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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.

Gonadotrophin stimulation (with or without clomiphene citrate) was followed by either timed intercourse or intrauterine insemination (IUI). A gonadotrophin-releasing hormone (GnRH) antagonist was used in patients with a high risk of premature luteinization including those with polycystic ovary syndrome and very elevated baseline LH concentration, a history of early recruitment of a dominant follicle and/or an unexpected premature LH surge in a previous cycle.

Urinary or recombinant exogenous FSH was used alone or in combination with LH in hypogonadotrophic hypogonadic states. The lowest possible gonadotrophin doses were initiated (as low as 25 IU FSH) with a slow step-up approach as indicated based on ovarian response. Patient age, infertility diagnosis and response to previous cycles were taken into account to decide the initial dose and subsequent increases if necessary.

Patients had a baseline pelvic ultrasound and serum oestradiol concentration was measured at the beginning of each cycle before stimulation to rule out any functional ovarian cysts. Ovarian response was monitored frequently every 1–4 days with serial ultrasounds and serum oestradiol and LH concentrations. Cycles were cancelled if there was an inadequate response after 6–8 days of stimulation. Cycle cancellation was also highly recommended when there were more than three follicles $\geq$16 mm in diameter and serum oestradiol concentrations >1500 pg/ml. Exceptions were made for patients of advanced maternal age >40 years. Ovulation was triggered with human chorionic gonadotrophin (HCG) when at least one follicle was >17 mm or if a rising serum LH was noted.

Statistical analysis

All statistical analyses were performed using SAS version 9.1. Descriptive statistics included frequency for categorical variables and mean ± SD for continuous variables. Bivariate associations between categorical variables were examined using Pearson's chi-squared test. In addition, the Cochran–Armitage trend test was used to evaluate dose–response relationships between pregnancy, miscarriage, live-birth and multiple-birth rates and age group. Binary logistic regression was used to construct predictive models for each outcome of interest adjusting for age as a continuous variable; odds ratios (OR) and their 95% confidence intervals (CI) were presented. Two-sided statistical tests were conducted at an alpha level of 0.05.

Results

Patient age ranged from 21 to 48 years with a mean of 34.9 years. Out of 1452 cycles, 8.4% were cancelled because of reasons mentioned above. Coasting was utilized in 10.3% of the cycles to decrease the risk of ovarian hyperstimulation and multiple pregnancy. Peak serum oestradiol concentration was 771 ± 617 pg/ml (median (interquartile range) 635 (701) pg/ml) (n = 1438 cycles). The mean number of follicles $\geq$16 mm in diameter was 2.3 ± 1.4 and those between 10–16 mm was 2.5 ± 2.5. Clomiphene citrate was used in conjunction with gonadotrophins in a sequential manner in 40.8% of the cycles. A GnRH antagonist was used in 11.5% of the cycles. Table 1 summarizes the basic characteristics of the study cycles.

The per-cycle PR was 12%, which was defined as a positive serum βHCG test 2 weeks after timed intercourse or IUI. Out of the 175 pregnancies, there were 112 live births. The per-cycle LBR was 7.7% and the per-pregnancy LBR was 64%, with an expected significant linear trend towards higher rates in younger patients (P = 0.0002 and <0.0001, respectively). A threshold was noted whereby LBR declined considerably after age 35 (Table 2).

Out of the total 175 pregnancies, there were 38 multiple pregnancies (27 twins, 9 triplets, 2 quadruplets) resulting in 24 multiple live births (19 twins, 5 triplets). Multiple clinical PR was 21.7% per all pregnancies and 2.6% per cycle (15.4% twins, 5.1% triplets, 1.1% quadruplets per all pregnancies; 1.9% twins, 0.6% triplets, 0.1% quadruplets per cycle). Multiple LBR was 13.7% per all pregnancies and 1.7% per cycle (10.8% twins, 2.9% triplets per all pregnancies; 1.3% twins, 0.3% triplets per cycle). There were no births with higher-order multiples above triplets. The two quadruplet clinical pregnancies were either spontaneously or electively reduced, resulting in a twin delivery and a singleton delivery.

Overall miscarriage rate was 32.9%, which included biochemical pregnancies but excluded ectopic pregnancies. First-trimester miscarriages were the most common, representing 87.5% of all losses. Miscarriages between 12–20 weeks and after 20 weeks' gestation were only 8.3%

Table 1 Basic characteristics of the study cycles.

