Clinical consequences of ovarian stimulation in assisted conception and in PCOS
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Chapter I

Introduction
To date, multifollicular development is an integral part of ovarian stimulation in assisted conception cycles. Pharmaceutical preparations of human gonadotrophins play an important role to achieve this goal (1). In the late 1970s, human menopausal gonadotrophin (hMG) was the most widely used gonadotrophin for ovarian stimulation in assisted reproduction containing FSH and LH in a 1:1 ratio with urinary proteins. However, the often concurrent problem of premature luteinizing hormone (LH) surges and premature luteinizations, resulted in cancellations of many cycles. (2). This was efficiently overcome by reversible medical 'hypophysectomy', performed by gonadotrophin releasing hormone (GnRH) analogs, introduced in 1982. As a consequence, human chorionic gonadotrophin (hCG) was necessary to induce final follicular maturation and triggering of ovulation. Accordingly, in the 1980s, the use of gonadotrophins, gonadotrophin-releasing hormone (GnRH) agonists and human chorionic gonadotrophin (hCG) became a standard successful protocol for ovulation induction in assisted conception cycles.

This standard protocol was challenged in the 1990s by the introduction of two important products: recombinant FSH and GnRH antagonists. The manufacture of human follicle stimulating hormone (FSH) by recombinant DNA technology made production independent of urine collection and guaranteed the availability of an almost pure FSH preparation (>99% free from urinary protein contaminants) with minimal batch to batch variation. The high purity and low immunogeneity allowed S.C administration (3). Despite proven efficacy of recombinant FSH (rFSH), its wide-spread use was hampered by its relatively high cost as compared with human menopausal gonadotrophins (4). Both effectiveness and cost are important to decide whether to prefer one drug over the other. We therefore systematically reviewed current evidence comparing clinical pregnancy rate achieved with recombinant versus urinary gonadotrophins (hMG, purified FSH, and highly purified FSH) in controlled ovarian hyperstimulation in women undergoing IVF/ICSI cycles. Although clinical pregnancy rate is important, other outcomes such as amount of gonadotrophins used, live birth rate, miscarriage rate, multiple pregnancy rate and incidence of ovarian hyperstimulation syndrome should also be considered. Based on these results, a cost effectiveness analysis between hMG and recFSH was conducted to estimate the cost of an ongoing pregnancy in an IVF/ ICSI cycle from a perspective of a
developing country like Egypt. The rationales to do this are the limitations in medical insurance and/or government support for infertility treatment in Egypt and other developing countries.

One important step in controlled ovarian hyperstimulation is final follicular maturation and triggering ovulation and for the last few decades urinary human chorionic gonadotrophin (hCG) has been used. Recombinant technology has allowed the production of two drugs that can be used for the same purpose i.e. to mimic the endogenous LH surge. However, to change practice, the recombinant drugs should at least be as effective as the currently used urinary hCG.

The GnRH antagonists emerged as an alternative to GnRH agonists in preventing premature LH surges. In comparison with the GnRH agonists, the pharmacological mechanism by which GnRH antagonists suppress the release of gonadotrophins is completely different. (5). While the agonists act on chronic administration through down-regulation of receptors and desensitisation of the gonadotrophic cells, the antagonists bind competitively to the receptors and thereby prevent the endogenous GnRH from exerting its stimulatory effects on the pituitary cells. The competitive blockade of the receptors leads to an immediate arrest of gonadotrophin secretion (6). This mechanism of action is dependent on the equilibrium between endogenous GnRH and the applied antagonist. Because of this, the antagonistic effect is highly dose-dependent in contrast with the GnRH agonists (7). The efficacy and safety of GnRH antagonists was demonstrated in a number of studies (8-10).

In addition, GnRH antagonists for controlled ovarian hyperstimulation in assisted conception reduced the amount of gonadotrophin needed for stimulation, lowered the risk for developing severe OHSS and avoided estrogen deprivation symptoms (e.g. hot flushes, sleep disturbances, headache) as frequently observed in the pre-stimulation phase of a long GnRH agonist protocol. (11, 12) Whether the benefits mentioned above justify a change in routine treatment from the standard long GnRH agonist protocol to the newly designed GnRH antagonist regimen depends on whether the clinical outcome using these protocols is equivalent. Although multicenter randomized controlled trials showed that there was no statistically significant difference between GnRH agonist and antagonist in prevention of premature LH surge, there was a consistent trend towards lower pregnancy rate with the antagonist. (9, 13) This could be attributed to several factors.
First, the RCTs were not powered enough to detect a difference in clinical pregnancy rate. We therefore systematically reviewed the literature to summarize the evidence on effectiveness of GnRH agonist versus antagonist administered on a fixed day.

