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REVIEW ARTICLE

The Multiple Birth Epidemic: Revisited

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Abstract The modern era of infertility treatment was heralded over half a century ago with the introduction of new hormonal drugs that could effectively induce ovarian ovulation. However, it was quickly recognized that the birth of these new "miracle drugs" was associated with a remarkable increase in the incidence of high-order multiple births. Despite the fantastic improvement in our ability to monitor ovarian response during ovulation induction, and our power to control the number of embryos introduced into the womb through IVF, multiple births remain a leading cause of long-term child morbidity among infertility patients. Efforts to prevent what was coined in the 1960s as the "multiple birth epidemic" remain an urgent concern. A new body of research clearly points at our capacity to reduce the risk of multiple births and their associated long term morbidity without diminishing current high success rates of infertility treatment.

Keywords Ovulation induction · Gonadotropins · Assisted reproductive technology · Elective single embryo transfer · Perinatal outcome

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Introduction

The modern era of fertility treatments was launched in 1958, when Gemzell et al. [1] reported their success in ovulation induction with pituitary-derived gonadotropins. Further advancement was made by Donini and Lunenfeld, who were able to extract human gonadotropins from human menopausal urine in sufficient quantities. After satisfactory reports of successful outcomes following ovulation induction, Pergonal 75 was registered in Israel in 1963 and in Italy in 1965 [1]. The concern regarding a "multiple birth epidemic" was raised in the Life Magazine issue of August 25, 1965, which was among the first few to recognize Pergonal as "the fantastic drug that creates quintuplets." The same epidemic is repeatedly referred nowadays as a challenge to be overcome by the reproductive community and pediatricians and is even noted as "the cost of irresponsibility" [2, 3]. In this article, we will review the changing attitude toward the meaning of a successful fertility treatment and the methods to achieve it.

The Current Epidemic

According to the Centers for Disease Control and Prevention (CDC), 1 in every 30 babies born in the United States (USA) in 2009 was a twin, compared with only 1 in every 53 babies in 1980. Over this period, twin birth rates rose in the USA by nearly 100 % among women aged 35–39 and by more than 200 % among women aged 40 and over. A part of this increase can be explained by the shift in the overall age

distribution of women giving birth in the USA due to delayed childbearing and an older female population. However, about two-thirds of the increase in the twin birth rate in the last three decades is likely associated with assisted reproductive technology (ART) and non-ART infertility treatments. The average increase was more than 2 % a year from 1980 to 2004, but from 2005 to 2009, the pace of increase slowed to less than 1 % annually [4]. A similar trend was reported in other Western countries. The rates of triplet or higher-order multiple pregnancies increased by 310 % in France, 430 % in England and Wales, and 696 % in the US between 1970s and 1998 [5]. Reports from Japan showed an overall increase in non-ART multiple births during 1979–2008, whereas ART multiples tended to increase from 1983 to 2005, and then rapidly decreased thereafter [6].

Risks and Impact of Multiple Pregnancies

The Society of Obstetricians and Gynecologists of Canada (SOGC) published guidelines concerning perinatal outcomes of ART pregnancies, based on the literature analysis from the years 1990–2005 [7]. They found that pregnancies achieved by ovarian stimulation with gonadotropins and intrauterine insemination are at higher risk for perinatal complications, and that multiple gestations remain a significant risk. They stated that infertile couples need to be informed of the increased risks of multifetal pregnancies in ART treatments, with dichorionic twins as the most common outcome, but with an elevated incidence of monochorionic twins as well. Multiple pregnancies were associated with higher rates of perinatal mortality, preterm birth (PTB), low birth weight (LBW), gestational hypertension, placental abruption, and placenta previa.

A prospective, population-based study [8] reported 10.1 % twin births in subfertile women treated with in vitro fertilization (IVF) compared to 1.3 % in untreated women. In that study, LBW was related to multiple pregnancy or PTB, but not to use of treatment itself. The last finding did not correlate with outcomes from earlier review [9] that found IVF twins at a significant increased risk of PTB, LBW, and lower mean birth weight compared with spontaneously conceived twins.

Another important aspect of multiple births is the psychological impact. Parents of twins and triplets present difficulties related to greater material necessities, higher social stigma, lower marital satisfaction, more depression, and inferior quality of life [10].

The Economic Burden

Multiple-birth ART infants also pose a significant challenge from a cost perspective. The economic consequences placed on healthcare systems due to the need for care of ART twins and triplets was shown to be substantially greater than if the infants had been born as singletons. These costs were found to extend beyond the perinatal period [11]. In 2006, 30 % of all ART live births were multiple infant deliveries in the US. Sixty-two percent of ART twins and 97 % of ART triplets were delivered preterm. It was estimated that the mean cost of each preterm was 51,600 US dollars, or a total of approximately 1 billion US dollars annually [12].

