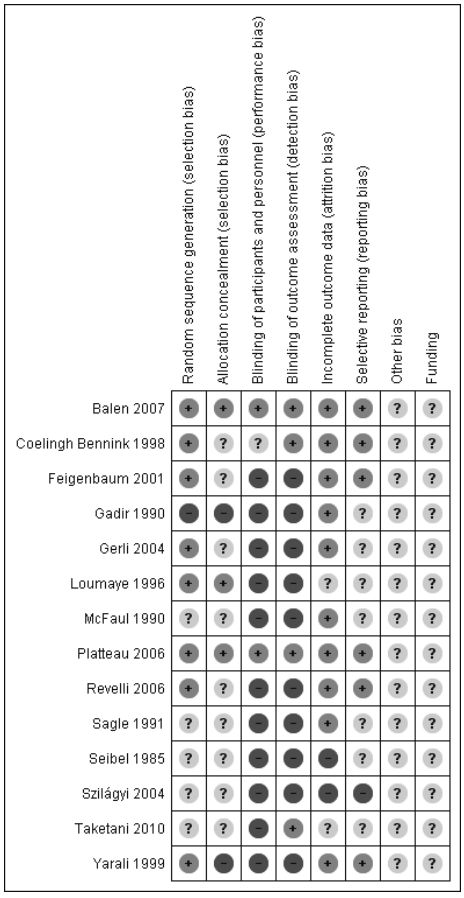


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Blinding

Four trials were assessor-blinded (Balen 2007; Coelingh Bennink 1998; Platteau 2006; Taketani 2010). Blinding was not performed in the remaining studies.

Incomplete outcome data

Two trials had a high risk of attrition bias (Seibel 1985; Szilágyi 2004). For another two trials this was unclear (Loumaye 1996; Taketani 2010). All other trials had a low risk for this domain.

Selective reporting

We rated six studies as having a low risk of selective reporting bias; seven as having an unclear risk of bias in this domain, and one study as having high risk (Szilágyi 2004).

Other potential sources of bias

We rated this as unclear for all studies. Some studies provided too few details to make a judgement. Within all the trials, the baseline characteristics appeared balanced over the two treatment groups. Only five of the 14 trials mentioned the duration of the trial (Balen 2007; Coelingh Bennink 1998; Loumaye 1996; Platteau 2006; Taketani 2010).

Effects of interventions

rFSH versus urinary-derived gonadotrophins

Live birth rate per woman (Figure 4)

Five trials including 505 women reported on live birth (Balen 2007; Feigenbaum 2001; Platteau 2006; Revelli 2006; Szilágyi 2004). After pooling the results, the overall OR per woman was 1.26 (95% CI 0.80 to 1.99, 5 RCTs, n = 505, I^2 = 17%, low-quality evidence), indicating no evidence of a difference. Translated into absolute risks, this means that for a woman with a 16% chance of achieving live birth with the use of urinary-derived FSH, the chance of a live birth with the use of rFSH would be between 13% and 26%. Statistical heterogeneity for this outcome was low. The live birth rate varied from 16% to 40% in the rFSH group and from 0% to 25% in the urinary gonadotrophin group.

When dividing the urinary-derived gonadotrophins into subgroups (three trials compared rFSH versus HP-HMG, two trials compared rFSH versus FSH-HP), we found no evidence of a difference between the subgroups (P = 0.09). The OR for rFSH versus HP-HMG/HMG was 1.04 (95% CI 0.63 to 1.73, 3 RCTs, n = 409, I^2 = 0%, low-quality evidence) and for rFSH versus FSH-HP was 3.11 (95% CI 0.98 to 9.91, 2 RCTs, n = 96, I^2 = 26%, low-quality evidence).

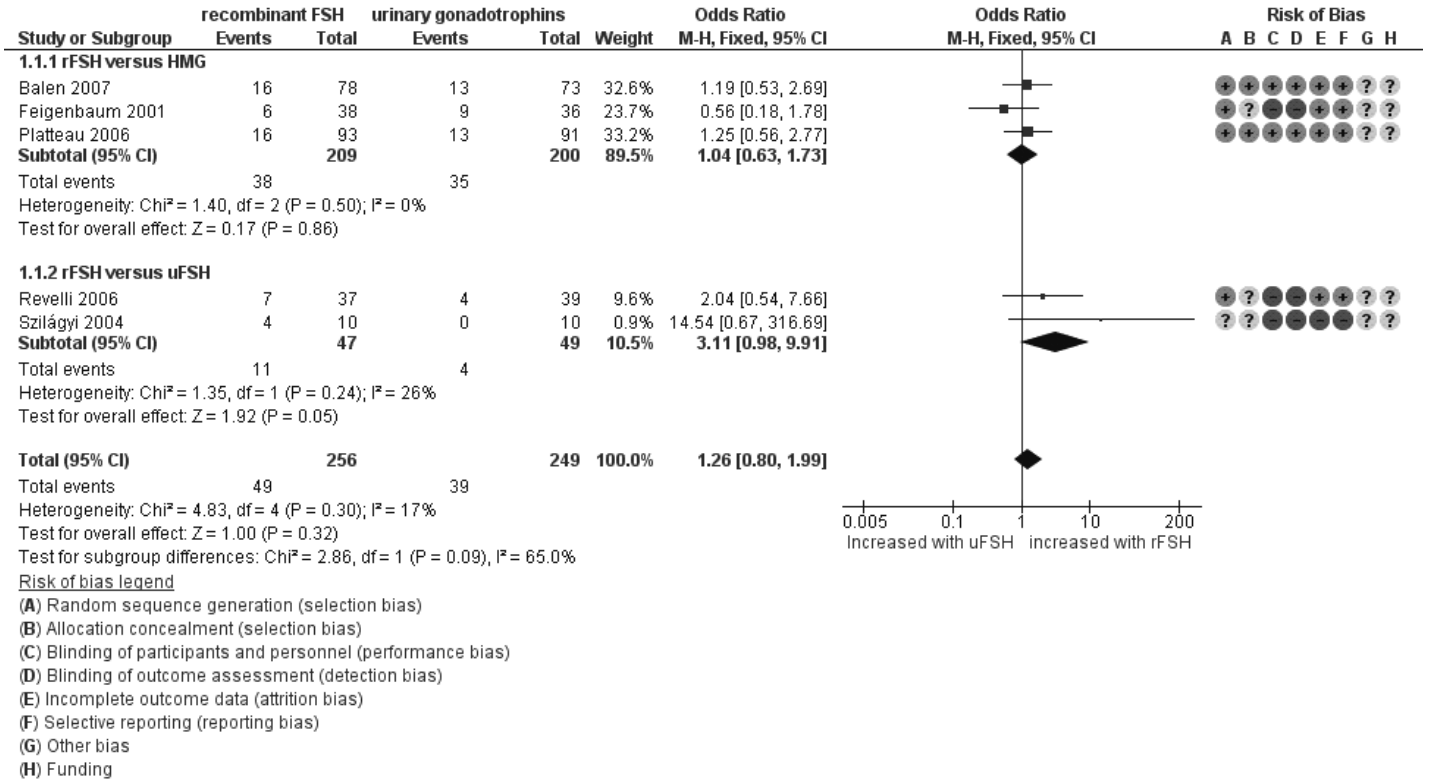


Figure 4. Forest plot of comparison 1: recombinant FSH versus urinary-derived gonadotrophins, outcome: Live birth rate per woman.

All trials comparing rFSH and HP-HMG were sponsored by Ferring, while for the other two trials comparing rFSH and FSH-P the sponsor was not reported. Subgrouped results per sponsor were therefore similar to the gonadotrophin comparison, i.e. subgrouping did not result in differences between subgroups (P = 0.09)

Incidence of ovarian hyperstimulation syndrome (OHSS) per woman

Ten studies reported OHSS, including 1565 women (Balen 2007; Coelingh Bennink 1998; Feigenbaum 2001; Gerli 2004; Loumaye 1996; Platteau 2006; Revelli 2006; Szilágyi 2004; Taketani 2010; Yarali 1999). After pooling the results, the overall OR for OHSS per woman was 1.52 (95% CI 0.81 to 2.84, 10 RCTs, n = 1565, I^2 = 0%, very low-quality evidence), indicating no evidence of a difference). This means that for a woman with a 2.2% chance of OHSS urinary-derived gonadotrophins, the chance of OHSS with the use of rFSH would be between 1.2% and 5.2%. The OHSS rate varied from 0% to 20% in both groups.

When dividing the urinary-derived gonadotrophins into subgroups (three trials compared rFSH versus HP-HMG, seven trials compared rFSH versus FSH-HP), we found no evidence of a difference between the subgroups (P = 0.53). The OR for rFSH versus HP-HMG was 1.12 (95% CI 0.37 to 3.44, 3 RCTs, n = 409, I^2 = 0%, very low-quality evidence) and for rFSH versus FSH-HP was 1.74 (95% CI 0.81 to 3.72, 7 RCTs, n = 1156, I^2 = 0%, very low-quality evidence).

Clinical pregnancy rate per woman

Eight studies including 1330 women reported on clinical pregnancy (Balen 2007; Coelingh Bennink 1998; Feigenbaum 2001; Gerli 2004; Loumaye 1996; Platteau 2006; Taketani 2010; Yarali 1999). There was no evidence of a difference in clinical pregnancy (OR 1.08, 95% CI 0.83 to 1.39; 8 RCTs, n = 1330, I^2 = 0%, low-quality evidence).

When dividing the urinary-derived gonadotrophins into subgroups (three trials compared rFSH versus HP-HMG, five trials compared rFSH versus FSH-HP), there was no evidence of a difference between the subgroups (P = 0.49). The OR for rFSH versus HP-HMG was 1.25 (95% CI 0.76 to 2.04, 3 RCTs, n = 409, I^2 = 0%, low-quality evidence) and for rFSH versus FSH-HP 1.02 (95% CI 0.75 to 1.38, 5 RCTs, n = 921, I^2 = 0%, low-quality evidence).

Miscarriage rate per woman

Seven studies including 970 women reported on miscarriage (Balen 2007; Coelingh Bennink 1998; Gerli 2004; Loumaye 1996; Platteau 2006; Szilágyi 2004; Yarali 1999). There was no evidence of a difference in miscarriage (OR 1.22, 95% CI 0.69 to 2.15; 7 RCTs, n = 970, I^2 = 0%, low-quality evidence).

When dividing the urinary-derived gonadotrophins into subgroups (two trials compared rFSH versus HP-HMG, five trials compared rFSH versus FSH-HP), we found no evidence of a difference between the subgroups (P = 0.70).

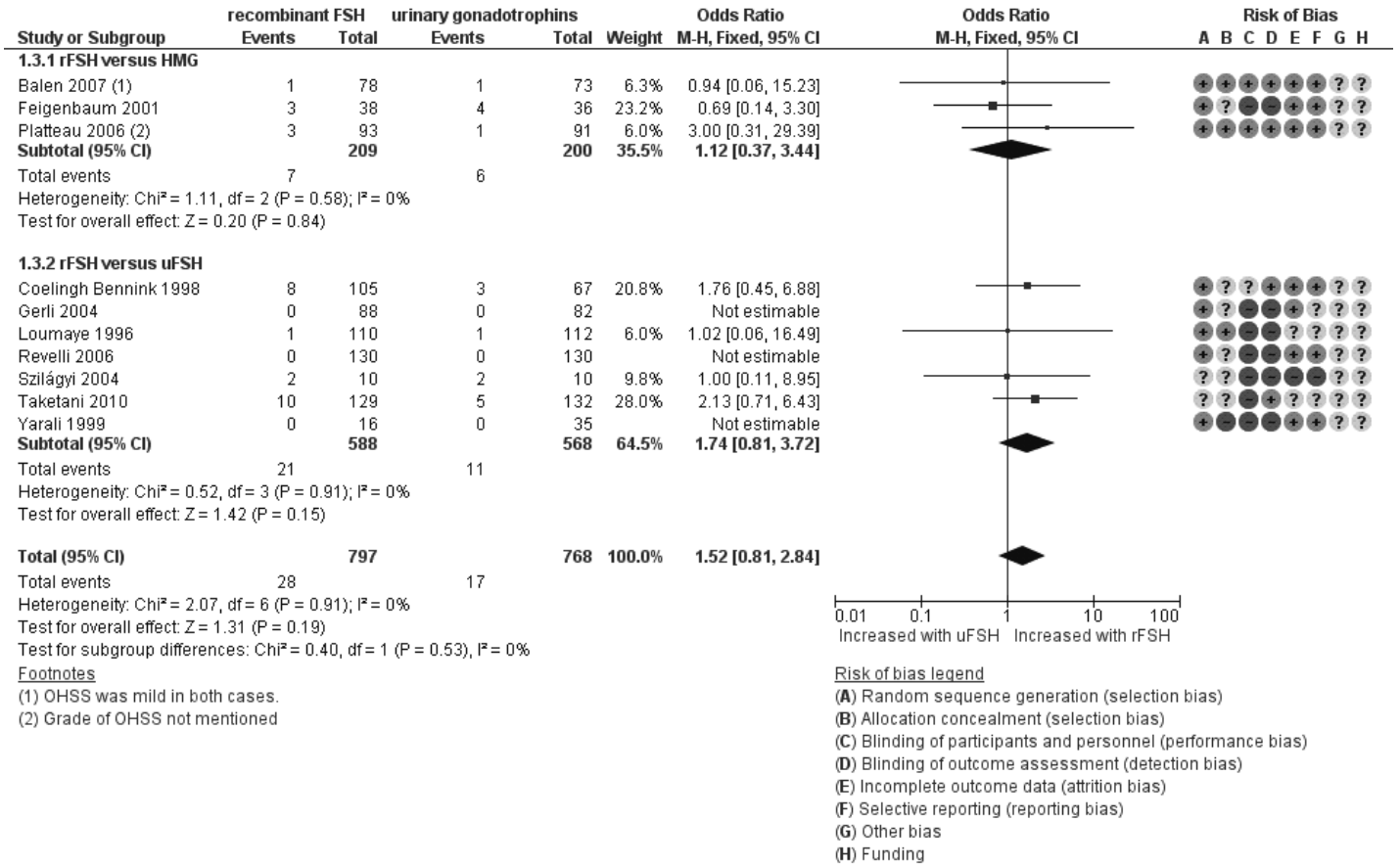


Figure 5. Forest plot of comparison 1: recombinant FSH versus urinary-derived gonadotrophins, outcome: Incidence of OHSS per woman
Subgrouping by sponsor did not result in differences between subgroups (P = 0.88).

Incidence of multiple pregnancy per woman

Eight studies including 1368 women reported on multiple pregnancy (Balen 2007; Coelingh Bennink 1998; Feigenbaum 2001; Gerli 2004; Platteau 2006; Revelli 2006; Taketani 2010; Yarali 1999). There was no evidence of a difference in multiple pregnancy (OR 0.86, 95% CI 0.44 to 1.65; 8 RCTs, n = 1368, I^2 = 0%, low-quality evidence).

When dividing the urinary-derived gonadotrophins into subgroups (three trials compared rFSH versus HP-HMG, five trials compared rFSH versus FSH-HP), there was no evidence of a difference between the subgroups (P = 0.34).

Tabel I. Summary of findings for the main comparison: recombinant FSH versus urinary-derived gonadotrophins for ovulation induction in women with polycystic ovarian syndrome.

Patient or population: women with polycystic ovarian syndrome
Settings: women visiting the outpatient clinic
Intervention: recombinant FSH versus urinary-derived gonadotrophins as second-line treatment

	Illustrative comparative risks* (95% CI)				
	Assumed risk	**Corresponding risk**			
Outcomes	**Urinary-derived gonadotrophins**	**Recombinant FSH**	**Relative risk (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**
Live birth rate per woman	157 per 1000	191 per 1000 (127 to 257)	OR 1.26 (0.80 to 1.99)	505 (5 studies)	⊕⊕⊖⊖ **low**[1,2]
Incidence of OHSS per woman	22 per 1000	33 per 1000 (18 to 60)	OR 1.52 (0.81 to 2.84)	1565 (10 studies)	⊕⊖⊖⊖ **very low**[1,2,3]
Clinical pregnancy rate per woman	239 per 1000	253 per 1000 (207 to 304)	OR 1.08 (0.83 to 1.39)	1330 (8 studies)	⊕⊕⊖⊖ **low**[1,2]
Miscarriage rate per woman	47 per 1000	57 per 1000 (33 to 95)	OR 1.22 (0.69 to 2.15)	970 (7 studies)	⊕⊕⊖⊖ **low**[1,2]
Incidence of multiple pregnancy (per woman)	30 per 1000	26 per 1000 (13 to 48)	OR 0.86 (0.44 to 1.65)	1368 (8 studies)	⊕⊕⊖⊖ **low**[1,2]

*The basis for the **assumed risk** is the median risk in the controle groups. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; OR: Odds ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Imprecision around the absolute effect
[2] Inconsistency in results across studies
[3] In each study a different definition or no definition of OHSS, downgraded one further level

Incidence of multiple pregnancy per clinical pregnancy

We found no evidence of a difference in multiple pregnancy per clinical pregnancy (OR 0.69, 95% CI 0.33 to 1.43; 8 RCTs, 315 pregnancies, $I^2 = 0\%$).

Mean total gonadotrophin dose per woman

We found evidence of a statistically significant mean difference in total gonadotrophin use in favour of rFSH (MD -105 IU, 95% CI -154 to -57, 6 RCTs, n = 1046, $I^2 = 81\%$). Use of a random-effects model in view of the high statistical heterogeneity resulted in no evidence of a difference (MD -127 IU, 95% CI -258 to 3.26).

Total duration of stimulation per woman (days)

We found evidence of a statistically significant mean difference in total duration of stimulation favour of rFSH (MD -0.66 days, 95% CI -1.04 to -0.28, 6 RCTs, n = 1122, $I^2 = 72\%$). Use of a random-effects model in view of the high statistical heterogeneity resulted in no evidence of a difference (MD -0.80 days, 95% CI -1.66 to 0.05).

HMG or HP-HMG versus uFSH

Live birth per woman

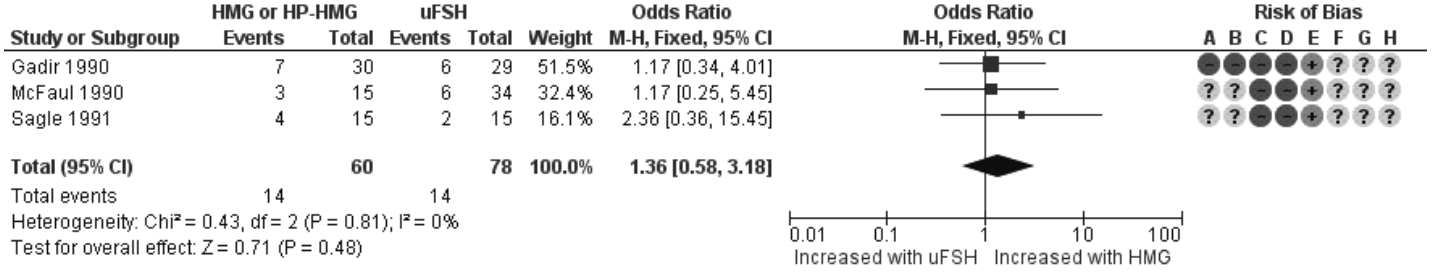
Three trials including 138 women reported on live birth (Gadir 1990; McFaul 1990; Sagle 1991). We found no evidence of a difference in live birth rate (OR 1.36, 95% CI 0.58 to 3.18, 3 RCTs, n = 138, $I^2 = 0\%$, low-quality evidence) (Figure 6).

Incidence of OHSS per woman

Two studies reported OHSS including 53 women (Sagle 1991; Seibel 1985). We found no evidence of a difference in OHSS (OR 9.95, 95% C 0.47 to 210, 2 RCTs, n = 53, very low-quality evidence).

Clinical pregnancy rate per woman

One study reported clinical pregnancy rate per woman (Sagle 1991). McFaul 1990 presented pregnancy rates without defining this outcome. For this study, we calculated the clinical pregnancy rates by adding the number of live births to the number of miscarriages in each group. Seibel 1985 reported conception rates, which we used as clinical pregnancy rate.
This analysis covers 102 women. After pooling the data, we found no evidence of a difference (OR 1.44, 95% CI 0.55 to 3.77, 3 RCTs, n = 102, $I^2 = 0\%$, low-quality evidence).



Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias
(**H**) Funding

Figure 6. Forest plot of comparison 2: HMG or HP-HMG versus uFSH, outcome: Live birth rate per woman.

Miscarriage rate per woman

We found no evidence of a difference in miscarriage rate (OR 0.30, 95% CI 0.04 to 2.05, 2 RCTs, n = 98, I^2 = 0%, low-quality evidence).

Incidence of multiple pregnancy per woman

We found no evidence of a difference in multiple pregnancy rate per woman (OR 2.26, 95% CI 0.47 to 10.95, 4 RCTs, n = 161, I^2 = 0%).

Table II. Additional summary of findings for the comparison HMG or HP-HMG versus uFSH for ovulation induction in women with polycystic ovarian syndrome.

Patient or population: women with polycystic ovarian syndrome
Settings: women visiting the outpatient clinic
Intervention: HMG or HP-HMG versus uFSH as second-line treatment

	Illustrative comparative risks* (95% CI)				
	Assumed risk	**Corresponding risk**			
Outcomes	**uFSH**	**HMG or HP-HMG**	**Relative risk (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**
Live birth rate per woman	179 per 1000	230 per 1000 (90 to 370)	**OR 1.36** (0.58 to 3.18)	138 (3 studies)	⊕⊖⊖⊖ **low**[1,2]
Incidence of OHSS per woman	No events	4/28[3]	**OR 9.95** (0.47 to 210)	53 (2 studies)	⊕⊖⊖⊖ **very low**[1,2,4]
Clinical pregnancy rate per woman	203 per 1000	269 per 1000 (123 to 490)	**OR 1.44** (0.55 to 3.77)	102 (3 studies)	⊕⊖⊖⊖ **low**[1,2]
Miscarriage rate per woman	82 per 1000	26 per 1000 (4 to 154)	**OR 0.30** (0.04 to 2.05)	98 (2 studies)	⊕⊖⊖⊖ **low**[1,2]
Incidence of multiple pregnancy (per woman)	23 per 1000	50 per 1000 (11 to 203)	**OR 2.26** (0.47 to 10.95)	161 (4 studies)	⊕⊖⊖⊖ **low**[1,2]

*The basis for the **assumed risk** is the median risk in the controle groups. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; OR: Odds ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Imprecision around the absolute effect
[2] Inconsistency in results across studies
[3] Event rate derived from the raw data. A 'per thousand' rate is non-informative in view of the scarcity of evidence and zero events in the control group
[4] In each study a different definition of OHSS, downgraded one further level. Two of our studies did not report this outcome

Incidence of multiple pregnancy per clinical pregnancy

The total number of multiple pregnancies within the studies that reported clinical pregnancies were too small to compare.

Mean total gonadotrophin dose per woman

The studies of Gadir 1990 and McFaul 1990 reported mean values for total doses but they did not state standard deviations (HMG/HP-HMG versus uFSH): 1568 versus 1478 (Gadir 1990) and 1770 versus 1995 (McFaul 1990). The authors declared that they found no significant difference.

Sagle 1991 also observed no significant difference. They reported values in mean total dose per cycle: 1080 (min - max: 525 - 1950) versus 1447.5 (min - max: 675 - 2887.5).

Total duration of stimulation per woman (days)

McFaul 1990 reported no significant mean difference between HMG and uFSH (11.8 versus 11.9 days respectively). They did not provide standard deviations.

DISCUSSION

Summary of main results

This review compared the effectiveness of recombinant gonadotrophin (rFSH) with the three main types of urinary gonadotrophins (i.e. HMG, FSH-P and FSH-HP) as a second-line treatment for ovulation induction in women with CC-resistant PCOS. We found 10 studies that compared rFSH versus urinary-derived gonadotrophins, and four trials that compared uFSH with HMG. There was no evidence of a difference in pregnancy outcomes when rFSH was compared to urinary gonadotrophins as a whole, nor when comparing rFSH with HMG/HP-HMG or rFSH with FSH-HP. There was no evidence of a difference observed in OHSS for any of the comparisons. We found no trials which compared rFSH and FSH-P or FSH-HP with FSH-P.

Overall completeness and applicability of evidence

For the trials that compared rFSH and urinary-derived gonadotrophins, outcome data needed to make the planned comparisons were largely available; these trials were all published after 1996. The data of trials that compared rFSH and uFSH-P and uFSH-HP were incomplete, probably because these trials had been published between 1985 and 1991 when there were no CONSORT or PRISMA guidelines and clinical pregnancy or ovulation rate were still accepted endpoints.

Seven trials did not define the outcome OHSS. The remaining studies used very different definitions (see Characteristics of included studies, available online). Nowadays, it is common to categorise cases of OHSS by three degrees; mild, moderate or severe.[27] Since this ranking was almost never used in the included studies of this review, it may be inappropriate to pool the data on OHSS. Also, different starting dosages were used varying from 50 to 150 IE per day, with various criteria to withhold from injecting human chorion gonadotrophin (hCG). This may influence the incidence of OHSS, regardless of the type of gonadotrophin used.

The data on gonadotrophin dose used and duration of stimulation were never presented per woman randomised, and showed high statistical heterogeneity. These outcomes are therefore likely to be biased, and conclusions on the basis of these data should not be drawn.

Three of the included studies used IUI in addition to ovulation induction with gonadotrophins. IUI may or may not have increased the pregnancy rate, but as in these studies IUI was always provided in both study arms, its effect on differential pregnancy rates is likely to be small.

No women were included that had been treated with electrocautery in the past. We can therefore draw no conclusions on this specific population.

The included population represents women with PCOS who are either CC-resistant or failed to conceive with CC. The evidence is broadly applicable as a second-line treatment for ovulation induction in these women.

Quality of the evidence

GRADE assessment found that evidence for most outcomes was of low to very low quality, due to the limited amount of studies, small study size, statistical heterogeneity, and the quality of the individual studies.

Potential biases in the review process

Strengths of this review include comprehensive systematic searching for eligible studies, rigid inclusion criteria for RCTs and data extraction, and analysis by three independent review authors. The possibility of publication bias was minimised by inclusion of both published and unpublished studies (such as abstracts from meetings). However, as with any review, we cannot guarantee that we found all eligible studies.

Agreements and disagreements with other studies or reviews

Our results are in line with the outcomes of the previous Cochrane review of Bayram 2001,[21] in concluding that rFSH and urinary-derived gonadotrophins are equally effective for ovulation induction in women with PCOS in terms of ovulation rate, pregnancy rate, miscarriage rate and multiple pregnancy rate. Our results are also in line with the outcomes

of the previous Cochrane review of Nugent 2000,[22] who concluded that comparing FSH and HMG showed no evidence of a difference in pregnancy rate. Nugent 2000 did find a significant reduction in OHSS rate per cycle in women treated with FSH-P compared to HMG. We focused on OHSS rate per woman and did not find any difference, although only two trials were available for this analysis.

Bayram 2001 and Nugent 2000 did not evaluate the outcome of live birth. We found no evidence of a difference in live birth rate for the comparisons rFSH versus urinary gonadotrophins and HMG or HP-HMG versus uFSH, but the quality of evidence was low.

Another review compared rFSH with urinary-derived FSH products. The authors found that follitropin alpha, beta and urinary FSH products appeared to be as effective in terms of clinical, ongoing and multiple pregnancy rates as in live birth rates. This review did not pool data on OHSS.[28]

AUTHORS' CONCLUSIONS

Implications for practice

It appears that differences in effectiveness and safety between the available gonadotrophins are small. The choice of one or the other product will depend upon the availability of the product, the convenience of its use, and the associated costs.

Implications for research

We chose ovarian hyperstimulation syndrome (OHSS) as a safety outcome, since this review is an update of two older Cochrane reviews which have also used this outcome. Both reviews and the current review included mainly older studies, performed at a time when OHSS was a complication after ovulation induction. At present, OHSS is mainly a complication that occurs after treatment with IVF.[27] Nowadays it seems more relevant to investigate the occurrence of multiple pregnancies after ovulation induction. In this respect, we found no evidence of a difference in multiple pregnancy rates per woman when comparing the different types of gonadotrophins, but the included studies were of low quality. We therefore feel that new research should be specifically directed at preventing multiple pregnancies while retaining the highest live birth chances. Another reason for the need for new research is the low quality of most of the included studies in this review.

