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Gonadotropin Therapy: A 20th Century Relic

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Abstract

Gonadotropin therapy has been a cornerstone of infertility therapy for half a century. From the very beginning, its use has been associated with a high rate of multiple births, particularly high order multiples, and ovarian hyperstimulation syndrome. Initially, success rates seemed acceptable when used for superovulation (SO)/IUI therapy. However, as data from RCTs have emerged, reported outcomes suggest that we question the use of injectible gonadotropins. This manuscript examines the studies that have challenged gonadotropin use for SO/IUI and other research that supports reduced doses of gonadotropins for IVF. We examine the challenges for its continued use for SO/IUI and for moving to lower doses worldwide for IVF. We propose a future that views gonadotropins as a relic of the twentieth century.

Introduction

Infertility therapy was in its infancy during the first half of the twentieth century. Few couples were willing to speak openly about their inability to conceive, much less seek medical help. The only treatment available was tubal surgery and by 1937, Greenhill published an article that reported low success rates after the repair of tubal obstruction (1). He concluded that, given the low probability of success, the risks of the surgery likely did not justify the procedure. While surgical approaches to tubal disease had sporadic proponents in subsequent years, overall success rates remained low.

The first area for advancement of infertility therapy was the treatment of anovulation. In 1935, Stein and Leventhal published their observations on the study of 7 women who had presented with amenorrhea and a phenotype that also included hirsutism and enlarged ovaries diagnosed by pneumoventerography (2). These patients all had characteristic polycystic ovaries. They performed laparotomy and large ovarian wedge resections of the ovarian cortex to remove the pathologic cysts with the hypothesis that such treatment would reverse the disorder. All of these women began to ovulate and menstruate following the surgery and one had become pregnant twice as of the publication. The positive effects of ovarian wedge resections were usually limited in duration and pregnancy rates were overall disappointing. For some women, the development of significant adhesions from this surgery rendered them sterile.

In 1960, one year before the initial reported studies of clomiphene citrate (3) use to induce ovulation, Lunenfeld in Europe first utilized urinary human menopausal gonadotropins for ovulation induction (4). Within several years, Van de Wiele and Turksoy reported their

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experience in the US (5). At that time, knowledge about follicular recruitment and tools needed to guide therapy were limited. Within the first years of gonadotropin use, two sets of sextuplets were reported worldwide. In addition to high order multiple births, reports of ovarian hyperstimulation syndrome (OHSS) emerged, with related deaths. In those early years of use, the double-edged sword of gonadotropin therapy was evident: for some couples it was their only hope for pregnancy and at the same time it was a potentially dangerous therapy.

For many years, infertility management was dominated by testing, as successful therapies had yet to emerge. Over what was often many months, couples had a myriad of tests performed, many of which have been relegated to history. Effective therapies just didn't exist at that time. The birth of Louise Brown changed the face of infertility management from an evaluation dominated approach to a therapeutic dominated strategy. Couples began to move from an abbreviated evaluation more quickly to treatment.

At the foundation of most treatment paradigms has been the use of injectible gonadotropins. Although many thousands of couples have benefited from superovulation (SO) either in preparation for intrauterine insemination (IUI) or IVF, the use of gonadotropins has added a disproportionate cost to both of these treatments and made them prohibitive for many patients. In addition, a significant number of women and infants have suffered the morbidity and occasional mortality resulting from gonadotropin therapy. The incidence of multiple births has skyrocketed, the high order multiple births peaking in 1999 with 77 quintuplets, 506 quadruplets, and 6742 triplets born in the US. OHSS, although less frequent in recent years because of newly developed prevention and treatment strategies, has plagued the use of gonadotropin therapy as well. Furthermore, studies have emerged that have posed a potential association of ovarian cancer with repeated ovarian overstimulation.

We examine here the outcomes of therapies, which include gonadotropin use, and strategies that have emerged to reduce the incidence of their untoward effects, particularly multiple births and OHSS. In so doing, we propose that the long term goals of infertility research should focus on the elimination of this potentially hazardous medication and the lowering of costs of treatment.

Gonadotropins for Superovulation with IUI

SO with IUI has become the mainstay of treatment for unexplained and mild male factor infertility. Historically, therapy was initiated with clomiphene and IUI, and when not pregnant, couples moved in a step wise fashion through gonadotropin and IUI treatments to IVF. This progression seemed logical as an initial literature-wide review (primarily observational studies) reported success rates of 1.3% to 4% for no treatment, 8.3% for CC/IUI, 17.1% for hMG/IUI, and 20.7% for IVF (6).

