Clinical consequences of ovarian stimulation in assisted conception and in PCOS
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Chapter 12

Summary
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The aim of this thesis was to find the best available evidence of various treatment regimens in ovarian hyperstimulation and to find new treatment options for ovulation induction in women with poly cystic ovaries.

In ovarian hyperstimulation, pharmaceutical preparations of gonadotrophins play an integral role to induce multiple follicle growth. To avoid premature LH surges with subsequent cycle cancellation, it is commonly agreed to use GnRH analogues. With the introduction of new drugs like recombinant FSH and GnRH antagonists, it has become necessary to choose one drug over a comparator based on the best available evidence. This can be obtained through conducting systematic review of medical literature or to perform randomized controlled trials.

Accordingly, the first part of this thesis aimed—as outlined in chapter 1—to answer seven specific questions

Chapter 2 addresses the first question

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?

To answer this question, we conducted a systematic review and meta-analysis of randomized controlled trials comparing urinary gonadotrophins (hMG, uFSH and HP-FSH) versus recombinant FSH for ovarian hyperstimulation in women undergoing IVF/ICSI. Our concept was that uFSH-P and uFSH-HP are subproducts of hMG and hence should be grouped together when compared to recombinant FSH, rather than to compare each separately. In support of this concept, in clinical practice, these products are given for the same purpose, for the same patients with similar effects and in similar doses.

We searched the Cochrane Menstrual Disorders and Subfertility Review Group specialized register of randomized controlled trials, MEDLINE and the abstracts of the ESHRE & ASRM meetings from 1999 to 2001 to identify all randomized controlled trials comparing recombinant FSH with FSH containing urinary gonadotrophins.

All published truly randomized controlled trials—using a long protocol of gonadotrophin releasing hormone (GnRH) agonist for downregulation—were reviewed. Data of clinical pregnancy rate/cycle started were extracted and odds ratio were calculated with the use of a
fixed effect model. Subgroup analysis was done to compare recombinant FSH to each product (hMG alone, FSH-P alone, and FSH-HP alone).

Pooling the data from twenty randomised trials (that included 4610 IVF/ICSI cycles) resulted in no statistically significant differences in clinical pregnancy rate / started cycle between recombinant FSH and FSH containing urinary gonadotrophins (O.R 1.07 (0.94-1.22)). Subgroup analysis showed no statistically significant difference in the clinical pregnancy rate per started cycle between recombinant FSH vs hMG (O.R 0.81 (95% C.I 0.63-1.05)), recombinant FSH vs uFSH-P, (O.R 1.24 (95% C.I. 0.98 –1.58)) and recombinant FSH vs uFSH-HP (O.R 1.14(95% C.I 0.94-1.40). There was no significant heterogeneity of treatment effect across the trials.

In summary, there is no evidence of clinical superiority in clinical pregnancy rate for the recombinant FSH over different FSH containing urinary gonadotrophins. Additional factors should be considered when choosing a gonadotrophin regimen, including safety, cost, patient acceptability and drug availability.

Chapter 3 addresses the second question:

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?

Due to the renewed interest in LH, more randomized controlled trials were published after the above mentioned meta-analysis comparing hMG versus recFSH for ovarian hyperstimulation in women undergoing IVF/ICSI cycles. To answer this specific question, we performed a systematic review in 2005 including eight truly RCTs enrolling 2031 participants.

Pooling data from included trials showed no significant difference between recombinant FSH and hMG regarding different outcomes (ongoing pregnancy/live birth rate O.R 1.18 (95% C.I 0.93-1.50), clinical pregnancy rate O.R 1.2 (95% C.I 0.99-1.47), miscarriage rate O.R 1.2 (95% C.I 0.70-2.16), multiple pregnancy rate O.R 1.35 (95% C.I 0.96- 1.90) and incidence of moderate/severe OHSS O.R 1.79 (95% C.I 0.74- 4.33).