Characteristic	*Cycles (n = 1452)*
Patient age (years)	
<25	40 (2.8)
25–29	252 (17.4)
30–34	475 (32.7)
35–39	400 (27.6)
40–44	256 (17.6)
45+	29 (2.0)
Medications used	
GnRH antagonist	166 (11.4)
Gonadotrophins (with Clomid)	592 (40.8)
Gonadotrophins (without Clomid)	860 (59.2)
Coasting	149 (10.3)
Cancellation	122 (8.4)
Main infertility diagnoses	
Endometriosis	300 (20.7)
Diminished ovarian reserve	126 (8.7)
Ovulatory dysfunction	267 (18.4)
Hypothalamic ovarian dysfunction	16 (1.1)
Pelvic adhesive disease	72 (4.9)
Polycystic ovary syndrome	465 (32.0)
Tubal factor	84 (5.8)
Unexplained infertility	292 (20.1)
Uterine – any	153 (10.6)
Uterine – nonspecified	56 (3.9)
Uterine – myoma	97 (6.7)
Male infertility	182 (12.5)

Values are n (%).
GnRH = gonadotrophin-releasing hormone.

Table 2 Per-cycle pregnancy, live-birth, miscarriage and multiple-birth rates by patient age.

Age (years)	*Cycles*	*Pregnancies* (n = *1452*)	*Live births* (n = *1452*)	*Miscarriages* (n = *167*)[a]	*Multiple births* (n = *175*)
<25	40 (2.8)	17.5	10.0	42.9	14.3
25–29	252 (17.4)	14.3	10.7	22.9	11.1
30–34	475 (32.7)	15.6	10.9	25.7	13.5
35–39	400 (27.6)	11.0	5.3	48.8	18.2
40–44	256 (17.6)	5.1	2.7	46.2	7.7
45+	29 (2.0)	3.5	3.5	0.0	0.0
Total	1452 (100)	12.0	7.7	32.9	13.7
P_{trend}	–	<0.0001	<0.0001	0.08	0.84

P_{trend} = Cochran-Armitage trend test two-sided *P*-value.
[a]Eight ectopic pregnancies identified.

Table 3 Age-adjusted effects of stimulation and patient characteristics on miscarriage status per pregnant cycle.

Variable	*Miscarriage* (n = *167*)[a]
Urinary gonadotrophins	1.12 (0.46–2.73)
Recombinant gonadotrophins	0.68 (0.35–1.30)
GnRH antagonist – ever used[b]	0.25 (0.07–0.89)
Clomid – ever used	1.65 (0.84–3.22)
Peak oestradiol concentration	1.00 (1.00–1.00)
No. of follicles ≥16 mm	1.04 (0.85–1.27)
No. of follicles ≥10 mm and <16 mm	1.11 (0.99–1.24)
Main diagnoses	
Diminished ovarian reserve	0.72 (0.06–8.69)
Endometriosis	1.23 (0.50–3.02)
Male factor	1.28 (0.52–3.17)
Ovulatory dysfunction (NOS)	1.28 (0.55–2.99)
Hypothalamic ovarian dysfunction	–
Pelvic adhesive disease	2.04 (0.39–10.49)
Polycystic ovary syndrome	1.28 (0.64–2.57)
Tubal factor	1.69 (0.49–5.89)
Unexplained infertility	0.55 (0.25–1.22)
Uterine – any	1.69 (0.36–7.90)
Uterine – nonspecified	2.15 (0.29–15.77)
Uterine – myoma	1.17 (0.10–13.30)

Values are OR (95% CI). Binary logistic regression models were adjusted for age (years) as a continuous variable.
GnRH = gonadotrophin-releasing hormone.
[a]Ectopic pregnancies excluded.
[b]Statistically significant.

Table 4 Age-adjusted effects of stimulation and patient characteristics on pregnancy status.

