The dilemma of the increased obstetric risk following assisted reproduction

Summary
of Ph.D. thesis

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2004

INTRODUCTION

Demography of infertility and its action on society

During the second half of the 20th century, developed countries have experienced both some degree of population growth and unprecedented declines in fertility rates. Couples in most European countries now have fewer than 2 children on average and they tend to postpone these births until a later age. In France, the mean age at first birth for women is now over 27 years, roughly 3 years more than 20 years earlier. This new trend has several causes: the lengthening of the period of education, the more frequent entry of women into the labor market, the uncertainties of this market, and the availability of effective contraceptive methods. It is therefore unlikely to be reversed in the near future.

The main reason for low birth rates is obviously that men and women want fewer children. Some couples, however, are not able to have the children they would like to have, and the question has been raised of whether fecundity is actually currently declining or not. The issue is made more crucial by the new behavior shown above: if women tend to postpone childbearing to an older age, they might also face a decline in fecundity due to advancing age. This decline is not easy to assess, because several features interfere: the risk of spontaneous abortion undoubtedly increases with increasing maternal age, permanent sterility comes well before the menopause, and fecundability might also decline after a particular age.

A possible decline in fecundity over time has been suggested by studies of sperm quality and counts, but not everywhere. We must be cautious, however, because couples tend to be more and more impatient when they decide to have a child, and a recent study has shown that the time to pregnancy is currently declining in Britain. The most likely possible reasons for the declining birth rates in most European countries are clearly social and economic rather than medical, since no clear correlation can be discerned between the availability and practice of contraceptive methods, nor between abortion rates and birth rates. Thus, countries such as Italy or Spain, where there has been a relatively low frequency of use of oral contraceptives (OCs) and other contraceptive methods in the past, and also relatively low and declining abortion rates, likewise have very low birth rates. In the same way, at least within the ranges observed within the European Union, there is no clear correlation between the age at first marriage and the fecundity rate. For example, the age at first marriage is around 26–27 years in Italy or Spain, with very low birth rates, but around 29 years in Denmark, Sweden and

Iceland, with appreciably higher birth rates. In the whole of eastern Europe, the mean age at first marriage is as low as 22 years, but the fecundity rates are still around or below 1.5.

The current prevalence of infertility in Western and developing countries is ~10% of married and cohabiting couples in which the female partner is aged 15–44 years, as indicated above. Since females aged 15–44 years comprise ~20% of the population in developed countries, 2% of a given country's population are infertile female partners. Thus, the current prevalence of infertility is one infertile couple for every 50 individuals in the population (or 20 000 per million population).

Women who seek help for fertility problems are older, have a higher income and are more likely to be married than infertile women who do not seek such help. Nevertheless, the distribution of occupations among those attending tertiary care infertility centers is typical of the distribution in the population. In five European countries, the proportion of infertile couples seeking medical attenion ranged from 19% in Poland to 61% in Denmark. The uptake of clinical services by infertile couples in some other surveys averaged <50% of those with infertility. If it is assumed that 50% of infertile couples seek medical care services, this is equivalent to 5000 couples seeking care for current infertility per million population.

The prevalence of subfertility remains close to 10%, and studies from a number of countries indicate that approximately 50% of infertile couples make use of infertility services, including *in vitro* fertilization - embryo transfer (IVF-ET) and intracytoplasmic sperm injection (ICSI), which are available in 45 countries covering 78% of the world's population. It is estimated that the current level of service is sufficient for less than one-third of the need.

Assisted reproduction and infertility

IVF-ET has been playing a crucial role in the treatment of infertility since 1978, and serves as the basis of various assisted reproductive techniques (ARTs). During recent decades, IVF-ET has become a widespread realistic alternative for infertile couples. In Europe, more than 200 000 IVF/ICSI cycles are started annually, which account for 500–1500 cycles per million inhabitants per year. In 2000, the clinical pregnancy rate per transfer was 28.6%, and the total multiple delivery rate was 26% (24% twins). The children born after ARTs constituted 1–3% of the overall number of live births in European countries. These figures indicate that ARTs are available and practised on a large scale. Numerous scientific studies have shown that ARTs furnish efficacious treatment in subfertile couples. In spite of their established efficacy,

little attention has been paid so far to the safety of ARTs, i.e. to their adverse events and complications.

