Pituitary down-regulation in IVF/ICSI: consequences for treatment regimens
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Chapter 9

Summary
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Chapter 1
covers the history of IVF in humans from the very first beginning in 1944, via the birth of Louise Brown, the first IVF baby in 1978, to the latest developments to date. Four key elements in IVF are recognized which have puzzled researchers in the past and are still topics of research in reproductive medicine today. They represent the quintessence of the IVF cycle and are addressed in this thesis. Firstly, pituitary downregulation for preventing premature LH surges (chapters 2 and 3), secondly, controlled ovarian hyperstimulation (chapter 4), thirdly, timing of the oocyte collection (chapter 5) and fourthly, luteal phase support (chapters 6 and 7).

Chapter 2
focuses on optimization of pituitary downregulation. Two forms of pituitary downregulation are available; an indirect form with GnRH agonists, and a direct form with GnRH antagonists. Unlike the indirect form of pituitary suppression by GnRH agonists, which requires ≥2 weeks of administration, the GnRH antagonists cause an immediate and direct suppression by competitive binding with the GnRH receptors. Theoretically, GnRH antagonists can thus be administered just before the expected LH surge for only a few days. Previous studies that had assessed the efficacy of GnRH antagonists in preventing LH surges showed promising results. However, a Cochrane meta-analysis pooling the pregnancy results of 2973 women showed a 4.3% lower ongoing pregnancy rate in GnRH antagonists treated group compared to GnRH agonists group Odds Ratio (M-H, Fixed, 95% CI) 0.82 [0.68, 0.97]. It was suggested that the way the GnRH antagonists were applied was the cause of this lower pregnancy rate. GnRH antagonists were administered in a set manner i.e always starting after 5 or 6 days of ovarian stimulation with recombinant FSH and not taking the growth of the individual follicle into account. In this chapter we explored an alternative protocol, comparing a regimen in which the GnRH antagonist was started when the dominant follicle reaches ≥15 mm, entailing variable starting moments during the stimulation phase (flexible regimen) with the standard protocol (fixed regimen).

Between April 2001 and October 2002, two hundred and five women of seven fertility clinics in The Netherlands were randomized in this randomized clinical trial. 102 to the flexible regimen and 103 to the fixed regimen. In the flexible regimen, 25 women started the GnRH antagonist administration on stimulation day 5 (one on day 4), 20 on stimulation day 6, 33 on day 7, 8
patients on day 8 and 13 on day 9. In the fixed regimen, all women, except one, started on stimulation day 6. No differences were found in the mean number of retrieved oocytes (primary endpoint), fertilization rate, quality or total number of obtained, transferred, and frozen embryos (secondary endpoints). Although not statistically significant, fewer clinical and ongoing pregnancies were found in the flexible regimen as compared to the fixed regimen; 22.7 versus 33.0% for clinical pregnancy (RR 0.69, 95% CI 0.44–1.08) and 21.8 versus 31.1% for ongoing pregnancy (RR 0.70, 95% CI 0.44–1.12) respectively.

We pooled the ongoing pregnancy results of our study and three similar previous studies. A total of 224 women in the flexible regimen were analysed versus 218 women in the fixed regimen. We found a Peto odds ratio of 0.68 (95% CI 0.45–1.03) against the flexible regimen for ongoing pregnancy rate. Therefore we concluded that, in case a GnRH antagonist is applied in COS, the fixed regimen is the best choice.

Chapter 3
assesses patients’ preference for a GnRH agonist or antagonist by means of a discrete choice experiment (DCE) which. Because of the lower chances of OHSS, shorter treatment duration and less side effects when using a GnRH antagonist, it is generally assumed that most women would express a preference for the antagonist above the agonist, but data substantiating this hypothesis are lacking.