Variable	*Pregnancy* (n = *1452*)
Urinary gonadotrophins	1.11 (0.70–1.75)
Recombinant gonadotrophins	0.88 (0.64–1.21)
GnRH antagonist – ever used	1.17 (0.73–1.89)
Clomid – ever used	0.90 (0.65–1.26)
Peak oestradiol concentration	1.00 (1.00–1.00)
No. of follicles ≥16 mm[a]	1.23 (1.11–1.37)
No. of follicles ≥10 mm and <16 mm	1.12 (1.06–1.19)
Main diagnoses	
Diminished ovarian reserve[a]	0.25 (0.08–0.81)
Endometriosis[a]	0.55 (0.35–0.87)
Male factor	1.27 (0.81–1.99)
Ovulatory dysfunction (NOS)	1.17 (0.77–1.78)
Hypothalamic ovarian dysfunction[a]	3.88 (1.38–10.88)
Pelvic adhesive disease	0.58 (0.25–1.37)
Polycystic ovary syndrome	1.06 (0.73–1.52)
Tubal factor	1.07 (0.55–2.07)
Unexplained infertility[a]	1.61 (1.10–2.35)
Uterine – any[a]	0.46 (0.23–0.93)
Uterine – nonspecified	0.82 (0.34–1.95)
Uterine – myoma[a]	0.26 (0.08–0.82)

Values are OR (95% CI). Binary logistic regression models were adjusted for age (years) as a continuous variable.
GnRH = gonadotrophin-releasing hormone.
[a]Statistically significant.

and 4.2% of all losses, respectively. There were eight ectopic pregnancies representing 0.6% of all cycles and 4.6% of all pregnancies. As mentioned before, a GnRH antagonist was used during stimulation in 166 cycles (11.4%), which significantly decreased the risk of miscarriage with an OR of 0.25 (95% CI 0.07–0.89), as seen in **Table 3**. While it did not impact pregnancy status when controlling for age, GnRH-antagonist use did positively impact live-birth status (OR 1.74, 95% CI 1.03–2.92), as seen in **Tables 4** and **5**. Such findings should be regarded with caution as more of an observation than a concrete conclusion given that the study was not designed to specifically test that treatment.

Patients with hypothalamic ovarian dysfunction were associated with the highest per-cycle PR and LBR of 37.5% (no miscarriages). The lowest per-cycle LBR was in women with diminished ovarian reserve and uterine myomas (1.5–2.7%). The number of follicles (both greater and less than 16 mm in diameter) and a diagnosis of hypothalamic ovarian dysfunction and unexplained infertility had a significant positive impact on both pregnancy and live-birth status. Conversely, endometriosis and uterine factors had a negative impact on both of those outcomes. As expected, diminished ovarian reserve negatively impacted pregnancy status (**Tables 4** and **5**).

Age, peak oestradiol concentrations, number of follicles ≥16 mm in diameter and type of stimulation protocol did

Table 5 Age-adjusted effects of stimulation and patient characteristics on live birth status.

Variable	*Live birth (n = 1452)*
Urinary gonadotrophins	1.13 (0.65–1.98)
Recombinant gonadotrophins	0.99 (0.67–1.46)
GnRH antagonist – ever used[a]	1.74 (1.03–2.92)
Clomid – ever used	0.75 (0.49–1.14)
Peak oestradiol concentration	1.00 (1.00–1.00)
No. of follicles ≥16 mm	1.19 (1.06–1.36)
No. of follicles ≥10 mm and <16 mm	1.08 (1.00–1.15)
Main diagnoses	
Diminished ovarian reserve	0.31 (0.073–1.30)
Endometriosis[a]	0.56 (0.32–0.97)
Male factor	1.10 (0.62–1.95)
Ovulatory dysfunction (NOS)	0.95 (0.55–1.63)
Hypothalamic ovarian dysfunction[a]	6.43 (2.27–18.17)
Pelvic adhesive disease	0.45 (0.14–1.45)
Polycystic ovary syndrome	0.96 (0.61–1.49)
Tubal factor	0.88 (0.37–2.07)
Unexplained infertility[a]	2.01 (1.29–3.14)
Uterine – any[a]	0.32 (0.12–0.89)
Uterine – nonspecified	0.39 (0.09–1.66)
Uterine – myoma	0.29 (0.07–1.18)

Values are OR (95% CI). Binary logistic regression models were adjusted for age (years) as a continuous variable.
GnRH = gonadotrophin-releasing hormone.
[a]Statistically significant.

not impact multiple-pregnancy status. The birthweight of a singleton survivor from a vanishing co-twin ($n = 8$) was significantly lower than the birthweight of a primary singleton (2882 g versus 3250 g, $P = 0.013$). Of the 90 singleton live births, 8.9% originated from a vanishing twin pregnancy.

