Polycystic ovary syndrome. A therapeutic challenge
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CHAPTER 1

General introduction
Introduction

Polycystic ovary syndrome (PCOS), the existence of which was already known in the 18th century, still represents a therapeutic challenge. To the best of our knowledge, Vallisneri was the first author to report on this condition in 1721. In his paper he focuses on the abnormal morphology of the ovaries which are described as large, bumpy, shiny and whitish, just like pigeon eggs (Insler and Lunenfeld, 1990). Since then occasional reports have been published regarding the origin of this morphological abnormality and its surgical treatment. In 1935, interest in the syndrome was revived by a landmark publication by Stein and Leventhal in which this anatomical abnormality was associated with amenorrhea, history of sterility, masculine type hirsutism, and less consistently, retarded breast development and obesity (Stein and Leventhal, 1935). Nowadays, polycystic ovary syndrome is considered to be a heterogeneous condition with a wide variety in clinical and biochemical presentation.

A patient with PCOS can be affected by one, all, or any combination of the following signs, symptoms and endocrine abnormalities: menstrual disturbance (oligomenorrhea, amenorrhea), infertility, hyperandrogenism (hirsutism, acne, alopecia), obesity, elevated LH/FSH ratio, insulin resistance, dyslipidaemia and appearance of polycystic ovaries on ultrasonography (Balen, 1999). A gold standard for the diagnosis of PCOS is lacking. Conclusive scientific arguments to prefer one definition of PCOS above another can not be given. Recently, a consensus was reached on the diagnostic criteria of PCOS at a meeting of the European Society of Human Reproduction and Embryology (ESHRE) and American Society for Reproductive Medicine (ASRM). The newly revised criteria for the diagnosis of PCOS are the presence of two out of the following three symptoms: oligo- or anovulation, clinical and/or biochemical signs of hyperandrogenism and polycystic ovaries. Other etiologies should be excluded (The Rotterdam ESHRE/ASRM-sponsored PCOS Consensus Workshop Group, 2004; The Rotterdam ESHRE/ASRM-sponsored PCOS Consensus Workshop Group, 2004a).

Since this consensus is quite recent, the reported prevalence of PCOS depends on the definition used and varies widely. A prevalence of approximately 4 to 7% has been reported when PCOS was defined by oligomenorrhea, clinical hyperandrogenism and/or hyperandrogenemia (Asuncion et al., 2000; Knochenhauer et al., 1998; Diamanti-Kandarakis et al., 1999) and approximately 21-33% when PCOS was diagnosed by the ultrasonographical image of polycystic ovaries (Polson et al., 1988; Clayton et al., 1992; Farquhar et al., 1994; Michelmore et al., 1999). Combining the presence of polycystic ovaries with one or more of the associated clinical symptoms or recognized biochemical disturbances, results in a prevalence of PCOS which varies between 8% and 26%, depending on how many criteria were applied to define the syndrome (Michelmore et al., 1999).

Treatment of PCOS is symptom oriented. Infertility due to chronic anovulation is the most common reason for patients with PCOS to seek treatment. The drug of first choice in ovulation induction is the anti-estrogen clomiphene citrate (CC). However, approximately 20 % of patients fail to ovulate on CC (Hull, 1987; Imani et al., 1998; Out and Coelingh-Bennink, 1998). Effective treatment of these clomiphene citrate resistant patients remains a significant challenge to the medical
profession. The second line therapeutic options are either ovulation induction with ovarian surgery or gonadotrophins.

The first effective treatment to restore ovulation was the bilateral ovarian wedge resection by laparotomy, introduced by Stein and Leventhal (Stein and Leventhal, 1935). Interest in this surgical intervention was lost because of the observed high incidence of adhesion formation after the wedge resection (Buttram and Vaquero, 1975; Kistner, 1969; Weinstein and Polishuk, 1975; Adashi et al., 1981) and the introduction of clomiphene citrate in 1961 (Greenblatt, 1961). Subsequently, laparoscopic ovarian biopsy was introduced by Palmer and De Brux in 1967 (Palmer and De Brux, 1967). Although this procedure is less invasive compared to bilateral ovarian wedge resection by laparotomy, it did not result in new interest for surgical treatment. Probably this was caused by the fact that laparoscopic surgery was not a common practice at that time, and by the fear for adhesion formation, as experienced after bilateral wedge resection.

The unilateral oophorectomy proposed by Hamerlynck in 1982 (Hamerlynck, 1982) was also not evaluated by others due to the introduction of in vitro fertilization and fear of premature ovarian failure, while at the same time attention was focussed on the further development of minimal invasive treatment options by laparoscopy. These new and less invasive techniques involved laparoscopic laser surgery and laparoscopic electrocautery of the ovaries. The laparoscopic laser surgery was introduced by Huber in 1988 (Huber et al., 1988). Despite certain advantages, such as a shorter operating time and a diminished risk of adhesions, the laser systems are expensive and require extensive and costly upkeep (Greenblatt, 1993).