The National Collaborative Reproductive Medicine Network designed and performed a randomized clinical trial to determine the effectiveness of gonadotropin/IUI treatments, given the significant risks of twins, high order multiple births, and OHSS (7). Nine hundred and thirty-two couples were randomized to one of four arms: intracervical insemination (ICI), IUI, FSH/ICI, and FSH/IUI. They concluded that "treatment with induction of superovulation and intrauterine insemination is three times as likely to result in pregnancy as is intracervical insemination and twice as likely to result in pregnancy as is treatment with either superovulation and intracervical insemination or intrauterine insemination alone." As such, they felt that FSH/IUI was an effective treatment for couples with unexplained infertility. Further examination of that study, however, revealed that the per cycle pregnancy rate for FSH/IUI was only 9%/cycle, a figure not that different from reported studies for CC/IUI, but with a far higher multiple (especially high order multiple) birth rate than had been

consistently found for CC/IUI. For couples treated with gonadotropins in that study, the 186 pregnancies included three sets of quadruplets, four sets of triplets, and seventeen sets of twins. In addition, six women developed OHSS requiring hospitalization.

The Fast Track and Standard Treatment Trial (FASTT) was designed to evaluate the role of FSH/IUI in a standard treatment paradigm for couples with unexplained infertility, when the female partner was younger than 40 years of age (8). 503 treatment naïve couples were randomized to either a conventional treatment arm or an arm that eliminated FSH/IUI from treatment. All couples in both arms initiated treatment with up to three cycles of CC/IUI. In the conventional arm, couples who were not pregnant then proceeded through a maximum of three cycles of FSH/IUI and, if not pregnant, to a maximum of six cycles of IVF. Couples in the accelerated arm proceeded directly from CC/IUI to IVF. CC/IUI was included in the accelerated arm (rather than have patients initiate treatment with immediate IVF) because a pretrial computer simulation demonstrated that an immediate IVF arm would not be cost-effective. The reason for this unexpected finding was the fact that, although IVF was much more successful than CC/IUI, its high twin pregnancy rate compared to the low twin rate of CC/IUI added sufficient cost to negate any savings.

An analysis of the FASTT data demonstrated that for couples with unexplained infertility (including some with mild male factor), and a female partner under age 40 years, moving directly from CC/IUI to IVF resulted in a 40% shorter time to pregnancy that was statistically significant(8). There was an estimated savings of \$10,000 per delivery when compared to couples whose treatment included FSH/IUI.

Computer simulations using the FASTT data demonstrated that an IVF cycle would have to cost \$17,749 in order for the conventional arm to have a lower cost per delivery. The per cycle pregnancy rates for CC/IUI and FSH/IUI cycles were not that different at 7.6% and 9.8%, respectively. In addition, 8% and 20% of pregnancies from CC/IUI and FSH/IUI, respectively, were multiple gestations. We concluded that the routine use of FSH/IUI did not add value to a contemporary infertility treatment paradigm.

For the reproductively younger women, beginning treatment with a minimum of three CC/IUI cycles using 100 mg for 5 days and timing the IUI with LH kits allows over 20% of couples to become pregnant with a therapy that, except for expectant management, costs less than most other infertility treatments. Few cycles are cancelled with this protocol in which ultrasound monitoring is used only if there is no LH surge by cycle day 16. In addition, this protocol allows the most fertile patients (i.e., those with the highest chance for multiple births) to become pregnant from a treatment with a low chance for multiple births.

Recently there has been an effort to use mild gonadotropin stimulation for SO as an alternative to conventional stimulation. In 2007, Dankert and colleagues from the Netherlands reported the outcome of a randomized clinical trial comparing the use of CC vs. low dose recombinant FSH in a SO/IUI protocol (9). Live birth rates per couple over a maximum of four treatment cycles for CC/IUI and FSH/IUI were 28% and 27%, respectively, and per cycle were 10% for CC/IUI and 8.7% for FSH/IUI. The Dankert study demonstrated that, for their mild protocol, FSH/IUI was no better than CC/IUI. Custers et al. reported data from a large Dutch multicenter cohort study of 15,303 cycles of IUI of which 51% included the use of CC and 19% the use of gonadotropins for SO (10). In a logistic analysis, they determined that controlled ovarian hyperstimulation did not have a significant influence on pregnancy outcome. This was explained by the fact that in the Netherlands patients have mild stimulation for both clomiphene and gonadotropin cycles and “mono or bifollicular cycles are quite common.” In 2006, Steures et al. reported findings from a randomized controlled trial comparing 6 months of COH/IUI to observation (11). The vast