Ways to Reduce Multiple Pregnancies

The best method to avoid multiple births in IVF–embryo transfer (IVF–ET) is obviously to transfer only one embryo. However, many physicians remain concerned that this strategy might result in an unacceptable decrease in birth rates per IVF–ET cycle. Another solution is fetal reduction in the first trimester of pregnancy, but this procedure is considered by many as a distressing experience for parents, and carries medical and ethical dilemmas [13, 14].

Elective single embryo transfer (eSET) is a method in which a patient undergoes the transfer of a single fresh embryo and, if no live birth results, the subsequent transfer of a thawed embryo takes place. The Society for Assisted Reproductive Technologies (SART) defines eSET as "an embryo to transfer in which more than one high-quality embryo exists, but it was decided to transfer only one embryo" [15].

A double-blind randomized trial [16] compared pregnancy rates and multiple births in 661 patients randomized to undergo eSET or double embryo transfer (DET). The researchers showed that eSET followed by the transfer of frozen and thawed embryo if necessary, resulted in a marked reduction in the rate of multiple gestations, but without a substantial reduction in pregnancy rates. The authors concluded that according to their results, eSET was an effective method for women younger than 36 years.

A recent systematic review [17] based on randomized controlled trials and cohort studies found that eSET was associated with decreased risks of PTB and LBW compared with DET. A policy of eSET combined with minimal ovarian stimulation with clomiphene citrate was suggested by Japanese researchers [18], based on a cohort retrospective study during 2008. Blastocyst formation and LBR showed an age-dependent decrease, with acceptable LBR per ET in infertile patients younger than 44 years, and high chances following frozen–thawed blastocyst transfer (compared with cleavage-stage embryos).

Multiple pregnancies that are attributed to non-ART treatments, such as intrauterine insemination with ovarian stimulation, were addressed by McClamrock et al. [19],

who suggested that high-dose gonadotropins regimens should be replaced with emerging alternatives, such as low-dose gonadotropins, clomiphene, and off-label letrozole regimens, whenever possible.

In order to predict reproductive outcome after IVF, including estimation of multiple birth, researchers developed a computerized multivariate risk assessment model, based on dataset from the Human Fertilisation and Embryology Authority (HFEA) [20]. They claimed that predictive tools would improve consultation and medical informed consent process by tailored outcome assessment to each patient, and reduce the potential for adverse outcomes with IVF.

Trends in ET Regimens

The CDC has been monitoring ART procedures performed in the United States since 1997. In a report that documented the treatments performed in 2002 [21], infants conceived with ART accounted for 1 % of the total births in the United States, but the proportion of twins and triplets or higher-order multiples attributed to ART were 16 and 44 %, respectively. Higher rates of multiple births were reported in procedures that involved fresh embryos and donor eggs, followed by fresh embryos and the patient's own eggs. The number of embryos transferred, embryo availability, and the woman's age were strongly associated with the risk of multiple births. The report stated that ART was a major risk factor for multiple births, and that efforts should be made to limit the number of embryos transferred. A study that investigated trends in embryo transfer practices in the US over the period 1996–2002 [22] found that the proportion of procedures in which three or more embryos were transferred declined, but single embryo transfer remained uncommon. Multiple gestation risk remained high, in part because of the increased multiple gestation rates associated with the transfer of two embryos.

Back in 1999 [23], a workshop group from the European Society of Human Reproduction and Embryology (ESHRE) called infertility specialists in all countries to address the prevention of multiple births. They even pronounced that if nothing was done, public concern might lead to legislation in many countries. Since then several guidelines have been published and revised over the years according to renewing practices and evidences.

Guidelines from Canada [24], based on literature from 1990 to 2006, aimed to minimize the occurrence of multifetal gestation while maintaining pregnancy and live birth rates (LBR) following IVF–ET. They recommended that in women younger than 35 years, no more than two fresh embryos should be transferred, and a transfer of single embryo should be considered in such women with an excellent prognosis. In women over the age of 39, they limited the number of transferred embryos to four. They also suggested that emphasis on healthy singleton live birth as a measure of success in IVF–ET may be beneficial in promoting a reduction in the number of embryos transferred. As for iatrogenic non-IVF–ET ovarian stimulation pregnancies, they called for efforts to limit them through cycle cancelation and removal of financial barriers to IVF–ET. According to accumulated updated researches, the same Canadian guidelines committee published new recommendations in 2010 [25]. They warranted that indiscriminate application of eSET in populations with less than optimal prognosis will result in significant reduction in LBR compared with DET. They suggested that it should be used in women aged 35 years or less, in their first or second IVF attempt, with at least two good quality embryos available for transfer.

Similarly, in 2009, guidelines revised by SART and the American Society for Reproductive Medicine (ASRM) [26] suggested that for patients under 35 years with good prognosis, the transfer of only a single embryo should be considered, and limited to no more than two embryos. For patients aged 41–42, no more than five cleavage-stage embryos or three blastocysts should be transferred. According to a report from 2012 [15], eSET transfers rates increased to 10 % of all transfers to patients under 35 years old in 2009, parallel to the increase in the number of DET, which led to unchanged rate of twin gestation. In order to maximize the acceptability and utilization of eSET, the report reviewed the latest data regarding ET and concluded that the use of eSET in the US has lagged behind that of many other countries, and that IVF centers should promote eSET when appropriate through provider and patient education. Among the recommendations in the report, it was suggested that women aged 35–40 may be considered for eSET if they had top-quality blastocyst-stage embryos available for transfer.