The study population comprised couples scheduled for their first IVF or ICSI cycle, who attended an IVF information gathering. These sessions were held at the fertility unit of the Maxima Medical Centre Veldhoven (MMC) and the Amsterdam Medical Center (AMC), between February 2008 and October 2008. By showing slides, the working mechanisms and the (dis-)advantages, the so-called attributes of GnRH agonists (labeled as medication A) and GnRH antagonists (labeled as medication B) were explained.

Subsequently, the couples were asked to fill out two questionnaires, a general preference questionnaire and a discrete choice experiment questionnaire. The chosen attributes were duration of administration (short for medication A and long for drug B), the risk of OHSS (2.6% for drug A and 4.2% for drug B), the occurrence of side effects such as headaches, hot flushes, insomnia (only for medication B) or the fact that a once missed dose or not would have consequences for the IVF treatment, and pregnancy rates (increasing from 20% to 25% with increments of 0.5%). Using Orthoplan (SPSS 6.1) random scenarios
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were generated from the selected attributes and the participants were asked their preference.

When equal pregnancy rates were assumed in both medication A and B, 176 of the 188 participants (95%) preferred the GnRH antagonist and nine participants (5%) preferred GnRH agonist. When a 5% increase in pregnancy rate the agonist group was assumed, 155 participants (82%) preferred the GnRH agonist and 33 participants (18%) kept their preference for the antagonist. At a mean trade off point of 2% (95% CI 1.8 to 2.2) 143 participants (82%) switched their preference from antagonists to antagonist. The chosen attributes were; levels of pregnancy rate during one cycle of IVF varied from 20% to 23% by incremental steps of 0.5%, the duration of treatment, long or short, the risk of OHSS 2.6% or 4.2% (Al Inany et al, 2006), adverse effects were present or not present and accidentally forgetting a single dose compromised the treatment or not.

The DCE showed that the most important attribute in the decision making of the participants was pregnancy rate, followed by an increase in OHSS risk. Contrary to our expectation, duration of use of medication was the least important attribute in the decision making of the participants. In summary, this preference and DCE study showed that patients’ preferences for GnRH antagonist or GnRH agonist are primarily influenced by pregnancy chances and least influenced by duration of administration. In a scenario of at least 2% higher pregnancy rates following GnRH agonist – which seems realistic in view of the data on effectiveness- most IVF patients preferred a GNRH agonist despite other advantages of antagonists above agonists.

Chapter 4

is a Cochrane meta-analysis on the effectiveness and safety of a combination of recombinant LH and recombinant FSH with recombinant FSH alone in COH protocols in IVF or ICSI followed by embryo transfer (ET). During IVF/ICSI cycles, GnRH agonists are used for the prevention of premature luteinizing hormone (LH) surges combined with recombinant follicle stimulating hormone (rFSH) for controlled ovarian hyperstimulation (COH). The GnRH agonists deprive the growing follicles of LH, since they block the output of LH. Since rFSH is completely devoid of LH, the question has arisen whether the lack of LH on growing follicles would have a negative impact, especially since a meta-analysis comparing urinary hMG (which contains LH activity) versus rFSH (completely devoid of LH activity) for COH following an long agonist down-
regulation protocol in IVF or ICSI treatment showed a significant increase in live birth rate (relative risk, RR = 1.18, 95% CI: 1.02–1.38, P = 0.03). Several trials have therefore studied the effect of adding rLH to rFSH for COH on pregnancy rates. Data of fourteen trials involving 2612 women were pooled. Eleven trials involving 2396 women used a GnRH agonist and three trials involving 216 women used a GnRH antagonist. There was no evidence of a statistical difference in ongoing pregnancy rates when rLH was added. However, the pooled pregnancy estimates of trials including only poor responders, showed a significant increase in pregnancy rates, in favour of co-administrating rLH (three trials: OR 1.85, 95% CI 1.10 to 3.11).