At this moment, laparoscopic electrocautery of the ovaries is the most commonly used surgical treatment in patients with clomiphene citrate resistant polycystic ovary syndrome. The original technique was first described by Gjonnaess in 1984 (Gjonnaess, 1984). A unipolar electrode with a power output of 200-300 Watts was pressed for 2 to 4 seconds against the ovary to penetrate the ovarian surface. The number of points cauterized varied between three to eight holes in each ovary. Gjonnaess reported an ovulation percentage of 92% and a pregnancy rate of 69% in a group of 62 patients. However, only 19 of these patients received clomiphene citrate before cauterization and only nine patients failed to ovulate with clomiphene citrate. Three out of those nine patients (33%) conceived after electrocautery (van der Weiden and Alberda, 1987).

Serious complications have not been reported with laparoscopic electrocautery of the ovaries. However, the use of unipolar cautery carries the potential risk of arcing, with damage to adjacent organs, particularly the bowel. One rare complication that has been reported is the development of ovarian atrophy (Dabirashrafi, 1989). This report emphasizes the need to avoid cauterizing the ovarian hilum, which might affect the blood supply, as well as individualizing the number of points of injury and maximum energy according to the size and bulk of the ovary. A more important possible complication of electrocautery is adhesion formation, although the incidence is not well established. Adhesion formation has been evaluated during second look laparoscopies because of persistent infertility or during caesarean sections and varies between 0-70% (Armar and Lachelin, 1993; Naether and Fischer, 1993; Weise et al., 1991; Farhi et al., 1995; Liguori et al., 1996; Pelosi, 1996).

At the time of writing the research protocol that is the basis for the present thesis, twelve uncontrolled studies had been published on laparoscopic electrocautery concerning
ovulation and pregnancy in patients with clomiphene citrate resistant polycystic ovary syndrome (Gjonnaess, 1984; Greenblatt and Casper, 1987; Greenblatt and Casper, 1993; Gurgan et al., 1991; Tasaka et al., 1990; Taskin et al., 1996; Lockwood et al., 1998; Taskin et al., 1999; Tulandi et al., 2000; Weerakiet et al., 1999; Alborzi et al., 2001; Zullo et al., 2000). Summary of the data from these studies results in a mean ovulation rate of approximately 73% (range 52-94) per patient and a mean pregnancy rate of approximately 50% (range 20-80) per patient.

Additional treatment with clomiphene citrate after laparoscopic electrocautery of the ovaries increased the ovulation rate to 87% (range 76-100) and the pregnancy rate to 70% (range 20-73) (Gjonnaess, 1984; Greenblatt and Casper, 1987; van der Weiden and Alberda, 1987); (Alborzi et al., 2001; Lockwood et al., 1998; Weerakiet et al., 1999).

The other treatment modality for clomiphene citrate resistant patients with PCOS is ovulation induction with gonadotrophins, which are available in the form of urinary derived human menopausal gonadotrophins (hMG) or follicle stimulating hormone (FSH). Human menopausal gonadotrophin was the first available preparation that contains 75 IU FSH, 75 IU luteinizing hormone (LH) and some urinary proteins. The next generation in this group was purified urinary FSH (uFSH) or urofollitrophins containing very little LH. Later highly purified FSH containing only traces of LH was introduced and finally the pure preparation of recombinant FSH (rFSH) became available. The conversion from hMG to uFSH was driven by the concept that lack of urinary proteins would diminish adverse reactions such as local allergy or hypersensitivity (Alban et al., 1996; Biffoni et al., 1994) whereas the absence of LH would have no negative influence on folliculogenesis (van Weissenbruch et al., 1993; Hayden et al., 1999). Although the fast introduction of rFSH was market driven, its purity, batch to batch consistency, high specific bioactivity and absolute source control made it an attractive alternative to the urinary FSH products.

It is however not clear whether using rFSH rather than uFSH for ovulation induction in patients with PCOS leads to any improvement in clinical endpoints like ovulation and ongoing pregnancy rate. We reviewed the literature to summarize the evidence on the effectiveness and safety of rFSH versus uFSH.

Ovulation induction with gonadotrophins in patients with PCOS is associated with the risk of multiple follicular development, consequently leading to complications such as ovarian hyperstimulation syndrome and multiple pregnancy. Various attempts have been made to achieve unifollicular growth and thereby to reduce these complications.

One of these attempts was the modification of the stimulation regimens. Currently, chronic low dose step up or step down regimens are used instead of the initially introduced high dose gonadotrophin regimens. The chronic low dose step up regimen employs a starting dose of one ampoule of 75 IU of FSH, which is only increased after 14 days if there is no response, and then by only half an ampoule every seven days (Hamilton-Fairley et al., 1991; Balen et al., 1994; Homburg et al., 1995). The aim of this regimen is not to exceed the FSH concentration above which more than one follicle will respond, the so-called FSH threshold for any given follicle (Brown, 1978).