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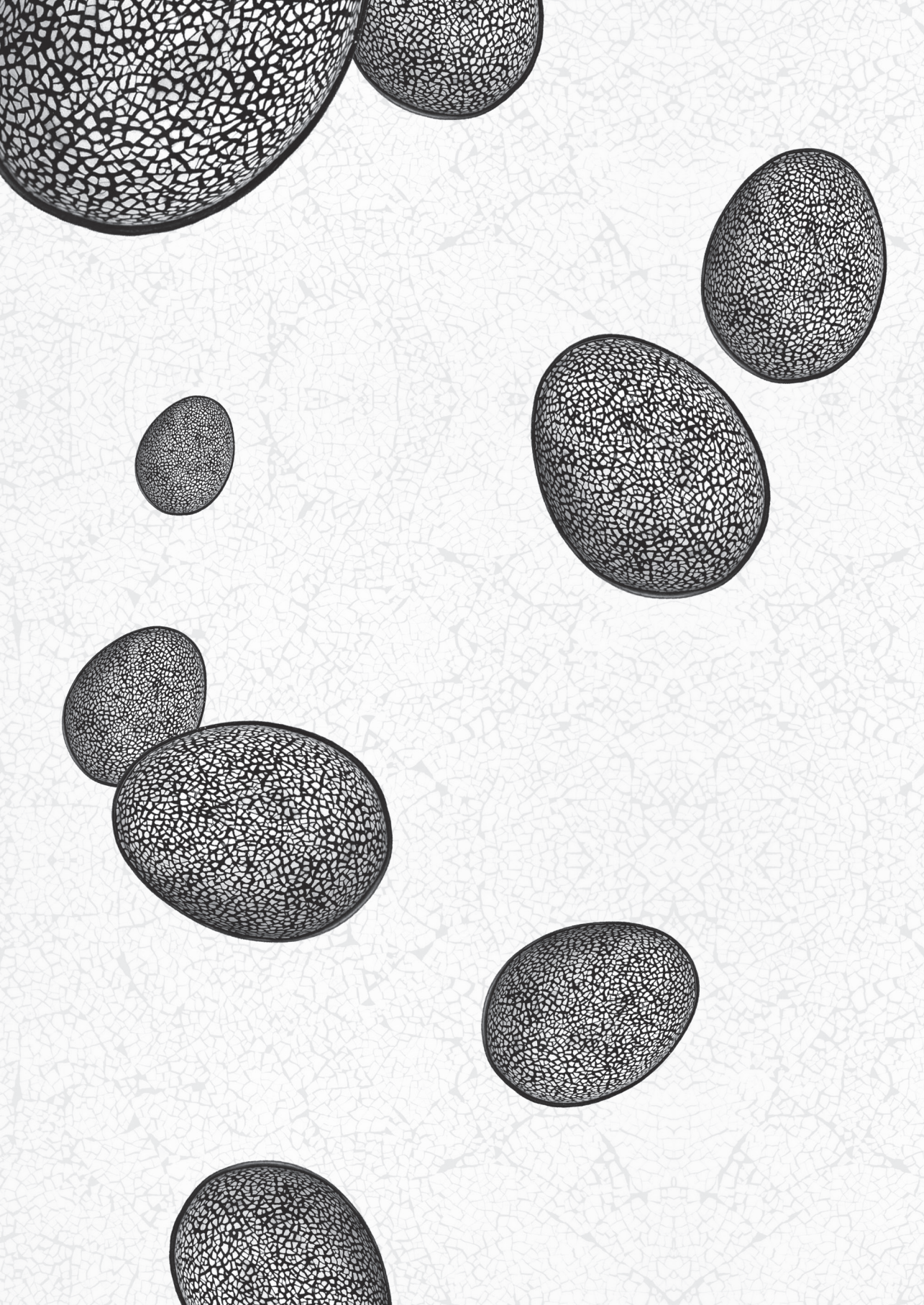
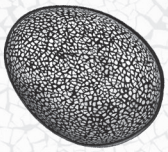


3

Does the postcoital test predict pregnancy in WHO II anovulatory women? A prospective cohort study



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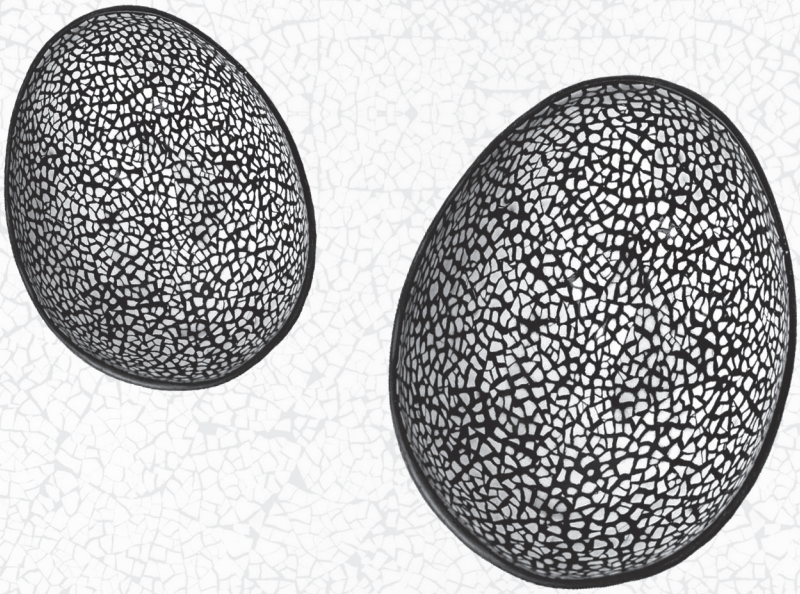

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ABSTRACT

Objective: To assess the capacity of the postcoital test (PCT) to predict pregnancy in WHO II anovulatory women who are ovulatory on clomiphene citrate (CC). In these women, an abnormal PCT result could be associated with lower pregnancy chances, but this has never been proven or refuted.

Study design: Prospective cohort study was performed between December 2009 and September 2012 for all women who started ovulation induction with CC in one university clinic and two teaching hospitals in the Netherlands. A PCT was performed in one of the first three ovulatory cycles. Ovulation induction with CC was continued for at least six cycles. The PCT was judged to be positive if at least one progressive motile spermatozo was seen in one of five high power fields at 400× magnification. The primary outcome was time to ongoing pregnancy, within six ovulatory cycles.

Results: In 152 women the PCT was performed. 135 women had a reliable, well-timed PCT. The ongoing pregnancy rate was 44/107 (41%) for a positive and 10/28 (36%) for a negative PCT. The hazard rate for ongoing pregnancy was 1.3 (95% CI 0.64–2.5) for a positive versus a negative PCT.
Thirty five of 77 (46%) women with clear mucus had an ongoing pregnancy versus 12 of 45 (27%) women in whom the mucus was not clear (HR 2.0; 95% CI 1.02–3.84, $p = 0.04$).

Conclusion: The present study suggests that the outcome of the postcoital test in women with WHO-II anovulation that undergo ovulation induction with CC does not have a large effect on ongoing pregnancy chances over time.

INTRODUCTION

Anovulation and oligo-ovulation are important causes of subfertility and are estimated to contribute to 20% of all cases of female subfertility.[1,2] The recommended first-line treatment for ovulation induction is the anti-oestrogen clomiphene citrate (CC) according to the ESHRE/ASRM-Sponsored PCOS Consensus Work- shop Group. [3,4] CC will restore ovulation in almost 80% and will result in pregnancy in 50% of all women.

Though CC results in high pregnancy rates, several studies have shown that CC has a negative effect on the cervical mucus.[5-7] The Dutch guidelines and the National Institute for Health and Clinical Excellence guidelines are not specific on the necessity to perform a PCT to exclude or demonstrate a cervical factor in women ovulating after induction as evidence on the relation between cervical factor and pregnancy chances does not exist.

The studies on the negative effect of CC on the cervical mucus did not evaluate whether abnormal cervical mucus was associated with lower pregnancy chances and the only prospective follow-up study on the relation between the result of the PCT and pregnancy rates describes the PCT outcome in some women, while the pregnancy rates are described in other women.[5-8] Therefore the association between outcome of the PCT and pregnancy chances cannot be determined from this study.

In view of this lack of knowledge we initiated a prospective cohort study to evaluate the relationship between the result of the postcoital test and time to ongoing pregnancy after ovulation induction with CC in women with WHO II anovulation.

MATERIAL AND METHODS

Between December 2009 and September 2012, we performed a multicenter prospective cohort study in one university clinic and two teaching hospitals in the Netherlands. All women with WHO II anovulation attending these clinics were asked to participate in this study. The study protocol was approved by the Institutional Review Board of the Medical Spectrum Twente of Enschede (registration number: P08-37), and had local approval from the board of the other participating hospitals.

Participants

We studied women with WHO class II anovulation who started ovulation induction with CC. Women needed to have oligo- or anovulation, combined with signs of hyperandrogenism or polycystic ovaries on ultrasound. Women younger than 18 years and women with other causes of anovulation, like thyroid disease or hyperprolactinaemia were not eligible for the study. The total motile sperm count had to be above 1 million in at least one semen analysis before starting ovulation induction. The cut-off point of 1 million was chosen to exclude severe male factor. Tubal patency tests before start of treatment were not mandatory, as the

incidence of bilateral tubal obstruction is low within this group of women and tubal patency testing is not without risks,[9] but women with already known bilateral tubal obstruction were excluded. Women could enter the study only once.

Study design and treatment regimen

Ovulation induction with CC was started after a spontaneous or progesterone induced menstrual bleed. From the third or fifth day until the seventh or ninth day after menstruation women took CC with a minimum of 50 mg to a maximum of 150 mg a day. If ovulation did not occur with the lowest dose of 50 mg/day, it was increased with steps of 50 mg to a maximum of 150 mg a day in the next cycles. Ovulation was established according to local protocol. Centres used a biphasic temperature curve, a follicle with a diameter ≤18 mm on transvaginal ultrasonography, progesterone ≤16 nmol/l in the second half of the cycle or a cycle length ≤35 days to define ovulation. The menstrual cycle was considered regular if the duration of the cycle was between 23 and 35 days. A PCT was performed during the basic fertility work-up in one of the first three ovulatory cycles. The test was planned based on cycle history or the basal body temperature (BBT) curve in the preceding cycle or ultrasound findings in the present or preceding cycle. In couples in whom the timing depended on the BBT and cycle length, the PCT was scheduled the day before the expected ovulation. In couples where the timing depended on ultrasound findings, the PCT was performed once the dominant follicle was ≤18 mm. The couple was asked to have intercourse four to sixteen hours before the appointment. The PCT was carried out by cleaning the cervix, followed by aspiration of endocervical mucus using a 1 ml disposable syringe or forceps. Clarity (clear or not clear) and spinnbarkeit were assessed and recorded. Mean number of progressive motile spermatozoa in a high power field at 400× magnification were determined. The PCT was judged to be positive if at least one progressive motile spermatozo was seen in one of five high power fields at 400× magnification. All other PCT results were considered to be negative. In case of a normal, positive test, only one PCT had to be performed. If progressive motile spermatozoa were absent, the test was scheduled again two days later or following the confirmation of a dominant follicle on ultrasound. In case the timing of the PCT was not optimal the test was planned again next month, based on ultrasound measuring of the follicle or LH tests. In case the test was negative again, and timing was appropriate the PCT test was considered to be negative. Follow-up started immediately after starting ovulation induction and ended at six ovulatory cycles. CC was continued for at least six cycles for both a positive and negative result of the PCT within a time horizon of 12 months.

Outcome measures

The primary endpoint of this study was time to an ongoing, viable intrauterine pregnancy, confirmed by ultrasonography, defined as a fetal heart beat seen by vaginal ultrasonography

at 12 weeks' gestation. The first day of the last menstrual period was considered to mark the end of time until natural conception. Time to pregnancy was censored at the day of start of any other treatment within six months after the start of ovulation induction with CC or at the day of the last contact during follow up, if the couple had no ongoing pregnancy.
Secondary outcomes were ovulation, clinical pregnancy, defined as any registered heart beat at sonography, ectopic pregnancy and miscarriage, defined as loss of an intra uterine pregnancy (confirmed by ultrasound or histological examination) before the 12th week of pregnancy and multiple gestation, defined as a registered heartbeat of at least two fetuses at 12 weeks of gestation.

Power calculation and statistical analysis

We planned a comparison between women with a positive and women with a negative result of the PCT. We anticipated that 50% of women would have an ongoing pregnancy within six ovulatory cycles, and that the ratio of a positive versus a negative PCT was 1.5:1. This ratio was based on data reported in the literature and a retrospective search in the clinics where women would be included. To prove that a negative PCT indicates a decrease of 20% chance for an ongoing pregnancy within six months compared to a standard of 50%, with a power of 80% and an alpha of 5%, 234 women needed to be included. To account for drop out, which we estimated not to be substantial, we aimed to include 250 women.
We compared time to ongoing pregnancy by constructing Kaplan Meier curves for women with a positive and negative result of the PCT. We performed Cox proportional hazard analyses to assess the association between the outcome of the PCT with time to ongoing pregnancy as a dependent variable adjusted for female age, total motile sperm count and duration of subfertility. Associations were expressed as hazard rate ratios (HR). We performed two sensitivity analyses. In the first we assumed that all the unrepeated negative PCTs would have been negative, in the second we assumed that all the unrepeated negative PCTs would have been positive.
We performed a separate analysis based on number of progressive motile spermatozoa per high power field and mucus quality. We classified the findings at PCT into four groups and compared pregnancy rates for women without progressive motile spermatozoa, for those with 1 progressive motile spermatozo, for those with 1–5 progressive motile spermatozoa and for women with more than five progressive motile spermatozoa per high power field at 400× magnification. Log rank test was used to test whether time to ongoing pregnancy differed significantly between groups. We classified the cervical mucus as clear or not clear. The effect of CC dose was not be taken into account since no evidence exists that the dose has any influence on pregnancy rates as long as women are ovulatory with CC.

RESULTS

PCT

The study profile is shown in Fig. 1. A total of 251 women with WHO class II anovulation starting ovulation induction with CC in three hospitals were included in this follow up study. There were 152 women (61%) with at least one PCT during one of the first three ovulatory cycles. The PCT was not performed in the remaining 99 women for various reasons, of which the main reason was pregnancy before the PCT could be planned.
Of the 152 remaining women, the PCT could be adequately performed in 135 women (89%) starting ovulation induction with CC, of whom 107 had a positive and 45 women had a negative PCT result. Baseline characteristics are shown in Table I. For all women included, 63% of the women had a BMI below 25 (159/251), 18% had a BMI between 25 and 30 (45/251), 11% had a BMI above 30 (28/251) and for another 8% the BMI was unknown. No differences between women with the three different test results were observed.

Table I. Baseline characeteristics of women with a PCT (n = 152)

	Results of the PCT			
	Positive n = 107	**Negative n = 28**	**Negative, not well timed n = 17**	**Significance (p < 0.05)**
Clinical parameters				
Female age in years (mean)	29.15	29.59	29.30	0.62
Duration of subfertility in months (mean)	16.1	18.2	14.7	0.46
Primary subfertility n (%)	77 (72)	22 (79)	13 (77)	0.51
Smoking n (%)	21 (20)	3 (11)	3 (18)	0.86
Amenorrhea n (%)	29 (27)	7 (25)	1 (6)	0.17
BMI (mean)	23.7	22.7	22.22	0.34
Male partner				
Total motile sperm count (median)	67	64	79	

A total of 200 PCTs were performed in the 152 women. In 131 women one ovulatory cycle was needed to perform an adequate PCT, while in 21 women PCTs in two or more ovulatory cycles were necessary. In 107 women who finally had a positive PCT more than one PCT was performed in 20% of the women, whereas in 28 women with a negative PCT more than one PCT was performed in 50% of women.

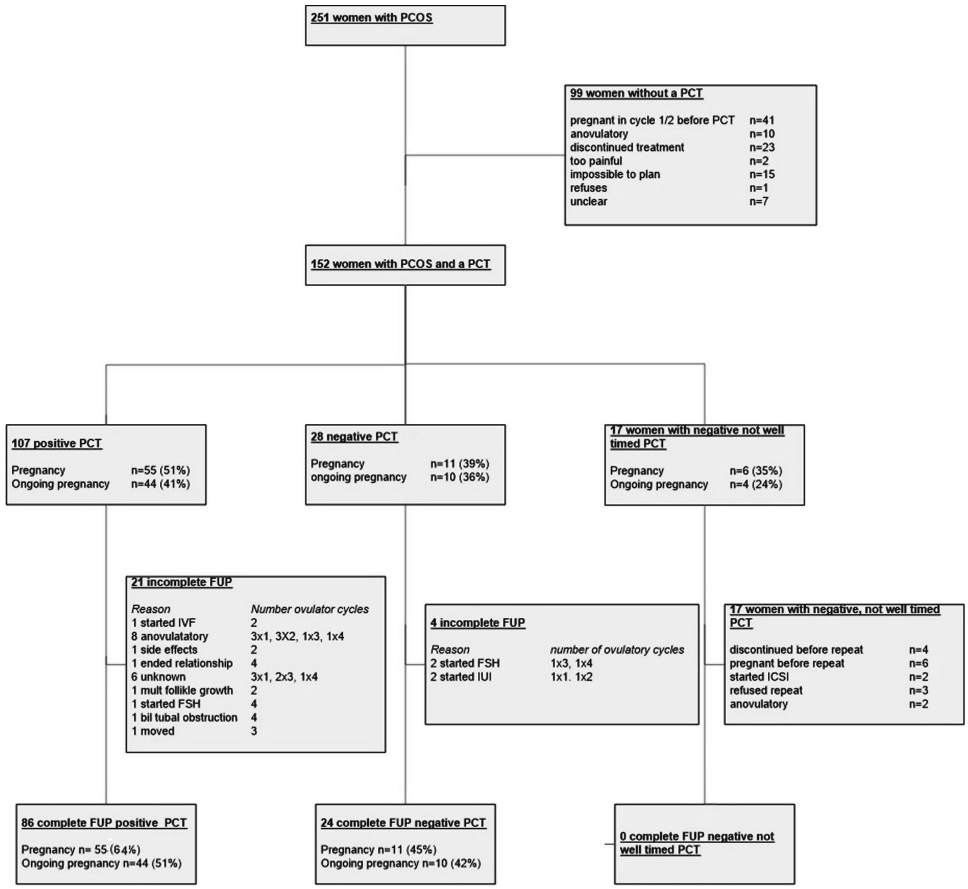

Figure 1. Study profile

Pregnancy

Overall, 72 of the 152 women (47%) had a clinical pregnancy (Fig. 1). Clinical pregnancy rate per cycle is shown in Table II.

Unsuccessful pregnancies occurred in 13 women (18%) of whom 12 miscarried and 1 had an ectopic pregnancy.

From the 152 women, 59 (39%) had an ongoing pregnancy within 6 ovulatory cycles after start with CC. From the 135 women with a well-timed, adequate performed PCT, 54 (40%) had an ongoing pregnancy within 6 ovulatory cycles after start with CC. Of the 107 women with a positive PCT, 44 women (41%) had an ongoing pregnancy. Of the 28 women with a negative PCT, 10 women (36%) had an ongoing pregnancy. Of the 17 women in whom the PCT was not well-timed and negative, but not repeated, 4 women (24%) had an ongoing pregnancy. All ongoing pregnancies were singleton pregnancies (Fig. 1). There

were 24 women who discontinued treatment before the sixth ovulatory cycle, without a pregnancy. Kaplan–Meier analysis of the cumulative probability of ongoing pregnancy up to six ovulatory cycles are shown in Fig. 2.

Table II. Pregnancy rate per ovulatory cycle

Ovulatory cycle	Women started	Pregnancy n (total)			Pregnancy rate per cycle (%)
		Positive	Negative	Negative, not well timed	
1	152	10	0	1	7
2	133	11 (21)	2 (2)	3 (4)	12
3	110	10 (31)	1 (3)	0 (4)	10
4	92	17 (48)	4 (7)	1 (5)	24
5	59	3 (51)	2 (9)	0 (5)	8
6	52	3 (54)	2 (11)	1 (6)	13
Total pregnancies		54/107 (50%)	11/28 (39%)	6/17 (35%)	72/152 (47%)

Pregnancy over time and associations

There was no evidence for a difference in ongoing pregnancy chance over time between women with a positive and women with a negative PCT result (HR 1.3; 95% CI 0.64–2.5). Under the assumption that all the unrepeated negative PCT would have been true negative PCT outcomes, the negative PCT group would entail 45 women of whom 14 women had an ongoing pregnancy. The ongoing pregnancy chance over time remained almost the same (HR 1.3; 95% CI 0.74–2.5). Under the assumption that the unrepeated negative PCT tests would actually have been positive PCT outcomes, the positive PCT group would entail 124 women of whom 48 women had an ongoing pregnancies. The ongoing pregnancy chance over time would also remain comparable (HR 1.2; 95% CI 0.61–2.4). For all these analyses there was no association of female age, total motile sperm count and duration of subfertility with ongoing pregnancy rates. Furthermore there was no interaction with between these variables and PCT.

Ranking motile spermatozoa and clarity of mucus

When ranking women, with a well-timed PCT, based on number of progressively motile spermatozoa per high power field, no differences in pregnancy rate were reported for women with none, one, one to five or more than five progressively motile spermatozoa per high power field (Table III). No statistically significant differences were found between those four groups in time to pregnancy (log rank test $p = 0.31$). When ranking women, with a well-timed PCT, based on clarity of the mucus, women with clear mucus had a significantly higher chance of an ongoing pregnancy. Thirty five of 77 (46%) women with clear mucus had an ongoing pregnancy versus 12 of 45 (27%) women in whom the mucus was not

clear (HR 2.0; 95% CI 1.02–3.84, p = 0.04). For all these analyses there was no association of female age, total motile sperm count and duration of subfertility with ongoing pregnancy rates. Furthermore none of these factors had any interaction with mucus clarity. There was no absence of mucus for any PCT (Table III).

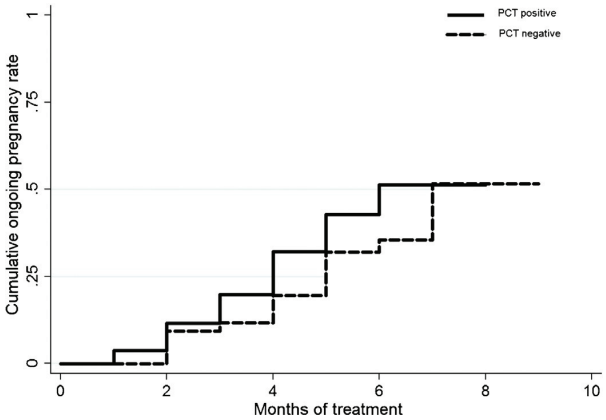

Figure 2. Cumulative proportion of women with a positive and negative result of the PCT (time in months from first ovulatory cycle).

Table III. Ongoing pregnancy rate per woman included in subgroup analysis based on 1) Number of progressive motile spermatozoa per high power field and 2) Mucus quality.

Progressive motile spermatozoa/ high power field		Positive	Negative	Negative, not well timed
0			10/28 (36)	4/17 (24)
1		4/11 (36)		
2-5		13/34 (38)		
>5		22/51 (47)		
Unknown		7/11 (63)		
Mucus	**Positive**	**Negative**	**Negative, not well timed**	**Total**
Clear	29/67 (43)	6/10 (60)	1/7 (14)	36/84 (42)
Not clear	8/27 (30)	4/18 (22)	2/7 (29)	14/52 (27)
Unknown	8/13 (62)	0/0	1/3 (33)	9/16 (56)

DISCUSSION

In this prospective cohort study we included 251 women with WHO II anovulation who started ovulation induction with CC. A PCT could be performed in 152 women who became ovulatory with CC. Women with an abnormal PCT had an ongoing pregnancy rate of 36%

compared to an ongoing pregnancy rate of 41% in women with a normal PCT. There was no evidence of a difference in time to ongoing pregnancy as expressed by a hazard rate of 1.3 (95% CI 0.64–2.5). In women with clear mucus the ongoing pregnancy rate was significantly higher (HR 2.0; 95% CI 1.02–3.84, p = 0.04).

The strength of our study is that we were able to assess the value of the PCT and cervical mucus in a prospective multicentre cohort. All women attending the fertility clinics with subfertility and WHO II anovulation were included. When ovulatory with CC a PCT was performed, or the reason for not performing was registered, which was usually due to pregnancy. The PCT was performed by various clinicians in different hospitals, but this is an adequate reflection of the true performance of the PCT in daily practice.

A limitation of our study is the sample size. The subset of women with a negative PCT was smaller than expected and from the 251 included women in only 152 women a PCT could be performed as a substantial number of women either got pregnant very fast, remained anovulatory and or just refused to do the test. Nevertheless, the differences in pregnancy rates between women with a positive and a negative PCT were small, and, more importantly, the absolute pregnancy rate was with 36%–41% rather high.

Women with clear mucus had a higher chance of pregnancy than women in whom the mucus was judged as not clear. Thirty five of 77 (46%) women with clear mucus had an ongoing pregnancy versus 12 of 45 (27%) women in whom the mucus was not clear. This difference could not be explained by a difference in female age, total motile sperm count and/or duration of subfertility. We could only speculate that spermatozoa migrate more easily through clear mucus than unclear mucus since evidence for this theory is lacking.

Compared to all other groups, the subgroup of women with a negative PCT and cervical mucus of poor quality had the lowest chance on an ongoing pregnancy (22%). This could in theory be the group that benefits from doing a PCT and a mucus determination. However, this group accounted for only 7% of the 250 women included in this study and therefore probably not worth of doing, especially since the PCT may result in emotional stress.[10] We noticed that several women refused the PCT, some thought it to be painful or the PCT was impossible to plan.

Performing PCTs may also have unnecessary side effects like switching treatment. In this study 4 out of 28 women (14%) with a negative test immediately switched treatment after the negative result of the PCT; two women started IUI and two women started ovulation induction with gonadotrophins. Also 6 out of 17 women (35%) with a negative and not well timed PCT stopped treatment or switched treatment before the PCT could be repeated as indicated. In daily practice this number may be higher. Finally, 17 out of 45 women (38%) with a negative PCT became pregnant.

In summary, the findings of this prospective cohort study demonstrated that the postcoital test has only limited value in women with WHO II anovulation, ovulatory with CC. Women

with clear mucus may have a higher chance of pregnancy than women with unclear mucus but an explanation for this is not available. We advocate that women who start ovulation induction with CC can safely do so without performing a PCT.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

FUNDING

None

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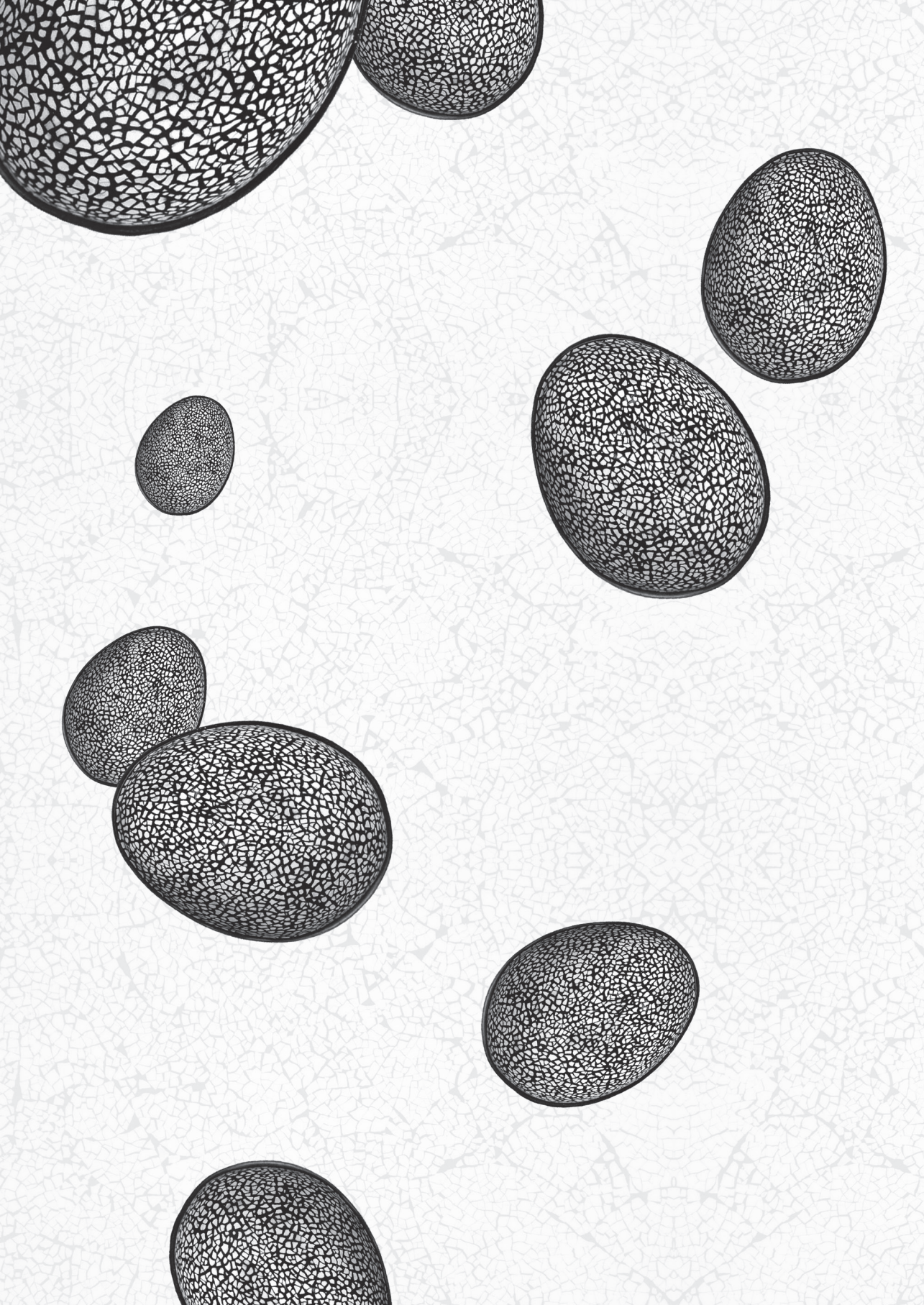

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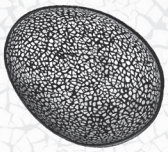
How long should we continue clomiphene citrate in anovulatory women?



