Is gonadotropin ovarian stimulation for unexplained infertility any longer warranted?

In December 2015, the Ministry of Health (MOH) of the Province of Ontario passed legislation funding one cycle of IVF lifetime for all women less than the age of 43 years. The funded cycle was accompanied by guidelines that included single ET under the age of 38 years in an attempt to lower the rate of multiple pregnancies in the Province and in the hopes of ultimately offsetting the costs of the program by decreasing the medical and societal costs of preterm birth related to multiple pregnancies. This funding of IVF cycles is laudable and makes sense for improving outcomes of treatment in women with infertility. However, in the same legislation, the Ministry of Health also provided funding for an unlimited number of IUI cycles per couple. If the goal of the Ministry of Health was to reduce the healthcare burden of multiple pregnancies, this latter funding program makes no sense.

Many couples have a definite diagnosis, such as tubal occlusion or severe male factor infertility, that requires IVF. Many other couples are diagnosed with subfertility related to anovulation, endometriosis, or mild male factor infertility. In an estimated 15%–30% of couples attempting pregnancy for more than 1 year, all tests are normal and a diagnosis of unexplained infertility is assigned. For most couples with anovulation, simple oral therapy for ovulation induction is available with a reasonable cumulative pregnancy rate (PR) up to six cycles with timed intercourse or IUI and a relatively low rate of multiple pregnancies, almost always twins (1). However, in women who are ovulatory with endometriosis, mild male factor or unexplained infertility, oral agents used for IUI, such as clomiphene citrate (CC) or letrozole, may result in PRs only slightly higher than simple cycle monitoring and IUI (2). In many of the cases of unexplained infertility, gonadotropin stimulation and IUI may result in a doubling of the pregnancy and live birth rate compared with oral agents but at the expense of a multiple PR of $\geq$30%, including higher order multiples (2). From a public health perspective, hospital expenses for each twin or triplet infant are several times that of a singleton, and lifetime costs to society (healthcare system and the community) could be 100–200 times higher compared with a singleton pregnancy (3). Therefore, avoiding multiple pregnancy with fertility treatment should be a major goal of all clinics.

The question that needs to be addressed is: Does the benefit of gonadotropin stimulation/IUI outweigh the risk? Part of the answer relates to patient selection. In the small proportion of women with polycystic ovary syndrome (PCOS) where oral agents are unsuccessful in inducing ovulation, gonadotropin-controlled ovarian stimulation is used to induce ovulation. Even starting with subthreshold doses of gonadotropins and with low, slow increases, monofollicular ovulation is difficult to achieve and three or more follicles may be induced to ovulate in about 15% of cases (4). In this good prognosis anovulatory group of women, multiple order pregnancies are quite frequent after gonadotropin stimulation with or without IUI.

In couples with unexplained infertility, if we can determine from history that intercourse frequency is adequate and appropriate ovulation timing was used by the couple for 1–2 years, we can presume that between 6 oocytes (at worst) and 24 oocytes (at best) were exposed to sperm and the chance of pregnancy. Preimplantation genetic screening studies suggest that about half of the oocytes are euploid in a woman at age 35 years. At that age then, between 3 and 12 euploid oocytes should have been exposed to fertilization. As a consequence, in a couple who have been diligently trying to conceive and generally having exposure to pregnancy in most months, it is difficult to determine what benefit will be accrued from stimulating two or more oocytes to ovulate with gonadotropins and then adding IUI. It represents more of the same attempt at natural conception that the couple has already done themselves. On the other hand, if the couple has unexplained infertility, but on history it can be determined that timing of intercourse has been inadequate because of travel or work schedules, or inaccurate (e.g., waiting for the temperature increase on a basal body thermometer before having intercourse), it is reasonable to offer a few cycles of oral medications with cycle monitoring and either timed intercourse or IUI to achieve a pregnancy. If patients in this latter group, who may have more of a timing problem than a fertility problem, are given aggressive gonadotropin stimulation/IUI as first-line therapy, it is foreseeable that a multiple pregnancy could be the result.

The classic publication that has often been cited in support of gonadotropin/IUI for unexplained infertility is the 1999 article by Guzick et al. (5). In that study, 932 couples (mean female age, 32 $\pm$ 4 years) were randomized to IUI or intracervical insemination (ICI) with or without gonadotropin stimulation. All couples had unexplained or male factor infertility (no female factor identified) of $>$1 year. The PR per cycle was 2% for ICI alone, 4% per cycle for IUI alone, 5% per cycle for gonadotropins and ICI, and 9% per cycle for gonadotropins and IUI. The cumulative PR for four cycles of treatment was 33% in the gonadotropin/IUI group. There was a 20% spontaneous abortion rate. There appeared to be a positive effect of IUI, although the study group included male factor infertility as well as unexplained infertility. Of note, in the two gonadotropin groups, there was about a 20% multiple PR including 3 quadruplet pregnancies, 4 triplet pregnancies, and 17 twin pregnancies, as well as 6 patients who were hospitalized for ovarian hyperstimulation syndrome (OHSS).

