Fertility treatment in women with WHO type II ovulation disorder

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CHAPTER 1

GENERAL INTRODUCTION AND OUTLINE OF THE THESIS
GENERAL INTRODUCTION

Infertility

Infertility is a disease of the reproductive system defined by the failure to achieve a successful pregnancy after 12 months or more of regular unprotected sexual intercourse.\(^1\) It affects about 10 to 15 percent of all couples that are trying to conceive.\(^2,3\) The main diagnoses of infertility are male subfertility, unexplained subfertility and ovulation disorders.\(^4-6\)

Ovulation disorders

The World Health Organization (WHO) categorizes ovulation disorders into three groups based on the state of gonadotrophin and oestrogen secretion. WHO type I anovulation is caused by hypothalamic pituitary failure and occurs in about 10% of women with ovulation disorders. WHO type II anovulation results from dysfunction of the hypothalamic-pituitary-ovarian axis, and concerns around 85% of women with ovulation disorders. WHO type III anovulation is caused by ovarian failure and affects only 5% of women with ovulation disorders.\(^7\)

In this thesis we focus on the treatment of the largest group, women with a WHO II ovulation disorder. WHO II ovulation disorder is characterised by normogonadotropic, normo-oestrogenic endocrine profiles and most of these women have polycystic ovary syndrome (PCOS), diagnosed by oligo- or anovulation, clinical or biochemical signs of hyperandrogenism and/or presence of polycystic ovaries on ultrasound.\(^8\)

Treatments

In women with WHO II ovulation disorder, ovulation induction using clomiphene citrate (CC) or letrozole, with or without metformin, are first-line treatments.\(^9\) Letrozole is more effective than CC, leading on average to 10% more live births within 6 months. However as letrozole is off-label medication, CC is still often used as first-line ovulation induction.\(^10,11\) When this is unsuccessful second-line treatments are ovulation induction with gonadotrophins and laparoscopic ovarian drilling. In vitro fertilization (IVF) therapy is the third-line therapy.\(^12\)

Risks

Ovarian stimulation is a crucial aspect of IVF. This stimulation leads to the development of multiple follicles, which can be aspirated to retrieve the oocytes produced. Subsequently these oocytes will be fertilized in vitro. Ovarian stimulation can lead to
ovarian hyperstimulation syndrome (OHSS). OHSS is the most threatening complication of IVF. The exact pathophysiology of OHSS remains unknown but it is mediated by human chorionic gonadotrophin (hCG) and characterized by a broad spectrum of signs and symptoms that include abdominal tenderness and swelling, enlarged ovaries, ascites and other complications of enhanced vascular permeability. Although there is no internationally agreed classification system, OHSS is usually divided into three different categories: mild, moderate and severe OHSS. Most cases of OHSS are mild but in its severe form it can cause multi organ failure and death.

The incidence of OHSS in IVF varies widely and used to be very high with an estimated prevalence of 20-33% in its mild form and 3-8% in its moderate or severe form. With the emergence of new treatment regimens, more judicious use of gonadotrophins, increased cycle monitoring and improved knowledge of OHSS risks, the incidence of OHSS has declined. However it remains a serious risk, especially for women with high antral follicle counts (AFC), such as in women with PCOS, and previous OHSS. It is known that these women are at increased risk of developing OHSS.

The treatment of OHSS merely consists of supportive management. Consequently, prevention of OHSS is the most effective way of avoiding serious health risks for the IVF patient. The only guaranteed method for prevention of OHSS is to cancel cycles during the stimulation phase before hCG is administered. Other preventative strategies that appear effective include individualized ovarian stimulation protocols with mild doses of gonadotrophins, natural-cycle IVF, use of gonadotrophin releasing hormone (GnRH) antagonists as pituitary downregulation and the use of GnRH agonists instead of hCG to trigger final oocyte maturation. Finally, in vitro maturation can be applied to prevent OHSS.

**In vitro maturation**

In vitro maturation (IVM) involves the retrieval of immature oocytes from antral follicles within unstimulated or minimally stimulated ovaries. Subsequently, these oocytes are matured in vitro. Matured oocytes can then be fertilized through standard IVF or ICSI. IVM offers great potential for women with high AFC or a previous OHSS, since there is no ovarian hyperstimulation and therefore no risk on OHSS. In addition, IVM is also applied to preserve the fertility of cancer patients.

Robert Edwards, the pioneer of IVF, first reported on IVM in humans. The first report of a pregnancy and live birth after IVM was published in 1991. Nowadays IVM is practiced more and more and the number of live births from IVM oocytes has been increasing over the past three decades. However, this technique requires specific
expertise and poorer pregnancy outcomes compared to IVF are a major barrier to the implementation of IVM in clinical practice worldwide. In addition, there have been concerns about the health of infants born following IVM. Although observational studies suggest that offspring from IVM are not adversely affected, most studies are based on small sample sizes.