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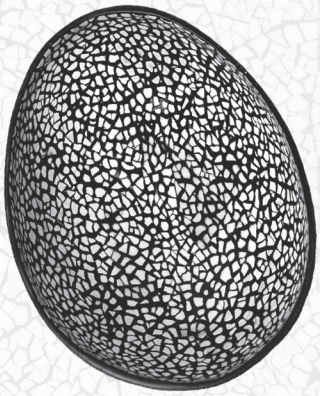

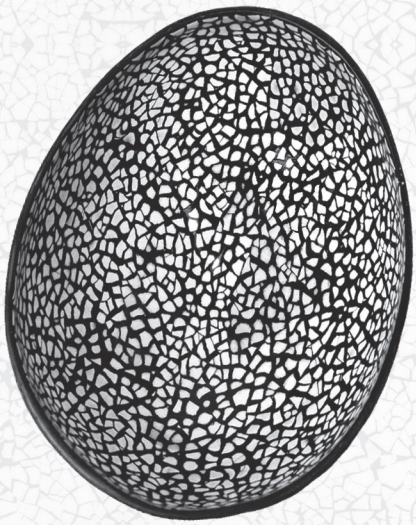

Human Reproduction. 2014 Nov

ABSTRACT

Study question: What is the effectiveness of continued treatment with clomiphene citrate (CC) in women with World Health Organization (WHO) type II anovulation who have had at least six ovulatory cycles with CC but did not conceive?

Summary answer: When women continued CC after six treatment cycles, the cumulative incidence rate of the ongoing pregnancy rate was 54% (95% CI 37–78%) for cycles 7–12.

What is known already: If women with WHO type II anovulation fail to conceive with CC within six ovulatory cycles, guidelines advise switching to gonadotrophins, which have a high risk of multiple gestation and are expensive. It is however not clear what success rate could be achieved by continued treatment with CC.

Study design, size, duration: We performed a retrospective cohort study of women with WHO II anovulation who visited the fertility clinics of five hospitals in the Netherlands between 1994 and 2010. We included women treated with CC who had had at least six ovulatory cycles without successful conception (n = 114) after which CC was continued using dosages varying from 50 to 150 mg per day for 5 days.

Participants/materials, setting, methods: Follow-up was a total of 12 treatment cycles. Primary outcome was the cumulative incidence rate of an ongoing pregnancy at the end of treatment.

Main results and the role of chance: We recruited 114 women that had ovulated on CC for at least six cycles but had not conceived. Of these 114 women, 35 (31%) had an ongoing pregnancy resulting in a cumulative incidence rate of an ongoing pregnancy of 54% after 7–12 treatment cycles with CC.

Limitations, reasons for caution: Limitations of our study are its retrospective approach.

Wider implications of the findings: Randomized trials comparing continued treatment with CC with the relatively established second line treatment with gonadotrophins are justified. In the meantime, we suggest to only begin this less convenient and more expensive treatment for women who do not conceive after 12 ovulatory cycles with CC.

Study funding/competing interest(s): None.

INTRODUCTION

Anovulation is a common cause of subfertility and is diagnosed in ~20% of all subfertile couples.[1] Eighty-five percent of these women have serum concentrations of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) within the normal range. This type of anovulation is classified as World Health Organization (WHO) type II. It results in irregularities in the pattern of menstrual bleeding or in amenorrhea.[2,3] In the majority of cases the anovulation is based on the polycystic ovary syndrome (PCOS). PCOS is characterized by oligo-anovulation, clinical or biochemical hyperandrogenism and polycystic ovaries.[4]

If women with PCOS or anovulation type II wish to conceive, guidelines state that clomiphene citrate (CC) is first line treatment. CC was first described in 1961. Before this time, women with anovulation due to polycystic ovaries could only be treated by a wedge resection of the ovaries. CC is a non-steroidal compound that resembles estrogen and blocks hypothalamic estrogen receptors, signaling a lack of circulating estrogen to the hypothalamus. This process changes the pattern of pulsatile release of GnRH which results in inducing a discharge of FSH from the pituitary gland and thereby folliculogenesis. Treatment results in a 70–85% ovulation rate, and a 40–70% conception rate after six cycles.[5,6] The Thessaloniki ESHRE/ASRMPCOS Consensus Workshop Group advices to limit treatment with CC to six (ovulatory) cycles, but to consider a maximum of 12 cycles on an individual basis. The NICE Fertility guideline of 2013 suggests to continue CC up to a maximum of six cycles. Both guidelines state that the next step in treating these women is ovulation induction with gonadotrophins (FSH).[7,8] Cumulative live birth rates of 50% after second line ovulation induction with gonadotrophins have been reported. Ovulation induction with gonadotrophins involves subcutaneous injections, requires close sonographic monitoring, is expensive and has a high risk of multiple pregnancy (14%).[9] In view of this; it might be preferable to continue CC for more than six cycles, but whether this continued treatment with CC for more than six ovulatory cycles is effective, is unknown.

The aim of this study was to investigate the effectiveness of continued treatment with CC for up to 12 ovulatory cycles in women with WHO type II anovulation.

MATERIALS AND METHODS

Subjects

We performed a retrospective cohort study of a series of consecutive women attending the fertility clinics of five hospitals in the Netherlands between 1994 and 2010 using the patient databases of each individual hospital. We included women aged between 18 and 41 years who were diagnosed with WHO type II anovulation. Serum prolactin and thyroid-stimulating hormone levels were within normal range. All women had been ovulatory for

at least six cycles on CC treatment, with a maximum of 150 mg daily for 5 days, but did not conceive. In the five participating hospitals it was standard policy to proceed with CC treatment up to 12 cycles in women that ovulated on CC. Ovulation was proved by ultrasound, basic body temperature, midluteal progesterone level or LH test. Tubal patency had been demonstrated based on hysterosalpingography, diagnostic laparoscopy with tubal testing or hydrolaparoscopy. Women were excluded if they were treated with a combination of CC and metformin or CC and intrauterine inseminations (IUI). Endometriosis proved by laparoscopy was also an exclusion criterion.
We studied charts from all women to confirm the number of ovulatory treatment cycles and to obtain data about the outcome of treatment. Follow-up was a total of 12 treatment cycles.
Primary outcome was the cumulative incidence rate of an ongoing pregnancy after 12 cycles. An ongoing pregnancy was defined as a fetal heartbeat seen on ultrasound by 12 weeks of gestation. Secondary outcomes were number of treatment cycles, miscarriages and multiple pregnancies.

Data analysis

A cumulative hazard function was used to estimate the cumulative hazard or incidence rate of an ongoing pregnancy over time where time was expressed as number of cycles. The cumulative incidence rate estimates the probability of having an ongoing pregnancy for women undergoing ovulation induction with of CC. Conceptions that ended in miscarriage before 12 weeks of gestation were ignored in this analysis, and in these cases follow-up continued until an ongoing pregnancy occurred. Women who did not become pregnant were censored at the time of last treatment. Second, the cumulative incidence rate of all pregnancies was calculated, i.e. including the conceptions ending in a miscarriage before 12 weeks of gestation.
Statistical analyses were performed with SPSS for Windows (version 20).

RESULTS

We analyzed 114 women that had ovulated on CC for at least six cycles but had not conceived. The baseline characteristics of these women are detailed in Table I. From these 114 women, 35 had an ongoing pregnancy (31%) within cycles 7–12. The number of women and ongoing pregnancies per cycle is displayed in Table II. Of the 35 ongoing pregnancies, 32 were singleton pregnancies and 3 (9%) were twin pregnancies. Eight women conceived but had at least one miscarriage before 12 weeks of gestation. One of these eight women had an ongoing pregnancy with CC at a subsequent time. The average ongoing pregnancy rate per cycle was 8.3%. Twenty-nine women (25%) completed 12

treatment cycles and 3 of these 29 women conceived. Fifty-five women (48%) dropped out before reaching 12 cycles, mainly because of a treatment switch to ovulation induction with gonadotrophins despite regular ovulation with CC (n = 34). Seven of the dropped out women (13%) changed treatment to CC combined with IUI and four (7%) to IVF or ICSI. Finally, six women (11%) stopped treatment because of personal reasons, two (4%) because of anovulation, one experienced severe side effects and for one woman the reason for dropout was unknown. We chose to include all these women in our analyses to follow the intention to treat principle.

Tabel I. Baseline characteristics

	114 women
Age years (mean ± SD)	30.4 ± 4.8
BMI kg/m^2 (mean ± SD)	25.0 ± 5.4
Primary subfertile n (%)	76 (67)
Duration of subfertility years (mean ± SD)	1.4 ± 0.9
LH IU/l (mean ± SD)	8.8 ± 5.0
FSH IU/l (mean ± SD)	5.8 ± 1.7
Total motile sperm count x 10^6 (median, min – max)	63 (3 – 557)

Table II. Ongoing pregnancies per cycle

Cycle number	**Women**	**Ongoing pregnancies per cycle**
7	114	8 (7%)
8	94	3 (3%)
9	80	12 (15%)
10	62	3 (5%)
11	45	6 (13%)
12	29	3 (10%)

The treatment cycles were evaluated in a hazard curve (Fig. 1). The cumulative incidence rate of an ongoing pregnancy was 54% (95% CI 37–78%) after 7–12 treatment cycles with CC. Pregnancy rates continued to rise until 12 cycles. The cumulative incidence rate of any pregnancy (including the early miscarriages) was 69% (95% CI 49–96%).

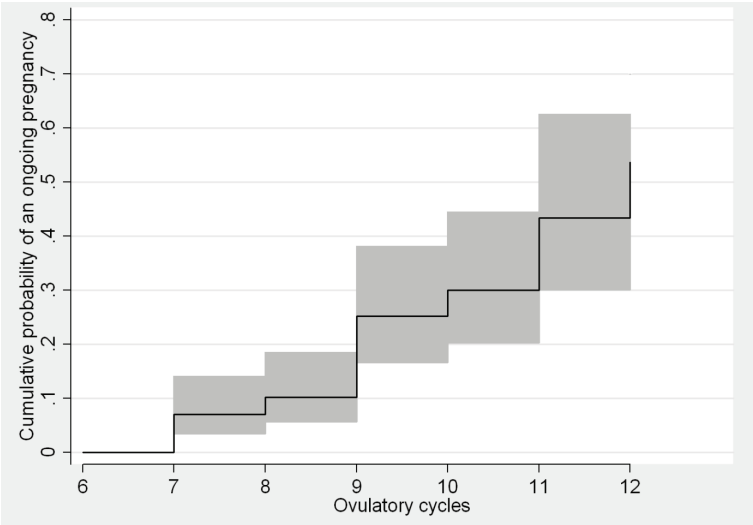

Figure 1. Cumulative probability of an ongoing pregnancy

DISCUSSION

Guidelines and reviews [2,6-8,10] agree on the effectiveness of CC in therapy naïve women with anovulation WHO type II and PCOS. All state that CC should be first in line after lifestyle changes in case of obesity. A recent multicenter randomized controlled trial that compared three cycles of ovulation induction with CC with three cycles of low-dose recombinant FSH in 255 therapy naïve women with PCOS found that cumulative live birth rates are higher with FSH than with CC (47 versus 37%, $P = 0.031$).[11] However, the authors state that this result should be balanced against convenience and costs which are in favor of CC. Another similar but smaller RCT (76 women randomized to either CC or FSH) showed no significant difference for both treatments after three cycles.[12] A prospective cohort study found a cumulative singleton live birth rate of 78% within 2 years after treatment with CC for a maximum of six to nine cycles followed by ovulation induction with gonadotrophins of 108 therapy naïve women with PCOS.[13]

There are no randomized studies that have focused on women who do ovulate on CC but do not conceive within six cycles. Only two small cohort studies performed a follow-up of women with PCOS that were treated with CC for 10 and 12 cycles. [14,15] In these limited studies, cumulative pregnancy rates were, respectively, 80 and 67% in women who ovulated on CC. Our study shows that continued treatment up to 12 ovulatory cycles with CC in women with WHO type II anovulation results in a cumulative incidence rate of 54% ongoing pregnancies in women not pregnant after six cycles. Some women however dropped out before reaching 12 treatment cycles. Reasons for dropping out were mostly based on reasons not

related to pregnancy chances. Main reasons were the wish of patients to change treatment or personal issues like divorces or moving elsewhere. Therefore, we assumed the women who dropped out had the same chances of conception with CC as the women remaining in the cohort. Cumulative incidence rate of an ongoing pregnancy represents the ongoing pregnancy chance of only those women who remained in the study. Though possibly overestimating real practice we find this estimate very informative. If a woman is prepared to undergo another six cycles of CC, the estimate is likely to represent her chances to reach an ongoing pregnancy. We acknowledge the number of women that dropped out and the retrospective design as limitations of our study. A further limitation of this study was its non-comparative nature. We do not know how CC in this group of women compares to ovulation induction with gonadotrophins.

Considering our results and the lack of large (randomized) trials with a focus on women who ovulate with CC but fail to conceive within a certain period of time, guidelines that state that there is no place for CC after six ovulatory cycles may reconsider this advice. Possible carcinogenic effects of extended use of CC are still debated but have never been proved.[16] A large cohort study of 3837 infertile women identified 11 women with a borderline or invasive malignant ovarian tumor, nine of which had used CC. Five of these women had taken CC for 12 cycles or more.[17] The authors of a histopathological study reviewing 35 cases of oophorectomies and cystectomies in women treated with IVF suggested a possible relationship between ovarian hyperstimulation and developing ovarian dysplasia. Two of the 35 women were treated with CC for more than six cycles.[18] Whether this ovarian dysplasia is clinically relevant is unclear since it has been shown that these lesions have a different genetic profile from ovaries from women with a genetic risk for ovarian cancer. Therefore it might be that this dysplasia will not develop into cancer.[19]

The ESHRE/ASRM PCOS Consensus Workshop Group proposes to combine CC or FSH with IUI when PCOS is associated with male subfertility or when women fail to conceive despite successful induction of ovulation.[7] Evidence for the value of combined treatment of ovulation induction and IUI in women with anovulation is, however, not available. So far, there has been one RCT conducted in women with anovulation comparing the effectiveness of IUI versus timed intercourse during ovulation induction.[20] This trial randomized 188 women with PCOS for either CC and IUI or CC and timed intercourse. Clinical pregnancy rates in both groups were comparable (23.6 versus 22.1%, $P = 0.33$). A retrospective cohort study of women with PCOS receiving ovulation induction (with CC, gonadotrophins or letrozole) with IUI ($n = 86$) or with timed intercourse ($n = 70$) also showed no significant difference in clinical pregnancy rates; 16.6 and 17.5%, respectively.[21] Therefore, more research is needed on what treatment regimen is most successful in women with anovulation WHO type II.

There have been speculations that CC, due to its anti-estrogenic effect, might negatively influence the thickness of the endometrium.[22-25] In view of this possible effect of CC,

various agents such as tamoxifen and aromatase inhibiters have been examined within trials but clear cut evidence to replace CC as first line therapy by these drugs has not been generated.[2,26-28]

Given the equipoise between continuing ovulation induction with CC after six failed cycles or starting gonadotrophins as second line treatment with or without IUI, a multicenter randomized controlled trial is now conducted, in which women are included after six ovulatory cycles with CC and randomized for continued treatment with CC, either with and without IUI or for six cycles with gonadotrophins with or without IUI.[29]

CONCLUSION

For women with WHO type II anovulation who are ovulatory with CC, pregnancy rates continue to rise until at least 12 treatment cycles with CC. This outcome, although unexpected, may be explained if we bear in mind that healthy ovulatory women also have high chances of conceiving within 12 cycles. [30] Whether treatment regimens like gonadotrophins and IUI give better outcomes should be investigated in a randomized setting. In the meantime, we suggest to only install the less convenient and more expensive treatment with gonadotrophins for women who do not conceive after 12 ovulatory cycles with CC.

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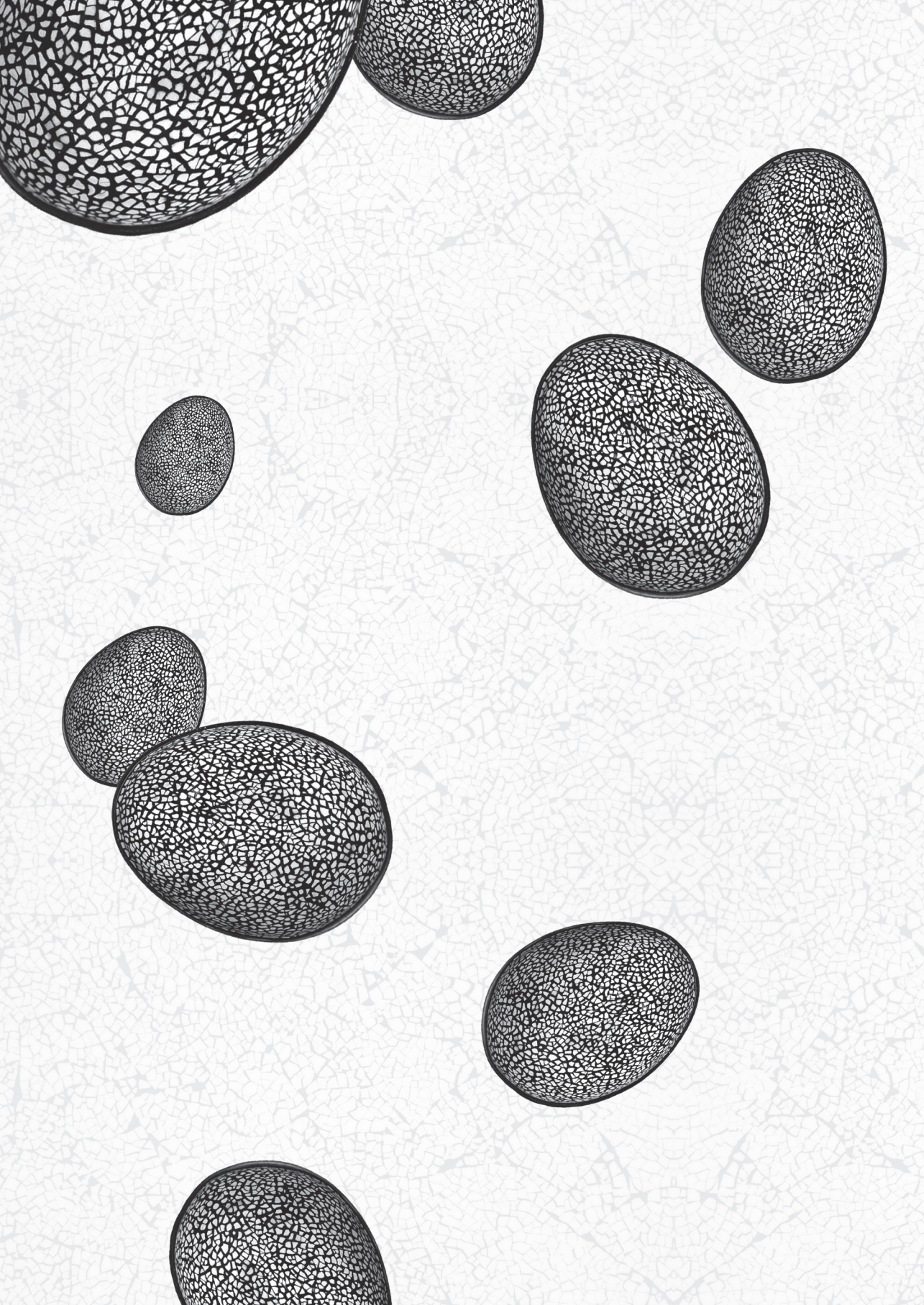
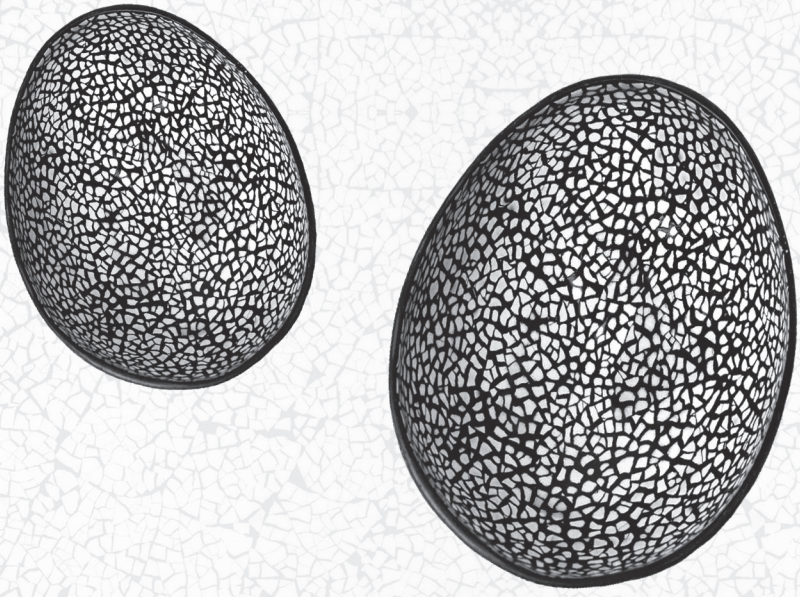


5

Gonadotrophins versus clomiphene citrate with or without intrauterine insemination in women with normogonadotropic anovulation and clomiphene failure (M-OVIN): a randomized, two-by-two factorial trial

Weiss NS, Nahuis MJ, Bordewijk EM, Oosterhuis GJ, Smeenk JMJ, Hoek A, Broekmans FJM, Fleischer K, de Bruin JP, Kaaijk EM, Laven JSE, Hendriks DJ, Gerards MH, van Rooij IAJ, Bourdrez P, Gianotten J, Koks CA, Lambalk CB, Hompes PGA, van der Veen F, Mol BWJ, van Wely M



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SUMMARY

Background: In many countries, clomifene citrate is the treatment of first choice in women with normogonadotropic anovulation (ie, absent or irregular ovulation). If these women ovulate but do not conceive after several cycles with clomifene citrate, medication is usually switched to gonadotrophins, with or without intrauterine insemination. We aimed to assess whether switching to gonadotrophins is more effective than continuing clomifene citrate, and whether intrauterine insemination is more effective than intercourse.

Methods: In this two-by-two factorial multicentre randomised clinical trial, we recruited women aged 18 years and older with normogonadotropic anovulation not pregnant after six ovulatory cycles of clomifene citrate (maximum of 150 mg daily for 5 days) from 48 Dutch hospitals. Women were randomly assigned using a central password protected internet-based randomisation programme to receive six cycles with gonadotrophins plus intrauterine insemination, six cycles with gonadotrophins plus intercourse, six cycles with clomifene citrate plus intrauterine insemination, or six cycles with clomifene citrate plus intercourse. Clomifene citrate dosages varied from 50 to 150 mg daily orally and gonadotrophin starting dose was 50 or 75 IU daily subcutaneously. The primary outcome was conception leading to livebirth within 8 months after randomisation defined as any baby born alive after a gestational age beyond 24 weeks. Primary analysis was by intention to treat. We made two comparisons, one in which gonadotrophins were compared with clomifene citrate and one in which intrauterine insemination was compared with intercourse. This completed study is registered with the Netherlands Trial Register, number NTR1449.

Findings: Between Dec 8, 2008, and Dec 16, 2015, we randomly assigned 666 women to gonadotrophins and intrauterine insemination (n=166), gonadotrophins and intercourse (n=165), clomifene citrate and intrauterine insemination (n=163), or clomifene citrate and intercourse (n=172). Women allocated to gonadotrophins had more livebirths than those allocated to clomifene citrate (167 [52%] of 327 women vs 138 [41%] of 334 women, relative risk [RR] 1·24 [95% CI 1·05–1·46]; p=0·0124). Addition of intrauterine insemination did not increase livebirths compared with intercourse (161 [49%] vs 144 [43%], RR 1·14 [95% CI 0·97–1·35]; p=0·1152). Multiple pregnancy rates for the two comparisons were low and not different. There were three adverse events: one child with congenital abnormalities and one stillbirth in two women treated with clomifene citrate, and one immature delivery due to cervical insufficiency in a woman treated with gonadotrophins.

Interpretation: In women with normogonadotropic anovulation and clomifene citrate failure, a switch of treatment to gonadotrophins increased the chance of livebirth over treatment with clomifene citrate; there was no evidence that addition of intrauterine insemination does so.

Trial registration: NTR1449

Funding: The Netherlands Organisation for Health Research and Development (ZonMw).

RESEARCH IN CONTEXT

Evidence before this study

We searched PubMed on Sept 15, 2008, before the trial started to identify all previous studies investigating women with clomifene failure with the following search terms: "ovulation induction", "polycystic ovary syndrome", "clomiphene citrate" (CC), "gonadotrophins", and "intrauterine insemination".

We identified only non-randomised studies suggesting that continued treatment with clomifene citrate and a treatment switch to gonadotrophins were both effective options for these women. Whether intrauterine insemination increases pregnancy rates in women with clomifene citrate failure is unknown.

In view of this research gap, we aimed to assess whether, in women who have failed to conceive after six ovulatory cycles with clomifene citrate, ovulation induction with gonadotrophins leads to higher livebirth rates than continued ovulation induction with clomifene citrate and whether intrauterine insemination leads to more livebirths than intercourse.

Added value of this study

The M-OVIN (Modified Ovulation Induction) study compared in anovulatory women with clomifene citrate failure two types of medication as well as addition of intrauterine insemination with intercourse. We found that a switch to gonadotrophins significantly increased the livebirth rate compared with continued treatment with clomifene citrate and that the addition of intrauterine insemination to gonadotrophins or clomifene citrate did not increase livebirth rates.

Implications of all the available evidence

Our findings imply that, for normogonadotropic anovulatory women with clomifene citrate failure who wish to conceive, continued treatment with clomifene citrate or a treatment switch to gonadotrophins are both effective options in terms of livebirth rates, whereas we could not prove this for intrauterine insemination. The choice between clomifene citrate and gonadotrophins should be made based on women's preferences, costs, and reimbursement. Considering recent randomised research suggesting that letrozole gives higher livebirth rates than clomifene citrate in the first six cycles, future research should establish whether continuing letrozole is also effective and safe if women have not conceived within the first 6 months of treatment.

INTRODUCTION

Women with normogonadotropic anovulation have absent or irregular ovulation due to hypothalamic-pituitary-ovarian dysfunction associated with normal concentrations of endogenous oestradiol.[1] In these women wishing to conceive, clomifene citrate has long been used as a first-line ovulation induction agent.[2,3] Findings of systematic reviews and meta-analyses have shown that clomifene citrate is an effective primary treatment option in therapynaive women with normogonadotropic anovulation and polycystic ovary syndrome.[4–6] Although ovulation is restored in about 75% of women starting ovulation induction with clomifene citrate, 6 months of treatment leads to conception in only about half of these women.[5,7] Women not conceiving after six ovulatory cycles are defined as having clomifene citrate failure.[8] The National Institute for Health and Care Excellence (NICE) guideline recommends not to extend treatment with clomifene citrate for more than six cycles, but this recommendation is not underpinned by any evidence.[9] In daily practice, these women usually switch to ovulation induction with gonadotrophins and intrauterine insemination is often initiated instead of relying on regular intercourse.[10] However, the effectiveness of a switch to gonadotrophins and intrauterine insemination compared with continued treatment with clomifene citrate has never been studied in randomised clinical trials.

To address this research gap, we aimed to compare, in women who had six ovulatory cycles with clomifene citrate but did not conceive, the effectiveness of a switch to gonadotrophins compared with continued treatment with clomifene citrate and the effectiveness of adding intrauterine insemination to either clomifene citrate or gonadotrophins.

METHODS

Study design and participants

The Modified Ovulation Induction (M-OVIN) study was a multicentre randomised clinical trial done in 48 Dutch hospitals within the infrastructure of the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynaecology. Eligible women were subfertile, aged 18 years and older with WHO type II anovulation (menstrual cycle >35 days, normogonadotropic, normo-oestrogenic, oligo-anovulation or anovulation), and had been ovulatory for six cycles on clomifene citrate treatment, with a maximum of 150 mg daily for 5 days, but had not conceived. Presence of ovulation was assessed by a basal body temperature curve, midluteal progesterone (>16 nmol/L), detection of a urinary luteinising hormone surge, or transvaginal sonography, depending on the local protocol. All women had undergone a basic fertility work-up including a semen analysis and endocrinology screening to rule out hyperprolactinaemia and uncorrected thyroid dysfunction. Couples with male subfertility could not participate. Women with abnormal

prolactin (0·05–0·80 IU/L) or thyroid-stimulating hormone (0·4–4·0 mU/L) were also not eligible. Tubal pathology had to be ruled out by either a negative Chlamydia antibody titre (CAT) or hysterosalpingography, transvaginal hydrolaparoscopy, or diagnostic laparoscopy showing at least one patent fallopian tube. Women with side-effects in previous clomifene citrate cycles were also not eligible. All women provided written informed consent.
The study was granted approval by the Medical Ethical Committee of the Medical Spectrum Twente Enschede (Netherlands) and from the Central Committee on Research involving Human Subjects (CCMO, Netherlands). The board of directors of each of the participating centres approved local execution of the study. The protocol was published previously.[11]
Two major adjustments to the protocol were made: in April, 2014, a change was made to the primary outcome from "ongoing pregnancy" to "livebirth". The second regarded the sample size. Both adjustments were approved by the Medical Ethical Committee.

Randomisation and masking

Eligible women were informed about the study during or immediately after their sixth treatment cycle either by their doctor or by a dedicated research nurse. Women were randomly assigned using a central password protected internet based randomisation program. The randomisation list had been prepared by an independent statistician with a variable block size and a maximum block size of 8. There was no masking.
We used a two-by-two factorial design to compare two pairs of interventions: a switch to ovulation induction with gonadotrophins versus continuing clomifene citrate and intrauterine insemination versus intercourse. Women were randomly assigned to six cycles with gonadotrophins plus intrauterine insemination, six cycles with gonadotrophins plus intercourse, six cycles with clomifene citrate plus intrauterine insemination, or six cycles with clomifene citrate plus intercourse.