Chapter 5 addresses the timing of an oocyte collection in IVF or ICSI in a randomized clinical trial. Although to date IVF is an effective mainstream procedure, planning an oocyte collection is still covered in mystery. It is widely agreed that follicles need to reach at least 17 mm in diameter before administrating hCG for follicular maturation for oocyte collection. This view, however dates back to a period in which the GnRH agonists were not yet introduced and a lot of cycles had to be cancelled because of detrimental premature LH surges. In the late ‘80 when the downregulation of the pituitary gland became fashionable, the concept of administering hCG at a follicle-diameter of 17 mm in downregulated IVF cycles was challenged. In 5 randomized studies the effect of delaying oocyte collection for 1 or 2 days after the leading follicle had reached a diameter of 18 mm or three follicles had reached a diameter of 17 mm, was assessed. The results however were contradictory and the design of the study was not robust. All studies used the criterion that the leading follicle had to reach at least a diameter of 17 or 18 mm. This may have lead to different sizes of follicle diameters, since “at least” implies that larger follicles than 17 or 18 mm. were also allowed. In view of these limitations, we aimed to seek more evidence on the impact of delaying oocyte collection on pregnancy rates. We compared the effect of planning oocyte collection when the leading follicle had a diameter of 18 mm versus planning oocyte collection when the leading follicle had a diameter of 22 mm on ongoing pregnancy rates.

Four fertility clinics in the Netherlands participated in this randomized clinical trial between April 2006 and April 2008. Ninety-seven patients were allocated to the 22 mm group and ninety-three to the 18 mm group. In the 22 mm group more women reached an ongoing pregnancy (primary endpoint)
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(37 of 97 women, 38%) compared to the 18 mm group (22 of 93 women, 24%) (RR 1.6, 95% CI: 1.03 to 2.5). As expected, the duration of controlled ovarian hyperstimulation was significantly higher in the 22 mm group compared to the 18 mm group and also a significantly higher amount of rFSH was used in the 22 mm group. In addition, in the 22 mm group the longer duration of ovarian stimulation yielded a significantly higher mean serum estradiol at the day of hCG administration, to significantly more follicles, significantly more oocytes and significantly more embryos and to significantly more top quality embryos, but there were no differences in the number of embryos transferred. The better pregnancy rates in the 22 mm group may have been the result of the sheer increase in number of oocytes and subsequent significant increase in the number of metaphase II oocytes leading to significantly more top quality embryos. We saw a beneficial effect if the oocyte collection was planned when the dominant follicle reached a diameter of 22 mm compared to a diameter of 18 mm. More and better quality oocytes and embryos were retrieved.

Chapter 6

describes a single center randomized clinical trial comparing two forms of luteal support in GnRH agonist downregulated IVF cycles. The advantages of gonadotrophin hormone-releasing hormone (GnRH) agonists have been well documented; the cancellation rate is decreased through the prevention of premature luteinizing hormone (LH) surges, follicular recruitment is improved, and the ovarian response to hyperstimulation is better synchronized, thus facilitating the scheduling of oocyte retrieval. This pituitary suppression results in an impaired gonadotrophin production later on, and the output of LH remains blocked for at least 10 days after cessation of GnRHa administration. As gonadotrophins are necessary to maintain progesterone output by the corpus luteum, luteal support is mandatory.

Administration of progesterone is a direct form of luteal support, i.e. the end-product of the corpus luteum is substituted. The advantage of this direct form of luteal support is its independence from corpus luteum function. This is important, because the amount of granulosa cells may be reduced by the oocyte retrieval. Administration of HCG is an indirect form of luteal support, i.e. the corpus luteum is stimulated. It generates an increase in both oestradiol and progesterone concentrations, thus rescuing the failing corpus luteum. As HCG stimulates all corpus luteum functions, we hypothesized that other, still unknown, products of importance for the maturation and sustaining of
the endometrium would be stimulated as well. These products might have a beneficial effect on the hormonal milieu and, as a consequence, might lead to higher pregnancy rates. We therefore performed a randomized clinical trial, comparing GnRHa/HMG-induced IVF treatment cycles supported with vaginal progesterone only, with an experimental group who received HCG i.m. in addition to the standard vaginal progesterone regime.

