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CHILDREN AFTER IN VITRO FERTILIZATION

An Overview of the Literature

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Abstract

This paper provides an overview of the effects of in vitro fertilization (IVF) on the children born from it. One of the main problems with IVF to date remains the high incidence of multiple pregnancies, which carry an inherent higher risk of preterm delivery and, therefore, of increased morbidity and mortality in newborns. Further, singleton pregnancies and twin pregnancies from IVF compared to control singleton or twin pregnancies appear to be at higher risk of preterm birth and low birth weight. Whether this is an effect of the procedure per se or is related to maternal factors, or a combination of both, remains to be studied. The risk of congenital malformations does not, with the available data, seem to be elevated. As of now, it remains unclear whether embryo freezing is a safe procedure. Psychomotor development of children born through IVF does not seem to be disturbed. Until further and more extensive studies are conducted, it remains unclear whether IVF poses long-term risks for the children.

Keywords: IVF, Side-effects, Follow-up Studies, Review, IVF Pregnancies, IVF Children

In vitro fertilization (IVF) was introduced in most western countries during the early 1980s as a new treatment for infertility. Its introduction was not accompanied by formal evaluation of the possible adverse effects on the health of the women, the course of the pregnancies, or the health of the babies and children born from it. IVF has nevertheless become widespread during subsequent years. In the Netherlands, the first baby was born after IVF in 1983. In 1997, approximately 1% of all Dutch babies were born after IVF. The development of IVF has led to the introduction of related new techniques, such as intracytoplasmatic sperm injection (ICSI). ICSI can help overcome severe male factor infertility. Instead of bringing together a number of egg cells with millions of sperm in a petri dish (as is the case with IVF), with ICSI each egg cell is injected with a single sperm cell. Even in 1998, many of the questions concerning short- and long-term effects of IVF on the children have not been sufficiently answered. Like IVF, spin-off techniques such as ICSI have become popular without careful evaluation of potential side effects.

Each of the different phases of the IVF may carry the risk of side effects for the developing embryo. First, hormonal treatment of the woman takes place to enable ripening of more than one follicle and, often, to better time the optimal moment of follicle aspiration. Most of the hormonal preparations used have not been studied sufficiently for potential teratogenic effects or for effects on the course of a subsequent pregnancy. Second, oocyte retrieval takes place. Theoretically, this phase could carry the risk of mechanical damage to the egg cells. Third, eggs and pretreated sperm are brought together in a petri dish to permit fertilization. Fertilized eggs are transferred into a special culture medium for further growth. It is as yet unclear whether substances in the culture medium may have teratogenic effects on the growing embryo. Fourth, if dividing embryos develop, they can be transferred back into the uterus. Potentially, the mechanical process of placing the embryo into the uterus may lead to a less optimal place of nidation and placentation than would be the case in a naturally occurring pregnancy. Fifth, surplus embryos may be frozen to be transferred in a later cycle. Freezing may potentially be harmful to the embryo.

Since the late 1970s, a vast number of articles have been published concerning the likelihood of pregnancy per IVF cycle. Patient characteristics, but even more, aspects of the treatment protocol, have been studied extensively for their effect on the success rate. The course of subsequent pregnancies and especially the development of children born after IVF have been much less extensively studied. This paper presents an overview of the published research data concerning the outcome of IVF pregnancies and the subsequent development of the children. Risks for the woman will not be discussed.