Procedures

In women allocated to ovulation induction with gonadotrophins, a transvaginal ultrasound was usually done on the third day of a menstrual bleed and medication was started on that same day, but women were allowed to start medication up to day 5. Treatment was not started if ultrasound showed ovarian cysts bigger than 25 mm in mean diameter. According to local protocol, urinary or recombinant gonadotrophins were used with a starting dose of 50 or 75 IU daily. Follicular growth was strictly monitored by transvaginal ultrasound and we aimed for mono-follicular growth. When at least one follicle with a diameter of at least 16 mm was present, ovulation was triggered with 5000 IU or 10 000 IU of human chorionic gonadotrophin. If four or more dominant follicles (≥18 mm) developed, the cycle was cancelled - ie, couples were advised not to have intercourse and the planned intrauterine insemination was not done. In women allocated to intrauterine insemination,

semen samples were processed within 1 h of ejaculation according to the local protocol and women were inseminated 36–40 h after human chorionic gonadotrophin injection. Intrauterine insemination was done once per cycle.

In women allocated to ovulation induction with clomifene citrate, treatment was started on the third to fifth day of a menstrual bleed, in the same dosage as used in the last ovulatory cycle, varying between 50 mg and 150 mg daily, for 5 days. Ovulation was monitored by a basal body temperature curve, midluteal progesterone (>16 nmol/L), a urinary lutenising hormone surge, or transvaginal ultrasound, depending on the local protocol. Women undergoing ovulation induction with clomifene citrate plus intrauterine insemination were monitored by ultrasound; women assigned to clomifene citrate with intercourse were usually monitored by basal body temperature curve, midluteal progesterone measurement, or urinary lutenising hormone surge. In case of ovulation not followed by pregnancy, women continued taking the same dose of clomifene citrate until pregnancy occurred, or until the end of the study (8 months after randomisation). If ovulation did not occur, the dosage was increased in increments of 50 mg to a maximum of 150 mg daily in the next cycles.

Follow-up started at the day of randomisation and ended on the first day of the last menstruation before a positive pregnancy test within six treatment cycles or at 8 months after randomisation, whichever came first. If pregnant, women had an ultrasound at 7 and 11 weeks of gestation and were followed up until delivery of their baby. If they miscarried or had an ectopic pregnancy within 8 months after randomisation, couples were advised to continue their allocated treatment.

Data were collected by trained research nurses and doctors. They used a structured case record form to register the actual interventions, the reproductive outcomes, the occurrence of gestational diabetes, hypertensive disorders, stillbirths, preterm labour, and fetal birthweight as well as the course and outcome of subsequent pregnancies. If the women's medical records did not give the necessary information, women were contacted by telephone to ask about their outcomes.

We expected some couples to drop out of the study as per usual clinical practice, particularly in this protocol in which women had already had six ovulatory treatment cycles before inclusion. Women who dropped out of the study were managed according to their preferences.

Outcomes

The primary outcome measure was conception leading to livebirth within 8 months after randomisation, defined as any baby born alive with a gestational age beyond 24 weeks. Secondary outcome measures were ongoing pregnancy, multiple pregnancy, miscarriage (defined as loss of an intrauterine pregnancy confirmed by ultrasound or histological examination before the 20th week of pregnancy), ectopic pregnancy, time from randomisation to the birth of a live child, fetal birthweight, and pregnancy complications -

ie, hypertensive disorders, gestational diabetes, and preterm labour.[11] We did not monitor adverse drug events because these are already widely known for both types of medication. We do not report on all outcomes mentioned in the statistical analysis plan here. Outcomes such as clinical pregnancy rate, ovulation rate, and gestational age will be reported elsewhere.

Statistical analysis

When we first planned our study, we designed the trial as a two-by-two factorial superiority trial. After recruiting 136 women, we received governmental funding that allowed enlargement of our trial. To assess whether either switching to ovulation induction with gonadotrophins or addition of intrauterine insemination would increase the livebirth rate from 40% to 55%,[12,13] we needed to include 600 women (alpha of 5% and a power of 88% at three degrees of freedom). We decided to include a total of 660 women because 10% of women became pregnant after randomisation but before starting the trial. With these 660 women we would have sufficient power to find a difference in livebirth rate for the two comparisons that we have made. A detailed description of all steps in establishing the sample size is provided in the appendix. A statistical analysis plan was established before data lock.

The primary analysis was on an intention-to-treat basis. For the livebirth rates and other binary outcome measures, we calculated absolute risks, relative risks, and 95% confidence intervals. Chi-square test statistics were used to assess statistical significance. We reported categorical data as absolute numbers and percentages. We summarised normally distributed continuous variables as means with standard deviations, and non-normally distributed continuous variables as medians with IQRs. We formally tested for interaction between the two comparisons. We constructed Kaplan-Meier curves for time to conception leading to livebirth for gonadotrophins versus clomifene citrate, for intrauterine insemination versus intercourse, and for all four treatment arms separately. They were compared with a log-rank test. Two-sided p values of less than 0·05 were considered to indicate statistical significance. We assessed whether there was interaction between treatment effect and body-mass index (BMI) at cut-off of 25 kg/m^2 as this was the mean BMI of our population. We also did a per-protocol analysis in which we only included women that were treated according to the predefined protocol. SPSS software (version 23.0; IBM Corp, USA) was used for statistical analysis.

This study is registered with the Netherlands Trial Register, number NTR1449.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Between Dec 8, 2008, and Dec 16, 2015, 762 women were registered as eligible. 96 women declined randomisation and 666 were randomly assigned. 166 women were allocated to ovulation induction with gonadotrophins combined with intrauterine insemination, 165 to ovulation induction with gonadotrophins, 163 to ovulation induction with clomifene citrate combined with intrauterine insemination, and 172 to continued ovulation induction with clomifene citrate (figure 1). We excluded five women after randomisation because they did not fulfil the inclusion criteria. None of these women became pregnant. The baseline characteristics were similar across the four groups (table 1).

Table I . Baseline characteristics of the participating couples.

	Gonado-trophins + IUI **n = 164**	**Gonado-trophins + intercourse** **n = 163**	**CC + IUI** **n = 163**	**CC + inter-course** **n = 171**
Age of women (years)	29·5 ± 3·7	29·9 ± 3·7	30·0 ± 3·6	29·9 ± 4·0
Ethnicity				
White	131 (85%)	134 (88%)	133 (86%)	141 (89%)
Non-white	24 (15%)	18 (12%)	21 (14%)	18 (11%)
BMI (kg/m^2)*	25·4 ± 5·1	25·6 ± 5·6	25·0 ± 4·9	25·4 ± 5·0
BMI >25.0 kg/m^2	76 (46%)	81 (49%)	64 (39%)	81 (47%)
Current smoker	29 (18%)	20 (12%)	22 (13%)	22 (13%)
Diabetes	1	1	3	2
Previous livebirth	32 (20%)	35 (21%)	36 (22%)	34 (20%)
Duration of subfertility (months)	26·3 ± 14·9	24·5 ± 12·5	24·5 ± 15·5	25·9 ± 19·0
Cycle pattern prior to treatment #				
Amenorrhea	124 (76%)	125 (77%)	115 (71%)	120 (70%)
Oligomenorrhea	21 (13%)	25 (15%)	27 (16%)	32 (19%)
Unknown	19 (11%)	13 (8%)	21 (13%)	19 (11%)
Median TMC *10^6	52 (20-106)	43 (16-113)	53 (15-132)	38 (16-99)
Polycystic ovaries on ultrasound ##	110 (67%)	103 (63%)	109 (67%)	117 (68%)
Mean serum biochemical values				
FSH (IU/L)	5·7 ± 2·1	5·7 ± 1·7	6·2 ± 2·2	6·0 ± 2·2
LH (IU/L)	9·7 ± 7·4	10·6 ± 7·8	10·6 ± 7·6	10·9 ± 10·8
Estrogen (pmol/L)	255 ± 295	239 ± 217	201 ± 159	271 ± 460
Total testosterone (nmol/L)	1·6 ± 1·7	1·6 ± 2·0	1·8 ± 2·2	1·8 ± 1·8

Data are mean (SD), n (%) or median (IQR). BMI = body-mass index. TMC = total motile sperm count. FSH = follicle stimulating hormone. LH = luteinizing hormone. CC = clomiphene citrate. IUI = intrauterine insemination.
*BMI was missing for 24 women; data were imputed by using multiple imputation.
Amenorrhea: absence of menstrual bleeding for >6 months. Oligomenorrhea: irregular menstrual bleedings with intervals of >35 days but ≤6 months
Defined as the presence of 12 or more follicles in each ovary measuring 2–9 mm in diameter

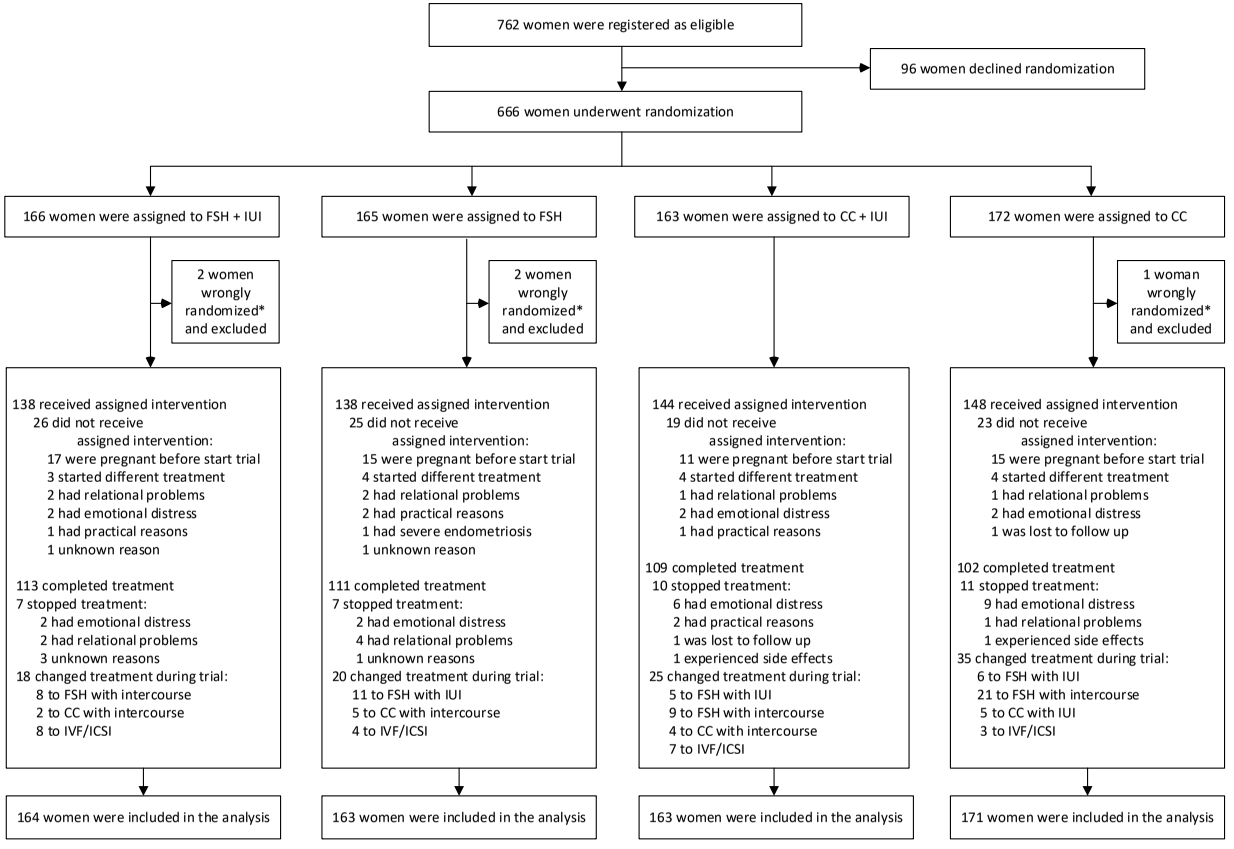

Figure 1. Trial profile

FSH = follicle stimulating hormone. CC = clomifene citrate. IUI = intrauterine insemination. IVF = in vitro fertilization. ICSI = intracytoplasmatic sperm injection. *2 women had thyroid disease, 1 woman had bilateral tubal pathology, 1 male partner had azoospermia, 1 woman only had two cycles with clomifene citrate before randomisation.

Table II. Cycle results

	Gonado-trophins + IUI n=164	Gonado-trophins + intercourse n=163	CC + IUI n=163	CC + intercourse n=171
Total nr of cycles	540	570	612	681
Mean nr of cycles per woman	3·3 ± 2·0	3·5 ± 2·1	3·8 ± 1·8	4·0 ± 1·9
Mean nr of IUIs per woman	3·2 ± 2·2	0·04 ± 0·3	3·5 ± 2·2	0·05 ± 0·4
Total nr of cancelled cycles	65 (12%)	61 (11%)	4*	2*
Total units of gonadotrophins per woman	2594 ± 2439	2640 ± 2577	153 ± 823*	223 ± 823*
Total mg of CC per woman	4·5 ± 43·4 #	18·2 ± 128 #	1401 ± 1152	1255 ± 1139

Data are n (%) or mean (SD)
*After switching to gonadotrophins
# After switching to CC
CC = clomiphene citrate. IUI = intrauterine insemination

Women allocated to gonadotrophins with intrauterine insemination underwent 540 cycles, women allocated to gonadotrophins only underwent 570 cycles, women allocated to clomifene citrate with intrauterine insemination underwent 612 cycles, and women allocated to clomifene citrate only underwent 681 cycles. Of these cycles, 65 (12%) were cancelled in the gonadotrophins with intrauterine insemination group and 61 (11%) in the gonadotrophins only group. Of these cancelled cycles, 35 (28%) were due to anovulation; the other cycles were cancelled because of multiple follicular growth (table 2).

Women allocated to gonadotrophins had significantly more livebirths than women allocated to clomifene citrate (167 [52%] of 327 women vs 138 [41%] of 334, relative risk [RR] 1·24 [95% CI 1·05–1·46]; p=0·0124; absolute difference 10·2% [95% CI 2·4–17·9]; table 3). The mean time to conception leading to a livebirth was 5 months (95% CI 4·7–5·4) following gonadotrophins and 5·5 months (5·1–5·8) following clomifene citrate (log-rank test; p=0·028; figure 2). Seven women (2%) allocated to gonadotrophins conceived a twin pregnancy versus eight women (2%) allocated to clomifene citrate (RR 0·89 [95% CI 0·33–2·4]; p=0·8262; absolute difference 0%).

Women allocated to intrauterine insemination had more livebirths than women allocated to intercourse, but this difference was not statistically different (161 [49%] of 327 women vs 144 [43%] of 334 women, RR 1·14 [95% CI 0·97–1·35]; p=0·1152; absolute difference 6·1% [95% CI –1·71 to 13·8; table 3). The mean time to conception leading to a livebirth was 5·2 months (95% CI 4·8–5·5) with intrauterine insemination and 5·3 months (5·0–5·7) with intercourse (log-rank test; p=0·27; figure 2).There were 11 (3%) twin pregnancies after intrauterine insemination and four (1%) after intercourse (RR 2·8 [95% CI 0·90–8·7]; p=0·0743; absolute difference 2·0%). There were no high order pregnancies.

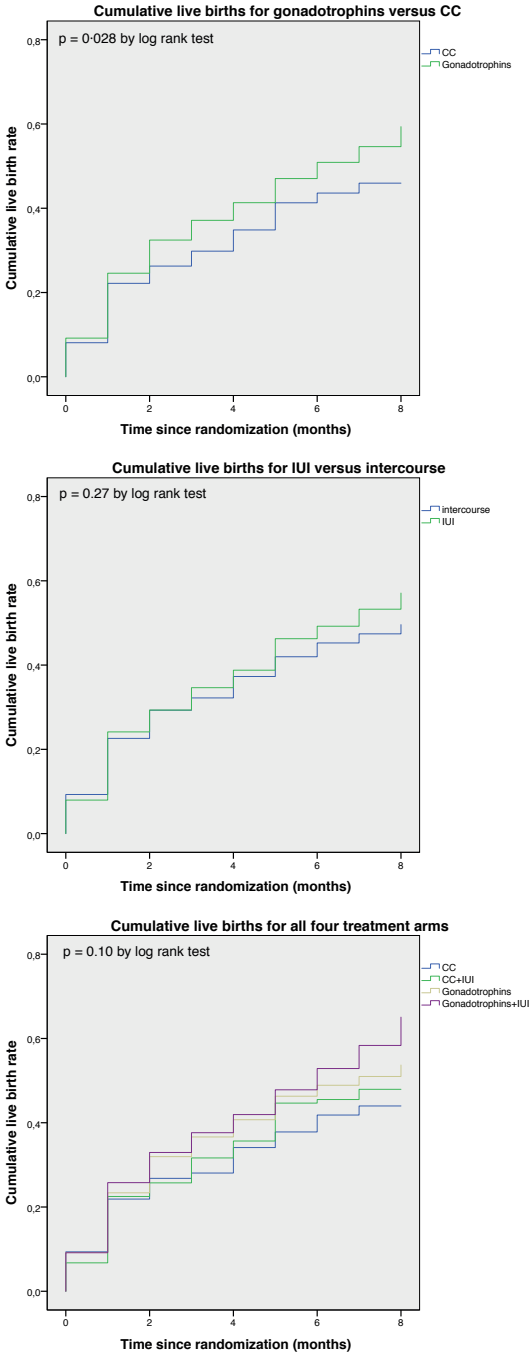

Figure 2. Time to conception leading to livebirth for the comparison gonadotrophins versus clomifene citrate, and intrauterine insemination versus intercourse.

Table III. Primary and secondary outcomes

	Gonado-trophins + IUI n = 164	**Gonado-trophins n = 163**	**CC + IUI n = 163**	**CC n = 171**	**Gonado-trophins vs CC RR (95% CI)**	**Gonado-trophins vs CC P value**	**IUI vs intercourse RR (95% CI)**	**IUI vs intercourse P value**
Livebirth	89 (54·3%)	78 (47·9%)	72 (44·2%)	66 (38·6%)	1·24 (1·05-1·46)	0·0124	1·14 (0·97-1·35)	0.12
Ongoing pregnancy	90 (54·9%)	80 (49·1%)	72 (44·2%)	66 (38·6%)	1·26 (1·07-1·48)	0·0063	1·14 (0·97-1·34)	0.13
Multiple pregnancy per woman	4 (2·4%)	3 (1·8%)	7 (4·3%)	1 (0·6%)	0·89 (0·33-2·4)	0·82	2·8 (0·90-8·7)	0.07
Miscarriages per woman	15 (9·1%)	9 (5·5%)	8 (4·9%)	3 (1·8%)	2·2 (1·11-4·5)	0·02	1·96 (0·99-3·9)	0·05
Ectopic pregnancy per woman	1 (0·6%)	1 (0·6%)	3 (1·8%)	1 (0·6%)	*		*	
Birth weight (g)	3279 ± 695	3302 ± 769	3178 ± 714	3408 ± 491		0·96		0·14
Pregnancy complications					*		*	
Hypertensive disorders	4 (2%)	6 (4%)	5 (2%)	2 (1%)				
Gestational diabetes	3 (2%)	5 (3%)	3 (2%)	3 (2%)				
Preterm labour	6 (4%)	2 (1%)	0	1 (1%)				

Data are n (%) or mean ± SD unless otherwise stated. All multiple pregnancies were twin pregnancies.
RR = relative risk. * No RR was calculated as the proportions are low.

The number of miscarriages was higher after treatment with gonadotrophins (n=24 [7%]) than after clomifene citrate (n=11 [3%]; RR 2·2 [95% CI 1·11–4·5]; p=0·0243; absolute difference 4·0%). The number of ectopic pregnancies was similar between all groups. We found no differences in mean birthweights and pregnancy complications (table 3). We noted no interaction between the two comparisons (p=0·932). Also, there was no interaction of BMI and treatment effect for both comparisons.

We included 563 women in the per-protocol analysis. We noted more livebirths after gonadotrophins compared with clomifene citrate (123 [44%] of 279 women after gonadotrophins vs 90 [32%] of 284 women after clomifene citrate, RR 1·38 [95% CI 1·11–1·72]; p=0·0027; absolute difference 13%). Addition of intrauterine insemination did not increase livebirths compared with intercourse: 113 (41%) of 277 women had a livebirth after intrauterine insemination versus 100 (35%) of 286 women after intercourse (RR 1·17 [95% CI 0·94–1·44]; p=0·1548; absolute difference 13%).

There were three adverse events: one woman treated with clomifene citrate conceived a child with congenital abnormalities resulting in second trimester pregnancy termination, one woman treated with gonadotrophins with intrauterine insemination delivered at a gestational age of 20 weeks due to cervical insufficiency, and one woman treated with clomifene citrate had a stillbirth at a gestational age of 19 weeks.

DISCUSSION

In this multicentre randomised trial, we found that, among normogonadotropic anovulatory women not pregnant after six ovulatory cycles with clomifene citrate, a switch to gonadotrophins with strict cycle monitoring increased the livebirth rate compared with continued treatment with clomifene citrate. The addition of intrauterine insemination did not increase livebirth rates. All four treatment groups resulted in acceptable pregnancy rates and low complication rates.

A strength of our study is the two-by-two factorial design. This design allowed us to dissect the effect of gonadotrophins and clomifene citrate and of intrauterine insemination versus intercourse. The per-protocol analysis limited to women that received the allocated treatment did not alter our results, suggesting that the treatment switches did not have a large effect on livebirth chances. A weakness could be that we allowed participating hospitals to use their local protocols for ovulation induction and intrauterine insemination. Alternatively, this pragmatic approach might increase the generalisability of the results. Plausible biological explanations for the finding of more livebirths with gonadotrophins than clomifene citrate may be the following. First, treatment with gonadotrophins requires strict cycle monitoring whereas treatment with clomifene citrate does not. Therefore, women given gonadotrophins have more specific knowledge on the timing of their

ovulation, which might lead to a better timing of their intercourse. Second, clomifene citrate might have negative effects on the endometrium; however, studies assessing this effect in relation to pregnancy rates show conflicting results.[14–16] Third, clomifene citrate might induce cervical factor subfertility by influencing the cervical mucus.[17–19]

We do not know whether the differential monitoring in the women that underwent ovulation induction with clomifene citrate affected the outcomes, but it is not something we expect. The addition of intrauterine insemination, in which monitoring was more strict, did not result in significantly higher pregnancy chances. We believe one of the merits of our study is that even with minimal monitoring good results can be obtained with continued ovulation induction with clomifene citrate.

We found a small, not statistically significant effect of intrauterine insemination on livebirth rates. Apparently, intrauterine insemination does not contribute to pregnancy chances in women with anovulatory subfertility. We reported 4% multiple pregnancies after gonadotrophins versus 6% after clomifene citrate, which can be explained by the very purpose of ovulation induction in women with anovulation, which is to induce mono-follicular growth with low doses of gonadotrophins.[9,11] There has traditionally been reluctance to continue treatment with clomifene citrate because of safety issues.[9] However, direct evidence that cancer risks are increased after six cycles of clomifene citrate is lacking. In our study, women given gonadotrophins had more miscarriages than women given clomifene citrate. Our study was not powered to detect a difference in miscarriage rate, hence this finding needs to be confirmed in future studies. We recorded only one second trimester miscarriage in the whole study population, which is very low and in contrast to the miscarriage rate seen after in-vitro fertilisation in a fresh transfer cycle in women with polycystic ovary syndrome.[20] This is probably due to the fact that ovulation induction aims to generate only one follicle in contrast to superovulation in in-vitro fertilisation, resulting in a thinner endometrium in ovulation induction. The cumulative livebirth rate after clomifene citrate in cycles 7–12 is similar to a previous observational study.[21] Similarly, the cumulative livebirth rate after gonadotrophins is in line with a previous prospective cohort study.[8] This underpins the reliability of our results.

Recent randomised trials and network meta-analyses reported that letrozole is associated with higher livebirth rates compared with clomifene citrate.[6,22] We therefore suggest that future research should aim to establish whether letrozole is also effective and safe if women have not conceived within the first 6 months of treatment. Based on our current finding that continued treatment with clomifene citrate is effective, one might hypothesise even higher livebirth rates for continued treatment with letrozole.

Our results can be used by couples treated with first-line ovulatory drugs who weigh the pros and cons of switching to gonadotrophins and addition of intrauterine insemination. Clomiphene citrate is known to cause more side-effects than gonadotrophins, whereas

gonadotrophins necessitate daily injections combined with ultrasound monitoring of follicular development and are more expensive.[23] Findings of a recent patient preference study of women with anovulation wishing to conceive showed that just over half of these women chose treatment with the least medical interference and lowest burden whereas less than 50% preferred a treatment with the highest success rates irrespective of the burden.[24] To evaluate cost differences we have planned a cost-effectiveness analysis that will be reported elsewhere.

Our study shows that subfertile women with anovulation who are given clomifene citrate or gonadotrophins with or without intrauterine insemination reach acceptable pregnancy rates and low complication rates even until their 12th treatment cycle. This means that, in contrast to the recommendation of the NICE guideline for unexplained subfertility, switching to in-vitro fertilisation after six failed ovulation induction cycles is not necessary. The choice between these alternatives should therefore be made based on couples' preferences, costs, and reimbursement.

DECELERATIONS OF INTEREST

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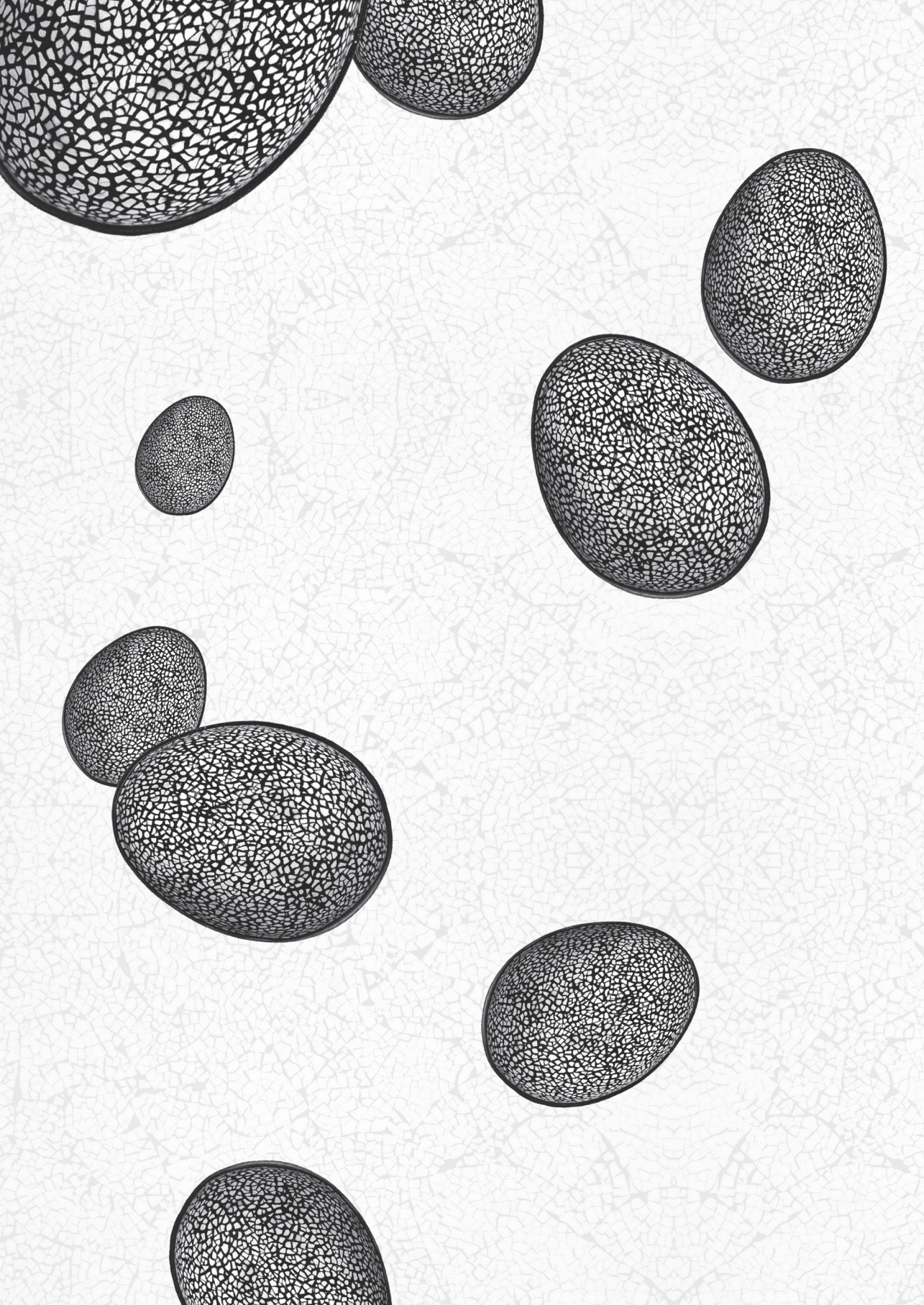
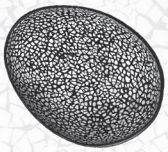


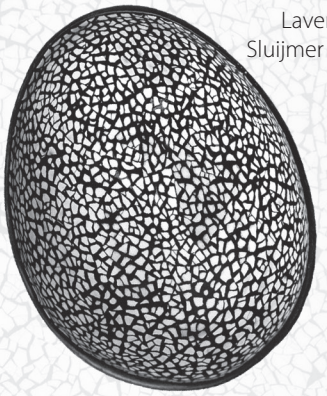
6

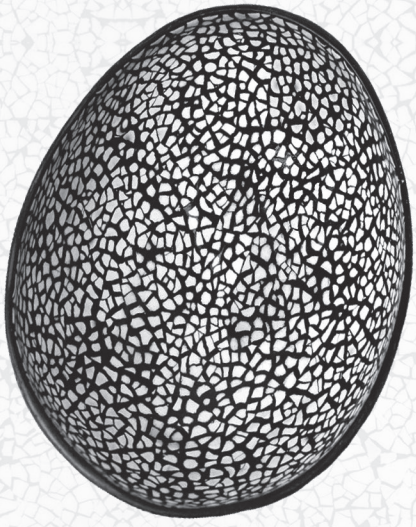
Gonadotrophins versus clomiphene citrate with or without intrauterine insemination in women with normogonadotropic anovulation and clomiphene failure: A cost-effectiveness analysis



Weiss NS#, Bordewijk EM#, Nahuis MJ, Bayram N, van Hooff MHA, Boks DES, Perquin DAM, Janssen CAH, van Golde RJT,Lambalk CB, Goddijn M, Hompes PGA,van der Veen F, Mol BWJ, van Wely M

Also on behalf of:
Bourdrez P, Broekmans FJM, de Bruin JP, Cohlen BJ, Fleischer K, Gerards MH, Gianotten J, Hendriks DJ, Hoek A, Kaaijk EM, Klijn NF, Koks CA, Kwee J, van de Laar-van Asseldonk TAM, Lambeek AF, Laven JSE, Nap AW, van Rijn-van Weert JM, Rijnsaardt-Lukassen HGM, Sluijmer AV, Smeenk JMJ, van Unnik GA, Vollebergh JHA, Vrouenraets FPJM





Submitted to Human Reproduction

ABSTRACT

Study question: Are six cycles of ovulation induction with gonadotrophins more cost-effective than six cycles of ovulation induction with clomiphene citrate (CC) with or without intra-uterine insemination (IUI) in normogonadotropic anovulatory women not pregnant after six ovulatory cycles with CC?