Concerns about *in vitro* fertilization

The major concerns about the obstetric risk of pregnancy after IVF-ET are related to the higher rate of multiplicity, previous infertility, primiparas aged over 35 and the technique itself. Studies on the obstetric outcome of such pregnancies, and especially twin gestations, have revealed differences from those conceived naturally. Higher rates of preterm deliveries, low birthweight of infants, a shorter duration of gestation, cesarean section, placenta previa and pregnancy-induced hypertension have been reported after IVF-ET. Some reports concluded that there is an increased risk of congenital malformation, though others did not. When controlled for maternal age, parity, ethnic origin and location of delivery, singleton IVF pregnancies have been reported not to involve an increased risk of prematurity, low birthweight, maternal or fetal complications. However, matched controls have yielded adverse results as concerns IVF-ET.

A comparison of the outcome of ART children and naturally conceived children may be hampered by the differences in characteristics of the infertile patients, such as age and genetic risks. Follow-up studies are further modified by the type of neonatal surveillance protocol, the number of individuals lost to follow-up, the size of the cohort study, and the lack of standardization, for example to define major anomalies. The different percentages of major and minor congenital malformations cannot be compared, but overall the data from large and reliable surveys do not indicate a significantly higher rate of malformations than among naturally conceived children, though the prevalence of heart malformations has reached the level of significance in some studies. To date, only a few studies have examined the medical and developmental outcome of ART children at 1 and 2 years. These do not reveal obvious problems, but in the future further comparison of matched cohorts of children and case-control studies are needed before final conclusions can be drawn.

Besides malformations and preterm delivery, the frequency of small-for-gestational age (SGA) is also an important issue to be investigated. Infants born SGA display a reduced cognitive capacity at a young adult age as compared with controls. However, this lower capacity is not considered sufficiently severe to affect the educational level or social adjustment. Being born SGA is associated with an increased risk of subnormal capacity in all

four dimensions (logical, spatial, theoretical and verbal capacity) of intellectual performance. The SGA status seems to have only modest independent effects on learning, cognition, and attention in adolescence. The severity, but not the symmetry of growth restriction predicts learning difficulties.

Multiple pregnancy as a major concern in all ARTs elevates both the maternal and the neonatal complication rate. An important point to be investigated is whether a twin pregnancy following IVF-ET presents a higher risk from all these aspects than in the spontaneous counterparts. Recent studies support the hypothesis that, after stratification for maternal age and parity in terms of maternal risks and perinatal outcome, no significant differences can be observed. Nevertheless, IVF twin mothers are more frequently on sick leave and hospitalized during pregnancy. Furthermore, the maternal risks are higher and the obstetric outcome is poorer in IVF twin versus IVF singleton pregnancies.

Multiple gestation is now recognized as a major problem associated with both ARTs and ovulation induction therapies. There is a clear need to ensure recognition and a correct approach to this problem worldwide in order to reduce its incidence.

AIMS OF THE STUDY

Though dozens of publications have evaluated the obstetric and neonatal outcome of pregnancies following IVF-ET, there is still an urgent need to accumulate knowledge on this field. The basic concept was to establish a correct database on the deliveries following ARTs at the Department of Obstetrics and Gynecology, University of Szeged. This tertiary center, working in conjunction with the Neonatal Intensive Care Unit (NICU), Department of Pediatrics, University of Szeged, collects all the high-risk pregnancies from the region, including multiples.

