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Obstetric Outcomes and Successful Reduction of Twin Pregnancies Achieved by *In Vitro* Fertilization

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Abstract

The use of *in vitro* fertilization methods around the world is constantly increasing. In some developed countries, up to 5% of newborns are as a result of pregnancies after IVF procedures. In vitro fertilization as one of the main and widespread methods for treatment of infertility is the main reason for the high frequency of multiple pregnancies, which, in many countries, is still too high. Most of the multiple pregnancies are in fact twin pregnancies. Twin pregnancies, regardless of how they are achieved, are associated with large number of complications compared with singleton ones. More often these pregnancies can lead to maternal complications and adverse pregnancy outcomes. Maternal complications include development of preeclampsia, gestational diabetes, placenta previa, placental abruption, premature rupture of membranes, antepartum and postpartum hemorrhage, and delivery by cesarean sections. Adverse pregnancy outcomes mostly include preterm birth (PTB), low birth weight (LBW), small for gestational age newborn (SGA), intrauterine growth restriction (IUGR), neonatal respiratory distress syndrome (RDS), and admission to neonatal intensive care unit (NICU). A number of studies have found differences in the course of twin pregnancies according to their mode of occurrence – spontaneous or after IVF. Some of them have found that twin pregnancies after IVF are associated with poorer obstetric and perinatal outcomes, others do not find such a difference, and there are even studies that find a better outcome in IVF twin pregnancies. Twin pregnancy is a common occurrence after IVF procedure, because multiple-embryo transfer is commonly regarded as an effective strategy to improve the likelihood of a successful pregnancy. Understanding the risks of these pregnancies should be a strong motive for the transfer of fewer embryos during IVF procedures. The most effective way to do this is to transfer a single-embryo into the uterus in cases, where this is justified and the chances of getting pregnant are high. An important element in achieving this goal is the use of methods for vitrification of embryos, which leads to a sufficiently high rate of clinical pregnancies after freezing of embryos obtained by IVF and their subsequent transfer after thawing in case of failure of fresh ET.

Introduction

In vitro fertilization (IVF) method has shown significant development worldwide in the last 40 years since its introduction into clinical practice after the birth of the first child as far back as 1978 [1]. The goal that should be set before each IVF procedure is the birth of a single healthy child, due to significantly lower obstetric and perinatal risk posed by singleton pregnancies compared to multiple pregnancies. All measures must be taken to maintain the highest possible rate of clinical pregnancy when performing assisted reproduction procedures, in particular IVF procedures. Unfortunately, most of the embryos achieved by IVF do not lead to successful pregnancy and delivery. This makes it difficult to decide on the number of embryos to be transferred during IVF. It is not uncommon for more than one embryo to be transferred into the uterus, which inevitably leads to an increase in the incidence of multiple pregnancies and the associated risks to the mother and fetus [2], [3], [4]. Moreover, the expectations of couples undergoing infertility treatment whose main goal is to achieve pregnancy, whether the pregnancy is singleton or multiple gestation, which should not be ignored. Some studies among patients with long-term infertility with the previous failures of assisted reproduction have shown that achieving a twin pregnancy is even a desirable outcome. In these patients, a larger number of embryos are transferred into the uterus, with the aim of achieving a higher rate of clinical pregnancies [5], [6]. Therefore, before performing IVF procedures, clinicians should not fail to explain to patients the risks of multiple pregnancies and thus make a reasoned decision on the number of embryos to be transferred into the uterus [7]. The aim of this review is to compare twin pregnancies achieved both after IVF and spontaneously occurring in terms of course and complications, as well as to analyze possible ways to reduce their frequency in clinical practice.

Comparison of the Course and Complications of IVF and Spontaneous Twin Pregnancies

A twin pregnancy, regardless of the mode of occurrence, carries a significantly higher risk of various complications for the mother, the fetus and for the newborn than for a singleton pregnancy. Complications such as gestational diabetes and preeclampsia, which significantly worsen the perinatal outcome of these pregnancies, are more common [8], [9]. Preterm birth, low birth weight, cesarean delivery, admission to the neonatal intensive care unit, stillbirth, and perinatal mortality are also more common [10], [11], [12], [13], [14], [15]. The main factors for the lower average weight of newborns in twin pregnancies are disorders of fetal growth and the preterm birth. The weight of the fetus in singleton and twin pregnancies does not differ significantly up to 28–30 weeks of gestation (w.g.). After this gestational period, however, the difference in weight increases significantly, as at 34–35 weeks and then the difference, becomes even more pronounced [16].