MULTIPLE PREGNANCIES

Since the success per cycle of IVF depends to a great extent on the number of embryos being placed in the uterus, in the majority of IVF treatments more than one embryo is transferred. Consequently, a large percentage of IVF pregnancies are multiple pregnancies. In most publications, mention is made of a multiple pregnancy rate of 25% to 30%. Approximately 3% of IVF pregnancies consist of triplet or higher order pregnancies (1;14;16). Thus, almost half of all children born after IVF are part of a multiple pregnancy. Multiple pregnancies inherently carry a higher risk of complications, of which prematurity, intrauterine growth retardation, and perinatal mortality are the most important (9;26). In most IVF cohorts an excess of prematurity, low birth weight, and perinatal mortality are observed, which seems primarily related to the high incidence of multiple pregnancies. A large French study of IVF pregnancies (16) showed a prematurity rate of 29%, a low birth weight rate of 36%, and a perinatal mortality rate of 27 per 1,000, with the excess in adverse outcomes mostly caused by the multiple pregnancy rate. D'Souza et al. (14), reporting outcomes of an IVF cohort, indicated that the higher percentage of preterm deliveries was largely due to the multiple births and that they contributed to adverse neonatal conditions in 45% of all IVF children in the cohort. These data are in accordance with figures on outcomes of multiple pregnancies in other IVF cohorts.

The rate of triplet and higher order pregnancies depends largely on the clinic's policy with respect to number of embryos being transferred. In the Netherlands, the present policy is not to transfer more than two embryos, unless their individual quality is very low and/or the woman is of higher age, in which case the expected chance of success per embryo is low. This policy is expected to lead to a reduced rate of multiple pregnancies in the near future.

LOW BIRTH WEIGHT, PRETERM BIRTH, AND SMALL FOR GESTATIONAL AGE IN IVF SINGLETONS

Many authors have reported an increased incidence of adverse pregnancy outcomes in singleton children conceived through IVF. A number of these studies involved population figures as controls, or employed no control groups at all, thus rendering it impossible to adjust for factors such as maternal age and parity, which are known to be different in the IVF population as compared to the general population of pregnant women. In an Australian cohort, the low birth weight rate in 700 singleton children conceived through IVF, was reported to be 15.6% (4). A study of 741 IVF singletons found a low birth weight scale of 12%, not compared to a control group (6). A study of 648 IVF singletons found 13% preterm deliveries compared with 6% in the general population, 11% versus 6% low birth weight, and 17% small for gestational age (SGA) compared to 10% (13). The study did not control for confounders such as maternal age and parity. Olivennes et al. (34) compared 162 singleton IVF pregnancies with 263 pregnancies from stimulated cycles without IVF and with 5,096 natural pregnancies. Prematurity occurred in 11.1% in the IVF group, in 6.1% in the stimulated group, and in 4.4% in the spontaneous group. Low birth weight occurred in 11.1%, 6.5%, and 3.6%, and SGA in 11.2%, 10.6%, and 5.9%, respectively. Only the differences between the IVF group and the spontaneous group reached statistical significance. The mothers who had undergone IVF were older and more often primiparous than mothers in the two other groups. No attempt was made to control for these differences in the analysis. Rufat et al. (42) compared IVF singletons to population controls (not adjusting for possible differences between the IVF group and the control group) and found a risk of prematurity of 12% compared with 5.6% and a 15% birth weight under the 10th percentile. A large national French study (16) found a prematurity rate of 9.4% and a low birth weight rate of 11.2% in almost 4,000 IVF singletons. These results also were not compared to those in a formal control group.

In a number of studies into outcomes of singleton pregnancies achieved through IVF, attempts have been made to control for certain factors. Tan et al. (47) compared 763 IVF pregnancies to a control group matched for maternal age and parity and found a twofold increased incidence of intrauterine growth retardation and preterm delivery in singleton pregnancies following IVF. A study of 140 singleton IVF pregnancies and an equal number of control pregnancies, matched for maternal age, height, weight, and parity, found that IVF pregnancies were 1 week shorter in duration and that the children weighed 175 g less than control subjects (49). Petersen et al. (36) in a small study compared 70 IVF singleton pregnancies to 70 pregnancies in women with fertility problems, of comparable age and parity, who had not undergone IVF. The preterm delivery rate was 7% in the singleton IVF group, compared with 4% in the singleton control group; the low birth weight rates were 16% and 0%, respectively. A study of 150 singleton IVF children, comparing them to an equal number of control subjects born at term and matched for sex of the child and social class, found that the IVF singletons were on average born one week earlier than the control subjects and weighed 400 g less (14). Reubinoff et al. (38) in a study of 260 IVF singletons, compared with 260 control subjects, found no difference in the percentage of low birth weight and SGA after pairwise matching for maternal age, parity, ethnic origin and location, and place of birth. The infants conceived through IVF were more premature, a difference that largely seemed due to the increase in cesarean sections before 37 weeks in the IVF group. A number of other studies comparing IVF singletons to other singletons also found that IVF singletons have shorter gestational age and low birth weight (19;30;44;50). A summary of these data is presented in Table 1.