Discussion

In a review of strategies to reduce multiple pregnancies from OI/OE cycles, Dickey (2009) stressed how less aggressive stimulations can limit HOMP rate to less than 2% while maintaining a reasonable overall PR of 10–20% per cycle. The overall per cycle PR of 12% and HOMP rate of <1% observed in the present study fall within those ranges. No pregnancies higher than quadruplets were noted, and ultimately, the goal is to eliminate high-order multiple pregnancies altogether. This study is reassuring in showing that the institutional guidelines have been successful in limiting HOMP to the ranges mentioned above while maintaining reasonable PR. However, the twin rate of 15.4% remains elevated and work must continue to further limit it in order to reduce the multiple-pregnancy rate of 21.7% since any multiple pregnancy is a high-risk pregnancy.

The main strength of this review is inclusion of live-birth outcomes in such a large sample size. While monitoring PR is important, full-term LBR is the ultimate measure of success for both the physician and the patient, although it is more difficult to track, especially in large cohorts. LBR data is limited in the literature, with most gonadotrophin OI/OE studies only measuring PR as an outcome. If LBR is included as well, it is usually cumulative LBR over a specific time period instead of per cycle LBR (Eikemans et al., 2003). The overall LBR encompassing over 1400 cycles is 7.7%, about which it must be noted that the patient population is large and heterogeneous with a wide variety of ages and diagnoses. Dankert et al. (2007) report a per-cycle LBR of 8.7% for 207 OE cycles with recombinant FSH and IUI. Erdem et al. (2009) report a per-cycle LBR of 9.3% in 204 OE cycles also using recombinant FSH and IUI. These two studies have similar per cycle LBR which is only slightly higher than ours; however, they are significantly smaller and more homogenous patient populations with unexplained infertility and/or male subfertility. A recent analysis of a large cohort of 1038 gonadotrophin OI/OE cycles with IUI studied prognostic factors for pregnancy but did not include LBR in the outcome measures (Merviel et al., 2010).

With respect to assessing predictive factors for multiple pregnancy, several studies have found that peak oestradiol concentrations, gonadotrophin doses, type of stimulation protocol and number of large follicles impact the risk of multiple pregnancy, especially HOMP (Dickey et al., 2001; Gleicher et al., 2000; Tur et al., 2001). The present data did not statistically show the impact of those factors but it included a very small number of multiples in the analysis, most of which were twins. In contrast, Tur et al. (2001) analysed a total of 1878 pregnancies, 107 of which were triplets and above in order to form a three-variable model for identifying patients at increased risk for HOMP. They emphasized the limitations of other published studies which show conflicting data about these variables due to the small sample sizes analysed.

Gleicher et al. (2000) argue that, although some of these variables may be associated with multiple pregnancy, guidelines that incorporate these variables are inadequate at reducing the incidence of HOMP without compromising overall PR. However, it is important to note that the guidelines used in their retrospective analysis are less stringent than the present study, recommending cycle cancellation if serum oestradiol concentrations were above 2500 pg/ml (instead of 1500 pg/ml) and in the presence of six (instead of three) or more dominant follicles. Thus, it is believed that it is important to establish and adhere to such institutional guidelines which can be effective in at least reducing HOMP if not twins.

The overall miscarriage rate of 32.9% (including biochemical pregnancies) may seem very high at first glance. However, two classic studies evaluating the rate of spontaneous pregnancy loss in young fertile women showed a rate of 31–34% when including preclinical pregnancies (Wang et al., 2003; Wilcox et al., 1988). Given that the present study's patient population includes a very heterogeneous group of ages and pathology that may lead to decreased oocyte/embryo quality and/or suboptimal endometrial environments, the miscarriage rate of 32.9% seems reasonable in comparison.