However, subgroup analysis showed a better clinical pregnancy rate with hMG in cycles where down regulation was done using long protocol. O.R.: 1.27 (95% CI 1.00-1.62). There was significant reduction in the amount of gonadotrophins in favor of hMG over
recombinant FSH. (OR -317.8 (95% CI -346.6 to -289.0). It would seem that in some women using recombinant FSH after GnRH agonist down-regulation, very low serum LH concentrations may occur, adversely effecting IVF outcome. However, identifying which women will require additional LH is costly and unreliable.

Chapter 4 addresses the third question:

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

To answer this question, a Markov model was developed to simulate the IVF treatment cycle with its key steps, to examine the costs and effectiveness of recFSH versus hMG. In addition, Monte Carlo micro-simulation was used to examine the potential impact of assumptions and other uncertainties represented in the model. The results of this study revealed that the estimated average cost of an ongoing pregnancy is 13,946 EGP and 18,721 EGP for an hMG and recFSH cycle, respectively. On performing a sensitivity analysis on cycle costs, it was demonstrated that the recFSH price should be 0.61 EGP/IU to be as cost-effective as hMG at the price of 0.64 EGP/IU which means a reduction of approximately 60% of its current price. The difference in costs between hMG and recFSH in over 100,000 cycles would result in an additional 4,565 ongoing pregnancies if hMG was used.

In conclusion, from an economic point of view, hMG is more cost-effective than recFSH. The decision to adopt a more expensive treatment could result in a lower number of cycles of IVF/ICSI treatment, especially if patients are paying for it.

Chapter 5 addresses the fourth question:

*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?*

To answer this question, a systematic review was conducted relying on an extensive search strategy [the Cochrane Menstrual Disorders and Subfertility Group trials register (27 August 2003), the Cochrane Central Register of Controlled Trials (CENTRAL on The Cochrane Library, issue 4, 2003), MEDLINE (1966 to Feb 2004) and EMBASE (1980 to Feb 2004)]. Only truly randomised controlled trials comparing rhCG or high dose rhLH with urinary
hCG for triggering ovulation in assisted conception for treatment of infertility in normogonadotrophic women were included.

Seven RCTs were identified, four comparing rhCG and uhCG and three comparing rhLH and uhCG. There was no statistically significant difference between rhCG vs uhCG regarding the ongoing pregnancy/live birth rate (OR 0.98, 95% CI 0.69 to 1.39), pregnancy rate, miscarriage rate or incidence of OHSS. rhCG was associated with a reduction in the incidence of local site reactions and other minor adverse effects (OR 0.47, 95% CI 0.32 to 0.70).

Pooling the data from the trials comparing recombinant rhLH versus urinary hCG demonstrated that clinical pregnancy rates were significantly lower in the rhLH group than in the uhCG group (p = 0.018 and p = 0.023, respectively). This information was sent to the pharmaceutical company after contacting them for additional data. As a consequence the manufacturer of rhLH has decided not to further develop this product.

In summary, there is no evidence of a difference in clinical outcomes of live birth/ongoing pregnancy, pregnancy, miscarriage and OHSS between urinary and recombinant gonadotrophins for induction of final follicular maturation. Minor adverse reactions such as skin irritation at injection site were more likely to occur after treatment with the uhCG. Additional factors should be considered when choosing gonadotrophin type, including safety, cost and drug availability.

Chapter 6 addresses the fifth question:

*Is gonadotrophin releasing hormone (GnRH) antagonist administered on a fixed day as effective as GnRH agonist long protocol?*

To answer this question, a systematic review was conducted. Search strategies included online searching of the MEDLINE and EMBASE databases and the Cochrane Menstrual Disorders and Subfertility Group's Specialised Register from 1982 to 2001, and hand searching of bibliographies of relevant publications and reviews, and abstracts of scientific meetings. Only five randomised controlled studies enrolling 1796 participants and comparing different protocols of GnRH antagonists with GnRH agonists in assisted conception cycles were included in this review.
In comparison to the long protocol of GnRHa, the overall OR for the prevention of premature LH surges was 1.76 (95% C.I. 0.75-4.16), which is not statistically significant. There were significantly fewer clinical pregnancies in those treated with GnRH antagonists (OR 0.79 95% C.I., 0.62-0.97). The absolute treatment effect (ATE) was calculated to be 5%. The number needed to treat (NNT) was 20. There was no statistically significant reduction in incidence of severe ovarian hyperstimulation syndrome between the two regimens (RR 0.51 (95% C.I. 0.22, 1.18).