Most of the studies into pregnancy outcomes after IVF singleton pregnancies have shortcomings in the sense that they do not employ a formal control group, or if one is used, the number of factors that is being controlled for is limited. The evidence, however, that IVF singleton pregnancies are more likely to end preterm and result in low birth weight babies is overwhelming. It is clear from the abovementioned literature that IVF singleton pregnancies have worse outcome than naturally conceived singleton pregnancies, although it is less clear whether this is related to the IVF procedure per se or to other factors. Women who give birth following IVF are older on average and more often primiparous. They may be of higher socioeconomic status and may have different risk-taking behaviors (such as smoking and drinking) during pregnancy. They may suffer more from certain chronic conditions that may influence fertility as well as the outcome of pregnancy. The infertility itself, instead of the procedure, may cause worse pregnancy outcomes. If after controlling for these potential confounders simultaneously, an effect of IVF remains, it would suggest a harmful effect of the procedure itself instead of a negative effect of maternal factors on the outcome. Unfortunately, none of the studies carried out so far has controlled for a large number of potential confounders at the same time, thus rendering it impossible to draw a firm conclusion as yet.

In a few studies, attempts have been made to control for the cause of infertility that led to IVF. In one of these studies (13), couples for whom tubal obstruction was the main indication for the IVF treatment had lower reported risks of adverse perinatal outcomes, such as low birth weight, than did couples who underwent IVF for reasons related to idiopathic or male infertility. Another study (43) compared spontaneous pregnancies to IVF pregnancies and to pregnancies in untreated women on the waiting list for IVF, finding that the rate of prematurity was comparable in the latter two groups and that both were higher than in the first group. These data suggest that infertility of male or unknown causes may be a risk factor in itself. Olivennes et al. (34) found higher risks of prematurity and low birth weight in the IVF singleton group than in the stimulated group, but still lower rates in the group of spontaneously conceived pregnancies, indicating there may be a risk attached to the ovulation stimulation and a separate risk attached to IVF itself.

If IVF is a contributing factor to the higher rate of low birth weight and/or the preterm labor in IVF singleton pregnancies, instead of the mothers' profile, a number of possible explanations can be offered. Some studies have linked superovulation to reduced birth weight and growth retardation in humans. Elevation of insulin-like growth factor–binding protein (IGFBP-1) is the suggested cause (21;22;24;25;52), which would imply that the ovulation induction within IVF may be harmful to fetal development. Another study suggests that there is a higher incidence of abnormal placental shapes in IVF singleton pregnancies (22% vs. 6% in the control group) and that abnormal umbilical cord insertions are found more often (23). The phenomenon may be related to inadequate orientation of the blastocyst after IVF embryo transfer, which may cause inferior placental functioning. In assisted reproduction with cattle and sheep, culture, embryo micromanipulation, and embryo transfer are known to lead to larger-sized offspring, which in these species is a sign of pathology (53;54). In animal assisted reproduction, neither the animals donating the gametes, nor the recipients, suffer from infertility. Therefore, these adverse effects, if real, have to be related to aspects of the procedure itself.

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MULTIPLE PREGNANCIES FOLLOWING IVF COMPARED WITH OTHER MULTIPLE PREGNANCIES

Multiple pregnancies following IVF may be at higher risk of complications than multiple pregnancies that have been conceived differently. A number of studies comparing naturally conceived multiple pregnancies to multiple pregnancies conceived through IVF either combine all multiple pregnancies in their analysis or suffer from numbers too low to permit firm conclusions (17;39;47).

