Treatment regimens in ovulation induction and ovarian hyperstimulation

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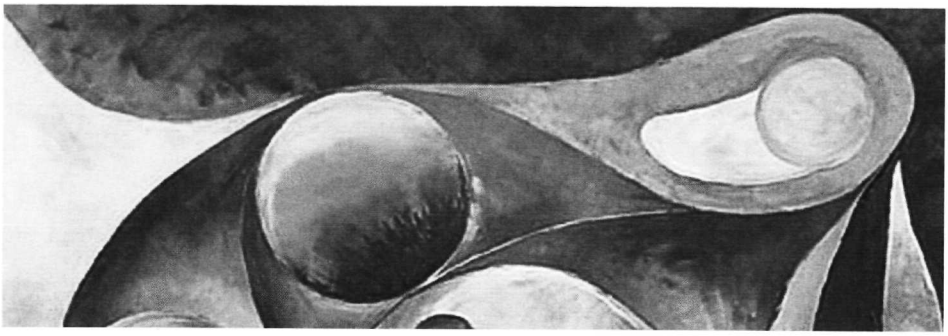
Chapter 1



Introduction

In reproductive medicine, manipulating ovarian function remains one of the more challenging topics. Two types of intervention can be distinguished, namely ovulation induction and ovarian hyperstimulation. In ovulation induction one aims for the development of one mature follicle, while in ovarian hyperstimulation one intends to stimulate the development of multiple mature follicles.

Ovulation induction

Ovulation induction is indicated in women with ovulation disorders. In about 90% of these women polycystic ovary syndrome (PCOS) can be diagnosed. PCOS is a leading cause of female infertility and is observed in approximately 4-7% of all women.[1-3] The disorder is characterised by oligo- or amenorrhea and the formation of multiple follicular cysts of 10 mm or smaller in the ovaries, a process related to the ovarian failure to develop a mature follicle. Symptoms may include infertility, hirsutism, acne, obesity and a pre-diabetic state with insulin resistance or hyperinsulinaemia. Furthermore, PCOS can have significant long-term effects, including diabetes and cardiovascular disease[4-10] and presumably endometrial or breast cancer.[2,11,12]

In North America diagnosis of PCOS used to be predominantly based on the presence of hyperandrogenism, while in Europe PCOS was generally diagnosed on the basis of the presence of polycystic ovaries.[4,6,13,14] Recently, consensus was reached on an international standard for the diagnosis of PCOS. The revised diagnostic criteria include at least two out of the following three criteria: oligo- or anovulation, clinical or biochemical signs of hyperandrogenism and presence of polycystic ovaries. A polycystic ovary is defined as 12 or more follicles in each ovary measuring 2–9 mm in diameter, and/or an increased ovarian volume, i.e. a volume of at least 10 ml.[15,16]

Strategies to induce ovulation include oral anti-oestrogens, parenteral gonadotrophin therapy, laparoscopic ovarian surgery and insulin sensitisers. The oral anti-oestrogen clomiphene citrate (CC) is at this moment the treatment of choice. It binds to oestrogen receptors in hypothalamus and pituitary gland. This results in secretion of gonadotrophin-releasing hormone (GnRH) with a consequent release of the gonadotrophins LH and FSH that trigger folliculogenesis. About twenty percent of the women with PCOS will not ovulate on CC.[7,11,17-19] The second line treatment in these clomiphene citrate resistant women may be ovulation induction with gonadotrophins or laparoscopic ovarian surgery. The basic idea behind ovulation induction with gonadotrophins is to stimulate the follicles directly and more vigorously than is done with CC therapy.

Human gonadotrophin preparations may contain FSH only or a combination of FSH and LH. Gonadotrophin preparations are derived from urine of post-menopausal women or can be

produced as recombinant FSH by transfected stable Chinese hamster ovary cell lines. Treatment leads to ovulation in about 70 - 80% of the cycles started and results in an average cumulative pregnancy rate of about 38% per woman.[20,21]

The major disadvantages of ovulation induction with gonadotrophins are the high cancellation rate due to multifollicular development and the risk of higher order multiple pregnancies. These treatment risks are even more significant in women with PCOS due to the high sensitivity of polycystic ovaries to exogenous gonadotrophins. Multiple pregnancy rates varying from 6 up to 35% have been reported depending on the protocol used.[21-23] Probably, the safest approach for ovulation induction with gonadotrophins in PCOS is the chronic low dose step-up regimen that employs a maximal starting dose of 75 IU of FSH.[21] If there is no response after 14 days, the starting dose is increased by 37.5 IU every seven days. Related to the notion of a "threshold" FSH concentration, the goal is to not exceed the FSH concentration above which more than one follicle will respond.[23,24] This approach may require as much as 20 to 25 days of stimulation, but carries the lowest risk for multifollicular development and an almost zero risk of the ovarian hyperstimulation syndrome.[25] A further disadvantage of ovulation induction with gonadotrophins are the high costs associated with this form of treatment.

