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## Clomiphene Citrate in PCOS

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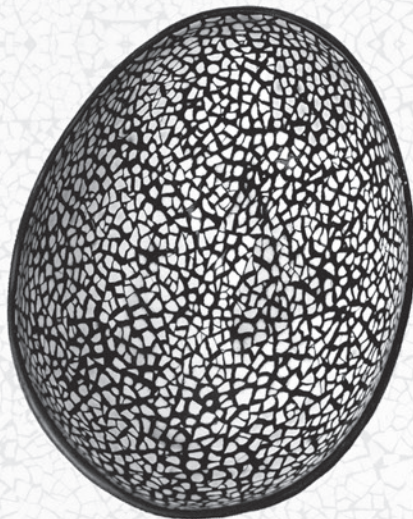
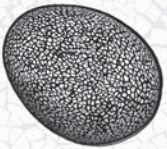
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# General Introduction and Outline of the thesis





## 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.<sup>1</sup> 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.<sup>2</sup>

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.<sup>3</sup>

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.<sup>4</sup> 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.<sup>5</sup> 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.<sup>6</sup>

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.<sup>2</sup>

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.<sup>7,8</sup> In around 75% of women starting ovulation induction with

CC, ovulation is restored and approximately half of those women will conceive with CC.<sup>9,10</sup> 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.<sup>11,12</sup> In 1988, recombinant FSH preparations entered the market.<sup>13</sup> Treatment with exogenous gonadotrophins elicit pregnancy rates of 45%.<sup>10</sup>

## **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.<sup>14</sup>

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.<sup>15</sup> 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.<sup>16</sup> 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.<sup>17</sup> 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.<sup>18</sup>

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.<sup>19</sup> 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.<sup>18,20</sup> 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.<sup>21</sup>

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.<sup>22</sup>

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.<sup>23</sup> 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.<sup>24</sup>

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.<sup>25</sup> 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.<sup>26</sup> 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.<sup>27</sup>

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.<sup>2,28,29</sup>

The second gap is the value of IUI in anovulatory women. IUI was originally designed to increase pregnancy chances in couples with male subfertility.<sup>30</sup> Subsequently, IUI was also introduced to couples with unexplained subfertility and subfertility based on a 'cervical factor', also referred to as cervical 'hostility'.<sup>2,31</sup> 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.<sup>32-34</sup>

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.<sup>35,36</sup>

## 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 multinomial 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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