Second, administration of the antagonist in these studies started on a fixed day i.e day 6 of FSH stimulation. This fixed regimen was advised to avoid any risk of premature LH secretion and to simplify the stimulation protocol. As there are individual variations in patient response to ovarian stimulation, a flexible protocol may be more justified. We therefore compared GnRH agonist in a long protocol versus a flexible protocol of antagonist by starting the antagonist according to the size of the follicle rather than a fixed day and at the same time, we systematically reviewed the flexible administration of antagonist versus the fixed regimen.

Third, in antagonist cycles, follicular growth depends on both exogenous and endogenous FSH and LH. When the antagonist is started, both endogenous FSH and LH secretion will fall which may be detrimental for further follicular development. Increasing the dose of gonadotrophins on the day of starting the antagonist may improve the pregnancy rate. To test this hypothesis in the best way, we conducted a randomized controlled trial to find out the possible effect of increasing the dose of gonadotrophins on the day of starting the antagonist on the pregnancy rate.

One important observation in the multicenter randomized controlled trials evaluating gonadotrophins and GnRH antagonists is that they had a common exclusion criterion which is women with polycystic ovary syndrome (PCOS). As the cause of infertility in patients with PCOS is anovulation -because of a failure of the follicles to develop beyond 10 mm-, induction of ovulation is essential. However, the risks of ovarian hyperstimulation and multiple pregnancy with gonadotrophin administration are substantial in this population. (14). Clomiphene citrate is particularly effective in inducing ovulation in PCOS patients. However, not all cases respond to this drug (15,16). Effective treatment of these clomiphene citrate resistant patients remains a significant clinical challenge. Laparoscopic electrocautery of the ovaries is the most commonly used surgical treatment in patients with clomiphene citrate resistant PCOS but it needs hospital setting usually with an overnight stay and the risk of postoperative adhesions cannot be ignored. Exploring other mechanisms to induce or augment ovulation in CC resistant patients is needed. Thermal aqua puncture (TAP) could be
an attractive option, through conveying thermal energy (hydro coagulation) using hot saline to coagulate areas of the ovarian stroma. Hot saline provides conduction exchange medium through which heat is gently conveyed to the ovarian stroma tissue without tissue substance loss or scarring (17) The ovarian stroma tissue in cases of PCOS is quite echogenic. It can be accurately targeted using the puncture needle. The injected fluid can be identified on real time ultrasound, thus can be done as an office procedure. To evaluate the feasibility of transvagal ultrasound guided ovarian stroma hydrocoagulation in clomiphene citrate resistant PCOS, we conducted a clinical trial.

With increasing evidence that insulin resistance constitutes a key metabolic element, it seems logical that improving insulin sensitivity and glucose disposal might wholly, or partially, reverse certain features of polycystic ovarian syndrome, including anovulation. (18) Accordingly, we conducted a randomized study, in which metformin 500mg versus placebo was given for 6 week prior to, and in conjunction with, clomiphene citrate induction of ovulation for both overweight and lean polycystic ovarian syndrome women vs. the use of placebo.

Another promising agent is N-acetyl cysteine (NAC). NAC is a safe and well tolerated mucolytic drug that softens tenacious mucous secretions. It is the acetylated precursor of both amino acid L-cysteine and reduced glutathione (GSH). It has been shown to have proven activity on insulin secretion in pancreatic cells, as well as on the regulation of the insulin receptor in human erythrocytes (19) In addition, it is a powerful antioxidant (20), anti-apoptotic (21) and induces a significant fall in testosterone levels and in free androgen index values (19). Accordingly, we performed a randomized controlled trial to evaluate the effect of NAC administration as an adjuvant to CC on ovulation and pregnancy rates as compared to CC plus placebo in patients with CC resistant PCOS.
**Aim of this thesis**

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

1. How do urinary and recombinant gonadotrophins compare in terms of clinical pregnancy rate when used for ovarian hyperstimulation in IVF/ICSI cycles in normogonadotrophic ovulating women?

2. Is recombinant FSH superior to human menopausal gonadotrophins regarding various clinical outcomes when used for ovarian hyperstimulation in IVF/ICSI cycles in normogonadotrophic ovulating women?

3. What is more cost effective for ovarian stimulation in IVF/ICSI cycles in a developing country like Egypt: human menopausal gonadotrophins or recombinant FSH?

4. How do urinary and recombinant gonadotrophins compare in terms of clinical outcome when used for final follicular maturation and triggering of ovulation in assisted conception cycles?