There is a lot of evidence in the literature for differences in the course of spontaneous twin pregnancies and those after IVF, which, however, is contradictory. Some studies have found that perinatal outcome in twin pregnancies after IVF is worse and that some obstetric complications of pregnancy are more common [10], [17], [18], [19], [20]. According to other authors, there is no such difference in course of pregnancy [2], [21], [22], [23], [24], [25], [26], and there are some studies that claim that the outcome of IVF twin pregnancies is even better than that of spontaneous twin pregnancies [27], [28]. The main outcomes measured in most of the studies available in the literature are maternal complications and adverse pregnancy outcomes. In most of them, maternal complications include development of preeclampsia, gestational diabetes, placenta previa, placental abruption, premature rupture of membranes, antepartum and postpartum hemorrhage, and delivery by cesarean sections. Adverse pregnancy outcomes mostly include preterm birth (defined as birth at <37 weeks of gestation); very PTB (VPTB; defined as birth at <32 weeks of gestation); low birth weight (defined as birth weight <2500 g); very LBW (VLBW; defined as birth weight <1500 g); small for gestational age newborn (birth weight below the tenth percentile for gestational age); perinatal mortality (defined as stillbirth, fetal death, or neonatal death); intrauterine growth restriction (growth below the third percentile for gestational age); and neonatal respiratory distress syndrome and admission to neonatal intensive care unit [29], [30], [31], [32].

A large cohort study found a higher incidence of placenta previa, 15% higher risk of PTB, 39% higher risk of VPTB, and 11% higher risk of LBW in twin pregnancies achieved by IVF compared with spontaneous twin pregnancies. IVF twins are more likely to be born by cesarean section than spontaneous twins [33]. In this study of IVF pregnancies, advanced maternal age and twin pregnancy were independently associated with adverse obstetric outcomes. The role of the age of women undergoing IVF on the outcome of pregnancy and delivery has been studied by other authors [34]. They found that women who became pregnant after IVF were older and, therefore, had a higher risk of some complications – preterm birth, cesarean delivery, and higher mortality. This requires further study of these pregnancies to better understand the difference in obstetric and perinatal outcomes compared with spontaneous twin pregnancies.

Several studies have established the effect of IVF on perinatal and neonatal outcome. It is clearly demonstrated that as the number of multiple pregnancies increases, the number of preterm births increases and, as a result, neonatal morbidity and mortality increase. The frequency of cesarean sections is also increased [35], [36].

To determine neonatal morbidity and mortality among twin pregnancies in Denmark, a large cohort national study was conducted, which included 3393 live-born IVF twins and 10239 live-born non-IVF twins born between 1995 and 2000. It was found that discordant growth of more than 20% between the two fetuses occurred in 20.6% of IVF twins, compared with 15.7% in the control group of twins achieved by spontaneous conception. In this study, the risk of preterm birth and low birth weight was found to be the same in both groups. When comparing only dizygotic twins, there was a certain difference in the course of pregnancy between IVF and spontaneous twins, which, however, disappear after equalization in age and parity. IVF twins had a higher rate of staying in the intensive care unit than spontaneous twins, which was even more pronounced in dizygotic twins. There was no difference in perinatal mortality or in the incidence of malformations in the two groups. This study has a strong point – a large number of pregnancies were covered. The main weakness was that the control group of twins could have been quite heterogeneous, including pregnancies in subfertile women, after stimulation and/or intrauterine insemination. It can be concluded from this study that dizygotic IVF twins have a higher risk of discordant fetal growth and NICU admission, while neonatal outcome is similar to twins conceived without the use of IVF [2].

A large meta-analysis compared the risk of preterm birth and low birth weight in spontaneous twins and those after IVF, after accounting for at least maternal age. The study covered the period 1978–2008 and included 4,385 pairs of IVF twins and 11,793 spontaneous twins. The results showed that IVF twins had increased rates of PTB and LBW, as well as a lower average birth weight compared with spontaneous twin pregnancies. They were at increased risk of VPTB before 32–33 w.g., although the risks of late PTB in the range of 32–36 w.g., and VLBW and difference in the duration of gestation were not significantly different compared to spontaneous twins after matching or controlling for maternal age and sometimes other factors. All this indicated that IVF twins have small but significantly higher risk of early PTB and LBW. There are several possible explanations for these results. The first is that the procedure itself affects the outcome of the pregnancy. The second reason may lie in the very cause of infertility. Third, it may be a consequence of greater monitoring of these pregnancies, often leading to elective preterm birth. There may be a combination of all factors. Some studies included in this meta-analysis took into account the chorionicity of pregnancies and still found significantly higher risks of PTB and LBW in IVF twins [37].

To determine the role of multiple pregnancies on perinatal outcome in women undergoing IVF, a study compared the outcome of two consecutive singleton pregnancies and one twin pregnancy in women who became pregnant through IVF. Preterm birth, very preterm birth, low birth weight, very low birth weight, and small for gestational age were dramatically increased for IVF twins compared with two IVF singletons with the same mother. Significantly higher rates of respiratory complications, sepsis, and jaundice were detected among the IVF twins. Furthermore, higher rates of pre-eclampsia and cesarean section were observed for IVF twins. Similar differences in the course of pregnancy are observed in singleton IVF pregnancies [38], [39], [40], [41], [42], but they are much more pronounced in twins. These results strongly support single-embryo transfer to minimize the risks associated with twin pregnancies [43].