The fixed GnRH antagonist protocol (i.e. start of the antagonist on day 6 of gonadotrophin stimulation) is a short and simple protocol with good clinical outcome but the lower pregnancy rate compared to the GnRH agonist long protocol and the non significant difference between both protocols regarding prevention of premature LH surge and prevention of severe ovarian hyperstimulation syndrome necessitates counseling subfertile couples before recommending a GnRH antagonist. The clinical outcome may be improved by developing more flexible antagonist regimens taking into account individual patient characteristics.

**Chapters 7-8** address therefore the sixth question

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

To answer this question we conducted a systematic review and meta-analysis of randomized controlled trials that compared GnRH antagonist administration on a fixed day versus starting it according to follicular size. In the mean time we performed a randomized controlled trial comparing GnRH agonist long protocol vs GnRH antagonist flexible administration according to follicle size.

In the systematic review, eleven trials were identified, but only four Randomized Controlled Trials were included. The other seven trials were only published as abstracts and attempts to obtain more data from the authors failed. There was statistically no significant difference in pregnancy rate per woman randomized although there was a trend towards a lower pregnancy rate in favor of the fixed protocol [O.R = 0.7 95% CI = 0.47 to 1.05]. There was no statistically significant difference in incidence of premature LH surge in both protocols. However, there was a statistically significant reduction both in number of antagonist ampoules and amount of gonadotrophins used in the flexible protocol (O.R -1.2
95% CI -1.26- -1.15). There was a trend to an increase in the number of oocytes retrieved with the flexible protocol (OR 1.28 95% CI 0.9-1.6).

In the clinical trial, one hundred women undergoing IVF/ICSI were randomized to receive either hMG/GnRH agonist long protocol or hMG/GnRH antagonist when the follicle reached 15mm in diameter using sealed envelopes as a method for randomization. The pregnancy rate per attempt was 30% in agonist group and 24% in antagonist group. Two women had a premature LH surge in the GnRH antagonist group. An economic evaluation was setup based on the results of this RCT. This analysis showed that the total cost per pregnancy was $6985 in the antagonist group and $5356 in the GnRH-a group, a difference found to be statistically significant.

In summary, flexible administration of a GnRH antagonist according to follicular size is not more beneficial in terms of obtaining pregnancies.

Chapter 9 addresses the seventh question:

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

To answer this question, a RCT was conducted in which one hundred and fifty one subfertile couples were randomly allocated using sealed envelopes on the day of starting the antagonist into two groups: no increase in hMG dose (group A), or an increase of75U of hMG on the day of antagonist administration (group B), and continued till the day of hCG administration. There was no statistically significant difference between both groups regarding number of oocytes retrieved, embryos obtained, implantation rate, clinical pregnancy rate, multiple pregnancy rate. The implantation rate was 19.1% in group B and 17.2% in group A. Clinical pregnancy rate was 32.1% in group A vs 36.2% in group B [O.R 1.3 (95% C.I 0.63-2.6)], The multiple pregnancy rate was 41.2% vs 38.9%.

In summary, there is no evidence of clinical value for increasing the dose of hMG on day of antagonist administration. The cost of increasing the dose of hMG should discourage such policy.

The second part of this thesis focused on new treatment options in polycystic ovary syndrome, a syndrome that affects about 5-10% of women in the reproductive age group and is associated with both reproductive and metabolic disorders.
Recent changes in treatment philosophy have implied a greater focus on the management of the metabolic disorders of PCOS. Insulin resistance has proven to be a key factor in the pathogenesis of PCOS, hence metformin—an insulin sensitizer—is a promising compound. Exploring other mechanisms to induce or augment ovulation in Clomiphene Citrate resistant patients is nevertheless desirable. N-acetyl cysteine could be such a promising agent as it is a safe, well tolerated antioxidant with insulin sensitizing properties. Not all women with PCOS respond to medical therapy and laparoscopic ovarian electrocoagulation is in these women a surgical option of proven benefit. To avoid general anesthesia and to implement the concept of office procedure, transvaginal ovarian electrocoagulation could be an interesting alternative.