majority of SO was achieved from gonadotropins. Their mild stimulation and cancellation protocols resulted in 14% of cycles being cancelled for > 3 mature follicles and 58% having only 1 mature follicle. Thus, 72% of cycles in the SO group had essentially no treatment effect when using their mild stimulation protocol. Pregnancy rates for mono- and multifollicular cycles were 4% and 5%/ cycle, respectively. They concluded that the pregnancy rate of their mild stimulation SO/IUI protocol was no different than the pregnancy rate of six cycles of observation. The data from the FASTT trial and studies evaluating the efficacy of FSH/IUI around the world do not support its use for the younger population of infertile couples having IUI, either in conventional or mild stimulation protocols. Given the lower costs, decreased health risks, and reasonable success of CC/IUI, this treatment seems to have borne the test of time for use in women younger than 40 years of age.

Data from the FASTT trial did not address the reproductively older woman. In particular, we sought to understand the most effective treatment strategy for women with unexplained infertility who were at the end of their reproductive years and demonstrated a reasonable chance for success. As a progression from the FASTT trial and our desire to understand the most appropriate treatment paradigm for the reproductively mature woman, we designed The Forty and Over Infertility Treatment Trial (FORT-T) (12).

Infertility care for women at or around age 40 years brings special considerations that are very different from the reproductively younger woman. It is well known that there is a limited window of opportunity for the reproductively mature woman to become pregnant. Data from the Hutterites have demonstrated that for women whose cultural pressure is to continue to bear children as long as possible and who don't use contraception, the average age of the last pregnancy is just before the 41st birthday (13). Some data have suggested that half of women attempting pregnancy at age 40 will become pregnant over one year. However, for the 50% who do not conceive, their fertility window may well have passed. Another difference for these reproductively older women has been the general belief that CC/IUI is not appropriate for them. Historically, the belief has held that, given their limited time for becoming pregnant, one should "pull out all stops" and immediately use FSH/IUI, despite the higher dosages required in this older population and thus much higher costs. Evidence in the literature has never supported this belief. On the other hand, adverse events, e.g., OHSS and high order multiple births, from treatment begin to drop.

The FORT-T trial was designed to test the hypothesis that immediate IVF is more effective than a treatment strategy that begins with either CC/IUI or FSH/IUI (12). Couples were randomized to begin treatment in one of three arms: 1) 2 cycles of CC/IUI, 2) 2 cycles of FSH/IUI, or 3) 2 cycles of IVF. If not pregnant and continuing to demonstrate a reasonable chance for success by study criteria, couples proceeded to a maximum of four fresh and two frozen IVF cycles. The preliminary data were presented at the ASRM annual meeting in October 2011 (12). That early analysis suggests that immediate IVF is the most effective strategy for couples with unexplained infertility in women age 38 years and older. If subsequent FORT-T data analysis is consistent with our preliminary findings, the combination of data from FASTT and FORT-T, we believe, will sound the death knell for the routine use of FSH in a standard treatment paradigm prior to IVF therapy.

Gonadotropin Therapy Outside of IVF: What's Left?

If gonadotropin use is eliminated from SO/IUI protocols, there remains the continued practice of giving FSH to PCOS patients who are resistant to clomiphene citrate for routine ovulation induction and HMG to hypogonadotropic hypogonadal patients who won't respond to clomiphene citrate. Seemingly, the patients left prior to IVF will be these

individuals, particularly the PCOS patients, who are at high risk from gonadotropin therapy for the development of hyperstimulation syndrome and high order multiple births. These are exactly the patients who most would prefer not using gonadotropins!! While pulsatile GnRH is ideally the safest treatment for the hypogonadotropic hypogonadal patients, it has not proven to be practical. Truly, new treatments and strategies are needed for them. In Vitro Maturation (IVM) brings the greatest hope of a safe and effective treatment for PCOS patients who ovulate and don't become pregnant or are resistant to routine ovulation induction (14).

Eliminating Gonadotropins in IVF: What are the possibilities?

If gonadotropin elimination from infertility treatment prior to IVF becomes a reality, one might also envision the elimination of gonadotropin therapy from IVF treatments. Reducing the risks, costs, required monitoring, time away from work, and patient discomfort may increase the acceptability of IVF treatment and make it available to far more couples than are currently helped. A number of studies demonstrate that even when insurance covers IVF, it is utilized primarily by the higher socioeconomic population of infertile couples (15).

Natural Cycle IVF

Natural cycle IVF was first utilized because it did not involve gonadotropin therapy and overall costs were much lower. In addition, it was popular in the early years of IVF when IVF success rates were low and cryopreservation of embryos was not possible or efficient. One might consider, thus, that natural cycle IVF warrants a renewed consideration as a therapy for couples with infertility given the numerous laboratory changes and improved IVF success.