A comparison of the outcome of ART children and pregnancies with naturally conceived ones may be hampered by the differences in the characteristics of the infertile patients, such as age, parity and previous obstetric outcome. A comparison of IVF-ET pregnancies with a clinical or national average is meaningless if we consider that the average age is higher and older primiparity is extremely frequent. The primary aims of our study were to evaluate the obstetric outcome of IVF-ET pregnancies, to establish a database from controls matched for age, parity and previous obstetric outcome, and to make an accurate statistical comparison between the two groups. With the help of this method, the roles of different risk factors (age,

primiparity, multiplicity and the ART) concerning the perinatal outcome of pregnancies after ARTs can be clarified.

The questions that we investigated were as follows:

1. Which pregnancy characteristics, intrapartum complications and neonatal parameters reveal differences from those in pregnancies conceived naturally?

2. Which risk factors can still be observed if we carry out examinations versus a control group matched for maternal age, parity, previous obstetric outcome and body mass index (BMI)?

3. What is the incidence of major congenital abnormalities among neonates delivered following IVF-ET as compared with a matched control group?

4. Further important aims were to examine the outcome of multiple pregnancies in comparison with spontaneous ones and triplets in their crude distribution, and to attempt to confirm our hypothesis that a multiple pregnancy is one of the major factors increasing the risk of ART.

5. Is it possible to reduce the rate of infertility therapy-associated multiple pregnancies by selecting and providing good-quality embryos and transferring the optimal minimum number of embryos for success?

MATERIALS AND METHODS

The births in the period between January 1, 1995 and February 28, 2002 were subjected to retrospective analysis. 230 (1.7%) of these deliveries were after IVF. 185 singleton and 36 twin pregnancies were evaluated and matched with spontaneous pregnancies as controls as regards age, parity, gravidity and previous obstetric outcome. The samples were comparable. The 13 triplet pregnancies were observed and analyzed in their crude distribution. Demographic and other selected maternal characteristics, pregnancy and labor complications and neonatal outcome were compared between the two groups. The following antepartum complications were examined: gestational diabetes mellitus, preeclamptic toxemia, myoma, placenta previa, malpresentation, placental abruption, premature rupture of the membranes, intrauterine infection, oligohydramnios and polyhydramnios. The following intrapartum characteristics were assessed: cesarean section, fetal distress, fetopelvic disproportion, retained placenta, postpartum hemorrhage, prolonged labor and prolonged second stage.

Macrosomia was taken as a birthweight of ≥ 4000 g. SGA was defined as a birthweight below the tenth percentile for that gestational age, according to the Hungarian data.

Intrauterine infection was recorded when the mother had fever and leukocytosis, and the neonate had tachycardia. Fetal distress was defined as the presence of repetitive late decelerations, severe variable decelerations, bradycardia, persistent fetal tachycardia or meconium-stained amniotic fluid. The BMI was calculated as the body weight (kg) per height (m^2).

Besides the matched control study, an evaluation was performed concerning inter-twin birthweight discordance among 75 twin pregnancies after ARTs (ovulation induction, intrauterine insemination and IVF-ET) and their 94 spontaneous counterparts. A birthweight discordance was defined as a difference of 20% or more. The discordance rate and the possible connection of the phenomenon with the prevalence of congenital anomalies, the rate of prematurity, SGA neonates, an Apgar score at 5 min <7, an umbilical cord arterial pH<7.20, NICU transfer and sex ratio were evaluated.

The reported rate of birth defects following IVF-ET varies from 3.4% to 9.0%. The major congenital anomalies, as one of the most important risk factors, were evaluated separately by comparison with a matched control group. Finally, the results from the Kaali Institute in Szeged in 2003 will be listed, with the focus on the pregnancy outcome and multiple rates, in comparison with the latest available European results.

Statistical analysis

Statistical analysis was performed with the SPSS 8.0 Windows program. Differences in the characteristics of the outcomes of singleton pregnancies between the two groups were assessed by the Fisher exact test for categorical variables and the Student t-test for continuous variables. Odds ratios (ORs) and 95% confidence intervals (CIs) were also calculated for categorical variables. Comparisons between the twin groups were performed with the Mann-Whitney U-test and the Wilcoxon test for categorical and ordinal variables. The significance level was set at 5%, two-tailed.