Summary answer: Both gonadotrophins and IUI are more expensive when compared with CC and intercourse, while gonadotrophins are more effective without any evidence of an increased effectiveness of IUI.

What is known already: In women with normogonadotropic anovulation who ovulate but do not conceive after six cycles with clomiphene citrate, medication is usually switched to gonadotrophins, with or without intrauterine insemination. Cost-effectiveness of these changes in policy is unknown.

Study design, size, duration: We performed an economic evaluation of ovulation induction with gonadotrophins compared with CC with or without IUI in a two-by-two factorial multicentre randomised controlled trial in normogonadotropic anovulatory women not pregnant after six ovulatory cycles with CC. Between December 2008 and December 2015 women were allocated to six cycles with gonadotrophins plus IUI, six cycles with gonadotrophins plus intercourse, six cycles with CC plus IUI or six cycles with CC plus intercourse. The primary outcome was conception leading to a live birth achieved within 8 months of randomisation.

Participants/materials, setting, methods: We performed a cost-effectiveness analysis from a health care perspective. We calculated the direct medical costs of ovulation induction with gonadotrophins versus CC and of IUI versus intercourse in six subsequent cycles. We included costs of medication, cycle monitoring, interventions, and pregnancy leading to live birth. Recourse use was collected from the case report forms and unit costs were derived from various sources. We calculated incremental cost-effectiveness ratios (ICER) for gonadotrophins compared to CC and for IUI compared to intercourse. We used nonparametric bootstrap resampling to investigate the effect of uncertainty in our estimates. The analysis was performed according the intention-to-treat principle.

Main results and the role of chance: We allocated 666 women to gonadotrophins and IUI (n=166), gonadotrophins and intercourse (n=165), CC and IUI (n=163), or CC and intercourse (n=172). Mean direct medical costs per woman receiving

gonadotrophins or CC were €4495 versus €3007 (cost difference of €1475 (95% CI €1457 to €1493)). Live birth rates were 52% in women allocated to gonadotrophins and 41% in those allocated to CC (relative risk 1.24: 95% CI 1.05-1.46). The incremental cost-effectiveness ratio was €15 258 (95% CI €8721 to €63 654) per additional live birth with gonadotrophins.
Mean direct medical costs per woman allocated to IUI or intercourse were €4497 versus €3005 (cost difference of €1510 (95% CI €1492 to €1529)). Live birth rates were 49% in women allocated to IUI and 43% in those allocated to intercourse (relative risk 1.14: 95% CI 0.97-1.35). The incremental cost-effectiveness ratio was €24 361 (95% CI €-11 290 to €85 172) per additional live birth with IUI.

Limitations, reasons for caution: We allowed participating hospitals to use their local protocols for ovulation induction and IUI, which may have led to variation in costs, but which increases generalisability. We did not implement indirect costs generated by transportation or productivity loss. We did not evaluate letrozole, which is potentially more effective than CC.

Wider implications of the findings: Because gonadotrophins are more effective, but more expensive than CC, the use of gonadotrophins in women with normogonadotropic anovulation who have not conceived after six ovulatory CC cycles depends on society's willingness to pay for an additional child. In view of the uncertainty around the cost-effectiveness estimate of IUI, data are not sufficient to make recommendations on the use of IUI in these women.

Study funding/competing interest(s): This trial was funded by the Netherlands Organisation for Health Research and Development (ZonMw).

Trial registration: NTR1449

INTRODUCTION

In women with normogonadotropic anovulation who wish to conceive, clomiphene citrate (CC) has long been used as first line treatment for ovulation induction.[1-4] Women not conceiving after six ovulatory cycles are defined as having CC failure.[5] In daily practice, these women often switch to ovulation induction with gonadotrophins and intrauterine insemination (IUI) is often initiated instead of relying on regular intercourse.[2]

The evidence for such a policy change has long been lacking. We recently reported the results of the Modified Ovulation Induction (M-ovin) study, a two-by-two factorial multicentre randomised controlled trial (RCT) comparing ovulation induction with gonadotrophins to CC with or without IUI in normogonadotropic anovulatory women with CC failure.[6] In that study, we randomly assigned women to either six cycles with gonadotrophins plus IUI, six cycles with gonadotrophins plus intercourse, six cycles with CC plus IUI or six cycles with CC plus intercourse. The primary outcome was a live birth achieved within 8 months of randomisation. We made two comparisons, one in which gonadotrophins were compared with CC and one in which IUI was compared with intercourse. This trial showed that a switch of treatment to gonadotrophins led to an absolute increase in live birth of 10% over treatment with CC. IUI did not lead to an increase in live births compared with intercourse.

In view of limited health care resources, costs are also important in deciding which treatment should be advised to patients. In contrast to CC, which is relatively cheap due to the low price of the tablets and limited monitoring requirements, ovulation induction with gonadotrophins is expensive due to the price of medication and the need for strict ultrasound monitoring.[7-10] Knowledge on the relative cost and effectiveness of these interventions with or without IUI is lacking. The aim of this study was to provide an economic evaluation of ovulation induction with gonadotrophins compared to CC with or without IUI in women with CC failure.

MATERIALS AND METHODS

Study design

This economic evaluation was performed alongside the M-ovin study, a two-by-two factorial RCT in 48 Dutch hospitals that compared ovulation induction with gonadotrophins with CC with or without IUI in normogonadotropic anovulatory women with CC failure. Details about the study design, sample size calculation, study procedures and outcomes have been described previously.[11,6] Ethical approval was obtained by the Medical Ethical Committee of the Medical Spectrum Twente Enschede (Netherlands) and from the Central Committee on Research involving Human Subjects (CCMO, Netherlands). The board of directors of each of the participating centres approved local execution of the study.

In short, sub-fertile women of at least 18 years of age with normogonadotropic anovulation who had been ovulatory for six cycles on CC, but who had not conceived, were eligible for the trial. Couples with male subfertility and double sided tubal pathology could not participate. Women were randomly assigned using a central password protected internet-based randomisation programme. The randomisation list had been prepared by an independent statistician with a variable block size and a maximum block size of 8. There was no masking. Consenting women were randomly allocated to any of four treatments on a 1:1:1:1 basis, i.e. six cycles of gonadotrophins plus IUI, six cycles of gonadotrophins plus intercourse, six cycles of CC plus IUI or six cycles of CC plus intercourse. We used a two-by-two factorial design to compare two pairs of interventions: a switch to ovulation induction with gonadotrophins versus continuing CC and IUI versus intercourse.

Ovulation induction, cycle monitoring, semen preparation and insemination were performed according to local hospital protocols. The starting dose of gonadotrophins was 50 or 75 IU daily and participating clinics used either urinary or recombinant gonadotrophins depending on their local protocol. Follicular growth was monitored by transvaginal ultrasound. We used 5000 IU of human chorionic gonadotrophin (hCG) to trigger ovulation. The dosage of CC was a minimum of 50 mg to a maximum of 150 mg daily, for five days. If ovulation did not occur, the dosage was increased with steps of 50 mg with a maximum of 150 mg daily in the next cycles. Women undergoing ovulation induction with CC plus IUI underwent monitoring by ultrasound, women undergoing CC plus intercourse were usually monitored by basal body temperature curve, mid luteal progesterone measurement or urinary luteal hormone surge depending on the local protocol. In the case of IUI, a single insemination per cycle was performed.

The primary outcome measure was conception leading to a live birth within eight months after randomisation. A live birth was defined as any baby that was born alive after a gestational age beyond 24 weeks. Secondary outcomes included multiple pregnancy rate, ongoing pregnancy rate, miscarriage, and ectopic pregnancy.

Economic evaluation

The economic evaluation was performed as a cost-effectiveness analysis from a health care perspective, thus focusing on direct medical costs during treatment.

Resource use

Data on resource use were collected from the individual case report forms of the RCT. For each woman, we registered the medication, cycle monitoring (number of ultrasounds), and interventions (cycles with IUI, cycles with IVF) they received within six subsequent cycles or until a live birth occurred within a time horizon of 8 months. If women changed their

treatment to IVF/ICSI, resource use was estimated on the basis of previously published data on resource costs for IVF/ICSI.[12] Within the M-ovin study, 21 women switched to treatment with IVF or ICSI during their study period i.e. before finishing their allocated treatment (8 women who were allocated to FSH+IUI, 4 women who were allocated to FSH, 7 women who were allocated to CC+IUI, 3 women who were allocated to CC). Because of the intention to treat principle that we have used, the pregnancies resulting from treatment with IVF/ICSI were included in the main analysis of our RCT.

Unit costs

Direct unit costs included the costs of medication, cycle monitoring, interventions, and the costs of pregnancy leading to live birth. The costs for medication and the unit costs of cycle monitoring and interventions were obtained from the costs as retrieved by an expert panel on cost-effectiveness from the Dutch Consortium for Research in Women's Health. The expert panel, consisting of gynecologists, economists and a methodologist, collected the actual total medical costs per cost unit from resources that are being used in fertility studies within our Consortium from two university hospitals and one general hospital. For our final calculation we used the average costs of the three Dutch hospitals.

We derived costs for pregnancy and delivery from a cost analysis of singleton versus twin pregnancies, in which the costs for a singleton and twin pregnancies up until 6 weeks after delivery was described.[13] The costs of a miscarriage with or without curettage, ectopic pregnancy and stillbirth were obtained from the pricelist of one general hospital. All costs were expressed in 2017 euros (€) and corrected for inflation or deflation whenever necessary using the consumer pricing index.[14]

Statistical analysis

For each of the four treatments we calculated the mean costs and effectiveness on the basis of the intention-to-treat principle. For effectiveness we calculated absolute risks, relative risks and corresponding 95% boundaries. Costs were calculated by multiplying the quantity of resource use and unit costs. For each treatment we calculated the mean cost per woman. For costs we calculated mean cost differences and 95% boundaries as estimated on the basis of bootstrapping by taking 1000 random samples. Costs were combined with effectiveness by calculating Incremental Cost-Effectiveness Ratios (ICER) for gonadotrophins compared with CC and for IUI compared with intercourse. The ICER was defined as the ratio between the differences in costs and the differences in effects between two interventions. We used a non-parametric bootstrap resampling to investigate the effect of uncertainty in our estimates. The uncertainty was visualized by plotting a cost-effectiveness plane. CC and intercourse were the reference strategies (in the origin of the cost-effectiveness plane).

We drew a cost-effectiveness acceptability curve, expressing the probability that a strategy will be cost-effective at a specific willingness-to-pay for an additional child, given the uncertainty. The range was from 0 to 135 000 euros.
In view of the factorial design, we investigated the interaction between IUI and ovulation induction with costs. We first evaluated if factors have a multiplicative effect and used a general linear model in transformed cost data.

Per protocol and sensitivity analyses

We did a per-protocol analysis in which we included women who were actually treated according to the predefined protocol.[11] We performed four one way sensitivity analyses to explore the impact of key factors in the cost-effectiveness analyses. In the first analysis we excluded IVF cycles (Model 1), in the second we used ongoing pregnancy as main measure of effectiveness (Model 2), in the third we calculated with unit costs used in the United Kingdom which were collected from a NHS hospital (Model 3), in the fourth we assumed that all CC-cycles were monitored by ultrasound (Model 4) and in the fifth that none of the CC-cycles were monitored by ultrasound (Model 5). All statistical analyses were performed using SPSS (version 23.0; IBM Corp., USA) and Microsoft Excel (version 2016) for the bootstrapping.

RESULTS

Study population and effectiveness outcomes

Between December 2008 and December 2015, we randomised 666 women: 166 women were allocated to ovulation induction with gonadotrophins combined with IUI, 165 to ovulation induction with gonadotrophins, 163 to ovulation induction with CC combined with IUI, and 172 to continued ovulation induction with CC. Five women were excluded since they had been erroneously randomised. The baseline characteristics of the participating women can be found in appendix 1.
Effectiveness outcomes are summarized in Table I. Live birth rates were 52% after gonadotrophins versus 41% after CC, RR 1.24 (95% CI 1.05-1.46); absolute difference 10.2% (95% CI 2.4–17.9). Live birth rates were 49% after IUI versus 43% after intercourse, RR 1.14 (95% CI 0.97-1.35); absolute difference 6.1% (95% CI –1.71 to 13.8). There was no interaction between CC or gonadotrophins and presence of IUI on live birth (p=0.0124). Multiple pregnancy rates were low and did not differ significantly for both comparisons. The mean time to pregnancy was 0.5 months shorter after ovulation induction with gonadotrophins compared to ovulation induction with CC (log rank p=0.028) whereas the mean time to pregnancy was the same when comparing IUI with intercourse (log rank p=0.27).

Table I. Primary and secondary outcomes

	Gonado-trophins + IUI n = 164	Gonado-trophins n = 163	CC + IUI n = 163	CC n = 171	Gonado-trophins vs CC Rate difference RR (95% CI)	IUI vs intercourse Rate difference RR (95% CI)
Live birth	89 (54.3)	78 (47.9)	72 (44.2)	66 (38.6)	1.24 (1.05-1.46)	1.14 (0.97-1.35)
Ongoing pregnancy	90 (54.9)	80 (49.1)	72 (44.2)	66 (38.6)	1.26 (1.07-1.48)	1.14 (0.97-1.34)
Multiple pregnancy	4 (2.4)	3 (1.8)	7 (4.3)	1 (0.6)	0.89 (0.33-2.40)	2.8 (0.90-8.70)
Miscarriages*	15 (9.1)	9 (5.5)	8 (4.9)	3 (1.8)	-	-
Ectopic pregnancy*	1 (0.6)	1 (0.6)	3 (1.8)	1 (0.6)	-	-
Stillbirth*	1 (0.6)	2 (1.2)	0 (0.0)	0 (0.0)	-	-

Data are n (%) unless otherwise stated.
All multiple pregnancies were twin pregnancies and live births.
* Secondary outcomes.

Economic evaluation

Resource use and unit costs

The mean resource use per woman is summarized in Table II. The number of ultrasounds were higher in the women who received gonadotrophins, which resulted in more hospital visits. Women who received CC were also monitored with basal body temperature curve, mid luteal progesterone measurement or urinary LH surge, which resulted in less monitory ultrasounds and therefore less hospital visits compared to gonadotrophins. Women allocated to gonadotrophins with or without IUI and CC plus IUI received a HCG-trigger. No HCG-trigger was given to the women allocated to CC plus intercourse. Unit costs are listed in Table III.

Table II. Resource use per woman*

	Gonadotrophins + IUI	Gonadotrophins	CC + IUI	CC
Cycle monitoring/Intervention				
- Ultrasound (N)	15.87 (10.53)	16.67 (10.66)	12.69 (7.72)	8.31 (5.98)
- IUI (N)	3.22 (2.26)	0.15 (0.71)	3.57 (2.30)	0.12 (0.55)
- IVF (N)	0.04 (0.20)	0.02 (0.16)	0.06 (0.36)	0.03 (0.25)
Medication				
- CC (50mg)	0.18 (1.27)	0.48 (2.91)	28.37 (22.74)	26.16 (21.02)
- FSH (75 IU)	36.00 (32.76)	39.94 (37.29)	2.87 (12.35)	4.84 (14.15)
- HCG (5000 IU)	3.27 (2.32)	3.42 (2.27)	3.69 (2.32)	0.49 (1.26)

* Data are mean (SD).

Table III. Unit costs

Cost item	Unit	Unit costs (Euros)	Reference
Cycle monitoring/Interventions			
- Ultrasound	1	62.50	Dutch Consortium*
- IUI	1	320.54	Dutch Consortium*
- IVF	1	1365.84	Dutch Consortium*
Medication			
- CC	50mg	0.53	Dutch Consortium*
- FSH	75 IU	24.75	Dutch Consortium*
- HCG	5000 IU	5.83	Dutch Consortium*
Pregnancy and delivery			
- Singleton	1	3107.00	Lukassen *et al* 2004
- Twin	1	16 419.00	Lukassen *et al* 2004
- Miscarriage	1	1494.76	One general hospital
- Ectopic pregnancy	1	4295.65	One general hospital
- Stillbirth	1	3107.00	One general hospital

Unit costs are based on Dutch price levels in 2017.
* Costs are derived from the expert panel Dutch Consortium for Research in Women's Health.

Costs

The mean costs per woman eight months after randomisation were €4984 for gonadotrophins plus IUI, €4003 for gonadotrophins plus intercourse, €4006 for CC plus IUI for €2045 with CC plus intercourse (Fig 1A).

For the comparison gonadotrophins versus CC we found mean costs per woman of €4495 with gonadotrophins and €3007 with CC (cost difference was €1475 (95% CI €1457 to €1493)) (Fig 1B). For the comparison IUI versus intercourse we found mean costs per woman of €4497 with IUI and €3005 with intercourse (cost difference was €1510 (95% CI €1492 to €1529)) (Fig 1C).

Cost-effectiveness

The ICER for ovulation induction with gonadotrophins compared with ovulation induction with CC was €15 258 (95% CI €8721 to €63 654) reflecting the additional costs necessary to achieve one additional live birth in women treated with gonadotrophins compared with CC. The majority of the bootstrap samples were located in the northeastern quadrant, reflecting higher costs with higher effectiveness for gonadotrophins versus CC (Fig. 2).

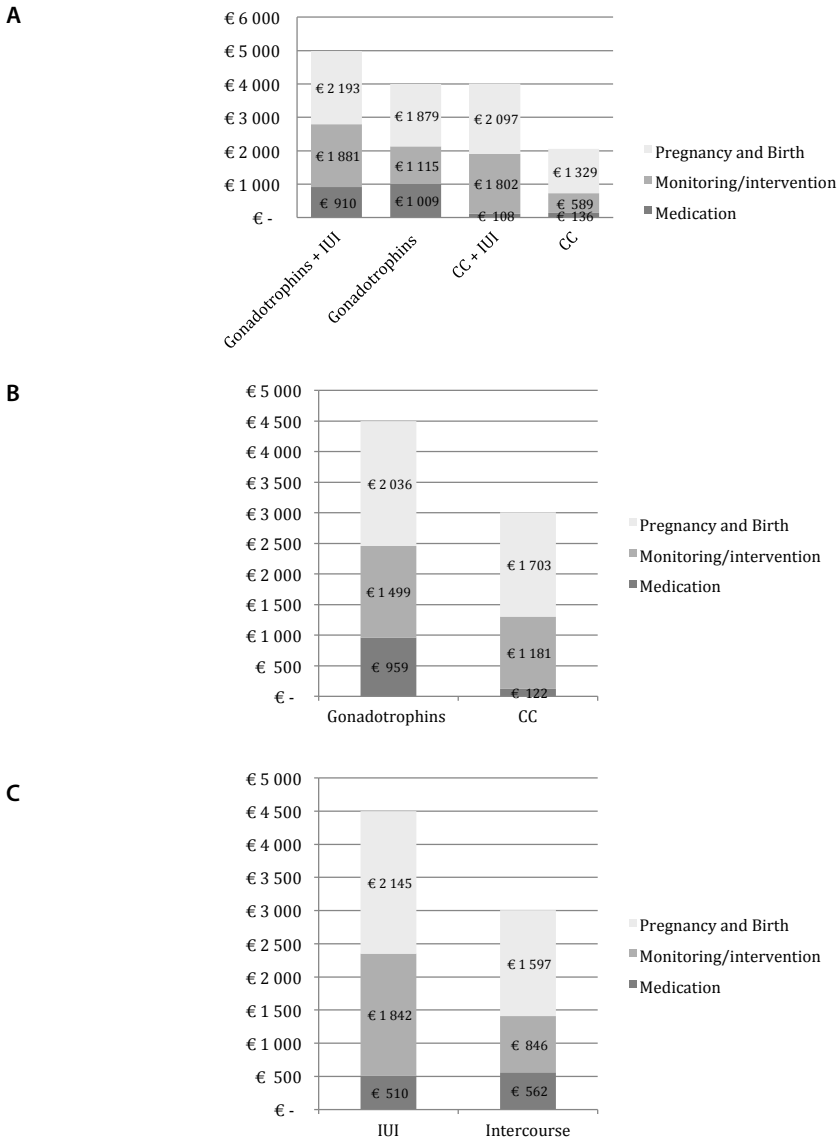


Figure 1. Mean costs per woman

A. Mean costs per woman for gonadotrophins plus IUI, gonadotrophins plus intercourse, CC plus IUI and CC plus intercourse split into the mean costs of medication, cycle monitoring/interventions (number of ultrasounds, cycles with IUI, use of IVF) and pregnancy leading to live birth. All costs are expressed in euros.
B. Mean costs per woman for the comparison gonadotrophins versus CC split into the mean costs of medication, cycle monitoring/interventions (number of ultrasounds, cycles with IUI, use of IVF) and pregnancy leading to live birth. All costs are expressed in euros.
C. Mean costs per woman for the comparison IUI versus intercourse split into the mean costs of medication, cycle monitoring/interventions (number of ultrasounds, cycles with IUI, use of IVF) and pregnancy leading to live birth. All costs are expressed in euros.

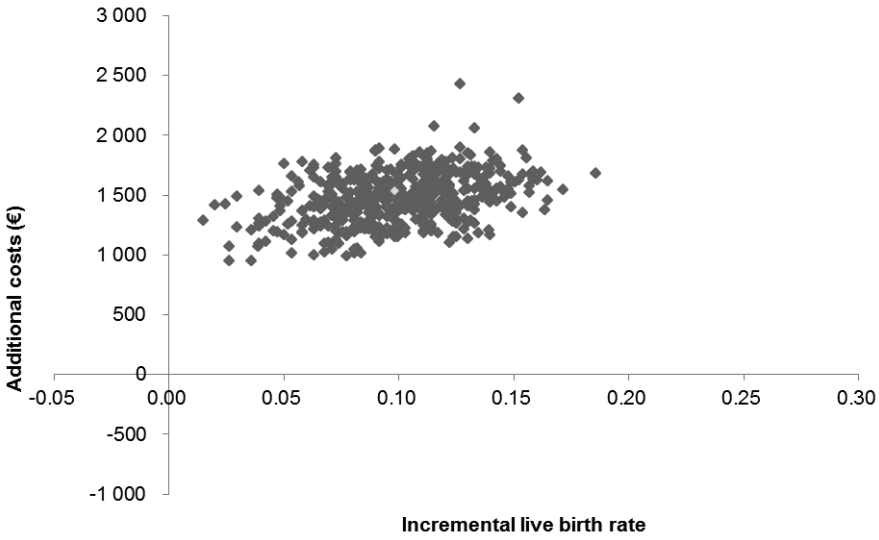


Figure 2. Cost-effectiveness plane gonadotrophins compared with CC

Cost-effectiveness plane: gonadotrophins versus CC. Each point in the cost-effectiveness plane represents the uncertainty of the additional costs and effect of gonadotrophins compared with CC after nonparametric bootstrap resampling (1000 random samples). The light grey dot in the middle represents the cost-effectiveness rate.

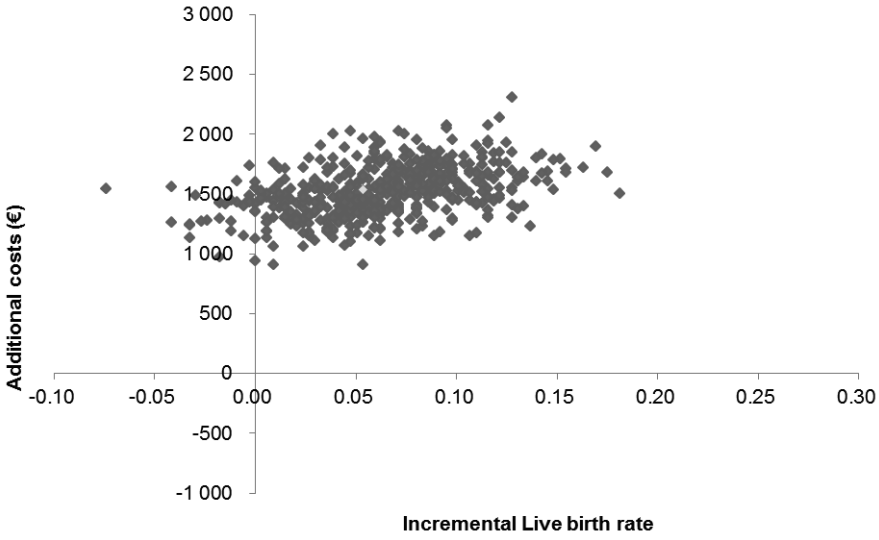


Figure 3. Cost-effectiveness plane IUI compared with intercourse

Cost-effectiveness plane: IUI versus intercourse. Each point in the cost-effectiveness plane represents the uncertainty of the additional costs and effect of IUI compared with intercourse after nonparametric bootstrap resampling (1000 random samples). The light grey dot in the middle represents the cost-effectiveness rate.

The ICER for IUI compared with intercourse was €24 361 (95% CI €-11 290 to €85 172) reflecting the additional costs necessary to achieve one additional live birth in the IUI group, compared with intercourse. The majority of the bootstrap samples were located in the north eastern quadrant (95%), reflecting higher costs with comparable effectiveness for IUI versus intercourse (Fig. 3).
For both comparisons we drew a cost-effectiveness acceptability curve (appendix 2). For a willingness-to-pay of €15 000 for an additional live birth, there is 51% chance that gonadotrophins is cost-effective compared with CC and this was 96% for a willingness to pay of €30 000. For a willingness-to-pay of €15 000 for an additional live birth, there is 15% chance that IUI is cost-effective compared with intercourse and this was 61% for a willingness to pay of €30 000.
Costs increased as more and more complex interventions were ordered, i.e. from CC, gonadotrophins, CC plus IUI, to gonadotrophins plus IUI. This implies costs were additive. The general linear model analysis did not indicate presence of interaction between IUI and ovulation induction on costs (p=0.62).

Per protocol and sensitivity analyses

Of the 666 women, 566 women were treated according to protocol and were included in the analysis. We noted more livebirths after gonadotrophins compared with CC, 125 (46%) of 274 women after gonadotrophins versus 95 (33%) of 292 women after CC (RR 1.39 (95% CI 1.10 – 1.57) absolute difference 13%). We found mean costs per woman of €4550 with gonadotrophins and €2596 with CC (cost difference was €2056 (95% CI €2040 - €2072)). The ICER for ovulation induction with gonadotrophins compared with ovulation induction with CC was €15 582 (95% CI €10 013 – €37 323) which is higher compared to the intention-to-treat ICER.
Addition of IUI did not significantly increase livebirths compared with intercourse: 118 (42%) of 281 women had a livebirth after IUI versus 102 (36%) of 285 women after intercourse (RR 1.14 (95% CI 0.96–1.36) absolute difference 6%). We found mean costs per woman of €4282 with IUI and €2578 with intercourse. The cost difference was €1586 (95% CI €1568 - €1604). The ICER for IUI compared with intercourse was €25 628 (95% CI €-11 870 – €72 340) which is higher compared to the intention-to-treat ICER.
For the comparison of gonadotrophins versus CC the results of the sensitivity analyses are shown in Table IV a. If we excluded IVF cycles (Model 1), the ICER was €15 426. When ongoing pregnancy was the main measure of effectiveness (Model 2) the ICER was €11 157. Calculating with unit costs of the United Kingdom (Model 3) resulted in a ICER was £19 744. If all CC-cycles were 100% monitored by ultrasound (Model 4) the ICER would lower to €13 460 and if none of the CC-cycles were monitored by ultrasound (Model 5) the ICER would increase to €17 222.

For the comparison of IUI versus intercourse the results of the sensitivity analyses are shown in Table IV b. If we excluded IVF cycles (Model 1), the ICER was €23 786. When ongoing pregnancy was the main measure of effectiveness (Model 2) the ICER was €17 531. Calculating with unit costs of the United Kingdom (Model 3) resulted in a ICER of £34 420.