A systematic review of the literature on natural cycle IVF studies was conducted in 2002 (16). Twenty studies which included 1,800 natural IVF cycles performed between 1989 and 2001 were summarized. The ongoing pregnancy rate on average was 7.2%/cycle and 15.8%/transfer. There was a high cycle cancellation rate usually because of an untimely LH surge. Cycles were also not completed because of failed retrieval or fertilization. Only 45.5% of cycles resulted in a transfer. In 2009, Verberg and colleagues summarized the literature and reviewed in more detail four randomized clinical trials (RCTs) for which one arm of the trial included natural cycle IVF (17). The pregnancy rates ranged from 0% to 6.1% /cycle for those couples who were followed prospectively. Nargund reported 52 couples with regular menstrual cycles who initiated 181 natural cycles of IVF (18). On average 3.49 cycles were completed per couple and 32% of the couples became pregnant. This suggests that approximately four natural cycles of IVF are equivalent to one cycle of conventional IVF.

Currently the high cancellation rates of natural cycle IVF combined with low success rates negate the cost savings that couples garner from this treatment. Even when GnRH antagonists are used to prevent the LH surge and increase the percentage of couples having transfer, eliminating gonadotropins from IVF does not yet appear to add sufficient benefit to warrant routine implementation.

Clomiphene Instead of Gonadotropins for IVF

The earliest outcomes of clomiphene for SO in IVF protocols were reported by Trounson in 1981 with a live birth rate of 17%/transfer and Marrs in 1983 with a pregnancy rate of 11%/laparoscopic retrieval (19, 20). Numerous additional studies reported similar outcomes. Two RCTs reported ongoing pregnancy rates of 13% and 18%/cycle and 0% and 47% cancellation rates, respectively (21,22). The use of clomiphene alone for SO by itself clearly is not the answer today to lower costs and side effects from IVF treatments.

Modified Clomiphene Protocols that Include FSH for IVF

In 1995, Dhont et al. reported an RCT comparing a protocol of CC followed by 150 IU of HMG to an oral contraceptive long GnRH agonist protocol that included 300 IU of HMG (23). The cancellation and ongoing pregnancy rates were 20.5% / 24.5% and 2.6% / 36.8%, respectively. Several subsequent RCTs added the use of a GnRH antagonist to the clomiphene/gonadotropin protocol and found no differences between the clomiphene/gonadotropin protocol and the conventional protocols (24–26). It is not certain whether the higher cost of the GnRH antagonists outweighed the benefits of lower total gonadotropin dosages in these patients.

Mild IVF Stimulation

There has been a renewed interest in using low dosages of gonadotropins for mild stimulation in IVF protocols. Overall, these milder stimulation protocols include doses of gonadotropins at or lower than 150 IU per day with the desire to achieve eight or less oocytes at retrieval. Studies have shown a number of benefits to these protocols (27–29). Each IVF treatment cycle is shortened from the conventional two menstrual cycles required of a long protocol to one menstrual cycle instead. Couples can complete more cycles of treatment in a given time period with mild stimulation protocols than they can from conventional protocols. The protocols are considered to be patient friendly as they include fewer injections and days of injections and less monitoring (29, 29). There is reduced risk of OHSS, discomfort, and stress, all documented in the literature. In addition, there is accumulating evidence in the literature that lower stimulation protocols result in better quality embryos and a lower percentage of aneuploid embryos when compared to embryos from conventional or high dose gonadotropin stimulation protocols (27, 30, 31). The challenges remain that cancellation rates are higher and per cycle pregnancy rates are lower with fewer embryos frozen from mild stimulation protocols compared to conventional stimulation. If one looks at accumulative cycles over a similar time period, however, the percentage of couples becoming pregnant from the two protocols is similar, albeit with one or more additional IVF cycles required for those couples having low dose protocols.

Despite the benefits of mild IVF stimulation protocols, there remain challenges for instituting these protocols worldwide. Enormous amounts of data have been collected in Europe that support this therapy. Several important differences exist that allow Europeans to more easily adopt such protocols. First, there has been a long cultural history, some of which has been mandated by law, for transferring fewer embryos. Additionally, for some of the mild stimulation IVF studies, when embryos that were frozen in fresh cycles of selective single embryo transfer were transferred back in a thaw cycle, both the fresh and frozen transfers were attributed to the fresh cycle for determining success; a practice that does not exist in the US and is not reflected in our national registries (29,31). It appears that overall Europeans have historically used milder protocols and have historically had fewer frozen embryo cycles. In contrast to European treatment approaches, a number of current US practices further challenge the adoption of mild IVF stimulation protocols. Couples seek the programs with the best success rates as reported in the SART and CDC registries. With the current configuration of these national registries, programs will be reticent to adopt protocols that will potentially place them at a competitive disadvantage with lower pregnancy rates as have been reported for the lower dose protocols. The fact that cumulative pregnancy rates for milder protocols are equivalent over time to conventional pregnancy rates but require one or more additional cycles will not be necessarily convincing to couples in the US, many of whom are paying out of pocket. Additionally, US programs have historically transferred more embryos. Fortunately, there is a trend for transferring fewer embryos and, when appropriate, single embryos, that may help change the culture and