For the evaluation of inter-twin birthweight discordance, statistical analysis was performed with the SPSS for Windows program (SPSS 11.0, Inc. Chicago). The Kolmogorov-Smirnov test was used to test the statistical normality in the surveyed groups. Univariate comparisons were assessed with the Mann-Whitney U-test and the Wilcoxon test for continuous and categorical variables, respectively. Normality was not proved in our samples, due to the low

number of statistical entries, and nonparametric tests were used to test the difference between the case and control groups. In the testing of the null-hypothesis, the statistical power at the defined statistical significance level of P<0.05 ranged between 0.8 and 0.68. The Mantel-Haenszel test was used to estimate the correlation of variables between the discordant and the nondiscordant twin pregnancies relative to the correlation in the case-control group.

RESULTS

Singleton births following IVF-ET

The first group evaluated comprises the singleton pregnancies following IVF-ET, compared with the matched spontaneous counterparts.

The singleton IVF-ET mothers were significantly less highly educated (P<0.05), whilst the mothers of twins had a higher educational level, but the difference did not reach the level of significance. The BMI before delivery did not differ between the two groups, whereas the weight gain during pregnancy was significantly higher among the singleton IVF-ET mothers. The rates of primiparity and primigravidity did not differ statistically significantly between the two groups, reflecting the success of the matching procedure. Congenital anomalies of the uterus were more common among the singleton IVF-ET pregnancies.

The birthweight of the neonates was significantly lower, whereas the incidence of prematurity was significantly higher among the IVF-ET cases. Statistical differences were not observed as concerns the gestational age and the rate of SGA. Macrosomia was significantly more common among the spontaneous pregnancies.

Threatened preterm delivery was significantly more prevalent among the IVF-ET pregnancies. Almost all pregnancy complications occurred with higher frequency among the IVF-ET pregnancies, with the exception of meconium-stained amniotic fluid, intrauterine infection and oligohydramnios. The rates of myoma, placental abruption and polyhydramnios were extremely low in both singleton groups.

Surprisingly, significantly higher levels of cephalopelvic disproportion, prolonged labor and a prolonged second stage were noted among the control singleton pregnancies. The incidence of cesarean section was noteworthy among the IVF-ET pregnancies, but the difference did not reach the level of statistical significance.

Twin births following IVF-ET

The mothers of twins following IVF-ET had a significantly higher educational level. The BMI before delivery did not differ between the two groups, whereas the weight gain during pregnancy was significantly higher among the mothers of spontaneously conceived twins. The rates of primiparity and primigravidity did not differ statistically significantly between the two groups, reflecting the success of the matching procedure.

The gestational age of the IVF-ET twins was longer, while the rates of premature birth and SGA were very similar. The birthweight of the IVF-ET twin neonates proved significantly higher. There were no statistically significant differences between the case and control twin groups in the rates of most obstetric complications. Gestational diabetes mellitus, preeclampsia, threatened preterm delivery, inertia uteri, meconium-stained amniotic fluid, malpresentation and premature rupture of the membranes exhibited similar rates in the two groups. The rates of myoma, placenta previa, placental abruption, oligohydramnios and polyhydramnios were very low in both groups.

The rates of intrapartum complications in the twin study groups were comparable. The difference in the incidence of cesarean section was considerable, but did not attain statistical significance.

Studies of inter-twin birthweight discordance and SGA

Besides the matched control study, an evaluation was performed concerning the inter-twin birthweight discordance among 75 twin pregnancies after assisted reproduction and 94 spontaneous counterparts. The discordance rate was 25.3% in the ART group versus 17.0% in the controls. The twin A neonates displayed a higher birthweight in both groups. There were no significant differences between the two members of the twins as regards the neonatal outcome. The difference in prevalence of congenital anomalies was not significant (2.7% vs. 1.1%). The prevalence of SGA was 18.7% vs 23.4% in the ART group and in the control group, without any significant difference. In contrast, SGA among the discordants was significantly increased in the case groups (discordant groups: ART 52.6% and non-ART 37.5% vs. nondiscordant groups: ART 7.1% and non-ART 20.5%).