Two recent studies, however, have specifically compared twin and triplet pregnancies from IVF to twin and triplet pregnancies conceived otherwise (7;18). One study comparing 105 IVF twins to 297 twins after natural fertilization (7) found a significantly higher incidence of low birth weight (72% vs. 59%) and discordant birth weight (23% vs. 14%) in the IVF twin pregnancies compared with the control twin pregnancies, after controlling for maternal age and parity. Prematurity rates did not differ between the two groups. Discordant fetal growth is a complication that especially occurs in monochorionic pregnancies, probably as a result of an imbalance in the blood flow through the placental arteries. It is less likely to occur in dizygotic twins, who have separate chorionic membranes. Therefore, one might expect that discordant birth weight is a phenomenon more likely to be seen in spontaneous twin pregnancies (25% of which are monozygotic) than in IVF pregnancies, which are essentially dizygotic pregnancies only. The authors offer the possible explanation that IVF twin pregnancies are more often of unlike sex than the control twin pregnancies. Unfortunately, no analysis was carried out comparing same-sex twins in both cohorts separately. Both the higher rate of discordant birth weight and higher rate of the low birth weight in the IVF group may be related to decreased functioning of the placenta, as also may be the case in IVF singleton pregnancies. The other study (18) compared 56 triplet pregnancies after unspecified ART to 82 triplet pregnancies after ovulation induction and 13 triplet pregnancies conceived spontaneously. Mean gestational age of triplets following ART (33.2 weeks) was not significantly different from those conceived following gonadotrophin stimulation (33.4 weeks) or stimulation with clomiphene citrate (34.2 weeks), but was significantly shorter than in the pregnancies after spontaneous conception (35.3 weeks). Mean fetal birth weight was 1,743 g, 1,683 g, 1,863 g, and 1,963 g, respectively. Only the difference between the birth weights in the ART and in the spontaneous group was statistically significant. No difference was found in low birth weight rates between the groups, although the very low birth weight rates (<1,500 g) following ART and ovulation induction were significantly different from those in the spontaneous group (31%, 30%, and 10%, respectively).

Although the groups compared are still small in terms of absolute numbers, these results seem to indicate that a possible adverse effect from ART (and therefore from IVF) is more likely to stem from the ovulation stimulation than from other aspects of the procedure. The analysis did not control for maternal characteristics. It is not possible, therefore, to conclude whether age, parity, or other maternal characteristics related to infertility may have (partially) determined the worse outcome in the ART and stimulation group compared with the group of naturally conceived pregnancies. In contrast, another recent study comparing a group of 72 IVF twin pregnancies, 82 twin pregnancies after ovulation induction, and 164 spontaneous twin pregnancies did not find a difference in prematurity rate (39%, 45%, and 40%), SGA (18%, 23%, and 23%) or perinatal mortality (3%, 3%, and 4%) between the three groups (32).

Table 1. Prematurity (Gestational Age <37 Weeks), Low Birth Weight (<2,500 Grams), and Small for Gestational Age (<10th Percentile) in IVF Singletons

Reference	Number of IVF children studied	Number of control subjects studied	Gestation		Birth Weight		SGA		Factors controlled for in the analysis
			IVF children	Control subjects	IVF children	Control subjects	IVF children	Control subjects	
Australian IVF Collaborative Group, 1988 (3)	700	—	18.5[e]	—	15.5[g]	—	—	—	—
Beral et al., 1990 (6)	741	—	—	—	12	—	—	—	—
MRC, 1990 (30)	1,267	Population	13[e]	6[e]	12[g]	—	—	—	—
Doyle et al., 1992 (13)	648	General population	13[e]	6[e]	11[g]	6	17[g]	10[g]	—
Olivennes et al., 1993 (34)	162	263[a] 5,096[b]	11.1[e]	61[a,e] 4.4[b,e]	11.1[g]	6.5[a,g] 3.6[b,g]	11.2[g]	10.6[a,g] 5.9[b,g]	—
Rufat et al., 1994 (42)	916	—	12.2[e]	—	12.3	—	—	—	
FIVNAT, 1995 (16)	3,822	—	9.4[e]	—	11.2	—	—	—	
Tan et al., 1992 (47)	494	978	14[e]	8	14	7.0	18.0[g]	—	Maternal age
Verlaenen et al., 1995 (49)	140	140	38.7[f]	39.8+	3,175+	3,393+	—	—	Maternal age, height, weight, parity
Petersen et al., 1995 (36)	70	70	7[e]	4	16	0	—	—	Age, parity
D'Souza et al., 1997 (14)	150	150	39.4[f]	39.5[a]	3,016	3,400[b]	—	—	Sex of child, social class, gestational age

