Clinical utility of ovarian-stimulation intrauterine insemination

In this issue, Huang et al. (1) provide their experience treating 8,583 couples with unexplained infertility using what has now become a standard approach using up with 3 cycles of ovarian-stimulation and intrauterine insemination (OS-IUI). They found that IUI live birth rates were significantly higher with stimulated cycles using clomiphene citrate (50–100 mg), letrozole (2.5–5.0 mg), or gonadotropins (75 IU) compared with natural cycles for couples with unexplained or mild male-factor infertility. Couples had to have attempted conception for 1 year, the female partner had to have at least one patent fallopian tube, and the male partner had to have a sperm concentration of 5–20 million/cc. Couples were followed with follicular monitoring and triggered with the use of 5,000–10,000 IU hCG when at least one follicle attained a size of 18 mm. All cycles were provided luteal phase support with the use of 200 mg/d progesterone or 20 mg/d dydrogesterone for 14 days. Of interest, the cumulative live birth rates were minimally different between clomiphene citrate and letrozole or gonadotropins. Stimulation compared with no stimulation was clearly more successful. The twin pregnancy rate was lowest with the use of letrozole. Results of their large experience are in keeping with and expand the inference reported by Farquahar et al. (2) in a relatively small pragmatic, open-label, randomized, controlled, two-center trial. In the present study, Huang et al. compared OS-IUI (three options) and IUI without ovarian stimulation. Ovarian stimulation was superior to expectant management and to IUI without stimulation.

Intrauterine insemination is widely used in the United States, the United Kingdom, and Europe. Of interest is that the practice has proceeded without randomized clinical trial evidence of superiority to natural cycle attempt. This seems to be driven by the desire to reduce costs associated with IVF and the natural desire to "do something to help." It has seemed to be the right thing to do despite the fact that until recently only two randomized controlled trials (RCTs) of IUI considered the question of whether IUI is superior to expectant management; and neither provided evidence of effectiveness.

Details of challenges and protocol variations in this study by Huang et al. and the RCT by Farquhar et al. are well documented. Both of these studies provide us with a realistic glimpse of how challenging it is to extract exact clinical precision from the findings. Yet they both inform. In the present large cohort study, the authors use improved methods for statistical analysis of clustered or correlated data to account for consecutive attempts within the same couple. The cumulative live birth rate provides a better insight of what a treatment can bring for a couple than per-cycle analysis. The cohort design always has the potential of selection bias, but because of the large sample size there is a better opportunity of observing adverse events.

The information provided is complementary. Although intention-to-treat analysis was used in the small RCT correctly, there were some practical challenges. Not all couples were evaluated consecutively in either study, some could conceive naturally, and clinical judgment is required for safety, usually in the form of cycle cancellation.

The large experience here and the findings of lower multiple pregnancy rates with the use of letrozole are consistent with RCT trial evidence reported by the National Institute of Child Health and Human Development Reproductive Medicine Network (3). Couples with unexplained infertility were enrolled in AMIGOS, a multicenter randomized trial. Ovulatory women 18–40 years of age with at least one patent fallopian tube were randomly assigned to ovarian stimulation (up to four cycles) with the use of gonadotropin (301 women), clomiphene (300), or letrozole (299). The primary outcome was the rate of multiple gestations among women with clinical pregnancies. Rates of conception, clinical pregnancy, and live birth in the letrozole group were within the prespecified noninferiority margin compared with clomiphene or gonadotropin. There was no significant difference in the time to conception among the three groups according to intention-to-treat analysis. Comparing individual groups, the incidence of multiple clinical pregnancy was significantly higher with gonadotropin than with clomiphene or letrozole (4). The only higher-order multiple gestations (all triplets) occurred after gonadotropin administration. In contrast, in the AMIGOS study, clomiphene and letrozole each resulted in significantly lower rates of conception, clinical pregnancy, and live births compared with gonadotropin. Many reports in the literature have suggested a similar or improved pregnancy rate with the use of an aromatase inhibitor compared with standard therapy (5). AMIGOS provided a randomized design, standardized criteria for the timing of gonadotropin administration, and standardized timing of insemination in all treatment groups. Methods of analysis and power considerations might explain differences.

Interestingly, the live birth rates after four cycles of ovarian stimulation plus IUI with the use of clomiphene, letrozole, or gonadotropins in AMIGOS were 23.3%, 18.7%, and 32.2%, respectively. The corresponding rates in the Huang et al. investigation after three cycles were 25.7%, 26.2%, and 23.7%. Although the lower live birth rate in the gonadotropin group is likely explained by less vigorous stimulation in the Huang et al. study, differences in letrozole, and to a lesser extent clomiphene, treatment outcomes between the studies are harder to explain. In the Huang et al. study, progesterone support for the luteal phase was routinely used. In AMIGOS, luteal support was not given. Additional investigations are needed to determine the role of luteal support in ovarian stimulation treatments.

Although distinct advantages of the RCT design include the ability to reduce selection bias, the very large experience reported by Huang et al. and the findings of lower

multiple pregnancy rate with the use of letrozole will likely inform practice. The advantage of using oral agents without the need for multiple injections, with less monitoring and issues of cost—none of which were studied—are important considerations for management of unexplained infertility.

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