

Low tolerance for complications

Patricio Donoso, M.D., Ph.D.,^a and Paul Devroey, M.D., Ph.D.^b

^a Clínica Alemana de Santiago, Facultad de Medicina Clínica Alemana, Universidad del Desarrollo, Santiago, Chile; and

^b Center for Reproductive Medicine, Brussels, Belgium

Assisted reproductive techniques can lead to medical complications such as multiple pregnancy and ovarian hyperstimulation syndrome. A critical appraisal and strategies to reduce the occurrence of these complications are discussed in this manuscript. (*Fertil Steril*® 2013;100:299–301. ©2013 by American Society for Reproductive Medicine.)

Key Words: Assisted reproduction, complications

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The widespread use of infertility treatments such as in vitro fertilization has led to the birth of >5 million babies worldwide. Ovarian stimulation represents a cornerstone for these therapies aiming to develop multifollicular growth through gonadotropin administration. However, these procedures can lead to medical complications such as multiple pregnancies and ovarian hyperstimulation syndrome (OHSS). In the United States, twin birth rates rose by 75% from 1980 to 2000 and the rates of triplet and higher order multiple pregnancies rose fourfold over the same period, which can be attributed almost entirely to infertility treatments (1, 2). Pregnancy complications related to multiple pregnancies include increased risks of miscarriage, preeclampsia, fetal growth restriction, preterm delivery, and elevated perinatal morbidity and mortality (1).

The reported incidence of OHSS is 3%–6% for the moderate form and 0.1%–2% for severe forms (3). It has been estimated that worldwide, ≥200 women suffer annually from severe OHSS (4). This syndrome remains a serious problem for specialists dealing with infertility, being an iatrogenic

complication of a nonvital treatment with a potentially fatal outcome. OHSS in The Netherlands and the United Kingdom demonstrate an incidence of ~3 deaths per 100,000 in vitro fertilization (IVF) cycles performed (5, 6).

The negative side effects of aggressive stimulation and multiple embryo replacement have raised many concerns in the medical community and world press (e.g., *New York Times*, July 7, 2012), encouraging centers to start mild stimulation protocols and to implement elective single-embryo transfer (eSET) policies.

Elective SET is defined as the transfer of a single cleavage-stage embryo or blastocyst selected from a cohort of good-quality available embryos. The largest randomized trial, which included 11 clinics in Sweden (661 patients <36 years old), demonstrated that cumulative live birth rates (one fresh SET plus one frozen-thawed SET) were not significantly different compared with one fresh double-embryo transfer (DET; 39% vs. 43%), but the multiple pregnancy rate decreased from 33% to 0.8% (7). Furthermore, extending embryo culture to the blastocyst stage in young women

(<36 years old) enhances embryo selection, leading to a 10% increase in delivery rate (8). An additional improvement by means of preimplantation genetic aneuploidy screening (PGS) has been proposed, but similar live birth delivery rates per randomized patient were found in a study including women <36 years old undergoing eSET (30.8% vs. 30.8%) (9). A plausible explanation is that even if PGS does select the best embryo, it is possible that cell removal decreases the benefit of this strategy. In addition, the analyzed cell is in many cases not representative of the whole embryo, owing to the high mosaicism rate (~50%) (10, 11).

Mild ovarian stimulation uses a low dose of gonadotropins to produce up to ten oocytes. Because GnRh antagonists are administered only in the middle to late follicular phase, an endogenous intercycle rise in FSH is allowed. Prospective randomized trials show that, compared with the conventional agonist protocol, antagonists require fewer days of stimulation, resulting in similar delivery rates (12). Furthermore, antagonist protocols have shown a lower incidence of OHSS in women with polycystic ovary syndrome (PCOS) (13). Additional potential advantages include a simpler protocol with less patient discomfort, a reduced dosage of gonadotropins, fewer days of monitoring, lower costs, and a reduced negative psychological

Received May 1, 2013; revised May 29, 2013; accepted June 7, 2013; published online June 24, 2013.

P. Donoso has nothing to disclose. P. Devroey has nothing to disclose.

Reprint requests: Patricio Donoso, M.D., Ph.D., Av. Vitacura 5951, Santiago, Chile (E-mail: pdonos@alemana.cl).

Fertility and Sterility® Vol. 100, No. 2, August 2013 0015-0282/\$36.00

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impact on infertile couples (14). A noninferiority effectiveness trial including 404 patients randomly assigned to undergo either mild treatment with GnRh antagonist combined with SET or a standard treatment using a GnRH agonist long protocol and transfer of two embryos found that the proportions of cumulative pregnancies that resulted in term live births after 1 year were 43.4% with mild treatment and 44.7% with standard treatment. The proportion of couples with multiple pregnancies was 0.5% with mild IVF treatment versus 13.1% with standard treatment. Mean total costs were €8,333 and €10745, respectively (difference €2,412, 95% confidence interval [CI] €703–€4,131) (15). A meta-analysis including three randomized studies demonstrated that the optimal number of retrieved oocytes depended on the ovarian stimulation regimen (16). Following mild ovarian stimulation, the retrieval of a low number of oocytes (4–6) was associated with the highest chance of ongoing pregnancy per embryo transferred (29%) (16).

Some studies have also suggested an increased chromosomal abnormality rate associated with high-dose stimulation protocols (17, 18). Haff et al. (19) found that a high oocyte yield increased the likelihood of chromosome errors in women <35 years and 35–40 years old undergoing the first ICSI cycle. A randomized clinical trial found a significantly lower aneuploidy rate in embryos derived from a mild stimulation protocol compared with a conventional protocol using a nine-chromosome panel (1, 7, 13, 15, 16, 18, 21, 22, X, and Y; 50% vs. 62%) (18).

Triggering final oocyte maturation with GnRH agonist is an effective alternative to hCG for inducing follicular maturation, with the potential benefit of preventing OHSS (20). Two randomized studies reported no OHSS cases with GnRH agonist triggering compared with 30% in the hCG groups (21, 22). More studies are needed to confirm this observation as well as to include normogonadotropic and not only PCOS patients. A significant drawback for this approach is that GnRH agonist triggering has a combined negative effect on the function of the corpus luteum and the endometrium (23). The addition of 1,500 IU hCG at oocyte retrieval has been shown to overcome the luteal-phase defect, however more studies are required to establish the best scheme and dosage protocol (24). A combination of daily intramuscular progesterone (50 mg) and transdermal E₂ patches on alternate days (0.3 mg) has also been proposed (22). This scheme starts after oocyte retrieval until the 10th week of gestation, achieving an implantation rate of 36% and ongoing pregnancy rate of 53% (22).

An alternative approach is to cryopreserve all oocytes or embryos in patients at risk of OHSS, given the high survival and pregnancy rates with the currently used vitrification protocols (25–27). Therefore, the achievement of an OHSS-free clinic relies on the segmentation of IVF treatment: 1) optimization of the ovarian stimulation, including GnRH agonist triggering in a GnRH antagonist cycle; 2) highly efficient cryopreservation methods for oocyte or embryo vitrification; and 3) embryo replacement in a receptive nonstimulated endometrium in a natural cycle or with artificial endometrial preparation.

In conclusion, contemporary assisted reproductive techniques should aim not only to improve delivery rates, but

also to increase the safety of these procedures, especially concerning multiple pregnancies and OHSS. Mild ovarian stimulation followed by eSET is the best choice for young women with good prognosis and high risk for these complications.

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