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ARTICLE

Gonadotrophin ovulation induction and enhancement outcomes: analysis of more than 1400 cycles

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Abstract Ovulation induction (OI) or ovulation enhancement (OE) with gonadotrophins can be a reasonable treatment option for patients with a variety of infertility diagnoses. It must be used with extensive monitoring and management given the risk of multiple pregnancy, especially high-order multiples. This retrospective study evaluated per cycle outcomes of a large cohort of 1452 gonadotrophin OI/OE cycles at an academic infertility centre, and the efficacy of specific guidelines in limiting multiple pregnancy. The lowest possible gonadotrophin doses were used and cycle cancellation was recommended if more than three dominant follicles were present, and/or if serum oestradiol was above 1500 pg/ml. Overall, pregnancy rate (PR) was 12% and live birth rate was 7.7%, with an increasing trend in younger patients ($P = 0.0002$ and <0.0001, respectively). Multiple clinical PR was 2.6% with 1.9% twins and 0.7% triplets and above. The birthweight of a singleton from a vanishing twin pregnancy ($n = 8$) was significantly lower than other singletons (2882 g versus 3250 g, $P = 0.013$). Reducing multiple pregnancies from OI/OE cycles remains an important and challenging goal. In this large cohort, high-order multiple clinical PR was limited to 0.7% per cycle by using specific management strategies while maintaining a reasonable PR.

KEYWORDS: birthweight, multiple birth, multiple pregnancy, ovulation enhancement, ovulation induction, vanishing twin

Introduction

Ovulation induction (OI) and ovulation enhancement (OE) with exogenous gonadotrophins has been a treatment option since the 1960s and 1980s, respectively (Practice Committee of ASRM, 2008), aiming to achieve monofollicular development in the anovulatory patient or enhanced follicular development in the already ovulatory (but infertile)

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patient. It offers a reasonable alternative when less complex and costly methods have failed, or when assisted reproduction technology (ART) is not indicated or possible.

Careful monitoring and management of these patients has become increasingly important, especially given the alarming rates of multiple pregnancy. In fact, OI/OE with non-ART has surpassed ART as the cause of higher-order multiple births (quadruplets and above) in 2003 (Dickey, 2007). First published in 1998 and most recently updated in 2009, the practice committee guidelines of the Society for Assisted Reproductive Technology (SART) and the American Society for Reproductive Medicine (ASRM) limit the number of embryos to be transferred in ART cycles, based on different patient variables such as age and prognosis (Practice Committee of SART/ASRM, 2009). These guidelines have resulted in a decrease in high-order multiple births of triplets and above from 7% in 1996 to 3.2% in 2003 with the most updated 2007 statistics showing a rate of 3.7% (CDC, 2009). The study centre's programme has found that the elective transfer of two embryos results in similar pregnancy rates but significantly reduced multiple gestations when compared with the elective transfer of three embryos in IVF and oocyte donation cycles (Dowling-Lacey et al., 2007).

In contrast to ART cycles, gonadotrophin OI/OE cycles cannot limit the number of embryos available for implantation, making them major contributors to the rise in multiple births. The lack of universal evidence-based specific guidelines for the management of gonadotrophin OI/OE cycles to decrease the risk of multiple pregnancy further complicates the issue. The following is a summary of some of the published opinions of different professional societies highlighting the lack of consensus in this matter: the American College of Obstetrics and Gynecology suggests the possibility of cancelling cycles when more than three follicles $>$15 mm in diameter are present (ACOG, 2002). The UK's Royal College of Obstetricians and Gynaecologists merely recommends close ultrasound monitoring during gonadotrophin treatment (RCOG, 2004). ASRM guidelines only address the treatment of anovulatory patients in whom cycle cancellation should be seriously considered when three or more dominant follicles or a large number of intermediate-sized follicles are present, as well as when serum oestradiol is $>$1000–1500 pg/ml (Practice Committee of ASRM, 2008). The European Society of Human Reproduction and Embryology Capri Workshop Group suggests cancelling cycles with more than three large follicles or converting to IVF (ESHRE, 2000).

Multiple pregnancy has serious health consequences including maternal complications, preterm delivery, and low birthweight with resultant perinatal morbidity and mortality (Reynolds et al., 2003) as well as delayed developmental challenges in these children when compared with singletons (Merenkov, 1995). When faced with a high-order multiple pregnancy (HOMP) of triplets or above, not only is there the increased risk of spontaneous death of one or more of the fetuses, but also the option of elective fetal reduction to decrease adverse maternal and perinatal outcomes. There are obvious ethical considerations with such an intervention as well as the risk of pregnancy loss and preterm delivery depending on operator experience (Practice Committee of ASRM, 2006). The benefits are traditionally most accepted for quadruplets and higher, but triplet reduction to twins has also been shown to be beneficial (Evans et al., 2004).

The major challenge and goal in OI/OE cycles is maximizing pregnancy rates while minimizing multiple gestations, especially triplets and above. Given the lack of universally accepted specific recommendations for reaching this goal, individual infertility centres must recognize the importance of contributing variables to the risk of multiple pregnancy, including patient age, serum oestradiol concentration, follicular development and gonadotrophin doses (Balasch, 2004). The establishment of specific institutional guidelines using these variables can at least attempt to limit multiple pregnancies. This retrospective study reports the clinical outcomes of a large cohort of gonadotrophin OI/OE cycles including live-birth rates. The institutional guidelines for reducing the risk of multiple pregnancy included using the lowest possible starting gonadotrophin doses and recommending cycle cancellation when more than three dominant follicles developed or serum oestradiol concentrations were $>$1500 pg/ml.

The aim of this retrospective review was to report on 10 years of experience with OI/OE treatment at the study institution using specific guidelines to help decrease the risk of HOMP. The main outcomes measured included pregnancy rate (PR), multiple clinical PR, miscarriage rate, live-birth rate (LBR), multiple LBR, and live birthweight and the impact of different variables on these outcomes was studied.

Materials and methods

Patient population

A total of 1574 gonadotrophin OI/OE cycles were performed at the Jones Institute for Reproductive Medicine (Norfolk, Virginia) between August 1998 and December 2008. Data on one or more outcome measures were missing from 49 patients resulting in a total of 1525 cycles from 694 patients for data analysis. In order to limit the analysis to infertility patients, those with recurrent pregnancy loss were excluded resulting in a total of 1452 cycles from 660 patients. The number of cycles per patient ranged from 1 to 12 with a mean of 2.2. No other inclusion or exclusion criteria were applied given that the objective was to review the outcomes of all OI/OE cycles in that given time period.

All patients had a comprehensive fertility evaluation prior to treatment, including basal serum-cycle day-3 FSH, LH, oestradiol, thyroid-stimulating hormone and prolactin, a hysterosalpingogram to assess uterine cavity anatomy and confirm at least unilateral Fallopian tubal patency, and a semen analysis. Those found to have thyroid dysfunction or hyperprolactinaemia were treated appropriately. Submucosal myomas were surgically removed. Patients with severe male factor infertility had a full urologic evaluation as well as genetic testing as it has been well established that such a diagnosis may be associated with abnormal karyotypes or microdeletions of the Y chromosome (Oehninger, 2001). Overall, the patients represented a wide range of infertility diagnoses and were ovulatory, oligo-ovulatory or completely anovulatory.