The rate of male infants did not differ significantly in the two samples. NICU admission was more prevalent among the discordant pregnancies (ART: 55.3%; spontaneous: 71.9%) than among the nondiscordant twins (ART: 36.6%; spontaneous: 49.4%). The incidence of a low Apgar score was higher among the spontaneous (18.8%) than the ART discordant group (2.6%), whereas the prevalence was higher among the nondiscordant ART cases than the

spontaneous counterparts (14.3% vs. 11.5%). The umbilical cord arterial pH levels were similar. Unlike-sexed twins were observed at a significantly higher rate among the discordant ART group (discordant groups: ART 73.7% and non-ART 37.5% vs. the nondiscordant groups: ART 37.5% and non-ART 33.3%). The educational level of the pregnants was higher in the case group, improving the cooperation of the mother during pregnancy and determining an optimized lifestyle (e.g. smoking habits). The significantly elevated risk of SGA in the discordant group (both ART and non-ART) is very important as regards the long-term consequences of multiple pregnancies.

The incidence of SGA and premature delivery in our study proved to be higher after IVF-ET, but without attaining the level of statistical difference as compared with the matched control. The incidence of SGA in the singleton IVF-ET group was 8.1% versus 4.3% among the spontaneous matched controls (statistically not significant; OR; 95% CI:1.95) and 30.6% (IVF-ET) vs. 30.6% (matched control) in the twin pregnancies overall. Triplets, with a 43.6% incidence of SGA, provide further evidence of the greatly increased neonatal risk associated with multiple deliveries. To summarize, the overall incidence of SGA (18.24%) in the IVF-ET group as compared with the Hungarian National Database (8.6%) indicates the harmful effects of multiple pregnancies.

Triplets following IVF-ET

The rates of cesarean section (100%) and threatened preterm delivery (92.3%) indicate the elevated obstetric risk, and the rates of prematurity (53.8%) and SGA (43.6%) the increased neonatal risk in this group.

Distribution of major congenital defects

The incidence of major congenital abnormalities was not significantly higher (P>0.05) among the cases (n=5, 1.90%) than among the controls (n=3, 1.15%). The 39 triplets exhibited no major malformations. Birth defects were diagnosed 4 weeks after delivery. The prevalence was lower than that reported by others. When the analysis included pregnancies terminated because of fetal abnormalities detected prenatally (+ 2 cases during the 6-year period vs. +1.0% in the Hungarian National Database control), the statistical relation (2.67% vs. 2.25%, P>0.05) was unchanged. The rate of major birth defects was comparable with the clinical average (1.90% vs. 2.20%, P>0.05).

Results at the Kaali Institute in Szeged

Finally, results from the Center for Assisted Reproduction, Kaali Institute, Szeged University are presented. The ultimate goal of our activity is to reduce the rate of infertility therapy-associated multiple pregnancies by selecting and providing good-quality embryos and transferring the optimal minimum number of embryos for success. After a thorough evaluation of the predictive factors and individualization of the number of embryos transferred, the multiple birth rate has been reduced, and in 2003 the incidence at the Kaali Institute in Szeged was below the latest accessible European average. In a 5-year period, we succeeded in reducing the number of embryos transferred from an average of 2.74 (1998) to 2.06 (2003). As we did not wish to deteriorate the pregnancy rates, this modification demanded a long process. We need to have better-quality embryos with a higher chance of implantation, and at the same time we have to be able to prognose which patient needs more than 2 embryos and which patient needs 1 embryo to achieve pregnancy. By applying all these methods and focusing on a reduction of the multiple pregnancy rate, in Szeged we have achieved an ongoing pregnancy rate of 29.0% per ET, with a 83% singleton rate from 571 embryo transfers (2003). The multiple birth rate was 16.9%, i.e. less than the European average of 26.4% (2000), and also less than the latest data available from the US: 53% (2000).