An interesting finding was the decreased risk of miscarriages (with a positive impact on live-birth status) with the use of a GnRH antagonist although it had no impact on pregnancy status. As mentioned before, the study was not designed to specifically test this variable, and this finding should be regarded with caution although it is an interesting observation worth noting. GnRH antagonists are traditionally

used in IVF stimulation protocols, but they may also be beneficial in preventing premature luteinization in gonadotrophin OI/OE cycles. The effect of GnRH antagonists on endometrial receptivity and PR has been controversial. Rackow et al. (2008) showed significantly decreased *HOXA10* expression (a well-characterized marker of receptivity) in endometrial stromal cells of patients treated with GnRH antagonists when compared with GnRH agonists or natural cycles. With respect to IVF outcomes, a Cochrane review by Al-Inany et al. (2007) initially reported a significantly lower clinical PR for women randomized to GnRH antagonists with an odds ratio of 0.83. A more recent randomized controlled study of 98 patients by Prapas et al. (2009) showed no adverse effect on endometrial receptivity in donor oocyte recipients taking a GnRH antagonist during endometrial priming (Prapas et al., 2009). Furthermore, an updated Cochrane review by Al-Inany et al. (2011) showed no significant different in pregnancy or live birth rates in GnRH antagonist IVF cycles. With respect to gonadotrophin OI/OE cycles, multiple studies have shown either similar or increased PR when using GnRH antagonists to prevent premature LH surges (Allegra et al., 2007; Crosignani et al., 2007; Gomez-Palomares et al., 2008; Lambalk et al., 2006).

Risks of multiple pregnancy include a lower birthweight of the surviving singleton originating from a twin pregnancy, as shown by the present data. This finding is concordant with prior studies examining survivors of the vanishing twin syndrome. Pinborg et al. (2007) compared the birthweights of 642 survivors of a vanished co-twin to 5237 primary singletons and 3678 primary twins from IVF. The survivor singletons were found to have a significantly higher rate of being small-for-gestational age. More recently, Shebl et al. (2008) compared birthweights of 46 survivors of a vanished co-twin with 92 matched singletons as the control from assisted reproduction technology cycles. The frequency of low birthweight (26.1% versus 12%) and being small-for-gestational age (32.6% versus 16.3%) was significantly lower in the control group. It is uncertain whether these findings are associated with impaired or delayed neurological development of the surviving children. Anand et al. (2007) did not find significant differences between 92 singletons and 33 survivors of a vanished co-twin when evaluated at 1 year of age with Griffiths mental and developmental scales. The vanishing twin syndrome has been reported to occur in 10% of live-born IVF singletons (Pinborg et al., 2005) which is comparable to the present study's incidence of 8.9% in these OI/OE cycles.

Reducing the risk of any multiple pregnancy, but especially HOMP, in gonadotrophin OI/OE cycles remains a challenging but important goal. Since there are no specific universal guidelines, establishing and following institutional guidelines is essential for providing a baseline standard of care to help to achieve this goal while understanding that some patients require individualized management because of the wide variety of ages and infertility diagnoses. Although IVF offers a better PR with a lower risk of HOMP, it may not be feasible for all patients due to economic or personal reasons making gonadotrophin OI/OE an alternative treatment modality.

The main weakness of this study is the retrospective nature of the analysis and heterogeneous nature of the study population that spans a 10-year period. Obviously, clinical management of patients evolves over time and with different providers in every aspect of every field, and OI/OE management is no exception to that phenomenon. While all patients have always been discussed in a team setting on a daily basis with a goal of following institutional guidelines, deviations may occur. Furthermore, time and experience has led to a more conservative approach and stricter adherence to the guidelines in order to prevent multiple births. Lower doses of gonadotrophins are used as well as a slower progression to higher doses. The fact that the quadruplet pregnancies occurred in 2003 with no others noted in the more recent years illustrates this more conservative approach.

The inclusion of a large data set as well as live-birth outcomes, though, makes this study a valuable addition to knowledge of gonadotrophin OI/OE cycles and especially to efforts at preventing multiple births. The following guidelines are recommended based on the present experience with over 1400 OI/OE cycles: ovulation induction should be considered a reasonably successful treatment for women who have ovulatory dysfunction due to hypothalamic causes, polycystic ovary syndrome or unexplained infertility but not as successful in women with diminished ovarian reserve, endometriosis and uterine factors. Identification of high-risk patients based on age and diagnosis as well as strategies including using the lowest possible dose of gonadotrophins and cycle cancellation using certain parameters can be used to reduce (but not eliminate) the risk of multiple pregnancy, and especially HOMP. Proper counselling is essential to give patients realistic expectations and understanding of the risks of multiple pregnancy and its associated morbidity and mortality.

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