Ovarian surgery is an alternative treatment option for ovulation induction in women with CC-resistant PCOS. Surgical ovarian wedge resection was the first established treatment shown to induce ovulation in women with PCOS.[26] The procedure was abandoned because of the risk of post-operative adhesion formation leading to mechanical infertility. In recent years the rapidly expanding field of operative laparoscopy has led to a renewed interest for surgical treatment for PCOS. A number of laparoscopic approaches have been used, including laser, unipolar electrocautery, and bipolar electrocautery. The advantages of laparoscopic laser surgery are a shorter operating time and diminished risk of adhesions compared to electrocautery. However, the laser systems are expensive and require more extensive and costly upkeep, which is probably why electrocautery is most commonly being used. In ovarian electrocautery multiple perforations of the ovarian surface and stroma are created.[27-36] This procedure has been shown to lower levels of LH, testosterone, and other hormones that are characteristically elevated in these women.[29,30,32,36] The working mechanism is as of yet unknown. One theory hypothesises that cautery reduces the enlarged cohort of available antral follicles in the ovaries of women with PCOS. A reduction in the number of antral follicles would lead to a lower basal inhibin B concentration being produced by the granulosa cells and consequently to a relative increase in FSH, inducing follicular growth and spontaneous ovulations.[9,10] A second theory suggests that cautery is effective

through the destruction of ovarian stromal cells, which produce androgens. The subsequent reduction of ovarian hyperandrogenism might restore ovulation. [37]

Laparoscopic electrocautery of the ovaries leads to ovulation in about 70 - 80% of the cycles started and results in approximately 40% of woman achieving a pregnancy.[38] Uncontrolled studies have demonstrated that some anovulatory women respond to clomiphene citrate after electrocautery of the ovaries.[27-29,33,34,36] The disadvantages of a laparoscopic procedure are that it is a surgical procedure, that general anaesthesia is needed, and that possible long term effects on ovarian function are unknown.

Both ovulation induction with recombinant FSH (rFSH) and laparoscopic electrocautery of the ovaries are standard treatments in women with CC-resistant PCOS. Whether gonadotrophins or laparoscopic electrocautery of the ovaries should be the treatment of choice in women with CC-resistant polycystic ovary syndrome was unclear when work on this thesis was started. To find out the best way to treat these women, we designed a randomised clinical trial comparing a treatment strategy that started with laparoscopic electrocautery of the ovaries followed by CC and rFSH if anovulation persisted versus ovulation induction with rFSH. We hypothesised that the electrocautery strategy would lead to more women getting pregnant at lower costs.

In deciding which treatment to give to a woman it would be helpful if we could predict ovarian response and treatment outcome beforehand. An informed decision to use electrocautery or ovulation induction with rFSH would benefit from knowledge about the chances of success or failure with these respective procedures in specific subgroups of women. Such knowledge was not available at the time we planned our studies.

Ovarian hyperstimulation

Some women with PCOS will not respond to ovulation induction, while in others ovulation induction is not opportune as other fertility problems co-exist. In these women, ovarian hyperstimulation for in vitro fertilisation and embryo transfer (IVF-ET), and intra-cytoplasmatic sperm injection (ICSI) in case of an additional male factor infertility, is considered a last resort treatment.[39-41] It is standard practice to use gonadotrophins for ovarian hyperstimulation to achieve multiple follicular development in women with infertility undergoing treatment with assisted reproductive techniques (ART). Both human menopausal gonadotrophins (hMG) and FSH preparations have been used successfully for this purpose. The presumed redundancy of LH and the wish for a more purified product drove the conversion from hMG to urinary FSH (uFSH). Subsequently, highly purified and

recombinant FSH (rFSH) entered the market and replaced earlier FSH products. Its purity, batch-to-batch consistency and availability make it an attractive alternative to the urinary FSH products.