DISCUSSION

1.   Threatened preterm delivery among singleton IVF-ET pregnancies was significantly more prevalent as compared with a matched control group. The birthweight of the neonates was significantly lower, whereas the incidence of prematurity was significantly higher among the IVF-ET cases. On the other hand, significantly higher levels of cephalopelvic disproportion and prolonged labor were noted among the control singleton pregnancies.

The overall pregnancy and labor complication rates were comparable, but controversial; no other significant difference could be observed.

The duration of gestation of the IVF-ET twins was longer, while the rates of premature birth and SGA were very similar. The birthweight of the IVF-ET twin neonates proved significantly higher. There were no statistically significant differences between the case and control twin groups in the rates of most obstetric and intrapartum complications. The difference in the incidence of cesarean section was appreciable, but did not attain the level of statistical significance. The twin pregnancies (like their spontaneous counterparts) exhibited

considerably increased rates of SGA (>30%) and premature birth (>60%) relative to the singletons. The triplets, with an extremely high premature rate and a >40% incidence of SGA, further demonstrate the greatly increased neonatal risk associated with multiple deliveries.

The rate of significant discordance (>20% inter-twin birthweight difference) was higher in the ART group than among the controls. SGA among the discordants was significantly increased as compared with the non-discordant group. Our study has provided further evidence that unlike-sex pairs are significantly more prevalent among discordant ART twins. Discordant ART pregnancies are associated with a high risk of SGA and an increased incidence of NICU admissions. The observed increased incidence of birthweight discordance following ARTs can be an important risk factor that is partly responsible for pregnancy complications and an adverse perinatal outcome.

The high frequency of cesarean section observed in our study accords with previous literature reports, though the difference in our matched control study did not reach the level of significance.

2. In our study, the incidence of SGA, premature delivery and cesarean section proved to be higher after IVF-ET, but without attaining the level of statistical difference as compared with the matched control. However, the overall incidence of SGA was 18%, that of premature birth was 36% and that of cesarean section was almost 50% in the IVF-ET group. The Hungarian National Database (SGA: 9%, premature birth: 8.7%) figures reveal the less optimal effects of multiple pregnancies on the incidence of SGA, premature delivery and cesarean section.

3. The prevalence of major congenital birth defects that we observed was lower than that reported by others. The incidence of major congenital abnormalities among the 262 IVF neonates was not significantly higher among the cases (1.90%) than among the controls (1.15%), and was comparable with the clinical average (2.20%). When the analysis included pregnancies terminated because of fetal abnormalities detected prenatally, the statistical relation was unchanged. The application of matched controls to evaluate the perinatal effects of IVF-ET on the incidence of major birth defects indicates that the risk due to the method itself is minimal. Differences in the absolute risk of congenital abnormalities can be influenced by maternal age, certain maternal diseases, medication, toxic habits, environmental toxic effects and population variation. The different prenatal screening methods applied (e.g. nuchal translucency and chorion biopsy) and national guiding principles concerning prenatally detected malformations can also significantly modify the

perinatal outcome concerning congenital anomalies. It is therefore very important to collect safety data prospectively as the use of ARTs in infertility therapy has undergone a dramatic increase worldwide.

4.　　The matching procedure for establishment of a control group will clearly most closely reflect the relative risk of the ART method. The application of matched controls to evaluate the obstetric and perinatal effects of IVF-ET on the incidence of pregnancy and labor complication rates demonstrates that the risk due to the method itself is minimal.

IVF-ET involves only a slightly increased obstetric risk. The neonatal outcome exhibits a very low difference as compared with that for naturally conceived pregnancies, with a significantly higher rate of premature birth in singleton pregnancies. The rate of triplet pregnancies following IVF-ET should be minimized in view of the much higher risk as concerns both the obstetric and the perinatal outcome. The comparison of pregnancies following IVF-ET with a population-based control reflects an unquestionably elevated obstetric risk.

5.　　Since 1980, there has been a dramatic increase in multiple births worldwide. This seems to be due to an increase in the age of reproduction, the introduction of ovulation induction, and the use of IVF. Unfortunately, almost a third of these pregnancies involve multiple gestations. Research is currently focusing on methods to improve IVF success rates while reducing twin and triplet pregnancies and their associated increased morbidity and mortality.