Strategies to Reduce Multiple Pregnancies after IVF

According to most studies available, multiple pregnancies are the main risk factor leading to complications during pregnancy achieved by *in vitro* fertilization. A policy to limit their occurrence should be considered and put into practice. Deciding on the number of embryos to be transferred during IVF procedures is not always easy and a number of factors must be taken into account to achieve a higher rate of clinical pregnancies. Among the most important factors are a woman's age. As a woman ages, the incidence of autologous oocyte pregnancy decreases [5], [44]. Another important factor in deciding the number of embryos to be transferred into the uterus is the number and quality of embryos obtained. The ability to select the best quality embryos would allow a smaller number of embryos to be transferred, without significantly affecting the frequency of live births. A number of methods have been developed to determine the quality of embryos, with morphological assessment remaining perhaps the most important [45]. Embryos that divide more slowly are less likely to be implanted. Additional morphological criteria are the presence of fragmentation, morphology of polar bodies, morphology and orientation of pronuclei, and time of first division. All this is used to evaluate the most suitable embryos for implantation. Assessment with time-lapse morphology, pre-implantation genetic testing for aneuploidy, and metabolic assessment of media culture are also used by some developed countries. It is hoped that these technologies will help in the future to select a single-embryo without reducing the chances of pregnancy [46], [47], [48]. The day of transfer affects the number of embryos transferred because implantation rates increase as embryos survive longer in culture. More day 3 cleavage stage embryos are transferred than day 5 blastocyst stage embryos [49].

The average number of embryos transferred in IVF cycles varies considerably over time and in different countries. Over the years, an increasing number of European countries have joined the European IVF Monitoring (EIM) and more and more information is being received about the course of IVF cycles in Europe. It is noteworthy that fewer embryo transfers of three or more embryos are taking place (Table 1). This inevitably leads to a reduction in the frequency of multiple, and in particular twin pregnancies. The incidence of twin pregnancies is still unreasonably high (Table 1), but clinicians are showing a tendency to reduce them, which will lead to fewer obstetric and perinatal complications [50], [51], [52], [53], [54].

Table 1: Number of embryos transferred and twin rates in Europe over the years

EIM year	Twins (%)	1 embryo transferred (%)	2 embryos transferred (%)	3 embryos transferred (%)
2002	23.2	13.7	54.8	26.9
2008	20.7	22.4	53.2	22.3
2012	17.3	30.2	55.4	13.3
2014	17.0	34.9	54.5	9.9
2016	14.9	41.5	51.9	6.2

The only completely safe way to avoid twin pregnancies is to limit the number of transferred embryos to one. Where this is not mandatory, this option is often rejected by couples who want to increase their chances of pregnancy, and some even want twins. The most effective method for avoiding multiple pregnancies is the so-called SET – single-embryo transfer, where only one embryo is being transferred into the uterus. Elective SET (eSET) is the transfer of one good quality embryo when there are at least two good quality embryos. The opinion of the ASRM (American Society for Reproductive Medicine) for eSET is that it is suitable for patients with a good prognosis [55]:

- Age of woman <35 years
- Presence of more than one good quality embryo
- First or second IVF attempt
- Recipients of embryos from donor eggs

Although many countries have adopted and introduced the practice of SET, the incidence of multiple pregnancies still varies considerably in different parts of the world. The highest share of SETs is observed in Australia, New Zealand, some Scandinavian countries and the United States, with some reaching 90% [56], [57]. However, in other parts of the world, more than one embryo is much more likely to be transferred, which inevitably increases the incidence of multiple pregnancies. In Europe, as shown in Table 1, the incidence of SET in 2016 reached 41.5%, mainly due to the lower frequency of SET in Eastern European countries.

A major obstacle to the lack of mass implementation of SET in some countries is the fear of a lower live-birth rate associated with SET compared to double-embryo transfer (DET) after a single fresh embryo transfer. With the development of vitrification of embryos techniques, the rate of clinical pregnancies after frozen/thawed embryo transfers has increased significantly. A policy for two consecutive SETs – one with fresh and the other with frozen/thawed embryos has been implemented in some countries as a relatively secure alternative to DET. Evidence for the efficacy of this policy has been found in a study that found similar pregnancy rate after DET and two consecutive SETs, one with fresh embryo and the other with frozen-thawed – 43% versus 39%. The difference in twin rate was significant – 15% twins when DET was performed and 0–2% in SET [58].

Conclusion

More of the studies available at this time confirmed the increased maternal and perinatal risks in IVF twin pregnancies compared to spontaneous ones. The risks of placenta previa, PTB, VPTB, and LBW are significantly higher in twin pregnancies after ART. In addition, the IVF twins were more likely to be delivered by elective cesarean sections. A priority in the management of twin pregnancy should be accurate prediction and early detection of these complications to improve the outcomes. Further, well-designed studies are needed to make a difference between IVF and spontaneous twin pregnancies. Where possible, SET must be applied during IVF procedures.

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