Pituitary down-regulation in IVF/ICSI: consequences for treatment regimens
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Chapter 8

General discussion
and implications for future research

“Therapeutics”, said Professor Pickering in his Presidential Address to the Section of Experimental Medicine and Therapeutics of the Royal Society of Medicine, “is the branch of medicine that, by its very nature, should be experimental. For if we take a patient afflicted with a malady, and we alter his conditions of life, either by dieting him, or by putting him to bed, or by administering to him a drug, or by performing on him an operation, we are performing an experiment. And if we are scientifically minded we should record the results. Before concluding that the change for better or for worse in the patient is due to the specific treatment employed, we must ascertain whether the result can be repeated a significant number of times in similar patients, whether the result was merely due to the natural history of the disease or in other words to the lapse of time, or whether it was due to some other factor which was necessarily associated with the therapeutic measure in question. And if, as a result of these procedures, we learn that the therapeutic measure employed produces a significant, though not very pronounced, improvement, we would experiment with the method, altering dosage or other detail to see if it can be improved. This would seem the procedure to be expected of men with six years of scientific training behind them. But it has not been followed. Had it been done we should have gained a fairly precise knowledge of the place of individual methods of therapy in disease, and our efficiency as doctors would have been enormously enhanced.”

(Professor Sir George Pickering, 1949).

From: A. Bradford Hill Ph.D.D.Sc. The clinical trial
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The first randomized trial is credited to Sir Austin Bradford Hill (8 July 1897 - 18 April 1991) epidemiologist and statistician. He became Professor of Medical Statistics in 1947. In 1948 he, as a member of The Tuberculosis Trials Committee at the Medical Research Council, studied the use of streptomycin in treating tuberculosis. This landmark study is generally accepted as the first randomized clinical trial and has been referred to as the “1948 watershed”\(^2\). Hill designed, based on random sampling numbers, a reference series by which it was determined whether a patient would be treated by streptomycin and bed-rest (S case) or by bed-rest alone (C case). The details of the series were unknown to any of the investigators and were contained in a set of sealed envelopes, each bearing on the outside only the name of the hospital and a number\(^3\).

In those days, doctors were trained in an authority based fashion and questioning the efficacy of an established treatment was not done. The relationship with the patient was based on the assumption that “the doctor knows best”. No questions were asked, not by the patient, and not by the doctor. Many clinicians found randomization an unnatural interference with their everyday practice and experienced ethical difficulties\(^4\). Changing the creed “the doctor knows best” into “the doctor doesn’t know what’s best for me” was a traumatic experience for both patients and doctors\(^4\). Only in the late 20th century RCT’s gradually became recognized as the standard method for “rational therapeutics” in medicine\(^5\) and their quantity increased logarithmic ever since.

Performing clinical research in everyday medical practice is not easy. In the often busy clinical setting it has proven to be difficult for doctors to include patients in studies. This was cleverly illustrated in 1979 by Lasagna. His commented on a trial, where out of 8,027 possible candidates only 100 people participated, led to what is now popularly called “Lasagna’s law” meaning that in any trial, the incidence of the disease studied will be reduced to 10% of the original estimate\(^5a\). We too experienced the difficulty of performing clinical research in everyday medical practice. Nevertheless, in the setting as described, we performed several randomized studies and addressed clinical problems in IVF, targeting treatment protocols which showed large practice variation of which the outcomes are still relevant to date.

In 1992 we studied the function of the luteal phase, which was a subject of interest from the very outset of IVF. The IVF pioneer and Nobel Prize winner Edwards experimented with ovarian hyperstimulation combined with ovulation triggering and he reported on 14 implantation failures\(^6\). Edwards thought that the ovarian stimulation itself was the cause of this failure.
his eyes, the abnormal steroid production deranged the luteal phase by interfering with the implantation window. Optimal synchronization between the embryo arrival in the uterus and an optimal prepared endometrium would be essential. In vivo, a small, but distinct, increase of endogenous progesterone is seen concurrently with the LH surge. It takes 36–48 hours for progesterone to transform the proliferative endometrium into secretory-phase endometrium. The in vivo fertilized embryo usually arrives at the uterine cavity 72–96 h after ovulation, leaving sufficient time for the completion of this transformation of the endometrium. Compared to in vivo fertilized embryos, the in vitro fertilized embryos arrive relatively earlier in the uterine cavity, i.e. 72 h after oocyte collection. Starting luteal phase support early to achieve a more advanced endometrium seems, therefore, preferable. However, retrospective cohort studies have associated premature progesterone elevation with lower pregnancy and implantation rates. To study more closely the impact of this early progesterone rise, we started a randomized clinical trial in which exogenous progesterone was started at the day of ovulation triggering and compared with starting at the day of oocyte collection or the day of embryo transfer. We could not demonstrate an increase nor decrease in pregnancy rate as a result of the early exogenous progesterone rise. Our study was limited to exogenous progesterone and was therefore not able to settle the issue of early endogenous progesterone rise which is even today still a topic of debate, especially in high responder women. These women produce much larger numbers of growing follicles and therefore secrete much more pre-ovulatory progesterone which exceeds the natural rise extensively with a deleterious effect. Back in 1992 the poor pregnancy results of cryo-preserved and thawed embryos made it impossible to carry out a randomized clinical trial assessing the impact of endogenous rise of serum progesterone, because the only option, in case of a premature progesterone rise, was to cancel the IVF cycle and hope for better luck next time. Since the pregnancy results of cryo-preserved and thawed embryos are much better now, we now have the opportunity to randomize between cryopreserving embryos or transferring fresh embryo's in a cycle with elevated pre-ovulatory serum progesterone. Such a study may give us a better understanding of the clinical significance of elevated pre-ovulatory serum progesterone.