SET Uptake and Acceptability

A study that analyzed global variations in the uptake of SET [27] observed major national differences across different countries. In 2005, 69.4 % of all ETs in Sweden were SETs, compared to 32.6, 48.3, 1.3, 11 %, in Denmark, Australia and New Zealand, the United States, and Canada, respectively. In an effort to understand these differences, several factors were compared. As for regulation, for example, apart from Sweden and Belgium, guidelines in most countries endorse DET as an acceptable option. In Sweden, state regulation allows for the replacement of more than one embryo only in exceptional circumstances according to that study. Those authors also suggested that

strict legislation, as that exists in Italy which bans the use of cryopreservation, could impede the use of eSET. Another important factor observed was economic. Acceptance of eSET by patients depended on access to financial support for multiple cycles of ART.

In the US, for example, lacking public sector coverage, physicians, and patients were more likely to accept the risk of multiples. Public reimbursement plans, which minimize private expenses, might relieve the pressure on both the physicians and the patients for achievement of pregnancy with minimum attempts, and as a consequence will hopefully decrease the number of embryos transferred and multiple pregnancies [28].

The concern that eSET can cause higher direct costs was refuted by a comparative study that found eSET superior to DET in terms of overall costs, because of incorporation FET and reduced incidence of multiple births [29].

Interesting results are expected to be reported from the ongoing INeS study [30] that aims to determine the safest and the most cost-effective primary treatment for couples with unexplained subfertility or mild male subfertility. The treatments in the three arms of the study will be six cycles of IUI-COH, six cycles of Modified Natural Cycle IVF (MNC IVF), and three cycles with IVF–-eSET plus cryo-cycles.

Cross-Border Reproductive Care and Multiple Births

Another challenge facing the attempt to reduce occurrence of multiple births was described by McKelvey et al. [31]. In 2004, HFEA limited the number of embryos transferred following IVF to a maximum of two, besides special exceptions. In a retrospective study, they investigated the influence of cross-border fertility treatment on high-order pregnancies in a fetal medicine unit in the United Kingdom (UK). One-quarter of all women with high-order multiple gestations, who had ART, received the treatment outside the UK, seeking, in some cases, lower cost, fast access to ART, and fewer limitations on the number of embryos transferred. These women were less likely to elect to undergo embryo reduction compared to those who were treated in the UK. Those authors warned that a further increase in this unregulated and under-recognized phenomenon of cross border reproductive care is likely. They noted possible significant financial implications on the national health services of this new trend because of need for additional antenatal care, obstetric complications, and neonatal costs related to high-order pregnancies. In a study of the UK residents with experience of cross-border care [32], it was reported that most patients had several reasons for traveling abroad, including costs, higher success rates, and in 71 % they mentioned desire for timely and affordable treatment with donor gametes. The majority of cycles involved the transfer of two embryos. Most participants reported that they were aware of the risks of multiple pregnancies, but some were willing to accept then as they saw multiple embryo transfer (MET) as their best chance of success. Twins constituted 19 % of the pregnancies reported. According to this study, caution should be taken when concluding that treatment abroad would inevitably result in more high-order pregnancies than similar treatment in the UK.

Cross-border reproductive care has many aspects to be discussed, but completely preventing it is probably impossible in a democratic system committed to free movement of persons [33]. As most medical tourists seek care in Asia and Latin America [34], the challenge is even greater because of lack of systematic data on the extent and experience of cross-border reproductive care outside of Europe and the US.

The International Federation of Fertility Societies (IFFS) [35] lists a range of clinical practices which carry differing regulations in various jurisdictions. One of these is poor regulation regarding the number of embryos transferred. The IFFS claims that economic aspects remain a problem because few countries offer insurance or state support, and that this in turn may influence the number of embryos transferred and contribute to the persistently high multiple pregnancy rates in most countries [35]. Some fertility specialists are concerned that the transfer of a high number of embryos may be applied in poorly regulated countries, as a means of luring foreign patients seeking high pregnancy rates.

Conclusions

Multiple births are strongly associated with an increased risk of obstetric complications, adverse perinatal outcomes, and poor life quality, and present a long-term economic burden on health care systems. eSET has been suggested by many studies as an effective means to reduce multifetal pregnancies, especially in women with good prognosis, and may significantly lower the overall costs. It seems that to improve eSET embracement, there is a need to consider balanced regulation, apply eSET in suitable patients whenever possible, encourage public sector coverage to favor single transfers, and improve patients' and medical providers' education. International data sharing and professional collaboration could improve public interests, while protecting those of the individual.

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