Table IV. One way sensitivity analyses in Euro

Model	Description	Mean cost gonadotrophins (SD)	Mean cost CC (SD)	Difference (95% CI[#])	ICER (95% CI[#])
0	Base case	4536 (2501)	2996 (2735)	1475 (1457 to 1493)	15 258 (8721 to 63 654)
1	Excluded IVF	4504 (4504)	3020 (2791)	1507 (1490 to 1525)	15 426 (8852 to 64 210)
2	Endpoint ongoing pregnancy	2495 (1858)	1356 (1283)	1190 (1180 to 1201)	11 157 (5567 to 43 736)
3	Costs UK*	5410 (3033)	3429 (2824)	1918 (1898 to 1938)	19 744 (11 036 to 86 114)
4	All CC cycles monitored with ultrasound	4609 (2699)	3195 (2586)	1311 (1293 to 1329)	13 460 (7592 to 55 704)
5	CC cycles not monitored with ultrasound	4496 (3109)	2662 (2830)	1677 (1659 to 1695)	17 222 (9923 to 72 383)

A. Gonadotrophins compared with CC.
Model 0: Base case, live birth as effectiveness outcome, Model 1: Excluded all IVF cycles; effectiveness outcome live birth remained fixed, Model 2: The costs of pregnancy and birth were excluded (costs for miscarriage and ectopic are still included), effectiveness outcome was changed to ongoing pregnancy, Model 3: Effectiveness outcome live birth remained fixed, and costs from a UK (NHS) were used as input, Model 4: All CC cycles monitored with ultrasound; effectiveness outcome live birth remained fixed, Model 5: None of the CC cycles are monitored with ultrasound but with basal body temperature curve, mid luteal progesterone measurement or urinary LH surge.
[#]Non-parametric confidence interval based on 1000 bootstrap replications.
* Costs UK are in pounds.

DISCUSSION

We performed an economic evaluation alongside a two-by-two factorial multicentre RCT comparing ovulation induction with gonadotrophins with CC, and IUI with intercourse in women with normogonadotropic anovulation and CC failure. Women allocated to gonadotrophins had significantly more live births than those allocated to CC, but at higher costs. These higher costs were generated by more ultrasound monitoring and higher costs of medication in the gonadotrophin group. The additional cost necessary to achieve one additional live birth was €15,258 (95% CI €8721 to €63,654).

Women allocated to IUI did not have significantly more live births than those allocated to intercourse. The costs were significantly higher for women assigned to IUI compared with intercourse. The additional cost necessary to achieve one additional live birth was €24,361

(95% CI €-11.290 to €85.172). The wide confidence interval, crossing unity, implicates a large degree of uncertainty around the cost-effectiveness.

The present study has several strengths. First, we designed the study to assess live birth rates which is the most important outcome from the patient's perspective. Second, this economic evaluation was based on a randomised study with prospective registration of resource use. We incorporated all interventions and associated costs that took place in eight months, closely reflecting daily practice. Third, by performing several sensitivity analyses, we showed that our outcomes were robust making the results applicable to other hospitals. Finally, in the per-protocol analysis and the four sensitivity analyses CC and intercourse remained less costly, indicating that our results are robust when varying several treatment details.

A weakness of our study is that we allowed participating hospitals to use their local protocols for ovulation induction and IUI, which resulted in heterogeneous data on cycle monitoring and that we did not take into account indirect costs generated by transportation or productivity loss.

Our finding that continuing CC is less costly than switching to gonadotrophins matches the results of a cost-effectiveness study in women with PCOS using fictional treatment scenarios.[9] In that study, continuing CC for another six cycles followed by six or twelve cycles with gonadotrophins, followed by IVF was more cost-effective than a direct switch to gonadotrophins followed by IVF. The cost-effectiveness of IUI was not included in that study.

Several recent studies have shown that first line treatment with the aromatase inhibitor Letrozole is associated with higher live birth rates than with CC as was summarized in a network meta-analysis.[15] Letrozole tablets are only slightly more expensive than CC tablets.[16] A cost-effectiveness analysis comparing Letrozole with gonadotrophins in women with CC failure could result in a smaller cost difference than with gonadotrophins, but this needs to demonstrated before conclusions are drawn.

Since our cost-effectiveness analysis used a health care perspective, we focused on direct medical costs during treatment. From a societal perspective, indirect costs generated by transportation or productivity loss can also contribute to the costs of the ovulation induction treatments. Treatment with gonadotrophins plus IUI leads to more visits to the clinic in view of cycle monitoring and interventions and would thus result in more indirect costs. As a consequence, including societal costs would enlarge the cost difference between gonadotrophins and CC, and IUI and intercourse. On the other hand, due to the higher live birth rates after gonadotrophins, fewer cycles would need to be performed. Thus, over the treatment period of eight months, this potential difference in costs may disappear.

The unit costs of the interventions vary between countries. Country-specific prices and assumptions need to be considered before generalizing these results to other countries. When using prices from a NHS teaching hospital in the United Kingdom, we found that

the mean costs were higher for both gonadotrophins and IUI, leading to more costs per additional live birth for gonadotrophins compared with CC and for IUI compared with intercourse. In countries where the unit costs are higher, such as the United States, it is likely that gonadotrophins and IUI will be even more expensive.

Cost-effectiveness of interventions have to be known, but are -in themselves- not decisive in finalizing the optimal treatment policy. Decisive is the 'willingness to pay' i.e. the monetary value that society is willing to pay for higher live birth rates, but the problem is that there is no consensus on the level of costs per extra live birth that is acceptable. The NICE Fertility Guideline suggests a threshold of £30.000 per quality adjusted life year (QALY), but also highlights that QALYs cannot be derived from live births arising from assisted reproduction as QALYs are intended to capture improvements in health among patients and not in creating life. Patient preference studies in subfertile women reveal that couples are willing to pay €100-€500 extra to increase pregnancy rates by a few percent.[17,18]

In conclusion, in women with normogonadotropic anovulation who have not conceived after six ovulatory CC cycles, gonadotrophins are more effective, but generate higher costs compared to CC. In countries where ovulation induction regimens are reimbursed, policy makers and health care professionals may use our results in their guidelines. Importantly, apart from the costs, couples must be counseled that CC is known to cause more side-effects than gonadotrophins, whereas gonadotrophins require daily injections combined with ultrasound monitoring of follicular development.[10]

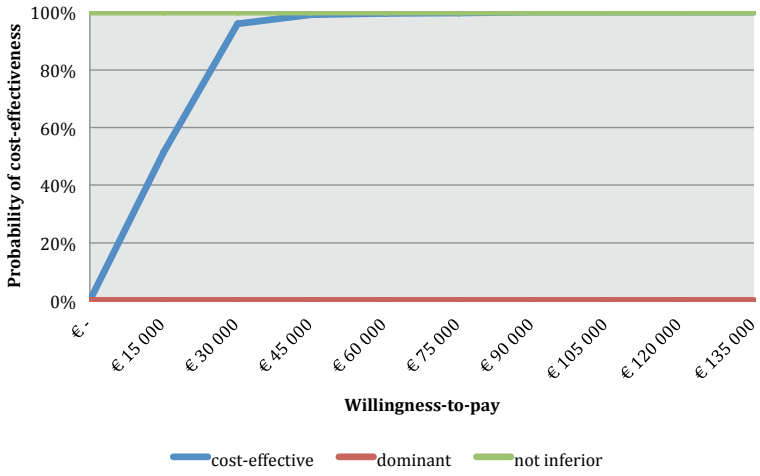
In view of the uncertainty around the cost-effectiveness estimate of IUI, we cannot make recommendations on the use of IUI in these women and more data are needed.

Appendix 1. Baseline characteristics of the participating couples

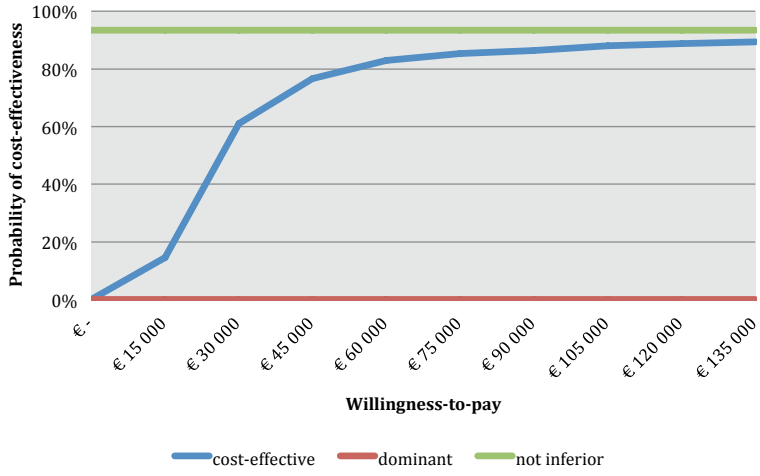
	Gonadotrophins + IUI n = 164	Gonadotrophins + intercourse n = 163	CC + IUI n = 163	CC + intercourse n = 171
Age of women (years)	29·5 ± 3·7	29·9 ± 3·7	30·0 ± 3·6	29·9 ± 4·0
Ethnicity				
White	131 (85%)	134 (88%)	133 (86%)	141 (89%)
Non-white	24 (15%)	18 (12%)	21 (14%)	18 (11%)
BMI (kg/m^2)*	25·4 ± 5·1	25·6 ± 5·6	25·0 ± 4·9	25·4 ± 5·0
BMI >25.0 kg/m^2	76 (46%)	81 (49%)	64 (39%)	81 (47%)
Current smoker	29 (18%)	20 (12%)	22 (13%)	22 (13%)
Diabetes	1	1	3	2
Previous livebirth	32 (20%)	35 (21%)	36 (22%)	34 (20%)
Duration of subfertility (months)	26·3 ± 14·9	24·5 ± 12·5	24·5 ± 15·5	25·9 ± 19·0
Cycle pattern prior to treatment #				
Amenorrhea	124 (76%)	125 (77%)	115 (71%)	120 (70%)
Oligomenorrhea	21 (13%)	25 (15%)	27 (16%)	32 (19%)
Unknown	19 (11%)	13 (8%)	21 (13%)	19 (11%)
Median TMC *10^6	52 (20-106)	43 (16-113)	53 (15-132)	38 (16-99)
Polycystic ovaries on ultrasound ##	110 (67%)	103 (63%)	109 (67%)	117 (68%)
Mean serum biochemical values				
FSH (IU/L)	5·7 ± 2·1	5·7 ± 1·7	6·2 ± 2·2	6·0 ± 2·2
LH (IU/L)	9·7 ± 7·4	10·6 ± 7·8	10·6 ± 7·6	10·9 ± 10·8
Estrogen (pmol/L)	255 ± 295	239 ± 217	201 ± 159	271 ± 460
Total testosterone (nmol/L)	1·6 ± 1·7	1·6 ± 2·0	1·8 ± 2·2	1·8 ± 1·8

Data are mean (SD), n (%) or median (IQR). BMI = body-mass index. TMC = total motile sperm count. FSH = follicle stimulating hormone. LH = luteinizing hormone. CC = clomiphene citrate. IUI = intrauterine insemination.
*BMI was missing for 24 women; data were imputed by using multiple imputation.
Amenorrhea: absence of menstrual bleeding for >6 months. Oligomenorrhea: irregular menstrual bleedings with intervals of >35 days but ≤6 months
Defined as the presence of 12 or more follicles in each ovary measuring 2–9 mm in diameter

Appendix 2. Cost-effectiveness acceptability curves



This cost-effectiveness acceptability curve shows the probability that FSH is cost-effective compared with CC, given the observed data, for a range of values of the willingness to pay for an additional live birth.



This cost-effectiveness acceptability curve shows the probability that IUI is cost-effective compared with intercourse, given the observed data, for a range of values of the willingness to pay for an additional live birth.

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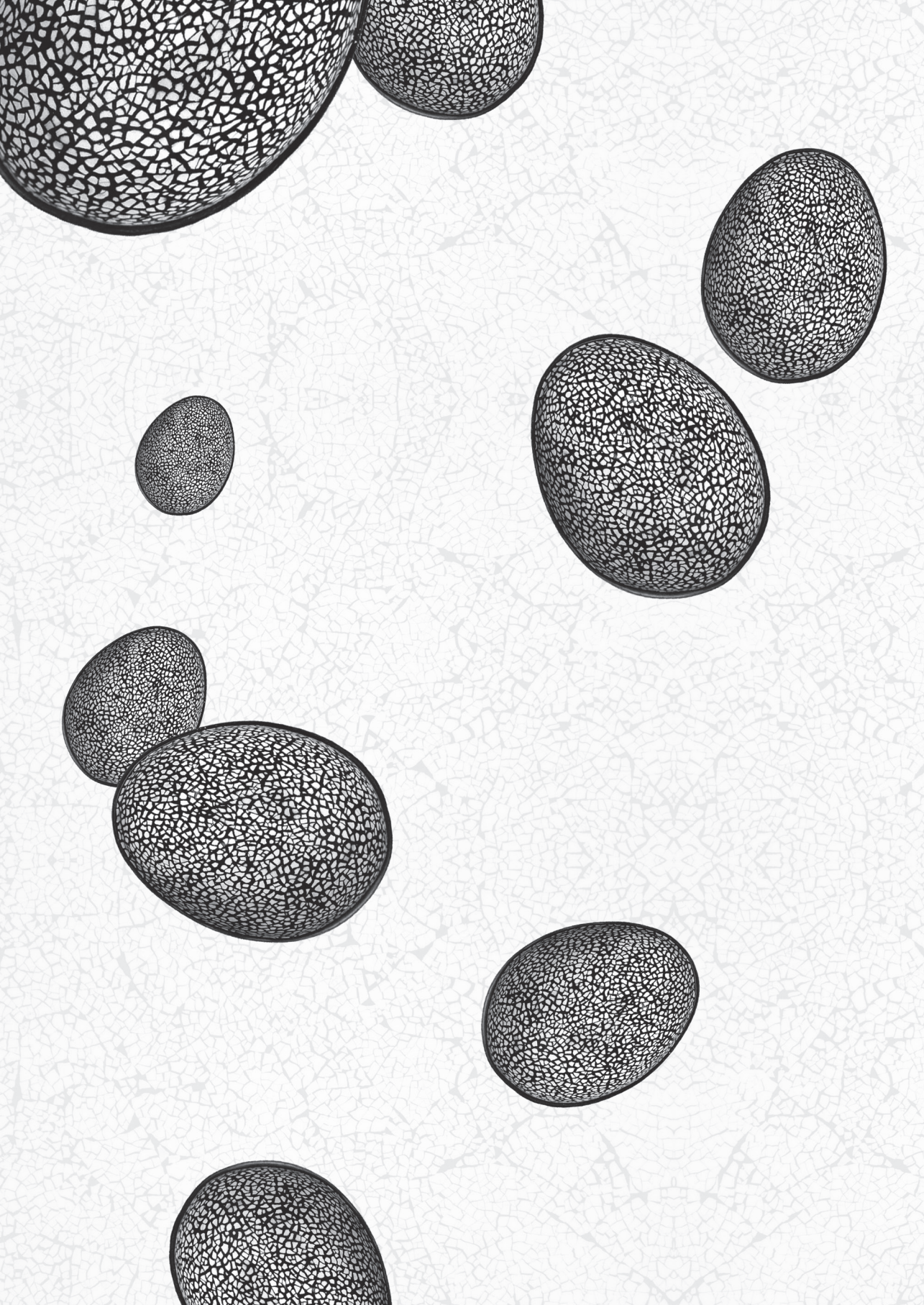

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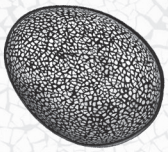
Women's perspectives on ovulation induction with or without IUI as treatment for normogonadotropic anovulation; A discrete choice experiment



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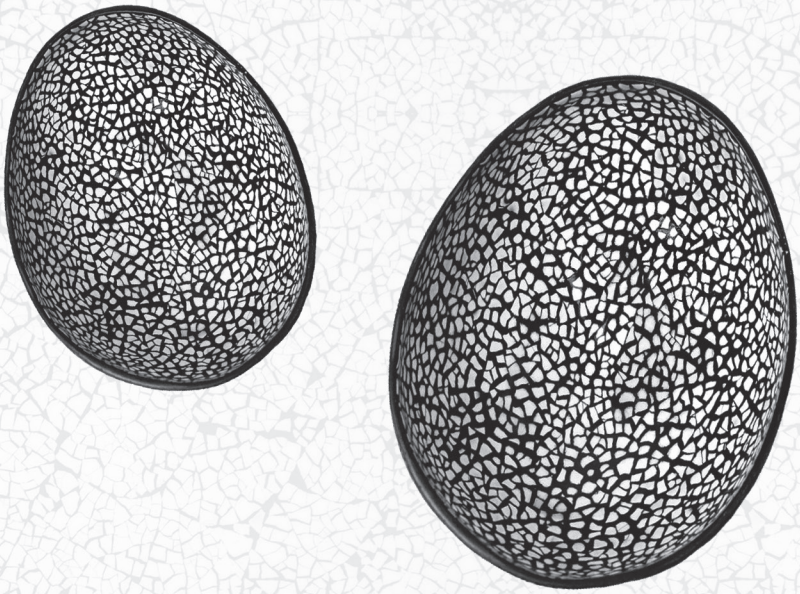

Human Reproduction Open, 2017 Oct

ABSTRACT

Study question: What are the treatment preferences of women with normogonadotrophic anovulation treated with ovulation induction with or without intrauterine insemination (IUI)?

Summary answer: Women with normogonadotrophic anovulation differ in their treatment preference; half of them base their preference on the lowest burden and half of them on the highest effectiveness.

What is known already: Common treatments for anovulatory women who wish to conceive are ovulation induction using clomiphene citrate or letrozole taken in tablet form or with injections containing gonadotrophins, all optionally combined with IUI. Patient preferences for these alternatives have not yet been examined in these women.

Study design, size and duration: Between August 2014 and February 2017 we conducted a multicentre discrete choice experiment (DCE). The target sample size was calculated by including 20 women for six attributes in the main analysis resulting in the inclusion of 120 women to be able to assess heterogeneity across choices.

Participants/materials, setting, methods: We invited treatment-naive women diagnosed with normogonadotropic anovulation and visiting the outpatient clinic of five Dutch centers (three teaching hospitals and two university hospitals) to participate in the DCE by completing a printed questionnaire. We asked women to indicate their preference in hypothetical alternative treatment scenarios by offering a series of choice sets from which they were to choose their preferred alternatives. The choice sets contained several treatment characteristics of interest, i.e. attributes concerning ovulation induction with clomiphene citrate or letrozole versus gonadotrophins, as well as intercourse and IUI. We selected six attributes: number of visits to the outpatient clinic during treatment; type of medication; intercourse or IUI; risk of side effects; willingness to pay; and pregnancy chances leading to the birth of a child after six treatment cycles.
We used a multinominal logit model to determine the preferences of women and investigated heterogeneity in preferences through latent class analysis. To determine if women were willing to make a trade-off for higher pregnancy rates at the expense of a higher burden, we calculated the marginal rate of substitution.

Main results and the role of chance: The questionnaire was completed by 145 women. All six attributes influenced women's treatment preferences and those valued as most important were low risk of side effects, a minimal number of hospital visits and intercourse. A total of 55% of women were driven by the wish to conceive with the least medical interference and lowest burden. The remaining women were success driven and chose mainly for the highest chances to conceive, regardless of the burden. Age and duration of subfertility did not significantly differ between these women. Women were willing to trade-off some burden and costs for higher pregnancy chances.

Limitations / reasons for caution: The sample size of our study is relatively small which made it not possible to perform inter- action tests and subgroup analyses.

Wider implications of the findings: Our results may be used during the counseling of couples about their treatment options. These findings are an argument to explore if a woman prefers potentially fast success or a medically less intense route that might take longer. The preference for the less intense route would lead to the continuation of ovulation induction with oral drugs such as clomiphene citrate or letrozole rather than treatment with injected gonadotrophins, or even IVF.

Study funding / competing interest(s): B.W.M. is supported by a NHMRC Practitioner Fellowship (GNT1082548). B.W.M. reports consultancy for Merck, ObsEva and Guerbet. CBL reports grants from Merck and Ferring.

INTRODUCTION

Shared decision-making begins with an understanding of patient preferences.[1] There is increasing interest in patient-centeredness within reproductive medicine since patients not only value the effectiveness of a treatment but also the burden, safety and costs. The trade-offs they make can be very different between patients.[2,3] Dropout rates in couples undergoing fertility treatment are reported to be ~50% and are mainly a result of emotional distress.[4] Insight into treatment preferences may help to counsel the woman for an individualized treatment strategy, thereby improving patient compliance by preventing dropout.[5,6]

Approximately 20% of fertility treatment concerns ovulation induction in women with normogonadotrophic normo-estrogenic anovulation, or oligo-ovulation.[7]

Ovulation may be induced with oral agents such as clomiphene citrate and letrozole or parenteral drugs such as gonadotrophins.[8-10] There are several meaningful differences between these medications. Although clomiphene citrate and letrozole can be taken orally, they can cause side effects. Clomiphene citrate may induce flushes and mood swings whereas letrozole can give headache and abdominal cramps. Gonadotrophins can only be administered by subcutaneous injection, but tend to have fewer side effects than clomiphene citrate.[9,11] Since the oral agents are much cheaper than gonadotrophins and monitoring of these cycles takes fewer hospital vis- its than monitoring cycles stimulated with gonadotrophins, the treatment with oral agents is remarkably less costly.[12,13] Around ovulation, conception can be realized by either intercourse or intrauterine insemination (IUI).[14]

To explore whether women prefer fast success or a medically less intense road that might take longer, we evaluated the treatment preferences of women with normogonadotrophic anovulation undergoing ovulation induction with or without IUI by means of a discrete choice experiment (DCE). DCEs have become a commonly applied approach over recent years.[15,16] The method involves asking individuals to indicate their preference in hypothetical alternative treatment scenarios by offering a series of choice sets from which they are to choose their preferred alternatives. The choice sets contain several treatment characteristics of interest, i.e. attributes.[17,18] The attributes are commonly defined by a literature review and by the expert opinions of focus groups of health care workers who are experienced in the subject under study.

MATERIALS AND METHODS

Women diagnosed with normogonadotrophic anovulation who were visiting the outpatient clinics of five Dutch hospitals and who had never undergone fertility treatment were invited to participate in the study. Being treatment-naive prevented any bias that

women might have based on their knowledge and experiences with previous treatments. Women who gave their informed consent to participate in this study received a printed questionnaire with 28 fictional scenarios, presented in 14 questions. Each question consisted of two fictional treatment options. The women were asked, for each scenario, to choose their preferred treatment (Table I). The scenarios included features concerning ovulation induction with clomiphene citrate or letrozole versus gonadotrophins as well as features about intercourse and IUI. Women had to be able to understand the questionnaire, which was written in Dutch. We asked women to complete the questionnaire before starting ovulation induction or when they had just started ovulation induction. If the questionnaire had not been returned within a few weeks, we sent out a reminder.

Table I. Example of discrete choice question in the DCE questionnaire.

Scenario 1	**Treatment A**	**Treatment B**
Number of hospital visits during one treatment cycle	2	4
Ovarian stimulation	Tablets for 5 days	Tablets for 5 days
Place of fertilization	Insemination at the hospital	Insemination at the hospital
Side effects per treatment	Existing	Non existing
Financial contribution	None	None
Chance of conceiving after six treatment cycles	45 out of 100 (45%)	40 out of 100 (40%)
I choose	A ☐	B ☐

The DCE design of this study was based on a report of the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) for good research practices for a Conjoint Analysis Task Force, which is a widely used guideline for designing a DCE study.[18,19] We defined the attributes in the DCE based on the expert opinions of a focus group consisting of gynecologists working in one of the participating hospitals and specialized in treating women with anovulation. Also experts on DCE testing from one of the hospitals were consulted to create the final questionnaire. We selected six attributes that were most frequently indicated by the experts: number of visits to the outpatient clinic during treatment; type of medication; intercourse or IUI; side effects; willingness to pay; and chances of the birth of a child after six treatment cycles. These six attributes cover the areas of 'burden', 'costs' and 'effectiveness'. The levels assigned to the attributes were also based on the opinion of the experts. A summary of the attributes and their features, i.e. 'levels' is shown in Table II.

The six attributes and their levels generated a total of 144 (24 × 32) possible scenarios. We selected an independent sample of 13 scenarios using a design meeting the main criteria

for an efficient DCE design.[20,21] We used Ngene design software to draw a most efficient design (version 1.1.1 Choicemetrics Pty Ltd, Sydney, NSW, Australia).

Table II. Attributes and levels used in the discrete choice experiment design

Attribute	Level
Number of hospital visits during one treatment cycle	0
	2
	4
Ovarian stimulation	Tablets for 5 days
	12 injections
Place of fertilization	Intercourse at home
	IUI at the hospital
Sides effects per treatment	Non existing
	Existing
Contribution	None
	€500
Chance of conceiving after 6 treatment cycles	40 out of 100 (40%)
	45 out of 100 (45%)
	50 out of 100 (50%)

Next, a check for internal consistency was included by adding a dominance test comprising a total of 14 scenarios in the questionnaire. The dominance test is a treatment scenario in which one option is set to be optimal, i.e. all levels are equal to or better than the other option (Table III). Therefore, if the woman chooses the suboptimal treatment one can conclude that she does not understand the questionnaire and the results cannot be used for analysis.

We included additional questions to collect baseline characteristics, i.e. age, educational level, duration of subfertility and possible fear of injections. There was also one open-ended question for the women to endorse their answers and add comments.

We introduced a pilot version of the questionnaire in one of the participating hospitals, to identify any inconsistencies in the questionnaire. After receiving 20 completed questionnaires, the pilot version was tested for internal validity. The dominance test was filled in correctly by all 20 women. Basic analysis suggested our expected direction of effect for all attributes. For the attribute 'chance of conceiving' a smaller effect was seen than we expected with much heterogeneity in response. We interpreted this as being caused by the relatively small differences in levels: a 40% versus 42% versus 44% chance of conceiving. Therefore, this attribute was adjusted by enlarging the thresholds of the levels to 40% versus 45% versus 50% chance of conceiving. The 20 women had no negative comments

on the DCE therefore no other changes were made. Subsequently, the DCE was expanded to the four other hospitals.

We calculated the sample size by using a rule of thumb of 20 women per attribute. Since our DCE contained 6 attributes, a minimum of 120 women was expected to be able to assess heterogeneity across choices. This was confirmed by assessing the size effect measures of the pilot data.

Table III. Dominance test included in DCE design for intern validity.

Scenario 4	Treatment A	Treatment B
Number of hospital visits during one treatment cycle	2	4
Ovarian stimulation	Tablets for 5 days	12 injections
Place of fertilisation	Intercourse at home	Insemination at the hospital
Side effects per treatment	Non existing	Existing
Contribution	None	€500
Chance of conceiving after 6 treatment cycles	50 out of 100 (50%)	40 out of 100 (40%)
I choose	A ☐	B ☐

Statistical analyses

We estimated the importance that women placed on each attribute level using a main-effects (no interactions) multinominal logit model, as recently described[22] We included the attribute 'chance of conceiving' as a continuous variable. All other attributes were included as categorical variables. A statistically significant coefficient indicated that women considered that attribute important.

We investigated preference heterogeneity through latent class analysis (LCA). With LCA one can study whether women have comparable pat- terns of preference in order to estimate the probability that each woman belongs to a certain class.[22] We assigned women to the latent class for which they had the highest probability. We determined the association between selected patient characteristics and latent class membership using univariable and multivariable logistic regression models. We included women's age, parity and duration of subfertility a priori in view of their expected preference effect to these attributes on choice-making. Finally, we determined the increase in the chances of conceiving required for women to accept a treatment with an undesirable attribute, called the marginal rate of substitution (MRS), i.e. the trade-off that women are willing to make for higher pregnancy rates.[22] The median and 95% CI of the MRS were estimated through Monte Carlo sampling.

All analyses were performed using SPSS 22 (IBM: IL, USA) and R (version 3.1.2; http://www.r-project.org).

Ethical approval

The Medical Ethical Committee of the Academic Medical Centre of Amsterdam approved the use of the DCE.

RESULTS

The study was performed between August 2014 and February 2017 in three teaching hospitals and two university hospitals in the Netherlands. A total of 234 women met the inclusion criteria and received the questionnaires. The response rate was 62%, with 145 returned questionnaires and these questionnaires were all included for analysis. The dominance question was answered correctly by all women.

Characteristics of participating women

The baseline characteristics of the women are shown in Table IV. The mean age was 30 years (range 23–40). The majority of women was highly educated (80%) and primary subfertile (81%) with a median duration of subfertility of 12.6 months. There were 29 women (23%) who reported having moderate to extreme fear of injections.

Attributes defining the choice for treatment

All attributes contributed to the choice for treatment (Table V). The most important attributes were intercourse versus IUI (coefficient 1.8 [95% CI 1.61–1.99]), no hospital visits compared to four visits (95% CI 1.68 [1.97–1.51]) and having no side effects versus having side effects (coefficient 1.68 [95% CI 1.8–1.46]). The chances to conceive showed a linear effect with women's preferences; for every 1% increase in chance, the coefficient increased by 10% (coefficient 0.10 [95% CI 0.075 to 0.125]).

Preference heterogeneity

LCA identified two subgroups of women. Over half of the women (Latent Class 1; 55%) preferred tablets over injections, having no side effects, no hospital visits and intercourse over IUI. The remaining women (Latent Class 2; 45%) chose mainly for the highest chances to conceive despite the need for injections, possible side effects and more hospital visits. Coefficients per attribute for both subgroups are shown in Table V.

We performed a univariable analysis on the characteristics 'age' and 'duration of subfertility' within the LCA. The women of Latent class 1 were on average 4 years younger and their duration of subfertility was on average 3 months shorter; these differences were not statistically different (P = 0.24 and 0.37 respectively, Table VI).

The MRS

The MRS analysis showed that women were willing to accept injections over tablets for an increase of 6.8% in the chances to conceive. Two hospital visits per treatment cycle versus no visits as well as personal costs of €500 were accepted if there would be an 8.9% increase in the chances to become pregnant.