Accordingly, the second part of this thesis aimed—as outlined in chapter I—to answer three specific questions.

Chapter 10 addresses the eighth question:

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

To answer this question, sixty anovulatory infertile women diagnosed with PCOS by clinical, chemical and ultrasound criteria were recruited for the study. All women were resistant to clomiphene citrate for more than 6 months. After local anesthesia, hot sterile saline (75°C) was injected into the ovarian stroma under transvaginal monitoring using a standard ovum pickup needle. Twenty three women (38.3%) experienced pain during the procedure, which was tolerable and insufficient to abort the procedure. Follow up was for 6 months to monitor ovulation rate as determined by regular cycles, transvaginal ultrasound and serum progesterone, and to diagnose pregnancy whenever the cycle was delayed after a period of ovulatory cycles.

Forty-three patients (71.7%) had an episode of bleeding a few days after the procedure. Forty-six patients (76.7%) had three spontaneous successive regular cycles and ovulation was documented by serum progesterone on day 20-22 in at least one cycle. Thirty eight women (63.3%) continued to do so for at least six cycles. Fourteen women (23.3%) became pregnant within the first 6 months of the procedure. Three of these women (21.4%) miscarried within the first trimester. There was no adverse effect recorded in any woman.
In conclusion, transvaginal ultrasound guided ovarian stroma hydrocoagulation in an office setting seems to be a safe, economic and practical procedure that is well tolerated by the patients. Obviously, more data are needed to collaborate these findings.

Chapter 11 addresses the ninth question:

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

A randomized controlled trial was conducted to answer this question and sixty infertile women were randomly divided into two groups: Group I: (n=30) had a BMI> 28 and Group II: (n=30) had a BMI< 28. Each group was further subdivided into two subgroups A & B. Subgroup A: consisted of 15 patients who were given metformin 500 mg t.d.s for 6 weeks prior to clomiphene citrate for three cycles and continued throughout induction. Subgroup B: consisted of 15 patients who were given placebo instead of metformin. Both subgroups were compared regarding BMI, biochemical criteria, regularity of the cycles and success of ovulation induction before and after taking metformin or placebo respectively.

There was a statistically significant lowering in LH level in subgroup 1-A (overweight-metformin) and subgroup 2-A (lean-metformin) after the intake of metformin. However, this was observed also in subgroup 1-B (overweight-placebo) after the intake of placebo. There was also statistically significant lowering in FSH level in subgroup 2-A (lean-metformin) after the intake of metformin. This was not observed in the other subgroups. There were no significant changes in the other hormones levels in any of the subgroups. A statistically significant difference both in the individual cycles and in the cumulative response regarding ovulation induction was observed between the two subgroups of each group. However, there were no pregnancies in both groups.

In conclusion, use of metformin (prior to and as an adjuvant to clomid), may be beneficial both in overweight and lean women with polycystic ovarian syndrome.

Chapter 12 addresses the tenth question:

*Does N-acetyl cysteine improve clinical outcome when act as an adjuvant to Clomiphene citrate in women with clomiphene citrate resistant PCOS?*
To answer this question, a RCT was conducted to evaluate the effect of NAC administration as an adjuvant to Clomiphene citrate. One hundred fifty CC resistant PCOS women undergoing therapy for infertility were assigned randomly to receive either NAC 1.2 gm/day (group I) or placebo (group II) with CC 100 mg/day for 5 days starting at day 3 of the cycle. Ovulation was monitored (number of follicles of ≥ 18 mm, serum E2 concentration, serum progesterone, endometrial thickness) and pregnancy rate was reported. Interestingly, the combination of CC and NAC significantly increased both ovulation rate and pregnancy rate in women with CC resistant PCOS (49.3% vs 1.3 and 21.3% vs 0% respectively) with two cases of miscarriage (12.5%). On performing subgroup analysis in the NAC group, it was found that at insulin level >20 u/mL; 8 pregnancies (one twin) out of 35 (22.8%) while at insulin < 20 u/mL; 8 pregnancies (three multiple pregnancies) out of 40 (20%) were observed (Odds Ratio = 1.14 95% CI = 0.38 to 3.36).