In recent years, virtually all IVF cycles undertaken include a gonadotrophin-releasing hormone (GnRH) agonist. Prolonged use of GnRH agonists results in down-regulation of the pituitary and is used in assisted reproduction cycles to prevent an LH surge that would induce premature ovulation. Studies have shown that the addition of GnRH agonists results in higher pregnancy rates, lower miscarriage rates and fewer cycle cancellations, compared to the use of gonadotrophins alone, both in women with and without PCOS.[41,42]

Whether a pure FSH preparation or a mixture of LH and FSH should be preferred for ovarian hyperstimulation in GnRHa down-regulated women has been a matter of debate in the literature over the last five years.[43-48] Especially in women with PCOS, who often have elevated LH levels, the use of pure FSH is theoretically appealing. Yet, when work on this thesis was started there was little evidence to support pure FSH preparations over LH-containing gonadotrophins.

There also is considerable difference between the available FSH preparations with regard to their composition. FSH is a glycosylated peptide hormone composed of two peptide subunits, an α- and a β-subunit. Each peptide subunit possesses two glycosylation sites on which oligosaccharides are normally attached. Each oligosaccharide may show single branched, di- tri- and even tetrabranched structures and each branch of the oligosaccharides may or may not terminate in a negatively charged sialic acid residue allowing FSH to exist as a number of isoforms.[49] These isoforms differ in their isoelectric points, the lower the isoelectric point the more acidic will be the FSH isoform. There is evidence that the acidity of the FSH isoforms affect its biological activity and circulatory half-life.[50-52] Recombinant and urinary FSH preparations are known to differ in isoform composition.[53] At the time we planned our studies, the FSH isoform profiles of commercially available gonadotrophin preparations had not been a factor when evaluating treatment outcome in connection with ART.

Aim of this thesis

The aim of this thesis is to answer the following questions:

1. How does a laparoscopic electrocautery strategy compare with ovulation induction with rFSH in CC-resistant women with PCOS in terms of clinical outcome and costs?

2. What are predictors of ovarian response after laparoscopic electrocautery of the ovaries and of treatment outcome after laparoscopic electrocautery of the ovaries followed by clomiphene citrate?

3. Which patient characteristics can predict treatment outcome following ovulation induction with rFSH

4. What is the effectiveness of hMG, uFSH and rFSH for ovarian hyperstimulation in IVF and ICSI cycles in women with PCOS?

5. How do hMG and rFSH compare in terms of clinical outcome when used for ovarian hyperstimulation in IVF and ICSI cycles in normogonadotrophic ovulating women ?

6. Is the FSH isoform profile of gonadotrophin preparations of clinical significance?

Outline of this thesis

The first part of this thesis (Chapters 2 to 5) addresses ovulation induction *in women with CC-resistant PCOS.*

Chapter 2 reports on the results of a randomised clinical trial that compared the effectiveness of a laparoscopic electrocautery strategy and ovulation induction with recombinant FSH in CC-resistant women with PCOS. This trial was performed in 29 Dutch hospitals between 1998 and 2001. Primary outcome was an ongoing pregnancy.

Chapter 3 reports on the economic evaluation of a laparoscopic electrocautery strategy compared to ovulation induction with recombinant FSH using data of the randomised clinical trial from Chapter 2. Data on used recourses were collected and costs of both treatment modalities were calculated. A scenario analysis was done to estimate the costs of ovulation induction with rFSH without a preceding laparoscopy.

Chapter 4 contains a study of clinical, ultrasonographic and endocrine characteristics obtained during initial screening of CC-resistant PCOS patients that can predict persistence of anovulation after laparoscopic electrocautery. Persistence of anovulation was defined as failure to ovulate within eight weeks after electrocautery. Subsequently it was studied whether clinical, ultrasonographic and endocrine characteristics during initial screening of cc-resistant PCOS patients may predict treatment failure after electrocautery followed by CC in case of persistent anovulation. Treatment failure was defined as failure to reach an ongoing pregnancy.

Chapter 5 documents the ability of clinical, ultrasonographic and endocrine characteristics during initial screening of CC-resistant PCOS patients to predict treatment success following ovulation induction with rFSH. Treatment success was defined as reaching an ongoing pregnancy.

The second part of this thesis (Chapters 6 to 8) deals with ovarian hyperstimulation.

Chapter 6 presents the results of a retrospective study comparing pregnancy outcome following treatment with hMG, uFSH and rFSH for IVF and ICSI in women with PCOS, while adjusting for other explanatory variables.

Chapter 7 provides a systematic review of the published literature in which hMG was compared to rFSH for ovarian hyperstimulation in IVF and ICSI in normogonadotrophic ovulating women. Primary outcome was ongoing pregnancy or live birth.

Chapter 8 reviews what is known on biological differences of various FSH isoforms and studies in a meta-analysis the clinical effectiveness of Metrodin-HP and Gonal-F, two FSH products that differ most profoundly in isoform composition.

Chapter 9 summarises the results of the preceding chapters, presents conclusions and gives suggestions for further research.

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