Perinatal Outcome of Pregnancies After Assisted Reproduction: A Case–Control Study

M. DHONT,[1] F. DE NEUBOURG,[1] J. VAN DER ELST,[1] and P. DE SUTTER[1]

Submitted: August 4, 1997
Accepted: September 22, 1997

Purpose: *A matched case–control study of all pregnancies obtained after either IVF or ICSI was conducted to investigate the perinatal outcome.*
Methods: *Three hundred eleven singleton and 115 twin pregnancies obtained after assisted reproduction were studied. Controls were selected from a regional register and were matched for maternal age, parity, singleton or twin pregnancy, and date of delivery.*
Results: *No significant difference was observed for gestational age at delivery, birth weight, incidence of congenital anomalies, and incidence of perinatal mortality between ART (singleton and twin) pregnancies and spontaneous controls. ART twin pregnancies showed a higher incidence of preterm deliveries than control pregnancies (52 vs 42%; $P < 0.05$)* and needed more neonatal intensive care (47 vs 26%; $P < 0.05$).
Conclusions: *From this case–control study it is concluded that the perinatal outcome of ART singleton pregnancies is not different from that in matched controls. ART twin pregnancies showed a higher incidence of preterm deliveries than control pregnancies and needed more neonatal intensive care.*

KEY WORDS: in vitro fertilization (IVF); intracytoplasmic sperm injection (ICSI); pregnancy; perinatal outcome.

INTRODUCTION

Almost 20 years after its introduction, more than 100,000 children have been conceived and born after in vitro fertilization (IVF). The initial skepticism surrounding this artificial method of conception has greatly waned but the perinatal outcome remains the focus of continuing critical scrutiny from both the medical world and the public at large. Overall the perinatal outcome of pregnancies obtained by assisted reproductive technology (ART) is worse than that following spontaneous conception but this is due mainly to the high incidence of multiple pregnancies, which are compounded by a higher rate of perinatal morbidity and mortality. Data about the outcome of singleton pregnancies after IVF have shown an increased incidence of small-for-gestational-age (SGA) infants and preterm delivery compared with population-based frequencies (1–8). IVF patients, however, are on average older than the normal obstetrical population, conferring an additional age-related risk of maternal and perinatal complications (9). Also, according to some reports, infertility itself could increase the risk of SGA and preterm birth, although other reports did not confirm these relationships (10–14).

The recent advent of intracytoplasmic sperm injection (ICSI) has added additional hypothetical risk factors such as the fact that the natural selection of the fertilizing sperm cell is surpassed and the potential risk of disrupting the cellular machinery by the mechanical invasion of the ooplasm. It has become clear that the incidence of sex chromosome anomalies is increased in conceptions obtained by ICSI (15–18). Most of these anomalies can be detected only by either prenatal cytogenetic diagnosis or chromosomal analysis at the time of birth. It is evident that the clinical assessment of malformations at the time of birth will underestimate the true incidence of congenital anomalies. As yet, however, there is no evidence that ICSI carries an extra risk to the perinatal outcome, which was the target of this study (19). In a comparative study we have shown that there is no difference in pregnancy outcome between women treated with IVF and those treated with ICSI (20). The question remains, however, whether IVF pregnancies, after subtraction of all known risk factors (e.g., zygosity, age, infertility, parity) still carry an additional risk. A number of case–control studies that address this question have been reported (21–23). These studies were concerned

[1] Department of Obstetrics and Gynecology, University Hospital, Ghent, De Pintelaan 185, UZ-Ghent, B-9000 Ghent, Belgium.

1058-0468/97/1100-0575$12.50/0

mainly with singleton pregnancies obtained after IVF. Although the results of these studies were not unanimous with respect to the different outcome measures, a common conclusion was that IVF pregnancies are associated with an increased risk of preterm birth and low-birth weight infants. We have extended the scope of our study by including both IVF and ICSI pregnancies and comparing both singleton and twin pregnancies with a matched control group. The objective of our study was to determine whether singleton and twin ART pregnancies carry a higher risk for perinatal complications and congenital malformations compared with naturally conceived pregnancies when age and parity of the mother are taken into consideration.