For the presence of side effects, requiring four hospital visits per cycle and IUI versus intercourse the trade-offs for the chance of pregnancy were 14, 14 and 15%, respectively (Table VII).

Table IV. Patient characteristics of responders at inclusion.[a]

Characteristic	
Mean age in years (range)	30 (23-40)
Median duration of subfertility in months (range)	12.6 (0.9-197.6)
Characteristic	**n (%)**
Highest level of education	
Primairy	0 (0)
Secondary	29 (20.0)
Tertiary	116 (80.0)
Income	
Below average	5 (3.4)
Average	32 (22.1)
Above average	101 (69.7)
Does not want to tell	7 (4.9)
Fear of needles/injections*	
None	49 (38.3)
Some	50 (39.1)
Moderate	20 (15.6)
Severe	6 (4.7)
Extreme	3 (2.3)
Parity	
1	27 (18.6)
0	118 (81.4)

[a] Responders, N=145
*Responders, N=128 (question was added during the pilot study)

Table V. Multinominal regression analysis and two latent class analyses

	Multinominal regression		Latent class 1 55%		Latent class 2 45%	
Attributes	**coeff**	**95% CI**	**coeff**	**95% CI**	**coeff**	**95% CI**
Intercept	-7.65		-7.67		-7.64	
Chance on conceiving per 1% (40% to 50%)	0.12	0.095 to 0.15	0.075	0.039 to 1.11	0.16	0.11 to 0.21
Side effects (yes vs no)	-1.68	-1.80 to -1.46	-1.89	-2.17 to -1.61	-1.37	-1.62 to -1.12
Stimulation (injections vs tablets)	-0.83	-0.99 to -0.66	-1.41	-1.78 to -1.04	-0.35	-0.02 to -0.68
Number of hospital visits						
0	ref		ref		Ref	Ref
2	-1.07	-1.33 to -0.81	-1.50	-1.97 to -1.03	-0.87	-1.05 to -0.59
4	-1.68	-1.97 to -1.51	-2.35	-2.86 to -1.85	-1.20	-1.53 to -0.87
Intercourse vs IUI	1.80	1.61 to 1.99	2.71	2.26 to 2.09	1.13	0.66 to 1.60
Costs vs no costs	-1.08	-1.26 to -0.88	-1.13	-0.83 to -1.43	-0.84	-1.14 to -0.54
2log likelihood	-611			-582		
Pseudo R2	0.322			0.328		
cAIC*	1185			1102		

*cAIC = consistent Akaike Info Criterion

Table VI. Two latent class analyses – patient characteristics

Patient characteristics	**Latent class I 55% of women mean (95%-CI)**	**Latent class II 45% of women mean (95%-CI)**	**Univariable analysis**
Age (years)	28.2 (25.0-31.5)	32.1 (29.0-35.2)	0.24
Duration of subfertility (months)	8.2 (6.0-10.4)	11.3 (8.9 - 13.7)	0.37

Table VII. Marginal rate of substitution

	% Increase in chance of conceiving to accept the undesirable attribute	
Attribute	**Level**	**Overall (95% CI*)**
Side effects	Yes versus no	14 (9.7 - 18)
Injections	Yes versus no	6.8 (1.9 - 12)
Number of visits	2 versus 0	8.9 (3.4 - 14)
	4 versus 0	14 (7.2 - 21)
Place of fertilization	IUI versus intercourse	15 (8.3 – 22)
Costs	€500,- versus no costs	8.9 (3.2 – 15)

*CI interval was based on the Krinsky Robb method adjusted for class probabilities.

DISCUSSION

This preference study among 145 women with normogonadotrophic anovulation who wished to conceive showed that all six selected attributes played a significant role in their preferences for treatment. Three attributes were valued as most important: low risk of side effects, a minimal number of hospital visits and intercourse. A small majority of women was driven by the wish to conceive with least medical interference and lowest burden, while the other women were primarily success driven and chose mainly for the highest chances to conceive. Age and duration of subfertility did not significantly differ between these women. Women were willing to trade-off some bur- den and costs for higher pregnancy chances.

A strength of our study is that it was designed following the checklist of the report of the ISPOR Conjoint Analysis Experimental Design Good Research Practices Task Force.[18] In addition, we performed a pilot study after which we made appropriate adjustments to the DCE. All women answered the dominance test correctly, which is why we assume that the questionnaire was easy to understand for the women, most of whom were highly educated. Another strength is that we solely included treatment-naive women; our rationale was that women who had previously undergone one of the treatments either successfully or unsuccessfully, may answer the questionnaire with a strong preference or dislike for one or the other treatment without actually considering the different features.

The main limitation of the present DCE is its relatively small sample size. For a full DCE, including interaction tests and subgroup analyses, a sample size of at least 500 women would be required. Another limitation is that the response rate was only moderate, possibly leading to selection bias. On the other hand, our sample size, composition of the population and response rate is comparable with other recently published DCEs, which is why we assume that our data are more widely applicable.[23,24]

Finally, our cohort is quite homogeneous including mainly highly educated women earning an above average income. Since women with a high educational level and income are less likely to have a positive perspective on care, whereas women with a lower occupational status experience more anxiety, our results may not necessarily extrapolate to all women.[25,26] Also, the facts that our population had easy access to fertility care (as most fertility clinics offer ovulation induction) and that IUI is reimbursed in the Netherlands have to be taken into account when generalizing the data.

There are no previous studies on women's preferences in the treatment of anovulation comparing oral agents with gonadotrophins, both with or without IUI. There is one preference study using inter- views with women with clomiphene citrate-resistant polycystic ovary syndrome comparing gonadotrophins with laparoscopic electrocautery of the ovaries.[27] There are two studies on subfertile women with various underlying causes, one of which used DCE-techniques and the other examined willingness to pay and con-joint analysis. All three preference studies show that pregnancy rates are the leading factor

for women when deciding on a specific treatment.[28-30] In contrast, in our study the majority of women chose mainly an approach with the lowest treatment burden. This discrepancy with the previous studies is probably caused by the fact that we, unlike the other studies, examined treatment-naive women. It seems likely that women who have experienced numerous failed treatment cycles, as was the case in the other studies, prefer a treatment with a high success rate and would therefore accept a fair amount of burden. This concept is supported by the comments found in the open-ended question of our DCE (data not shown).

Our results emphasize that effectiveness, i.e. pregnancy chances, are not the sole important issue in fertility care. This supports the outcomes of a focus group study, a survey study and a systematic review that found that aspects such as having a lead physician, seeing trained fertility nurses, physical comfort, accessibility and information provision can help to improve women's satisfaction with fertility treatment and care.[25,28,29,31] This, in turn, may prevent women dropping out of treatment.6

In our study, most women preferred having intercourse over IUI but were willing to accept IUI when pregnancy chances rise significantly. This trade-off is comparable with the results of a preference study that examined subfertile couples and their preferences on insemination.[32] On the subject of IUI, we must take into account the present discussion on the effectiveness of this treatment.[33,34]

Implications for practice and future research

The results of our study can be used during the counseling of couples about their treatment options. We suggest the development of a simple, practical decision tool that can help to distinguish the personal preference of an anovulatory woman consulting a fertility clinic before she starts treatment. These findings are an argument to explore whether a woman prefers possible fast success (i.e. time to pregnancy) or a medically less intense route that might take longer. The preference for a less intense route would lead to the continuation of ovulation induction with oral drugs, such as clomiphene citrate or letrozole, rather than treatment with gonadotrophins or even IVF.

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Conflict of interest

CBL reports grants form Merck and Ferring. BWM reports consultancy for Merck, ObsEva and Guerbet.

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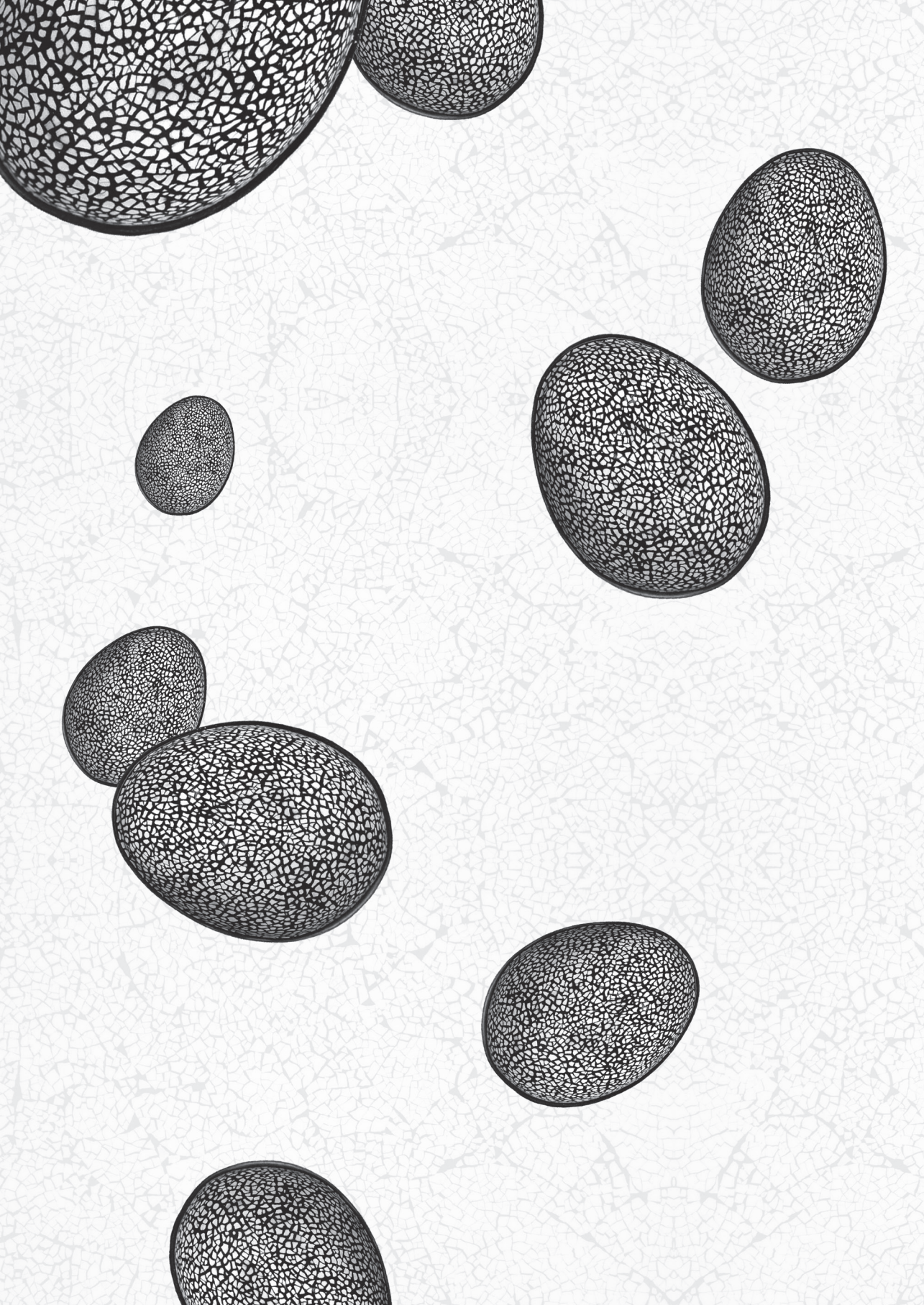
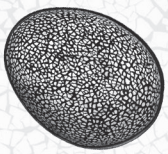
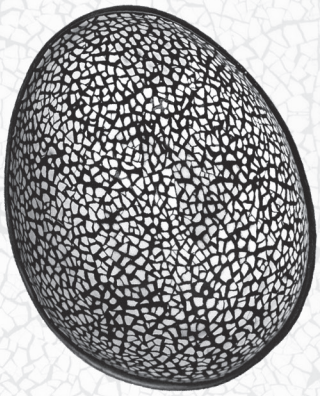


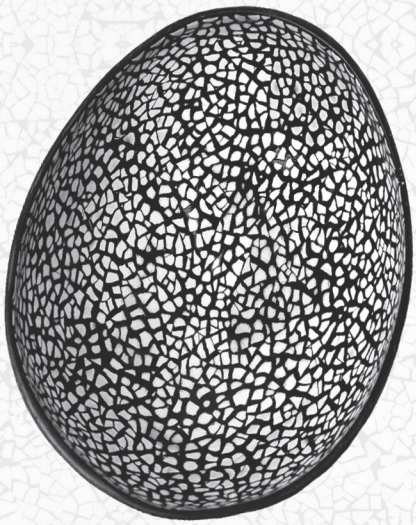
8

Summary

Implications for practice and future research







SUMMARY

Subfertility affects 10 to 15% of all couples who want to have a child. In 20 to 25% of these couples, the woman suffers from anovulation[1]. Ovulation disorders can be categorized as World Health Organization (WHO) type I, II and III. Type I ovulation disorders are caused by hypothalamic pituitary failure, type II ovulation disorders are defined as dysfunction of the hypothalamic-pituitary-ovarian axis and type III ovulation disorders are caused by ovarian failure.[2]

This thesis focuses on WHO type II anovulatory women i.e. normogonadotropic anovulatory women, who account for around 85% of the ovulation disorders. The majority of these women are diagnosed as having polycystic ovary syndrome (PCOS).[3] If normogonadotropic anovulatory women wish to conceive, strategies to induce ovulation include treatment with clomiphene citrate, letrozole and gonadotrophins. Also, intrauterine insemination (IUI) can be added to replace vaginal intercourse[2]. Clomiphene and gonadotrophins are both well established and effective treatment options and have been used for many years[2,4]. The use of letrozole is off-label for this indication.

The research presented in this thesis emerged from a collaboration of the Centers of Reproductive Medicine of the VU Medical Center of Amsterdam and the Academic Medical Center of Amsterdam. Both centers have a longstanding history of research in the field of subfertility and PCOS. This research line has contributed to our insight into the pathogenesis and endocrinology of PCOS [5-9], but also into the effectiveness and safety of treatment of therapy naïve women and women with clomiphene resistance.[10-16] This thesis follows up on this by studying how to effectively and safely treat women with clomiphene failure, taking into account patient preferences and costs associated with these interventions.[2,17,18]

In **chapter 1** we provide a general introduction and describe the objectives of this thesis.

In **chapter 2** we aimed to provide an overview on the effectiveness and safety of all gonadotrophin preparations available for ovulation induction in women with PCOS and clomiphene resistance or clomiphene failure. We performed a systematic review and meta-analysis including all randomized controlled studies that compared urinary-derived products such as urofollitropins (uFSH), human menopausal gonadotrophin (HMG), available in purified (FSH-P) and highly purified (FSH-HP and HP-HMG) forms, or recombinant FSH (rFSH). The review relied on the search strategy developed for the Cochrane Menstrual Disorders and Subfertility Group. Primary outcomes were live birth rate per woman and the incidence of ovarian hyperstimulation syndrome. We included 14 trials, covering 1726 women. We found no evidence of a difference for any of the gonadotrophin comparisons in terms of live birth (the overall OR per woman was 1.26 (95%CI 0.80 - 1.99, 5 RCTs, n = 505), for the comparison rFSH versus uFSH) or any other pregnancy outcome. There was also

no evidence of a difference in the occurrence of ovarian hyperstimulation syndrome. We suggest that the choice of one or the other product should depend upon the availability of the product, the convenience of its use, and the associated costs.

In **chapter 3** we aimed to establish the value of the postcoital test in women with WHO type II anovulation. It was questioned that the postcoital test would identify women with poor conception chances who might benefit from immediate IUI. We performed a prospective follow-up study to examine the capacity of the postcoital test to predict conception in WHO type II anovulatory women who became ovulatory with clomiphene. In this study, 251 women were included and a postcoital test was planned in one of the first three ovulatory cycles. Regardless of the test result, women continued clomiphene for at least six ovulatory cycles. The primary outcome was time to ongoing pregnancy. In 99 women the postcoital test was not performed; 41 women were pregnant before undergoing the test, 10 had persistent anovulation, and in 48 women the test was not performed for various reasons. Among the remaining 152 women, 107 had a positive test result and 45 women had a negative result. The ongoing pregnancy rate was 45/107 (42%) for women with a positive test and 10/28 (36%) for women with a negative test. The proportional hazard analysis showed that the postcoital test results was not a statistical significant predictor of time to ongoing pregnancy, (hazard rate (HR) for ongoing pregnancy 1.3 (95% CI 0.64 - 2.5). We concluded that the postcoital test has only limited value in women with WHO type II anovulation. We advocate that women who start ovulation induction with clomiphene can safely do so without undergoing a postcoital test.

In **chapter 4** we aimed to assess the effectiveness of continued treatment with clomiphene in women with WHO type II anovulation who have had at least six ovulatory cycles with clomiphene without successful conception. Guidelines advise switching to gonadotrophins after six cycles of clomiphene, but gonadotrophins carry a high risk of multiple gestation and are expensive. Even more importantly, the advice to switch is not underpinned by any evidence and we thus felt it opportune to assess success rates after continued treatment with CC.
We performed a retrospective cohort study that assessed the effectiveness of continued treatment with clomiphene in normogonadotropic women with clomiphene failure. We included 114 women from five Dutch hospitals that had not conceived after six ovulatory cycles and who had continued treatment with clomiphene. Follow-up was a total of 12 treatment cycles. Primary outcome was the cumulative incidence of an ongoing pregnancy at the end of treatment. Of these 114 women, 35 (31%) had an ongoing pregnancy resulting in a cumulative incidence rate of an ongoing pregnancy of 54% after 7–12 treatment cycles with CC. These results justified to start a randomized study comparing continued treatment with clomiphene with second line treatment.

In **chapter 5** we aimed to compare the effectiveness of gonadotrophins to continued treatment with clomiphene, both with or without IUI, in terms of live birth as it was unknown if gonadotrophins and IUI would increase pregnancy rates in women with clomiphene failure. We performed a multicenter, randomized, two-by-two factorial clinical trial in 48 centers in the Netherlands. We studied women with normogonadotropic anovulation not pregnant after six ovulatory cycles with clomiphene. Women were randomized to six cycles with gonadotrophins plus IUI, six cycles with gonadotrophins plus intercourse, six cycles with clomiphene plus IUI or six cycles with clomiphene plus intercourse, the latter being a continuation of the earlier treatment.

Primary outcome was conception leading to live birth within eight months after randomization. Secondary outcome measures were ongoing pregnancy, multiple pregnancy, miscarriage, ectopic pregnancy, time from randomization to the birth of a live child, fetal birth weight and pregnancy complications i.e. hypertensive disorders, gestational diabetes and preterm labour. Primary analysis was by intention to treat. We made two comparisons, one in which gonadotrophins was compared to clomiphene and one in which IUI was compared to intercourse. Between December 8th 2008 and December 16th 2015 we randomly allocated 666 women to gonadotrophins/IUI (N=166), gonadotrophins/intercourse (N=165), clomiphene/IUI (N=163), or clomiphene/intercourse (N=172).

Women allocated to gonadotrophins had more live births than those allocated to clomiphene (167 of 327 women [51.5%] vs. 138 of 334 [41.3%], (RR 1.24 (95% CI 1.05 -1.46). Addition of IUI did not statistically significant increase live births compared to intercourse (161 of 327 women [49·2%] vs. 144 of 334 [43.1%], RR 1.14 (95% CI 0.97-1.35). Multiple pregnancy rates for the two comparisons were low and not different.

The results of this study demonstrate that, in women with normogonadotropic anovulation and clomiphene failure, a switch to gonadotrophins increases chances of live birth over continued treatment with clomiphene. The addition of IUI does not seem to increase live birth rates in these women. More importantly, the study showed that all four treatment arms result in acceptable pregnancy rates and low complication rates.

In **chapter 6** we presented a cost-effectiveness analysis that was performed alongside the randomized clinical trial of chapter 5. We collected data on direct costs related to treatment and medication and we calculated unit costs from various sources. We calculated the mean costs of ovulation induction with gonadotrophins and clomiphene and the mean costs of IUI and intercourse. We calculated incremental cost-effectiveness ratios (ICER) for gonadotrophins compared to clomiphene and for IUI compared to intercourse. Nonparametric bootstrap resampling was used to investigate the effect of uncertainty in our estimates.

Mean medical costs were €4.495 per woman for gonadotrophins and €3.007 for clomiphene (cost difference €1.475 (95% CI €1.457 to €1.493), resulting in an incremental cost-effectiveness of €15.258 (95% CI €8721 to €63.654) per additional live birth. Mean medical costs were €4.497 for IUI and €3.005 for intercourse (cost difference €1.510 (95% CI €1.492 to €1.529). The incremental cost-effectiveness ratio was €24.361 (95% CI €-11.290 to €85.172) per additional live birth.
In conclusion, gonadotrophins are more effective, but generate higher costs compared to clomiphene. In view of the uncertainty around the cost-effectiveness estimate of IUI, we cannot make recommendations on the use of IUI in these women and more data are needed.

In **chapter 7** we investigated the treatment preferences of women with normogonadotropic anovulation. Between August 2014 and February 2017 we conducted a multicentre Discrete Choice Experiment (DCE) in the fertility clinics of five Dutch hospitals. We invited treatment-naive women diagnosed with normogonadotropic anovulation to participate in the DCE by completing a printed questionnaire. We asked women to indicate their preference in hypothetical alternative treatment scenarios by offering a series of choice sets from which they were to choose their preferred alternatives. The choice sets contained several treatment characteristics of interest, i.e. attributes concerning ovulation induction with clomiphene citrate or letrozole versus gonadotrophins, as well as intercourse and IUI. We selected six attributes: number of visits to the outpatient clinic during treatment; type of medication; intercourse or IUI; risk of side effects; willingness to pay; and pregnancy chances leading to the birth of a child after six treatment cycles.
We used a multinominal logit model to determine the preferences of women and investigated heterogeneity in preferences through latent class analysis. To determine if women were willing to make a trade-off for higher pregnancy rates at the expense of a higher burden, we calculated the marginal rate of substitution.
The questionnaire was completed by 145 women. All six attributes influenced women's treatment preferences and those valued as most important were low risk of side effects, a minimal number of hospital visits and intercourse. A total of 55% of women was driven by the wish to conceive with the least medical interference and lowest burden. The remaining women were success driven and chose mainly for the highest chances to conceive, regardless of the burden. Age and duration of subfertility did not significantly differ between these women. Women were willing to trade off some burden and costs for higher pregnancy chances.
The results of this study may be used during the counselling of couples about their treatment options. Our findings are an argument to explore if a woman prefers potentially fast success or a medically less intense route that might take longer. The preference for the

less intense route would lead to the continuation of ovulation induction with oral drugs such as clomiphene citrate or letrozole rather than treatment with injected gonadotrophins, or even IVF.

IMPLICATIONS FOR PRACTICE

Based upon the results of this thesis we have the following recommendation. Women with normogonadotropic anovulation and clomiphene failure should be counselled that continuing ovulation induction up until 12 ovulatory cycles still leads to considerable pregnancy chances. Inducing ovulation in these women can either be established by clomiphene citrate or any type of gonadotrophins, and one must realize that the latter treatment gives more live births for higher costs. Although we did not investigate the use of the aromatase inhibitor letrozole for this indication, it might be that women who ovulate on letrozole and continue treatment also continue to conceive.

We cannot make recommendations on the use of IUI to couples with clomiphene failure as IUI only marginally increases live birth rates and the cost-effectiveness estimate is uncertain. The explanation for this marginal increase may be that the fertility potential of women with anovulatory subfertility, once the anovulation has been dealt with, could be reduced by other, -so far unknown- factors. Hence, these women could possibly be considered to have unexplained subfertility in whom IUI seems to increase pregnancy chances when the prognosis on natural conception has decreased significantly.[24]

Obviously, patient preferences are crucial here. As our study in chapter 7 shows, anovulatory women presented with treatment scenarios make different choices. While in our trial a small majority preferred a less invasive treatment with clomiphene, a large minority preferred to maximize pregnancy chances even if treatment would be more invasive and intense. As a consequence, women should be offered different scenarios, and then, together with their partners, make their choices in a process of shared decision making.

Society can set boundaries to medical interventions that are not justified from an economical or safety perspective, by insurance mechanisms or through clinical guidelines. For example, we advocate that treatment naïve anovulatory women do not immediately start with gonadotrophins but always start with clomiphene or letrozole. Although a randomized trial comparing clomiphene and gonadotrophins in treatment naïve women showed that gonadotrophins give higher live birth rates than clomiphene (52% versus 39%, 95% CI 0.4–24.6)[25], gonadotrophins should be reserved for women with clomiphene resistance or clomiphene failure as gonadotrophins are more invasive and expensive.

IMPLICATIONS FOR FUTURE RESEARCH

While our study showed that ovulation induction with clomiphene or gonadotrophins can be safely and effectively continued for more than six cycles, it remains unknown if letrozole will lead to comparable, or even better pregnancy rates. Letrozole has been proposed as a new first line treatment in women with normogonadotropic anovulation and PCOS. A recent systematic review and network meta-analysis showed that this agent gives higher live birth rates compared to clomiphene.[26] Whether letrozole should indeed replace clomiphene in our Dutch population is yet to be sought out. A randomized study from the USA, also part of the review of Wang and colleagues, included 750 women and compared clomiphene to letrozole as a first line agent. It found that letrozole gave 8% more live births[27]. Within this trial, the mean BMI of participating women was 35 kg/m^2 and only women with a BMI > 30 kg/m^2 had higher live birth rates after ovulation induction with letrozole. For the slimmer women, there was no statistically significant difference in live births when comparing the two treatments[28]. As the women in the cohort study (chapter 4) and randomized clinical trial (chapter 5) of this thesis have a much lower mean BMI of 25 kg/m^2, we cannot simply assume that the results of that study extrapolate to the average Dutch woman with PCOS. Also, we must take into account that the trial was not powered to distinguish differences in live births according to BMI subgroups and that a differential effect between letrozole and clomiphene is thus not proven. We suggest that a similar randomized trial comparing clomiphene and letrozole in treatment naïve women is performed in the Netherlands. Ideally, this trial would contain a third treatment arm of ovulation induction with clomiphene plus metformin since the review of Wang and colleagues reported higher pregnancy rates (odds ratio of 1.81 (95% CI 1.35 - 2.42)), but comparable live birth rates for this combined treatment regimen compared to clomiphene alone, and higher pregnancy rates compared to letrozole (odds ratio of 1.14, (95% CI 0.79 – 1.65).[26]

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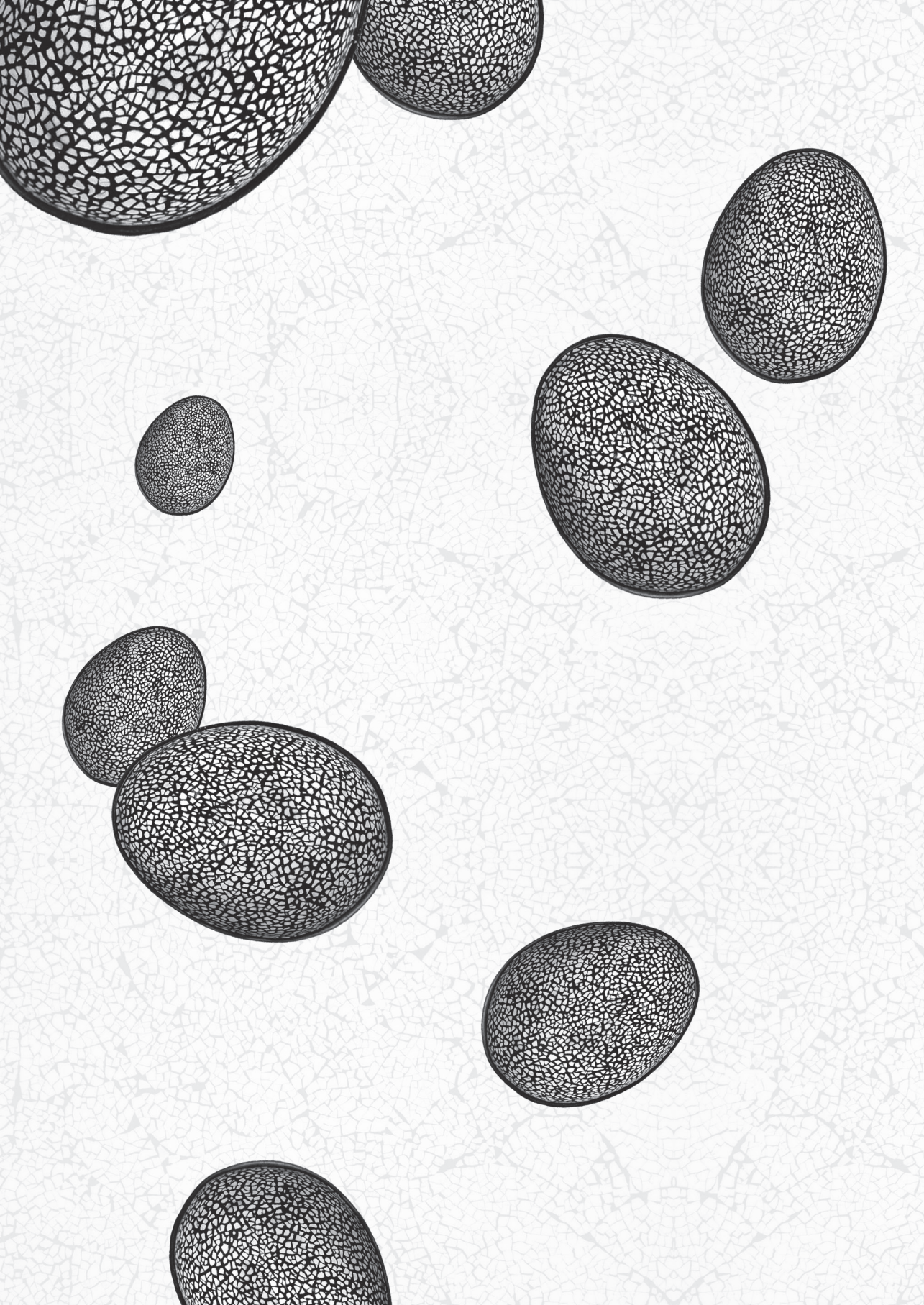
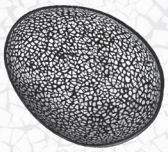
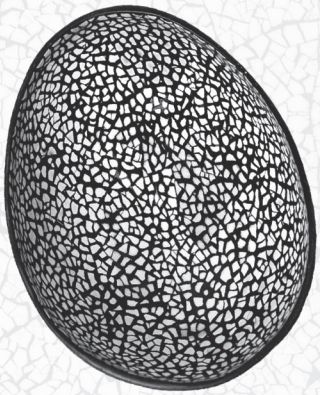


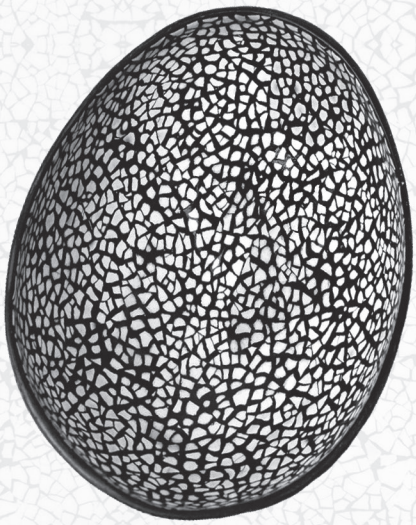
9

Nederlandse samenvatting

Implicaties voor de klinische praktijk en toekomstig onderzoek







SAMENVATTING

10 tot 15% van alle stellen met een kinderwens blijkt subfertiel. In 20 tot 25% van deze stellen lijdt de vrouw aan anovulatie.[1] Ovulatiestoornissen kunnen worden gecategoriseerd in World Health Organization (WHO) type I, II en III. Type I ovulatiestoornissen worden veroorzaakt door een stoornis in de hypothalaam-hypofysaire as, type II ovulatiestoornissen worden gedefinieerd als disfunctie van de hypothalame-hypofysaire-ovariële as en type III ovulatiestoornissen zijn het gevolg van ovarieel falen.[2]

Dit proefschrift focust op WHO type II anovulatoire vrouwen ofwel normogonadotrope anovulatoire vrouwen. 85% van alle vrouwen met een ovulatiestoornissen voldoen aan de criteria voor WHO type II anovulatie. De meerderheid van deze vrouwen wordt gediagnosticeerd met het polycysteus ovariumsyndroom (PCOS).[3] Indien normogonadotrope anovulatoire vrouwen zwanger willen worden, kunnen zij behandeld worden met clomifeencitraat, letrozol, en gonadotrofinen. Daarnaast kan intra-uteriene inseminatie (IUI) toegevoegd worden ter vervanging van coitus.[2] Clomifeen en gonadotrofinen zijn beide zeer gebruikelijke en effectieve behandelopties en worden sinds vele jaren gebruikt.[2,4] Het gebruik van letrozol is voor deze indicatie niet geregistreerd.