From September 1991 until February 1992, all consecutive patients scheduled for IVF treatment in our infertility centre of the Academic Medical Center, Amsterdam, The Netherlands, were asked to participate in this study. 176 women were included. The P/HCG group consisted of 87 cycles, and the P group of 89 cycles.

There were 9 ongoing pregnancies (10%) in the P/HCG group and 13 (15%) in the P group (OR 0.68, 99% CI 0.20-2.2). In the P/HCG group, eight patients had mild OHSS, two patients had moderate OHSS and one patient had severe OHSS. In these 11 cases, HCG was withheld after the second injection to avoid aggravating the OHSS. In the P group, three cases of mild OHSS were seen.

Significantly higher oestradiol and progesterone concentrations were found in the P/HCG group. As we expected, no mid-luteal decline in the concentrations of sex steroids was seen in the P/HCG group. To show the potential beneficial effect of high luteal sex steroids on pregnancy rates, we divided the cycles of both groups into those which resulted in a pregnancy and those which did not. We found that women with oestradiol concentrations >45 mM 9 days after oocyte collection had an odds ratio of becoming pregnant of 0.06 (99% CI 0.004-0.93) compared to women with an oestradiol concentration <4.5 mM. In conclusion, vaginal progesterone alone provides sufficient luteal support, despite a mid-luteal drop in sex steroids.

**Chapter 7**
reports on a single center randomized clinical trial regarding the time of onset of administration of luteal support.

The use of GnRH agonists for preventing premature LH surges in controlled ovarian hyperstimulation in IVF has greatly improved the success rate. This pituitary suppression blocks the output of LH for at least 10 days after cessation of the agonist, causing a luteal phase deficiency. Exogenous supplementation of progesterone or HCG, i.e. luteal phase support, proved to be mandatory as shown in several meta-analyses. The time of onset of...
administration of luteal phase support varied from the day before oocyte collection to 4 days after embryo transfer. Only three randomized studies have been performed to assess the impact of the moment of starting luteal phase support on pregnancy rates in GnRH agonist down-regulated IVF cycles. The chosen time points of the start of luteal support assessed in these randomized studies did not cover the complete implantation window, which includes the day of HCG administration for oocyte maturation until the day of embryo transfer.

The aim of this study was therefore to assess the impact of the onset of luteal phase support on ongoing pregnancy rate. We compared administration of vaginal progesterone starting before oocyte collection i.e. at the time of HCG administration for final oocyte maturation (HCG group), at oocyte collection (OR group) and at embryo transfer (ET group) in a randomized clinical trial, in infertile patients undergoing IVF in GnRH agonist down-regulated cycles. All consecutive patients between January 1993 and December 1997 who were scheduled for their first IVF treatment in the Center of Reproductive Medicine at the Academic Medical Center in Amsterdam, the Netherlands, were asked to participate in this study. 385 consecutive patients were included of which 30 left the study prematurely. 119 were allocated to the HCG group, 118 to the OC group and 118 to the ET group. We found no differences in mean number of stimulation days, mean number or quality of retrieved oocytes, mean number or quality of transferred embryos or the total number of frozen embryos. A significantly higher mean serum progesterone level was seen in the HCG group \( (P < 0.001) \) on the day of oocyte collection, no differences were seen in mean serum progesterone levels during the remainder of the luteal phase. No significant differences were found between the three groups in ongoing pregnancies or live birth.

**Chapter 8**

This chapter describes how medical practice has changed from “authority-based” to “evidence based”. A plea is made for large-scale structured cooperation in terms of new randomized trials, reducing chances of inclusions sufficient, good quality and faster implementation of the findings will accelerate. In addition, some concluding remarks concerning the investigations of this thesis and recommendations are made for future research.