The next intriguing topic we have addressed is the effect of the duration of exposure of the endometrium to endogenous serum estradiol (E₂) in the ovarian hyperstimulation phase. In comparing two different starting moments
of GnRH antagonists; i.e. starting on stimulation day 6 or starting at the day the dominant follicle exceeded 15 mm (Chapter 2) we found that a subgroup of women who received the GnRH antagonist from stimulation day 8 onward, had lower pregnancy rates compared to women with an earlier start of stimulation. We noticed that these women had higher E₂ levels. In accordance with a similar study\(^\text{12}\) with similar findings, we hypothesized that the exposure to the high E₂ is the cause of the negative effect on pregnancy rate, via the mechanism of prolonging the endometrium to E₂/LH exposure. Hence, we started a randomized controlled trial comparing early planning of the oocyte collection (shorter exposure to E₂) to late planning of oocyte collection (longer exposure to E₂) (Chapter 5). In contrast to our earlier findings, we found no deleterious effect on ongoing pregnancy rate and live birth rate when oocyte collection was planned earlier compared to delayed oocyte collection, which may safely rule out the impact of prolonged E₂ exposure on the endometrium. In view of the current trend to turn to mild stimulation regimens, it is noteworthy to find that delaying the timing of oocyte collection instead of using higher dosages of gonadotrophins, may also lead to a greater yield in oocytes. This has never been considered as an important factor in studies of mild stimulation\(^\text{13}\). To obtain better results in IVF, the real paradigm might not be the stimulation regimens (mild or conventional) themselves, but delaying oocyte collection to harvest more oocytes from the growing cohort, which then in turn lead to more high-quality embryos.

Mild stimulation regimens require the use of a GnRH antagonist, the third topic we studied. In comparison with the GnRH agonist, GnRH antagonists result in less ovarian hyperstimulation syndrome (OHSS), a shorter duration of treatment time and a lower amount of gonadotropine use\(^\text{14,15,16}\). Administration of GnRH antagonists in high dosages, however, can induce an acute arrest in follicular growth and can even cause atresia, caused by a sudden LH withdrawal\(^\text{17,18,19}\). Subsequent clinical studies on GnRH antagonists showed that endogenous LH in normogonadotropic women can be suppressed to such an extent, that follicle growth and pregnancy rates were adversely affected\(^\text{20}\). This effect of the GnRH antagonist depends not only on the dose and duration of the GnRH antagonist administration, but more importantly also on the moment of administration in the follicular phase. In the early follicular phase growing follicles are sensitive to FSH, whereas in the late follicular phase growing follicles become increasingly sensitive to, and ultimately dependent on, the presence of luteinizing hormone (LH). Applying a GnRH antagonist in
the mid-follicular phase, the ensuing sudden LH withdrawal causes the follicles to show a significant decrease in $E_2$ levels, which is a sign of atresia. We feel that this may be the cause of the significant lower ongoing pregnancy rates following GnRH antagonists compared to GnRH agonists. (OR 0.82 (95% CI 0.68 to 0.97) in a Cochrane meta-analysis, since in the GnRH agonist protocols no such withdrawal can occur. A currently performed meta-analysis using individual patient data may settle this debate between the GnRH agonist and antagonist.