The step down regimen employs a starting dose of two to three ampoules daily for three to four days followed by dose decreases once the lead follicle exceeds a mean diameter of about 10 mm (Schoot et al., 1992; Schoot et al., 1995; van Santbrink et al., 1995; Fauser
and Van Heusden, 1997). The rationale behind the step down regimen is that it mimics the normal menstrual cycle more closely (Fauser et al., 1993). In order to find out the most appropriate dose regimen we reviewed the literature to determine the effectiveness and safety of various dose regimens using rFSH.

Another attempt to achieve monofollicular growth was the introduction of pulsatile administration of gonadotrophin releasing hormone (GnRH). Following the positive effects in patients with hypogonadotrophic hypogonadism, Coelingh Bennink was the first author to select PCOS patients in whom other methods had failed or in whom ovarian hyperstimulation syndrome had occurred, for treatment with GnRH (Coelingh Bennink, 1983). Since then, a limited number of randomised controlled trials with small number of patients have been published, comparing GnRH with gonadotrophins. Although ovulation and pregnancies were achieved, the use of pulsatile GnRH in patients with PCOS did not lead to the same success rates as achieved in hypogonadotrophic amenorrhoea. To improve clinical outcome suppression of endogenous gonadotrophins through pre treatment with GnRH agonists was the next step. However, pulsatile GnRH has not become a standard treatment for ovulation induction in patients with clomiphene citrate resistant PCOS. To prove or to discard the value of pulsatile GnRH we reviewed the literature to determine effectiveness and safety of pulsatile GnRH versus gonadotrophins.

At present ovulation induction with laparoscopic electrocautery of the ovaries and recombinant FSH (rFSH) are standard treatments in patients with CC-resistant PCOS. Whether gonadotrophins or laparoscopic electrocautery of the ovaries should be the treatment of choice in patients with CC-resistant polycystic ovary syndrome was unclear when work on this thesis was started. To find out the best way to treat these patients, we designed a randomised controlled 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.
Aim of the thesis

The aim of the work reported in this thesis was to answer the following questions:

1. What is the effectiveness and safety of rFSH compared with uFSH and what is the effectiveness and safety of various dose regimens using rFSH in clomiphene citrate resistant patients with PCOS?

2. What is the effectiveness and safety of pulsatile GnRH compared with gonadotrophins in clomiphene citrate resistant patients with PCOS?

3. What is the value of electrocautery strategy compared to ovulation induction with rFSH in the treatment of clomiphene citrate resistant patients with PCOS in view of outcome measures, patients’ health related quality of life, costs and patients’ preferences?
Outline of the thesis

Chapter 2 reviews the literature on the effectiveness and safety of recombinant FSH versus urinary FSH and recombinant FSH in different dose regimens to induce ovulation in patients with clomiphene citrate-resistant PCOS. Studies were included according the principles of the Cochrane Menstrual Disorders and Subfertility Group. The results concerning ovulation, pregnancy, miscarriage, incidence of multiple pregnancy, incidence of ovarian hyperstimulation syndrome, total gonadotrophin dose and total duration of stimulation are described and compared.

Chapter 3 reviews the literature on the effectiveness and complications of pulsatile GnRH to induce ovulation in patients with PCOS. Studies were included according the principles of the Cochrane Menstrual Disorders and Subfertility Group. The results concerning ovulation, pregnancy, miscarriage, incidence of multiple pregnancy and incidence of ovarian hyperstimulation syndrome are described and compared.

Chapter 4 describes the first randomised controlled trial comparing the effectiveness of a laparoscopic electrocautery strategy entailing electrocautery of the ovaries followed by clomiphene citrate and recombinant FSH if anovulation persisted versus ovulation induction with recombinant FSH in patients with clomiphene citrate resistant PCOS. Ongoing pregnancy was the primary endpoint. Ovulation, miscarriage, ectopic pregnancy and the live birth rate were secondary endpoints.

Chapter 5 focuses on the health related quality of life of patients who participated in the randomised controlled trial described in Chapter 4. Health related quality of life was assessed by several standard self administered psychosomatic measures at different time points in both treatment groups.

Chapter 6 reports on the economic evaluation of the electrocautery strategy compared to ovulation induction with recombinant FSH using data from the randomised controlled trial described in Chapter 4. Data on used resources and lost production time were collected and costs of both treatment modalities were calculated to an ongoing pregnancy with a time horizon of 12 months. A scenario analysis was done to evaluate the costs of ovulation induction with rFSH without a preceding laparoscopy.

Chapter 7 contains a report of a study of patient preferences and trade-offs when offered a choice between laparoscopic electrocautery of the ovaries and ovulation induction with recombinant FSH. This study was performed among patients who had been treated in the randomised controlled trial described in Chapter 4 and among a control group of women undergoing ovulation induction with clomiphene citrate as they were potential candidates for treatment with either electrocautery of the ovaries or ovulation induction with recombinant FSH if they became resistant to clomiphene citrate.

Chapter 8 presents the summary and conclusions of the present study and gives directions for future research.
References