5. Is gonadotrophin releasing hormone (GnRH) antagonist administered in a fixed day as effective as GnRH agonist long protocol?

6. Is flexible administration of a GnRH antagonist according to follicular size more beneficial than starting on a fixed day?

7. Does increasing the dose of hMG at day of GnRH antagonist administration improve pregnancy rates?

8. Does office transvaginal ovarian stroma hydrocoagulation improve menstrual pattern and ovulation rate in clomiphene citrate resistant PCO cases?

9. Does metformin improve clinical outcome when given as an adjuvant to clomiphene citrate in women with Clomiphene citrate resistant PCOS?

10. Does N-acetyl cysteine improve clinical outcome when act as an adjuvant to Clomiphene citrate in women with clomiphene citrate resistant PCOS?
Outline of this thesis

The first part of this thesis (Chapters 2 to 9) addresses controlled ovarian hyperstimulation in women undergoing IVF/ICSI cycle.

Chapter 2 reports on results of a systematic review and meta-analysis of randomized controlled trials that compared between urinary and recombinant gonadotrophins in terms of clinical pregnancy rate when used for ovarian hyperstimulation in IVF/ICSI cycles in normogonadotrophic ovulating women. The studies were included and assessed according to the principles of the Cochrane Menstrual Disorders and Subfertility Group. Primary outcome was clinical pregnancy rate.

Chapter 3 presents a systematic review and a meta-analysis of randomized controlled trials that compare between recombinant FSH and human menopausal gonadotrophins regarding various clinical outcomes when used for ovarian hyperstimulation in IVF/ICSI cycles in normogonadotrophic ovulating women. The studies were included and assessed according to the principles of the Cochrane Menstrual Disorders and Subfertility Group. Primary outcome was live birth rate/ ongoing pregnancy rate.

Chapter 4 presents a cost effectiveness analysis comparing recombinant FSH and human menopausal gonadotrophins to estimate the cost of an ongoing pregnancy in an IVF/ICSI cycle from a perspective of a developing country like Egypt.

Chapter 5 provides results of a systematic review and meta-analysis of randomized controlled trials that compared urinary and recombinant gonadotrophins when used for final follicular maturation and triggering of ovulation in assisted conception cycles. The studies were included and assessed according to the principles of the Cochrane Menstrual Disorders and Subfertility Group. Live birth rate was primary outcome.

Chapter 6 reports on results of a systematic review and meta-analysis of randomized controlled trials that compared gonadotrophin releasing hormone (GnRH) antagonist administered in a fixed day to GnRH agonist long protocol. The studies were included and assessed according to the principles of the Cochrane Menstrual Disorders and Subfertility
Group. Primary outcomes were prevention of premature LH surge and clinical pregnancy per woman randomized. Secondary outcomes considered were number of oocytes retrieved, clinical pregnancy per oocyte retrieval and per embryo transfer, spontaneous abortion, incidence of severe ovarian hyperstimulation syndrome and the amount of gonadotrophins used.

Chapter 7 presents the results of randomized controlled trial that compared flexible administration of GnRH antagonist to GnRH agonist long protocol. Primary outcome was clinical pregnancy rate per woman randomized.

Chapter 8 reports the results of systematic review and meta-analysis comparing GnRH antagonist administration in a fixed day vs flexible administration according to follicle size. Primary outcome was ongoing pregnancy / live birth rate.

Chapter 9 presents the results of a randomized controlled trial that investigated increasing the dose of hMG at day of GnRH antagonist administration aiming to improve the results. Primary outcome was clinical pregnancy rate per woman randomized.

The second part of this thesis (Chapters 10-12) deals with ovulation induction in women with PCOS.

Chapter 10 presents the results of the first clinical trial of office transvaginal ovarian stroma hydrocoagulation to improve menstrual pattern and ovulation rate in clomiphene citrate resistant PCOS women. Primary outcome was ovulation rate and cycle regularity, clinical pregnancy rate was our secondary outcome.

Chapter 11 documents the ability of metformin in a randomized clinical trial to improve clinical outcome when given as an adjuvant to clomiphene citrate in women with Clomiphene citrate resistant PCOS. Primary outcome was ovulation rate and biochemical criteria. Clinical pregnancy rate was secondary outcome.

Chapter 12 presents the results of the first randomized controlled trial evaluating the value of N-acetyl cysteine to improve clinical outcome when act as an adjuvant to Clomiphene
citrate in women with clomiphene citrate resistant PCOS. Primary outcome was ovulation rate and clinical pregnancy rate per woman randomized.

Chapter 13 presents the summary and conclusions of the preceding chapters and gives directions for future research.
References