As concerns the question of whether it is possible to reduce the rate of infertility therapy-associated multiple pregnancies, my answer is a clear yes. In a 5-year period, we have succeeded in reducing the number of embryos transferred from an average of 2.74 (1998) to 2.06 (2003). By selecting and providing good-quality embryos and transferring the optimal minimum number, the multiple pregnancy rate in Szeged in 2003 remained below 18%.

Multiple pregnancies

If 25% of all pregnancies after IVF/ICSI are twin pregnancies, 40% of all babies born after ARTs are born as twins. Many physicians and patient couples underestimate the negative consequences of twin pregnancies.

Both perinatal and maternal mortality and morbidity are increased in multiple pregnancies as compared with singleton pregnancies, due to the higher rates of prematurity and low birthweight in the children, and due to pregnancy complications in the mothers. Furthermore,

parents of multiple births suffer more stress, and siblings of multiples are more likely to reveal behavioral problems.

ART programs do not consistently report success. The rate varies with the definition used. Success must reflect the delivery of healthy babies, and the burden of the treatment of the couples. The leading quest for infertility experts should be a further reduction of the rate of multiple pregnancies following IVF-ET. The ethical dilemma for the infertility practitioner is to create a balance between the desire to maximize the opportunity for the infertile couple to have a child and the need to minimize the risk of harm to the future child and the family.

The policy at the Kaali Institute in Szeged since 2001 has been to transfer only 2 embryos to females under 35 years of age during the first 2 IVF attempts. Accordingly the decision to optimize the outcome is made by the physician together with the infertile couple after a thorough evaluation of the anamnesis, the reaction to the stimulation, the quality of the pre-embryos and the age of the female partner. One of the most important factors is the patient age, but many other features are known to influence the possibility of a successful outcome. Additional, but important factors include the duration and type of infertility, previous IVF treatment and previous pregnancy, particularly a live birth, the hormonal status and the endometrium thickness on the day of embryo transfer. Every practitioner active in the field of ART treatment is aware of the risks and complications involved in twin and higher-order multiple pregnancies. The possible introduction of single embryo transfer (SET) into IVF/ICSI in the near future is one of the potential ways of reducing the rate of twin pregnancies. Careful selection of the patients, in combination with elective SET, has been shown to decrease the twin pregnancy rate while maintaining a stable ongoing pregnancy rate. The combination of a woman younger than 38 years of age, in her first or second IVF/ICSI cycle, with an embryo with a high implantation potential is the key to successful SET.

Offering an individualized embryo transfer policy together with strict quality control during the whole ART process can result in an acceptable multiple pregnancy rate without causing a decrease in the overall pregnancy rate.

CONCLUSIONS

From the outset, the invasive nature of IVF and ICSI led to concerns about the safety and potential risks, especially for the general health, growth and future fertility of the offspring. One of the main difficulties in determining the health outcome of ART offspring relative to that of their spontaneously conceived counterparts is the heterogenous nature of both the cause of infertility and the wide range of possible health effects. To detect such differences will require infertility specific stratification within very large studies or studies of specific diagnostic groups. We now have a body of evidence which suggests that children born following ARTs are at a slightly increased risk of a diverse range of adverse health outcomes. Some of these findings are controversial and would benefit from replication.

In terms of our current understanding, given the certainty of the outcome and the magnitude of the effect, the single most important impact of all forms of ARTs on the health of the offspring remains the multiple pregnancy rate. The risk of conception of a multiple pregnancy is directly related to the number of embryos replaced. This is the reality accompanying the hope that must be conveyed during the counseling of all couples contemplating treatment.

Safety, efficacy and quality in ARTs should mean encouragement of the transfer of fewer embryos, in order to diminish the number of multiple pregnancies without seriously compromising the pregnancy rates, as an ultimate answer for this challenging triple target.

ACKNOWLEDGMENTS

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