Because the technology for gonadotropin/IUI has not changed, it is likely that the results of the 1999 study would reflect the present results. This suggestion is confirmed by the results of the AMIGOS trial (2) of $>$900 women, also aged 32 $\pm$ 4 years, with unexplained infertility who were randomized to oral medications (CC and letrozole) or to gonadotropins for ovarian stimulation and IUI. Gonadotropin/IUI had a cumulative PR during four cycles of 35.5%, and a

multiple birth rate of 32% including 10 sets of triplets (2). On the other hand, IVF technology has advanced dramatically since 1999. Current IVF PRs in this age group (32 ± 4 years) with a single fresh or vitrified/warmed blastocyst transfer should be in the range of 50%. The cumulative single cycle PR in this age group, considering elective single fresh and frozen transfers, is likely closer to 80%–90%. Therefore, a single IVF cycle in a young patient should result in a success rate about three times higher than the cumulative PR of four gonadotropin/IUI cycles and without the risk of multiple gestations. Granted, the cost of an IVF cycle in Canada is about 10 times higher than that of a gonadotropin/IUI cycle. However, the low success rates with gonadotropin/IUI, the stress of serial cycle monitoring, and the emotional cost of repeated failure to conceive must be considered. Taking into account the added risk of multiple gestations, as the number of embryos produced cannot be controlled with gonadotropin/IUI, the argument of moving directly to IVF in cases of unexplained infertility of >1 year is appealing. Again, patient selection is the key to making this decision as patients with inappropriate timing of intercourse may benefit from a few months of simple cycle monitoring plus or minus oral fertility medications or IUI. In cases of true unexplained infertility, gonadotropin/IUI has a low success rate, as it is simply providing more cycles of natural in vivo insemination. In contrast, IVF has the ability to bypass every potential undiagnosed infertility factor (including tubal, cervical, fertilization, and embryo chromosomal problem) with the exception of an endometrial implantation abnormality.

In summary, it is difficult to make a convincing argument that there is any place for gonadotropin stimulation and IUI in women with unexplained infertility, or in women with PCOS who are resistant to ovulation induction with oral agents. If cycle monitoring with oral agents plus IUI is unsuccessful in couples with subfertility of short duration, moving to IVF and elective single ET is likely the safest, most efficacious therapy. In vitro fertilization with single ET and surplus embryo vitrification may also turn out to be the most economical treatment for completing a family in patients with infertility from an emotional, financial, and societal perspective.

Robert F. Casper, M.D.
Department of Obstetrics and Gynecology, Division of Reproductive Sciences, University of Toronto, Lunenfeld-Tanenbaum Research Institute, Toronto, and TRIO Fertility, Toronto, Ontario, Canada

http://dx.doi.org/10.1016/j.fertnstert.2016.07.1074

You can discuss this article with its authors and with other ASRM members at
https://www.fertstertdialog.com/users/16110-fertility-and-sterility/posts/11016-is-gonadotropin-ovarian-stimulation-for-unexplained-infertility-any-longer-warranted

REFERENCES

1. Legro RS, Brzyski RG, Diamond MP, Coutifaris C, Schlaff WD, Casson P, et al, the NICHD Reproductive Medicine Network. Letrozole versus clomiphene for infertility in the polycystic ovary syndrome. N Engl J Med 2014;371:119–29.
2. Diamond MP, Legro RS, Coutifaris C, Alvero R, Robinson RD, Casson P, et al, the NICHD Reproductive Medicine Network. Letrozole, gonadotropin, or clomiphene for unexplained infertility. N Engl J Med 2015;373:1230–40.
3. Diamond MP, Mitwally M, Casper R, Ager J, Legro R, Brzyski R, et al, the NICHD Reproductive Medicine Network. Estimating rates of multiple gestation pregnancies: sample size calculation from the Assessment of Multiple Intrauterine Gestations from Ovarian Stimulation (AMIGOS) trial. Contemp Clin Trials 2011;32:902–8.
4. Lan VT, Norman RJ, Nhu GH, Tuan PH, Tuong HM. Ovulation induction using low-dose step-up rFSH in Vietnamese women with polycystic ovary syndrome. Reprod Biomed Online 2009;18:516–21.
5. Guzick DS, Carson SA, Coutifaris C, Overstreet JW, Factor-Litvak P, Steinkampf MP, et al, the National Cooperative Reproductive Medicine Network. Efficacy of superovulation and intrauterine insemination in the treatment of infertility. N Engl J Med 1999;340:177–83.