Clomiphene Citrate in PCOS

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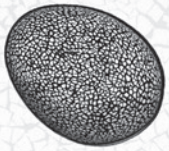
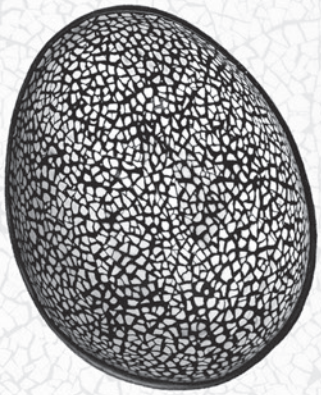
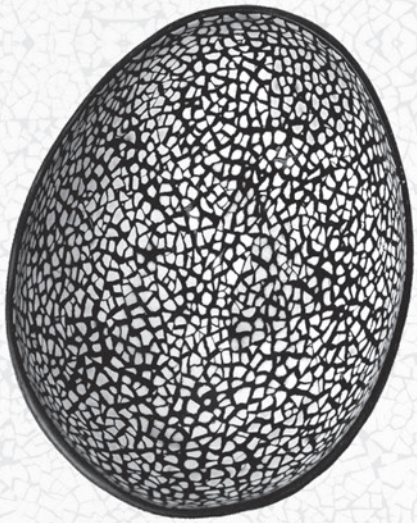
8

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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