(*Continued*)

Table 1. (*Continued*)

Reference	Number of IVF children studied	Number of control subjects studied	Gestation		Birth Weight		SGA		Factors controlled for in the analysis
			IVF children	Control subjects	IVF children	Control subjects	IVF children	Control subjects	
Wang et al., 1994 (53)	465	21,547	13.8[e]	9[e]	—	—	16.3[c,g] 5.6[d,g]	10[g] 3[g]	Age, parity
Gissler et al., 1995 (19)	1,015	190,697	11.0[e]	4.5[e]	6.2[g]	3.7[g]	—	—	Smoking, marital status, education, parity
Saunders et al., 1996 (44)	194	111	38.5[f]	38.7[f]	3,196 grams	3,294 grams	—	—	Gestational age
Reubinoff et al., 1997 (38)	260	260	8.8[e]	3.9[e]	11.2[g]	1.6[g]	12.5[g]	12.9[g]	Maternal age, parity, ethnic origin, location, and date of delivery

Abbreviation: SGA = small for gestational age.
[a] Stimulated cycles.
[b] Natural cycles.
[c] All.
[d] Primiparous.
[e] Prematurity (weeks).
[f] Mean gestational age (weeks).
[g] Low birth weight (grams).
[h] Mean birth weight (grams).

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CHILD BEHAVIOR

Several investigators have studied the behavior and cognitive and psychomotor development of children conceived through IVF. One of the first studies (31) investigated 33 IVF children with the Bayley Scales of Infant Development, between the ages of 12 and 20 months, comparing them with a normal population. The IVF children performed within the normal range, and the subgroup with developmental problems consisted mainly of IVF children that were born prematurely. Morin et al. (29) studied 83 children conceived through IVF and compared them with 93 control subjects matched for age of the infant, multiple conceptions, sex, race, and maternal age. No differences were found between the IVF and the control groups. The largest so far (10) studied 116 IVF children at 12 to 45 months of age and compared them with a control group matched for gestational age, multiple pregnancy, and a number of maternal characteristics, using the Bayley Scales and the Stanford Binet Scales. The development of the IVF children did not differ from that of the control group. A small study (37) compared 33 children born after IVF to 33 children born after ovulation induction without IVF and to 33 naturally conceived children at the age of 3 years. Only term singletons were studied. No differences in development were found between the three groups. Another small study (41) looked at 30 children born after IVF, who were at least 2 1/2 years of age, and compared them with a singleton control group.

Recently, a study compared 99 IVF children aged 33 to 85 months to a population control group in terms of their development (measured with the Griffith Scale) and their behavior (measured with the Child Behaviour Check List) (11). Thirty-four percent of the IVF children were part of a multiple birth and 28% were born prematurely. Although both the IVF group as a whole and the preterm group had scores comparable with the normal population group, IVF children who had experienced normal conditions did have higher developmental quotients on the Griffith Scale than those who had been born prematurely. These studies have been summarized in Table 2.