Het onderzoek wat in dit proefschrift wordt gepresenteerd is ontsproten uit een samenwerking tussen de Centra van Voortplantingsgeneeskunde van het VU Medisch Centrum van Amsterdam en het Academisch Medisch Centrum van Amsterdam. Beide centra hebben een langdurige geschiedenis van onderzoek binnen het veld van subfertiliteit en PCOS. Deze onderzoekslijn heeft bijgedragen aan ons inzicht in de pathofysiologie en endocrinologie van PCOS,[5-9] maar ook in de effectiviteit en veiligheid van de behandeling van therapie-naïeve vrouwen en vrouwen met clomifeenresistentie.[10-16] Dit proefschrift geeft hieraan een vervolg door te onderzoeken hoe vrouwen die niet zwanger zijn na zes cycli ovulatie-inductie met clomifeen, effectief en veilig behandeld kunnen worden, met inachtneming van patiëntenpreferenties en de kosten die geassocieerd zijn met deze interventies.[2,17,18]

Hoofdstuk 1 vormt een algemene introductie en beschrijft de onderzoeksdoelen van dit proefschrift.

In **hoofdstuk 2** gaven wij een overzicht van de effectiviteit en veiligheid van alle gonadotrofinepreparaten die beschikbaar zijn voor ovulatie-inductie in vrouwen met PCOS en clomifeenresistentie. We hebben een systematische review en meta-analyse verricht van alle gerandomiseerde studies die urinaire producten, zoals urofollitropins (uFSH), human menopausal gonadotrophin (HMG), zowel beschikbaar 'purified' (FSH-P) als 'highly purified' (FSH-HP en HP-HMG), of recombinant FSH (rFSH) vergeleken. De review gebruikte de zoekstrategie ontwikkeld voor de Cochrane Menstrual Disorders and Subfertility Group.

Primaire uitkomsten waren levend geboren kind, uitgedrukt per vrouw, en de incidentie van het ovarieel hyperstimulatiesyndroom. We includeerden 14 studies met daarin in totaal 1726 vrouwen. We vonden geen bewijs voor een verschil voor de vergelijkingen van de gonadotrofinen voor de uitkomst levend geboren kind (de totale OR per vrouw was 1.26 (95% BI 0.80 - 1.99, 5 RCTs, n = 505), voor de vergelijking rFSH versus uFSH) of voor de andere zwangerschapsuitkomsten. Er was tevens geen bewijs voor een verschil in het vóórkomen van het ovarieel hyperstimulatiesyndroom. Wij suggereren dat de keus voor het ene of het andere product moet afhangen van de beschikbaarheid van het middel, het gebruikersgemak en de geassocieerde kosten.

In **hoofdstuk 3** was ons doel om de waarde van de post coïtum test bij vrouwen met WHO type II anovulatie te bepalen. We onderzochten of de post coïtum test vrouwen kon identificeren die een lage kans op conceptie hadden en daarbij mogelijk gebaat waren bij directe behandeling met IUI. We verrichtten een prospectieve follow-up studie om vast te stellen of de post coïtum test conceptie kan voorspellen in vrouwen met WHO type II anovulatie die ovulatoir worden met clomifeen. In deze studie werden 251 vrouwen geïncludeerd en een post coïtum test werd gepland in een van de eerste drie ovulatoire cycli. Vrouwen gingen, ongeacht het resultaat van de test, door met clomifeen voor ten minste zes ovulatoire cycli. De primaire uitkomst was tijd tot doorgaande zwangerschap. Bij 99 vrouwen werd de post coïtum test niet uitgevoerd; 41 vrouwen waren reeds zwanger voordat de test gepland was, 10 vrouwen bleven anovulatoir en bij 48 vrouwen werd de test niet uitgevoerd vanwege verschillende redenen. Van de 152 vrouwen hadden 107 vrouwen een positief testresultaat en 45 vrouwen een negatief resultaat. Het aantal doorgaande zwangerschappen was 45/107 (42%) voor vrouwen met een positieve test en 10/28 (36%) voor vrouwen met een negatieve test. De 'proportional hazard' analyse toonde dat de resultaten van de post coïtum test geen significante voorspeller was voor de tijd tot doorgaande zwangerschap, (hazard rate (HR) voor doorgaande zwangerschap 1.3 (95% BI 0.64 - 2.5). We concludeerden dat de post coïtum test slechts beperkte waarde heeft bij vrouwen met WHO type II anovulatie. We menen dat vrouwen veilig kunnen starten met ovulatie-inductie met clomifeen zonder het ondergaan van een post coïtum test.

In **hoofdstuk 4** onderzochten we de effectiviteit van doorgaande behandeling met clomifeen in vrouwen met WHO type II anovulatie die ten minste zes ovulatoire cycli met clomifeen hadden ondergaan zonder succesvolle conceptie. Richtlijnen adviseren om na zes cycli met clomifeen over te stappen op gonadotrofinen, maar gonadotrofinen geven een hoog risico op meerlingzwangerschappen en zijn duur. Nog belangrijker is echter, dat het advies om over te stappen niet gebaseerd is op enig wetenschappelijk bewijs. Daarom vonden wij het gepast om de succeskansen na doorgaande behandeling met clomifeen vast te stellen. We

verrichtten een retrospectieve cohortstudie die de effectiviteit onderzocht van doorgaande behandeling met clomifeen, in normogonadotrope vrouwen niet zwanger na zes eerdere cycli met clomifeen. We includeerden 114 vrouwen van vijf Nederlandse ziekenhuizen die niet zwanger waren na zes ovulatoire cycli en die doorgingen met hun behandeling met clomifeen. Follow-up periode was een totaal van 12 behandelcycli. Primaire uitkomst was de cumulatieve incidentie van een doorgaande zwangerschap aan het einde van de behandeling. Van deze 114 vrouwen hadden er 35 (31%) een doorgaande zwangerschap wat leidde tot een 'cumulative incidence rate' van een doorgaande zwangerschap van 54% na 7-12 behandelcycli met clomifeen. Deze resultaten rechtvaardigden de start van een gerandomiseerde studie die doorgaande behandeling met clomifeen vergelijkt met tweedelijns behandelingen.

In **hoofdstuk 5** vergeleken we de effectiviteit van gonadotrofinen met doorgaande behandeling met clomifeen, beide met of zonder IUI, met als uitkomst het verschil in aantal levend geboren kinderen. Het was immers nog onbekend of gonadotrofinen en IUI zwangerschapscijfers verhogen bij vrouwen die niet zwanger zijn na zes eerdere ovulatoire cycli met clomifeen. We verrichtten een multicenter, gerandomiseerde, twee-bij-twee factoriële klinische studie in 48 centra in Nederland. We bestudeerden vrouwen met normogonadotrope anovulatie die niet zwanger waren na zes ovulatoire cycli met clomifeen. Vrouwen werden gerandomiseerd in vier groepen: zes cycli met gonadotrofinen plus IUI, zes cycli met gonadotrofinen plus coitus, zes cycli clomifeen plus IUI of zes cycli clomifeen met coitus. De laatste groep is de doorgaande behandeling van de eerst gestarte behandeling.
Primaire uitkomst was conceptie leidend tot levend geboren kind binnen acht maanden na randomisatie. Secundaire uitkomstmaten waren doorgaande zwangerschap, meerlingzwangerschap, miskraam, ectopische zwangerschap, tijd van randomisatie tot de geboorte van een levend kind, foetaal geboortegewicht en zwangerschapscomplicaties zoals hypertensieve aandoeningen, diabetes gravidarum en premature partus. Primaire analyse volgde het 'intention to treat' principe. We maakten twee vergelijkingen: een waarbij gonadotrofinen werden vergeleken met clomifeen, en een waarbij IUI werd vergeleken met coitus. Van 8 december 2008 tot 16 december 2015 werden er 666 vrouwen gerandomiseerd: 166 vrouw lootten voor gonadotrofinen plus IUI, 165 voor gonadotrofinen plus coitus, 163 voor clomifeen plus IUI, en 172 voor clomifeen plus coitus.
Vrouwen die geloot hadden voor gonadotrofinen hadden meer levend geboren kinderen dan vrouwen die geloot hadden voor clomifeen ((167 van de 327 vrouwen [51.5%] versus 138 van de 334 [41.3%], (RR 1.24 (95% BI 1.05 -1.46). Toevoeging van IUI gaf geen statistisch significante toename van het aantal levend geborenen vergeleken met coitus (161 van de 327 vrouwen [49.2%] versus 144 van de 334 [43.1%], RR 1.14 (95% BI 0.97-1.35). Het aantal

meerlingzwangerschappen was voor beide vergelijkingen laag en niet verschillend.
De resultaten van deze studie demonstreren dat, bij vrouwen met normogonadotrope anovulatie en niet zwanger na zes cycli met clomifeen, het overstappen op gonadotrofinen de kans op een levend geboren kind verhoogt in vergelijking met doorgaan met clomifeen. De toevoeging van IUI lijkt het aantal levend geboren kinderen niet te verhogen. We willen benadrukken dat deze studie laat zien dat alle vier de behandelingen resulteren in acceptabele zwangerschapscijfers en weinig complicaties.

In **hoofdstuk 6** presenteren we de kosteneffectiviteitsanalyse die gelijktijdig werd verricht met de gerandomiseerde studie van hoofdstuk 5. We verzamelden data van directe kosten gerelateerd aan behandeling en medicatie, en we berekenden eenheidskosten van verschillende bronnen. We berekenden de gemiddelde kosten van ovulatie-inductie met gonadotrofinen en clomifeen, en de gemiddelde kosten van IUI en coitus. We berekenden 'incremental cost-effectiveness ratios' (ICER) voor gonadotrofinen vergeleken met clomifeen, en voor IUI vergeleken met coitus. Non-parametrische 'bootstrap resampling' werd gebruikt om het effect van de onzekerheid in onze schattingen te onderzoeken.
Gemiddelde medische kosten waren €4.495 per vrouw voor gonadotrofinen en €3.007 voor clomifeen (kostenverschil €1.475 (95% BI €1.457 tot €1.493), wat resulteerde in een incremental cost-effectiveness van €15.258 (95% BI €8.721 tot €63.654) per extra levend geborene. Gemiddelde kosten waren €4.497 for IUI en €3.005 voor coitus (kostenverschil €1.510 (95% BI €1.492 tot €1.529). De incremental cost-effectiveness ratio was €24.361 (95% BI €-11.290 tot €85.172) per extra levend geboren kind.
Concluderend zijn gonadotrofinen effectiever maar duurder vergeleken met clomifeen. Vanwege de onzekerheid rondom de schatting van de kosteneffectiviteit van IUI kunnen we geen aanbevelingen geven ten aanzien van het gebruik van IUI bij deze vrouwen. Meer onderzoeksgegevens zullen duidelijkheid moeten bieden.

In **hoofdstuk 7** onderzochten we de behandelvoorkeuren van vrouwen met normogonadotrope anovulatie. Tussen augustus 2014 en februari 2017 verrichtten we een multicenter 'Discrete Choice Experiment' (DCE) in de fertiliteitsklinieken van vijf Nederlandse ziekenhuizen. Behandel-naïve vrouwen met normogonadotrope anovulatie werden uitgenodigd om deel te nemen aan de DCE door een papieren vragenlijst in te vullen. We vroegen vrouwen hun voorkeur aan te geven binnen verschillende, hypothetische behandelscenario'sdoor een aantal keuzesets te bieden. De keuzesets bevatten verschillende belangrijke behandelkarakteristieken, zoals attributen aangaande ovulatie-inductie met clomifeen of letrozol versus gonadotrofinen, en attributen aangaande coitus en IUI. We selecteerden zes attributen: aantal bezoeken aan de polikliniek tijdens de behandeling, type medicatie, coitus of IUI, kans op bijwerkingen, 'willingness to pay', en de

kans op zwangerschap leidend tot de geboorte van een kind na zes behandelcycli.
We gebruikten een 'multinominal logit model' om de preferenties van vrouwen vast te stellen, en we onderzochten de heterogeniteit van de preferenties met 'latent class' analyse. Om te bepalen of vrouwen bereid waren om hogere belasting van een behandeling uit te ruilen tegen hogere zwangerschapskansen, berekenden we de 'marginal rate of substitution'.
De vragenlijst werd ingevuld door 145 vrouwen. Alle zes attributen beïnvloedden de behandelvoorkeuren van de vrouwen. De attributen die als meest belangrijk werden beoordeeld waren lage kans op bijwerkingen, een minimaal aantal polikliniekbezoeken en coitus. 55% van de vrouwen koos voor een behandeling met de minste medische interventies en de laagste belasting. De overige vrouwen gingen primair voor succes en kozen voor de hoogste zwangerschapskansen, ongeacht de behandellast. Leeftijd en duur van de subfertiliteit waren niet significant verschillend bij deze vrouwen. Vrouwen waren bereid om enige belasting van een behandeling uit te ruilen voor hogere zwangerschapskansen.
De resultaten van deze studie kunnen gebruikt worden wanneer stellen gecounseld worden over hun behandelopties. Onze uitkomsten zijn een argument om te exploreren of een vrouw potentieel snel succes prefereert boven een medisch minder intensieve route die mogelijk langer duurt. De voorkeur voor de minder intensieve route zou pleiten voor doorgaan met ovulatie-inductie met orale medicatie zoals clomifeen of letrozol in plaats van behandeling met de injecteerbare gonadotrofinen, of zelfs IVF.

IMPLICATIES VOOR DE KLINISCHE PRAKTIJK

Gebaseerd op de resultaten van dit proefschrift hebben we de volgende aanbeveling. Vrouwen met normogonadotrope anovulatie die niet zwanger zijn na zes cycli met clomifeen moeten worden gecounseld dat het continueren van ovulatie-inductie tot 12 ovulatoire cycli nog steeds leidt tot aanzienlijke zwangerschapskansen. De ovulatie kan bij deze vrouwen worden opgewekt door clomifeencitraat of door elk type gonadotrofinen, en men moet zich realiseren dat gonadotrofinen meer levend geboren kinderen geeft tegen hogere kosten. Ondanks dat we het gebruik van de aromatase-inhibitor letrozol voor deze indicatie niet hebben onderzocht, is het mogelijk dat vrouwen die ovuleren met letrozol en deze behandeling continueren, ook continueren zwanger te raken.
We kunnen geen aanbeveling doen ten aanzien van het gebruik van IUI bij koppels die niet zwanger zijn na zes cycli met clomifeen aangezien IUI slechts een marginale toename van het aantal levend geboren kinderen geeft, en de schatting van de kosteneffectiviteit onzeker is. De verklaring voor deze marginale toename kan zijn dat het fertiliteitspotentieel van vrouwen met anovulatoire subfertiliteit, zodra de anovulatie is behandeld, verminderd kan zijn door andere, -nog onbekende– factoren. Ergo, deze vrouwen kunnen mogelijk

worden beschouwd als zijnde onverklaard subfertiel waarbij IUI de zwangerschapskansen lijkt te verhogen als de prognose op natuurlijke conceptie significant verlaagd is.[24]
Uiteraard zijn patiëntenpreferenties cruciaal. Uit onze studie in hoofdstuk 7 blijkt dat anovulatoire vrouwen bij de optie van verschillende behandelscenario's, verschillende keuzes maken. Terwijl in onze studie een kleine meerderheid de voorkeur gaf aan een minder invasieve behandeling met clomifeen, koos een grote minderheid voor maximale zwangerschapskansen, zelfs als dat een meer invasieve en intensieve behandeling betekende. Hieruit vloeit voort dat vrouwen verschillende scenario's aangeboden moeten krijgen waarna zij, samen met hun partners, een keus kunnen maken in een proces van 'shared decision making'.
De maatschappij kan grenzen stellen aan medische interventies die vanuit een economisch perspectief en veiligheidsperspectief niet gerechtvaardigd zijn. Zij kan dit doen door middel van verzekeringsmechanismen of door klinische richtlijnen. Wij adviseren bijvoorbeeld dat anovulatoire vrouwen die nooit eerder behandeld zijn, niet direct starten met gonadotrofinen maar altijd eerst behandeld worden met clomifeen of letrozol. Een gerandomiseerde studie, die clomifeen met gonadotrofinen vergeleek bij niet eerder behandelde vrouwen, liet zien dat gonadotrofinen meer levend geboren kinderen geeft dan clomifeen (52% versus 39%, 95% BI 0.4–24.6)[25]. Desondanks moeten gonadotrofinen bewaard blijven voor vrouwen met clomifeenresistentie of vrouwen die na zes cycli clomifeen niet zwanger zijn, aangezien gonadotrofinen invasiever en duurder zijn.

IMPLICATIES VOOR TOEKOMSTIG ONDERZOEK

Terwijl onze studie liet zien dat ovulatie-inductie met clomifeen en gonadotrofinen veilig en effectief kunnen worden voortgezet gedurende meer dan zes cycli, is het nog onduidelijk of letrozol zal leiden tot vergelijkbare, of zelfs betere zwangerschapscijfers. Er is geopperd dat letrozol een nieuwe eerstelijns behandeling is voor vrouwen met normogonadotrope anovulatie en PCOS. Een recente systematische review en netwerk meta-analyse toonde dat dit middel meer levend geboren kinderen geeft in vergelijking met clomifeen.[26] Of letrozol in onze Nederlandse populatie clomifeen moet vervangen, moet nog worden onderzocht. Een gerandomiseerde studie uit de Verenigde Staten, die ook deel uitmaakt van de review van Wang en collega's, includeerde 750 vrouwen en vergeleek clomifeen met letrozol als eerstelijns behandeling. Er ontstonden 8% meer levend geboren kinderen na behandeling met letrozol.[27] De gemiddelde BMI van de deelnemende vrouwen van deze studie was 35 kg/m^2 , en alleen vrouwen met een BMI > 30 kg/m^2 hadden meer levend geboren kinderen na ovulatie-inductie met letrozol. Voor de slankere vrouwen was er geen significant verschil wat betreft levend geboren kinderen als men deze twee behandelingen vergeleek.[28] Aangezien de vrouwen in de cohortstudie (hoofdstuk 4) en

de gerandomiseerde studie (hoofdstuk 5) van dit proefschrift een veel lagere gemiddelde BMI hebben van 25 kg/m^2, kunnen we niet zomaar aannemen dat de resultaten van de Amerikaanse studie toepasbaar zijn op de gemiddelde Nederlandse vrouw met PCOS. Daarnaast moeten we rekening houden met het feit dat de studie niet 'gepowered' was om een verschil aan te tonen in aantal levend geboren kinderen per BMI-subgroep waardoor een ongelijk effect van letrozol en clomifeen niet bewezen is. Wij stellen daarom voor dat een vergelijkbare gerandomiseerde studie, die clomifeen met letrozol vergelijkt in niet eerder behandelde vrouwen, in Nederland gaat plaatsvinden. Idealiter bevat deze studie een derde behandelarm met ovulatie-inductie met clomifeen plus metformine, aangezien de review van Wang en collega's hogere zwangerschapscijfers rapporteerde (OR van 1.81 (95% BI 1.35 - 2.42)), maar met een vergelijkbaar aantal levend geboren kinderen voor deze gecombineerde behandeling in vergelijking met alleen clomifeen, en hogere zwangerschapscijfers vergeleken met letrozol (OR van 1.14, (95% BI 0.79 – 1.65).[26]

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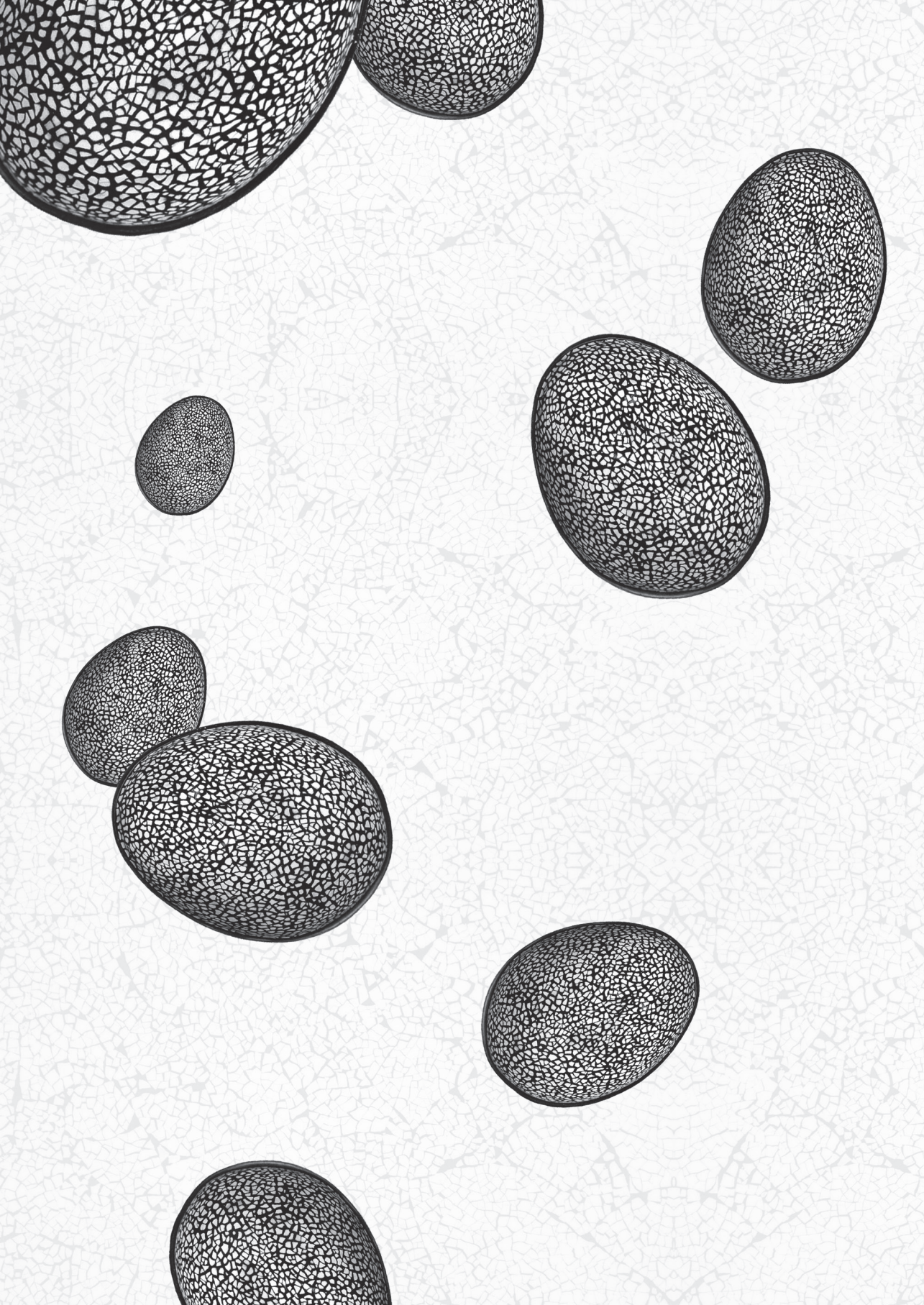


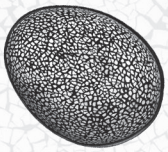
Appendices

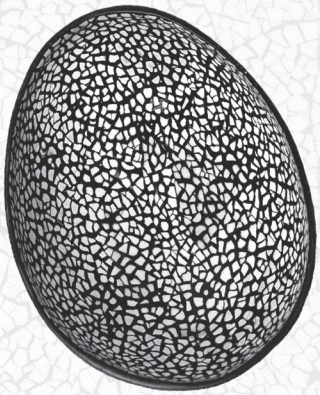
List of co-authors and affiliations

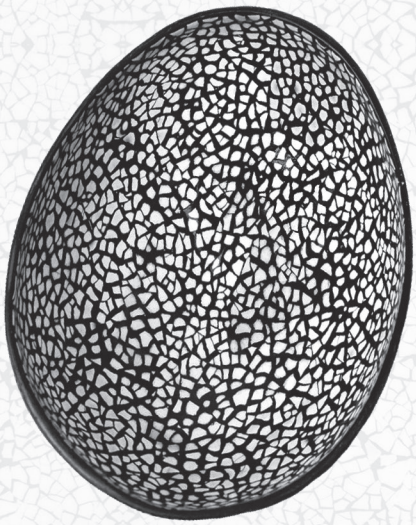
List of publications

Dankwoord

Curriculum Vitae







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Noor van der Heijden: veel dank voor het ontwerpen van de kaft! Gelukkig heb jij een groot creatief talent wat mij totaal ontbreekt …

Mijn paranimfen Floor en Rosa: Fijn dat ik altijd even kon spuien maar ook vooral lol kan maken met jullie en het NIET over de wetenschap hebben. Uiteraard ook dank voor de mental support tijdens mijn verdediging! Als ik een vraag niet kan beantwoorden weet ik jullie te vinden ;).

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dankbaar genoeg voor zijn. Daarnaast zal ik ook niet vergeten met hoeveel drive jij mijn eeuwige 'Excel-file' hebt helpen strak te trekken wat ik echt nodig had voor de M-OVIN studie. Ik heb enorm veel zin om, samen met mijn 'Schoemannen', te gaan genieten van onze verdere tijd samen.

CURRICULUM VITAE

Nienke Sanne Weiss werd op 25 maart 1985 geboren in Bussum. Zij groeide op in Naarden en behaalde in 2003 haar VWO diploma aan het St Vitus College te Bussum. In datzelfde jaar begon zij aan de studie Geneeskunde aan de Vrije Universiteit van Amsterdam.

Na het behalen van haar artsentitel in 2010 startte zij als ANIOS op de afdeling Gynaecologie en Verloskunde van het (destijds) Spaarne Ziekenhuis in Hoofddorp. Begin 2012 begon zij aan haar promotietraject als arts-onderzoeker binnen het Consortium onder leiding van prof.dr. Ben Willem Mol en prof.dr. Fulco van der Veen in het kader van een samenwerkingsproject tussen het Academisch Medisch Centrum Amsterdam en de Vrije Universiteit van Amsterdam. Zij maakte in 2013 de stap naar fertiliteitsarts in het Onze Lieve Vrouwe Gasthuis in Amsterdam Oost.

In 2015 is zij gestart met de opleiding tot gynaecoloog binnen het cluster VUmc (opleider prof.dr. J.I.P. de Vries). De eerste periode van de opleiding vond plaats in de Noordwest Ziekenhuisgroep te Alkmaar (opleider dr. J.M.J. Bais) en sinds eind 2017 werkt zij aan het vervolg van de opleiding in het VUmc.

Nienke woont, samen met Niels Schoeman en hun twee zoons Toby en Milo, in Amsterdam.