expectations of couples. In addition, couples in the US are accustomed to having high dose protocols and to having more embryos for cryopreservation than their European counterparts. Couples seeking care in the US “shop” for the IVF center that has “the best protocol,” particularly for low responders. “The best protocol” often requires huge doses of gonadotropins despite the paucity of evidence, if any, to suggest that “more” is better for success rates. Recent data are emerging to support the long held adage that “if the oocytes aren’t there we can’t make them and if it takes large gonadotropin doses to get them we probably don’t want them.” In particular, embryo quality has been found to be better for IVF cycles with low stimulation, and embryo biopsy data demonstrate a higher percentage of euploid embryos from milder protocols than from conventional stimulation (30, 31).

In summary, for milder protocols to become popular in the US, there will first need to be a wider acceptance of single embryo transfer. In addition, CDC and SART registries will need to have separate categories for reporting mild stimulation outcomes and it may be advisable to include the first thaw cycle in the success of a selected fresh single embryo transfer. We need to educate our patients about outcomes from high, conventional, and mild stimulation protocols, particularly for those patients with excessive stimulation and others with reduced ovarian reserve for whom data are emerging that do not support the use of either conventional or high dosage protocols (i.e., embryos from milder stimulations for both may be actually better). Moving toward mild stimulation will allow for more patient-friendly IVF that is less time consuming and associated with reduced overall cost, risk, and patient stress. Clinicians and patients, however, will need to become accustomed to having fewer embryos for transfer and cryopreservation and on average lower pregnancy rates but with time a similar portion of couples becoming pregnant over time. While mild stimulation IVF is most intriguing, it is not ready yet for prime time world wide!

Conclusions

When gonadotropin therapy was first given to women in 1960, the only prior successful treatment for anovulatory patients was ovarian wedge resection, a treatment that resulted in a time-limited response and associated adhesion-causing sterility. The hope that gonadotropin therapy would become the Holy Grail was very quickly dashed by the reports of sextuplets. Its use has been plagued with unpredictable multiple births, morbidity of OHSS, and high costs when compared to other most other infertility medications. The FASTT and FORT-T trials have demonstrated that there is really no place for the routine use of gonadotropins in SO / IUI protocols today. Other studies have similarly demonstrated that even when given as mild protocols for SO / IUI, gonadotropin therapy is not helpful; in fact, in such protocols observation performed equally as well. The only current use for gonadotropin therapy before IVF is in anovulatory patients either resistant to clomiphene or for whom clomiphene is not effective (i.e., hypothalamic patients). These patients, especially those with PCOS, have a high risk for multiple births and OHSS. Clearly, new techniques such as In Vitro Maturation of oocytes are needed to provide such patients with a safer more successful outcome. Even when used with IVF, gonadotropins provide a high cost, added stress of treatments, and risks of OHSS. While natural cycle IVF and clomiphene alone for IVF have low ongoing pregnancy rates and high cancellation rates, the emergence of mild stimulation protocols is quite intriguing. Success rates are lower and there are fewer embryos for cryopreservation for mild stimulation IVF cycles than are found from conventional stimulation. However, numerous benefits exist that include shortened protocols, fewer injections, less stress, lower costs, and probably better quality embryos. While these protocols have been popularized in Europe, there exist a number of barriers that make them not ready for prime time worldwide. In the US, our national registries are not designed to separate success rates of mild stimulation cycles from those of conventional protocols; combining success rates from both types of protocols will lower clinic success

rates and make these protocols less acceptable. Couples believe, usually wrongly, that for gonadotropin use in IVF “more is better.” Moving toward mild stimulation with gonadotropins in the US as has become popular in Europe will be the final step towards weaning ourselves from these high cost medications fraught with difficulties for nearly a half century. We need to continue to develop infertility treatments that decrease the cost, time involvement, stress, and dangers and do not limit infertility treatment to couples of higher socioeconomic status. In so doing, we believe gonadotropin therapy will be considered a relic of the twentieth century.

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