Most studies into child development after IVF carried out to date include relatively small numbers of children and have a limited period of follow-up. Many disorders, such as school performance problems and attention deficit disorders, can be diagnosed only at older ages. Still, the figures published so far do not seem to give rise to great concern. One possible explanation of why children conceived through IVF may be developing well is that the quality of care given by IVF parents is superior to that of control parents, thus overcoming the possible adverse effects of the IVF per se or of the prematurity related to it. One study compared 45 families with a child conceived by IVF with 45 families with a child conceived by donor insemination, 45 families with a naturally conceived child, and 55 families with an adopted child (20). The families were matched for social class of the parents and age and sex of the child. The children were between the ages of 4 and 8 years. No differences were found between the groups in terms of emotional or behavioral variables, but parent–child interaction was superior in the IVF families, possibly indicating a higher degree of "wantedness." This difference in interaction patterns may well influence the IVF childrens' score on developmental tests. A study looking at behavior of 65 primiparous IVF mothers toward their infants 4 months postpartum, however, found that IVF mothers, more often than the control subjects, reported lower self-esteem and lower maternal self-efficacy (28). Mothers who had

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Table 2. Behavior and Psychomotor Development of IVF Children Compared with Control Subjects

Reference	Number of IVF children	Number of control subjects	Age	Test used	Outcome	Factors controlled for in the analysis
Mushin et al., 1986 (31)	33	Norm population	12–20 months	Bayley Scales of Infant Development	Development within range	
Morin et al., 1989 (29)	83	93	?	Bayley test: Mental development index (MDI) Psychomotor development index (PDI)	No difference on MDI; slightly better outcome for IVF children on PDI:114 vs. 108	Age of infant, multiplicity, sex, race, maternal age, parental education, income
Brandes et al., 1992 (10)	116	116	12–45 months	Bayley Scales, Stanford, Binet	No difference between the groups	Birth weight, gestational age, birth order, mode of delivery, sex, age of child, age of mother
Raoul-Duval et al., 1994 (37)	33	33	3 years	Brunes-Lézine	No difference	Parity, socioeconomic status, mother's age, number of children
Ron-El et al., 1996 (41)	30	30	>28 months	General Cognitive Index Test	No difference	Maternal age, gestational age, birth weight
Cederblad et al., (11)	99	Norm population	33–85 months	Griffith Scale of Mental Development Child Behavior Check List	Development within range	

received more than one treatment cycle received lower scores. It is not clear whether the mothers' perception of themselves persists until later in their childrens' lives.

BIRTH DEFECTS

A number of authors have studied the occurrence of birth defects in children born after IVF (1;3;4;12;29;30;39;45;48). The number of newborns studied ranged from fewer than 100 to over 3,000. None of these studies found an increased risk of birth defects compared with the general population estimates, for all defects combined nor for specific groups of defects. Only one study (27) mentions a statistically significant increase in two types of birth defects, namely a higher prevalence of transposition of the great vessels and of spina bifida in children conceived through IVF than in the general population. This report has not yet been confirmed in other studies. Theoretically, birth defects after IVF may be increased in incidence because of the induction of chromosomal aberrations, an increase in fertilization rate by abnormal spermatozoa, or the actions of physical and chemical teratogens (8). At the moment there is no evidence of such effects. However, to find a significant increase in groups of birth defects or in isolated defects, instead of in all defects combined, larger numbers of cases are often needed than are part of the studies here mentioned. In order to test specific hypotheses concerning IVF and well-defined birth defects, in the future, pooled analyses of some of the larger studies may provide the necessary numbers.

