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Superovulation and Multiple Birth: In Search of Kryptonite

Richard S. Legro, M.D

Department of Obstetrics and Gynecology, Pennsylvania State University College of Medicine,
Hershey, PA

Abstract

The contribution of superovulation and ovulation induction to the multiple pregnancy epidemic in the U.S. is substantial. Further understanding of the contributing factors, and most importantly preventive strategies are needed.

Recognition and prevention of iatrogenic multiple pregnancy in infertility treatment remains an important public health goal. The CDC's Center for National Health Statistics announced early in 2012 that the epidemic of multiple pregnancy in the U.S. was still upon us (1). The twinning rate which was 1 in 53 babies in 1980, was 1 in 30 in 2009 (a 76% increase) with no decrease in sight. Twins make up 96% of multiple births in the U.S., and while high order multiple rates have decreased likely due to more restrictive embryo transfer policies in ART programs, the twinning rate continues to rise at slightly less than 1 percent annually from 2005-09 (down from more than 2% annually prior to 2005) (1).

This Views and Reviews section started with the instructions to the authors to explore the contribution of ovarian stimulation and specifically superovulation to the multiple pregnancy epidemic in the U.S. and discuss the risk/benefit ratio and solutions to current treatments. These authors have rightfully broadened the issue beyond superovulation to ovarian stimulation per se and the relationship between ovarian stimulation within and without IVF. It is intriguing to view the history and interrelationship of these practices.

The authors were specifically encouraged both to summarize their own experience and that from the literature, but also to editorialize and express their opinions about where to go next. Thus many of these articles are provocative and meant to stir debate and further initiatives to understand and prevent multiple pregnancy with the use of ovarian stimulation. Thus common themes run between the articles.

Drs. Beall and DeCherney will review the history of ovulation induction including the development of clomiphene and gonadotropins, and review the history leading to the adaptation of superovulation for IVF, spurred largely by Dr. Howard and Georgeanna Jones (and please note that Dr. Jones continues to be our most senior voice in the field and is co-author of one of the contributions). A particular intriguing vignette is that the eventual Nobel Prize Winner, Prof Robert Edwards along with Fowler noted as early as 1959 that superovulation in mice led to increased litter size and fetal mortality. They note the lack of

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Corresponding author: Richard S. Legro, M.D., Department of Obstetrics and Gynecology, Penn State College of Medicine, M.S. Hershey Medical Center, 500 University Drive, H103, Hershey, PA 17033, Telephone: (717) 531-8478, FAX: (717) 531-6286, RSL1@PSU.EDU.

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formal federal regulation of ovarian stimulation or IVF in the U.S., but suggest that the Fertility Clinic Success Rate and Certification Act requiring clinic specific reporting of cycles and outcomes contributed to the practice of multiple embryo transfer and high multiple pregnancy rates to maintain competitive advantage in a consumer driven marketplace.

Drs. McClamrock, Jones, and Adashi document the contribution of ovarian stimulation and intrauterine insemination to multiple pregnancy, and conclude that multiple pregnancy will always likely accompany ovarian stimulation. They sound the alarm that we are at a crossroads and some form of action is necessary. They make multiple excellent suggestions including forming a national registry for ovarian stimulation analogous to the existing one for ART.

Likely that would require similar legislative action from Congress, as efforts to achieve funding from the NIH and various other sources has been unsuccessful to date. They further make a clear recommendation to avoid high dose gonadotropin regimens (150U/day) and to consider oral ovarian stimulation therapy as first line treatment. Finally newer ovarian stimulation protocols based on our emerging knowledge of follicular development should be developed.

Drs. Diamond and Singh argue that there still is a role for gonadotropins in ovarian stimulation for infertility therapy in the U.S. and the benefits of these therapies must be rightfully recognized along with the risks. The economics of health care are such that often unduly aggressive approaches are pursued before coverage is exhausted and for many there is never any chance of coverage such that some form of ovarian stimulation remains the only out of pocket choice. They discuss methods for reducing the chance of multiple pregnancies and advocate for further trials in this area.

Drs. Reindollar and Goldman finish up with a powerful and provocative argument to remove gonadotropins from ovarian stimulation, both as a primary or secondary treatment for infertility, and toy with the idea of removing it from stimulation protocols for IVF. These authors have had extensive research experience in this area as principal investigators in The Fast Track and Standard Treatment Trial (FASTT)(2) and The Forty and Over Infertility Treatment Trial (FORT-T) (3), so there arguments are bolstered with some of the most important clinical trial data that exists in this field.

The U.S. lacks a national health insurance program, and coverage for infertility varies from state to state, and in most states from insurance program to insurance program, with many couples having no coverage at all. Thus many decisions about infertility care are made according to the coverage of the patient or their ability to pay out of pocket. This has been a major contributing factor to the continued reliance on superovulation and ovulation induction in the U.S. for the treatment of infertility. Affordable and accessible health care for all Americans is a major issue in the upcoming presidential elections

We Americans invented and promoted Superman (he certainly was needed during the Depression and WWII), the original and still most powerful superhero. The prefix super- in the U.S. is associated with the best of the best: Superhighways, Superconductors, Superpowers (with the U.S. as #1), and the Super Bowl (which in my Weltanschauung trumps the term "World Cup"). It is only natural that the appendage of this word to ovulation would imply a similarly powerful and effective method to treat infertility. Come to think about it, all of these super designations come with particular and in most cases elevated risks compared to their non-super comparators. As these authors all recognize in this section, we are need of further strategies to take the super out of superovulation, or at least sap its power to multiply pregnancies.

References

1. Martin, JA.; Hamilton, BE.; Osterman, MJK. NCHS data brief, no 80. Hyattsville, MD: National Center for Health Statistics; 2012. Three decades of twin births in the United States, 1980–2009.
2. Reindollar RH, Regan MM, Neumann PJ, Levine B, Thornton KL, Alper MM, et al. A randomized clinical trial to evaluate optimal treatment for unexplained infertility: the fast track and standard treatment (FASTT) trial. *Fertility and Sterility*. 2010; 94(3):888–899. [PubMed: 19531445]
3. Reindollar RH, Thornton KL, Ryley D, Alper MM, Fung JL, Goldman MB. A randomized clinical trial to determine optimal infertility therapy in couples when the female partner is 38–42 years: preliminary results from the forty and over infertility treatment trial (FORT-T). *Fertility and Sterility*. 2011; 96(3):S1. [PubMed: 22393576]