In conclusion, NAC may be a novel adjuvant treatment for PCOS patients. It is a simple, well tolerated and inexpensive agent but more randomised, controlled trials are needed before clinical guidelines can be determined.
Implications for future research

What can we expect from recombinant drugs?
Recombinant gonadotrophins (FSH, hCG, LH) are effective in IVF/ICSI program; however, the results of this thesis question whether they should replace urinary gonadotrophins. Recombinant gonadotrophins offer future advances in reproductive medicine but the issue of price is a significant one internationally that needs to be addressed by the pharmaceutical companies as they gradually recover their expenses in R & D of recombinant hormones. The current thesis showed that human menopausal gonadotrophins is more cost effective in ovulation induction, hence, it would be sensible to direct research efforts towards discovery-based research in the form of oral or long acting gonadotrophins even if initial results are not encouraging (Balen et al, 2004).

What is the place of exogenous luteinizing hormone (LH) supplementation in different protocols?
The need for LH in ovulation induction was the issue of debate for a long time with conflicting results and it is now even believed by some that human chorionic gonadotrophin (HCG) can play an important positive role if administered in the follicular phase in IVF cycles (Filicori et al., 2005). The current thesis showed that some downregulated women (long protocol) would benefit from hMG rather that recombinant FSH but there is lack of evidence regarding the need of LH in GnRH agonist microdose protocol, short protocol or ultrashort protocol. The same question can be applied for women undergoing IVF/ICSI cycles using GnRH antagonist.

It would also be of interest to answer the question: **Which gonadotrophin is more suitable for poor responders and which is more suitable for older women!!**
Little evidence is available in the literature but it seems that outcome differs by age and ovarian function between the urinary and recombinant gonadotrophins, with younger patients benefiting from the FSH/LH combination offered by urinary products, while older women and young women with ovarian resistance apparently benefiting from pure FSH stimulation. On the other hand, a post hoc analysis (Marrs et al., 2004) suggested supplemental LH is potentially beneficial in older women and this needs to be confirmed in prospective trials.
If both have similar effectiveness, then research efforts should be directed to **How to prevent ovarian hyperstimulation syndrome.** OHSS is an iatrogenic condition caused by administration of gonadotrophins and it is unclear which drug to use in women of high risk to develop OHSS (polycystic ovary). There is no published study directly comparing rFSH with HMG in ovulation induction in polycystic ovary women.

It was demonstrated from the current thesis, the necessity of continuing to use HCG to trigger ovulation but these results were driven after GnRH agonist desensitization, and with a high dose recombinant LH, thus more efforts should be devoted to undertake the necessary trials in order to **tailor the correct use of LH** especially it was evident to reduce the incidence of OHSS.

The production of GnRH antagonists allowed avoiding many of the agonist side effects but the lower pregnancy rate observed with the antagonist should devote research to find out **whether or not GnRH antagonist has direct effect on the ovary and the endometrium** !! and If GnRH antagonist has direct effect on the ovary, **could it be used in women down regulated with GnRH agonist and with high risk of OHSS** !!!! The reduction in E2 level after administration of GnRH antagonist would allow retrieval of oocytes without coasting . It would be interesting to study this in a randomized controlled trial

Clomiphene citrate is still the gold standard for treatment of polycystic ovary patient but resistance to CC occur in 20% of cases. During the last years, metformin has become a co-treatment to enhance successful ovulation. N-Acetyl-cystein appears to be promising agent and other randomized controlled trials are needed to confirm its beneficial effect as a co-treatment to clomiphene citrate.