EFFECTS OF CRYOPRESERVATION

The superovulation method as it is employed in most IVF treatments often yields a high number of oocytes to be fertilized. If too many embryos are thus created, surplus embryos can be frozen to be thawed in subsequent cycles. The first successful pregnancy after cryopreservation was described in 1983 (48). Cryopreservation and thawing involve major cellular changes and it is not clear whether they may have adverse effects for the offspring. A number of studies into the perinatal outcome of pregnancies after cryopreservation have been reported (35;38;46;50;54;55). Wada et al. (50) found no chromosomal abnormalities in the cryopreserved group and found that the prevalence of congenital malformation was smaller in the cryopreserved group than in the fresh embryo group. Stutcliffe et al. (46) studied perinatal outcomes in 91 children from cryopreserved embryos directly after birth. Compared with 83 normally conceived control children, their risk of congenital malformations was 31.9% versus 21.7% for minor and 3.3% versus 2.4% for major congenital malformations, respectively. Both increases were not statistically significant. Olivennes et al. (35) studied perinatal outcome and 1 to 9 years follow-up in terms of psychomotor development of a group of 82 children born after cryopreservation. No control group was employed. The singleton preterm birth rate and low birth weight rate were 14.7% and 9.3%, respectively. The congenital malformation rate was 3.4%. No pathology was found in psychomotor development. Wennerholm et al. (55) compared 270 infants after cryopreservation to equal numbers of control subjects after fresh embryo transfer and after spontaneous conception. No differences were found in preterm or low birth weight rate, nor in malformation rate. In a later study of the same cohort (54), no differences were found between 255 children born from cryopreserved embryos, 255 born after IVF with fresh embryos, and 252 children from spontaneous pregnancies in development nor in the prevalence of chronic illnesses during the first 18 months. Obviously, the number of

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studies of the effects of cryopreservation on human embryos is limited, the number of subjects per study is rather small, and data on follow-up are scant. So far, no evidence exists from human data that cryopreservation may carry risks for the fetus, but clearly more research is needed. A recent French study of long-term effects of embryo freezing in mice showed differences in morphophysiological and behavioral features between cryopreserved and control mice, some of which only appeared at older age. The relevance of these data for humans remains to be determined (15).

MISCELLANEOUS LONG-TERM EFFECTS

Growth and physical outcome at 2 years of age was measured in 314 children conceived through IVF and compared with that of 150 control subjects matched for plurality and gestational age (44). IVF status was not an independent factor for physical outcomes, although poorer outcomes were related to the effects of multiple births.

Recently, sleep apnea in a group of 50 newborns conceived through IVF compared with a control group of 50 infants who were all born at term and were matched for gestational age and birth weight has been reported (2). Sleep apnea seems to occur more often in babies born from multiple pregnancies and with growth retardation (5). No difference was found in incidence of apnea in the IVF versus the control group, although IVF children had significantly more periodic breathing episodes than control children, possibly indicating a more immature respiratory pattern. IVF singleton babies were more prone to breathing abnormalities than IVF twins, which led the authors to conclude the phenomenon is related to IVF per se and not to the infants being part of a multiple pregnancy. The importance of these results cannot yet be decided. It is the first time this relationship has been reported, and it is unclear from the description of the data whether this is a primary or a secondary analysis. Moreover, no biological explanation was offered.

CONCLUSION

Twenty years after the birth of the first baby conceived through IVF, many of the effects of the procedure on the children born from it have become clear, although a substantial number of questions remain unanswered. One of the main problems with IVF to date is the high incidence of multiple pregnancies. Further, singleton and twin pregnancies following IVF compared with control singleton or twin pregnancies appear to be at higher risk of adverse outcomes, such as preterm birth and low birth weight. Whether this is an effect of the procedure per se or is related to maternal factors, or a combination of both, remains to be studied. The risk of congenital malformations does not seem to be elevated. In the future, adequate numbers of subjects should be studied for specific defects before it can be concluded definitively that IVF does not increase the risk of congenital malformation. More data are urgently needed on the possible effects of embryo freezing on the health of the children. Until then, it remains unclear whether embryo freezing is a safe procedure. Psychomotor development of IVF children does not seem to be disturbed, possibly because the quality of IVF parenting appears to be high. Longer follow-up of children conceived through IVF is necessary, however, before long-term adverse effects can be excluded. In the future, data on fertility of IVF children will be needed to determine whether the parental fertility problem has been passed on to the next generation.

It is clear that procedures involved in IVF carry certain short-term risks for the offspring. Until further and more extensive studies are conducted, we will not know whether IVF poses additional long-term risks for the children.

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