Pituitary suppression with a GnRH agonist also results in an impaired gonadotrophin (FSH and LH) production. Since the output of gonadotropins remains blocked for at least 10 days after cessation of GnRH agonist administration, the luteal phase is also affected. As gonadotrophins are necessary to maintain progesterone output by the corpus luteum, exogenous luteal support is mandatory. Without luteal support, a mid-luteal decline in sex steroids is seen, which adversely affects implantation. We performed a randomized trial comparing HCG as a indirect form of luteal support to stimulation of the mid-luteal sex steroids, to progesterone as a direct form of suppletion of the sex steroid itself. We found that the indirect form of luteal support had a no beneficial effect on the pregnancy rate and lead to an increase of OHSS. (chapter 7) Follicular recruitment seemed unaffected by the lack of LH when using a GnRH agonist and adequate follicle growth may be achieved, even with pure FSH preparations. The presumed redundancy of LH for ovarian hyperstimulation and the wish for more purified products drove the pharmaceutical industry to the conversion from human menopausal gonadotrophins (hMG), which contains both FSH and LH, to recombinant FSH (rFSH) which is completely devoid of LH. rFSH became the treatment of first choice in most European countries. However, as described in the classic “two cell - two gonadotrophin” theory, LH is needed to provide the granulosa cells with androgen precursors for estradiol biosynthesis by FSH and LH is needed for the resumption of meiosis and for progesterone production after ovulation to sustain the endometrium. The beneficial effects of LH-like activity was shown in a meta-analysis comparing hMG to rFSH which is completely devoid of LH activity. In normogonadotropic GnRH agonist down regulated patients hMG leads to significant higher clinical pregnancy-rates than rFSH alone (risk ratio 1.18 (95% confidence interval 1.02 to 1.36). The role of LH in ovarian stimulation thus became again a matter of debate. Meanwhile, recombinant LH (rLH) entered the market, which can serve, in combination with rFSH,
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alternative to hMG\textsuperscript{30}. Hence, we addressed the question whether or not there is need for rLH co-administration to rFSH for controlled ovarian hyperstimulation in IVFor ICSI patients down regulated with a GnRH agonist or antagonist in a systematic review (Chapter 4) The pooled data on ongoing pregnancy showed no difference. However the pooled pregnancy estimate of trial of poor responder women showed a significant beneficial effect in favour of co-administrating rLH (three trials: OR 1.85, 95% CI 1.10 to 3.11). We hypothesize that this increase in ongoing pregnancy rates in this population is an effect of rLH on oocyte and embryo quality. Exogenous LH has been suggested to have an intrinsic effect embryo competence\textsuperscript{31}. We are now assessing the embryo quality of poor responder women with or without co-treatment with recLH in a randomized controlled trial.

To date there still is a large center-to-center variation in the choice of treatment regimens for IVF or ICSI. For example, the preference of clinicians in treating women with GnRH agonists or GnRH antagonists. Although there was no obvious clinical need for an alternative product for GnRH agonist downregulation, the GnRH antagonist, unsolicited, entered the market. The development and marketing of this product was in fact entirely pharmaceutically driven. Together with the introduction of the GnRH antagonist, the slogan “patient friendly IVF” or “friendly IVF” became fashionable. Patient friendly IVF was used as equivalent to “short duration of drug use”. Clinicians do not realize that they are greatly influenced by the representatives of pharmaceutical industries. It is known that representatives intensely study different doctors’ personalities and learn to get along with them all\textsuperscript{32}. Since some doctors prefer to be addressed by their representative as a friend and others prefer a business like approach, the representatives learn to switch their behavior accordingly. The term “patient friendly” appealed to clinicians in their wish to be(come) a patient friendly doctor. In contrast, we feel that the term “patient friendly” should be considered a commercially based catchphrase, without any scientific underpinning whatsoever. We performed the first discriminatory choice experience study comparing patients preference for GnRH agonists or antagonists and found that the most important factor is pregnancy outcome and shorter duration of drug use the least important. We now know that patient friendly IVF is the equivalent of effective IVF.
Chapter 8

General discussion

“If bureaucrats were in charge, physicians might have to prescribe the newest hypertension drugs as a first-line therapy, do MRIs to diagnose back pain and give regular Pap tests to women who have had total hysterectomies. Oh, wait—they do. All these medical practices are common, despite rigorous studies showing how useless or wrongheaded they are. Definitive studies over many years have shown that old-line diuretics are safer and equally effective for high blood pressure compared with newer drugs, for instance, and that MRIs for back pain lead to unnecessary surgery. And those Pap tests? Total hysterectomy removes the uterus and cervix. A Pap test screens for cervical cancer. No cervix, no cancer. Yet a 2004 study found that some 10 million women lacking a cervix were still getting Pap tests.

- Newsweek 2004

Time has come to halt this kind of quackery. Large scale collaboration of clinicians in evaluation research is the only effective way forward to achieve evidence, adherence to medical practice and improvement in guidelines.

In 2003, “The network of Dutch consortium studies” was instituted. Medical centres, grouped in clusters, are now collaborating. In this way, substantial funding can be accomplished, part of which is earmarked for research nurses who assist busy clinicians with the selection and counselling of patients. This, of course, has lead to higher inclusion rates. It is expected that the evidence generated in cooperative networks, will be easier accepted and implemented. This will eventually lead to evidence based medicine and a higher quality of care. For the near future, the consortium also has to address the role of the pharmaceutical companies and consider contracted collaboration. It is also very important to channel the relationship of clinicians with the pharmaceutical companies.

Becoming pregnant is not an efficient process, and is only successful about 10–15% of the time. The small contribution of changing ovarian hyperstimulation protocols to gain more success is therefore very hard to prove. So it is essential to gain evidence from large randomized trials, and to achieve this goal, collaboration of clinicians is imperative. Through these large trials it becomes possible to identify several subgroups of women with different patient and cycle characteristics which may contribute to success or failure. The aim of the future is to develop prediction models based on treatment selection markers that predict pregnancy chances for the first and all subsequent IVF treatment cycles, if any, on an evidence and personalized basis.
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References

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33. Sharon Begly, journalist of Newsweek