**Background and scope of the thesis**

Several questions concerning the treatment of women with WHO II ovulation disorder remain unanswered. In this thesis the following of these knowledge gaps will be addressed.

First, the effectiveness of various individual fertility treatment options for ovulation induction has been widely investigated. However, frequently women need to undergo multiple consecutive first-, second- and third-line treatments, so called treatment strategies, in order to reach pregnancy. Knowledge is lacking on the distribution of occurring pregnancies throughout the treatment strategy.

Second, with regard to ovulation induction with CC as first-line treatment two questions remain. The first question concerns the use of ultrasound monitoring. There is no consensus on whether ultrasound monitoring of follicle development should be applied to prevent multiple pregnancies in women in whom ovulation is induced by CC. The second question concerns women that ovulate on CC but do not become pregnant after six cycles. These women may switch to ovulation induction with gonadotrophins or they may continue to use CC for another six cycles. The effectiveness of continued treatment with CC for up to 12 ovulatory cycles is unknown.

Third, when it comes to second-line treatment the effectiveness of ovulation induction with gonadotrophins and laparoscopic ovarian drilling has well been investigated. However, some women are difficult to stimulate or do not conceive after six or more gonadotrophin cycles. The next step is a third-line treatment with IVF with accompanying risks, in particular the risk on OHSS. IVM is a potentially safer, cheaper and more “patient-friendly” alternative. The role of IVM in the treatment of women at risk for OHSS (i.e. WHO II ovulation disorder) is at present unclear. Little is known about the relative effectiveness, treatment costs and patient preferences and perspectives. All these aspects need to be taken into account in clinical decision-making.

Though IVM research has progressed in recent years, unfortunately there is still no evidence from properly conducted randomised controlled trials upon which to base any practice recommendations regarding IVM before IVF.
With regard to the position of IVM the Netherlands, IVM is not part of standard fertility treatments and is rarely applied. The professional boards Nederlandse Vereniging voor Obstetrie en Gynaecologie (NVOG) and Vereniging voor Klinische Embryologie (KLEM) did approve the use of IVM in clinical trials, after considering the results and outcomes of IVM outside the Netherlands. We aim to introduce this technique in the Netherlands with a pilot study. After successful introduction, a randomized controlled trial to compare the effectiveness of IVM versus IVF in women with an increased risk of OHSS is the next appropriate step.

OUTLINE OF THE THESIS

Chapter 2 presents a retrospective multicenter cohort study which was performed to assess the cumulative live birth rate in women with WHO II ovulation disorder and the proportion of women that need second- or third-line treatments if the initial therapy fails.

Chapter 3 evaluates safety and cost-effectiveness of ultrasound monitoring in clomiphene citrate treatment cycles. We studied follicular growth and multiple pregnancies that occur in clomiphene citrate ovulation induction cycles in a cohort of treatment naïve women with WHO II ovulation disorder. Second, we applied this knowledge in a decision model on basis of effectiveness, safety and cost.

Chapter 4 presents the results of a retrospective cohort study of women with WHO II ovulation disorder who did not conceive within their first six ovulatory cycles with clomiphene citrate and continued treatment with clomiphene citrate. Follow up was a total of 12 treatment cycles and primary outcome measure was the cumulative incidence rate of an ongoing pregnancy at the end of treatment.

Chapter 5 reports on the results of a multicenter prospective cohort study on IVM in women eligible for IVF and at risk for ovarian hyperstimulation syndrome. The primary endpoint of the study was the live birth rate per started IVM cycle. Furthermore, we followed women who were not pregnant after IVM and committed to a conventional IVF procedure.

Chapter 6 reports two cases of spontaneous pregnancies after IVM treatment in women with WHO II ovulation disorder.
Chapter 7 describes the effectiveness and safety of IVM compared with IVF for the treatment of women with high antral follicle count in a retrospective cohort study. The main outcome measures were live birth rate after first embryo transfer and cumulative live birth rate after one complete cycle. The incidence of ovarian hyperstimulation syndrome is also reported.

Chapter 8 reports on the results of a cost-effectiveness analysis of the cohort study on IVM compared to IVF presented in chapter 7. We calculated the mean costs and effectiveness for both treatments and estimated the incremental cost-effectiveness ratios.

Chapter 9 provides the results of a patient preference study in women with an increased risk of ovarian hyperstimulation syndrome on characteristics of IVF treatments. We performed a Discrete Choice Experiment on several treatment characteristics of interest concerning safety, burden, chance of pregnancy and willingness to pay.

Chapter 10 summarizes this thesis, provides implications for clinical practice and provides suggestions for future research.
REFERENCES