MATERIALS AND METHODS

All singleton ($n = 316$) and twin ($n = 118$) pregnancies beyond 20 weeks of gestation conceived after assisted reproduction (IVF and ICSI) at our center between January 1, 1991, and December 31, 1995, were considered for this study. Gestations of a higher order than twins were excluded because of their small numbers (triplets, 33; quadruplets, 2). Pregnancies conceived after conventional IVF and ICSI were pooled because a comparative study of the perinatal outcome of children conceived at our center after IVF ($n = 325$) and ICSI ($n = 429$) had shown no statistically significant differences between the two groups (18). There was no deliberate case selection. Cases were selected whenever an appropriate control was available. Controls were computer-selected from a register compiled by the Study Center for Perinatal Epidemiology (SPE) according to the following criteria: natural conception, same maternal age, parity, order of gestation, zygosity, and delivery date maximally 99 days (singletons) or 365 days (twins) apart from that of the cases. For each case the best possible match was selected and each selected control was unique. To enhance the statistical significance two spontaneous pregnancies were selected to act as a control for each singleton ART pregnancy. This was not possible for twin ART pregnancies given the incidence of naturally conceived twins. In total, an appropriate control was available for 311 singleton (IVF, 131; ICSI, 180) and 115 twin (IVF, 61; ICSI, 54) ART pregnancies.

Information about the obstetric and perinatal outcome of ART pregnancies was obtained either through questionnaires sent to referring physicians or from our own hospital files for patients who delivered at our department. Data about the outcome of spontaneous control pregnancies were retrieved from the SPE register. The SPE collects information about the obstetric and perinatal outcome of pregnancies in the Flemish general population. These data are also based on questionnaires completed by obstetricians.

In the study group, gestational age was calculated from the day of oocyte retrieval, which was defined as day 14. Delivery before 37 completed weeks of gestation was considered preterm. Low birth weight (LBW) and very low birth weight (VLBW) were defined as birth weights of less than 2500 and 1500 g, respectively. Congenital malformations were classified into 17 categories according to the affected organ system. No distinction was made between major and minor anomalies. Perinatal mortality included stillbirths from the completed 24th week of gestation and deaths during the first postnatal week.

In singletons, continuous variables were compared using the unpaired t test, whereas in twins the paired t test was used. For comparison of binary variables the chi-square test was used. The significance level was set at 5%, two-tailed.

RESULTS

Maternal characteristics are listed in Table I. Due to the accurate matching of subjects in the ART and the control group, maternal characteristics were exactly the same in both groups.

A significant difference was seen between both groups with respect to the onset of delivery. Spontaneous onset of labor was more frequent in the control group. Delivery was induced in, respectively, 39.5% (singleton) and 42.6% (twin) of ART pregnancies versus in 27.7% ($P = 0.0003$) and 20.9% ($P < 0.0001$) of naturally conceived pregnancies. However, ART pregnancies were not associated with a higher cesarean rate, the incidence in singleton and twin ART pregnancies being, respectively, 18.4 and 37.7%, versus 17.5 and 40.0% in spontaneous pregnancies.

The distribution of gestational age at delivery is shown in Table II. In singleton pregnancies, no difference was seen in the mean gestational age and incidence of preterm delivery between ART and control

Table I. Maternal Characteristics

	Singleton ($n = 311$)	Twin ($n = 115$)
Mean age ± SD (yr)	31.3 ± 3.9	30.8 ± 3.8
Range	21–40	23–39
>35 yr (%)	16.4	10.4
Nulliparous (%)	75.9	75.7

Table II. Gestational Age at Delivery

	Singleton			Twin		
	ART (n = 311)	Control (n = 622)	P	ART (n = 115)	Control (n = 115)	P
Mean ± SD (wk)	38.73 ± 1.9	38.70 ± 2.5	0.84	36.19 ± 5.4	36.33 ± 2.3	0.74
Range[a]	26–42	24–42		23–41	28–40	
Distribution (%)[a]						
<32 wk	1.3	2.9		7.0	5.2	
32–36 wk	7.1	7.6		45.2	37.0	
>36 wk	91.6	89.5		47.8	57.8	
Preterm (%)	8.4	10.5	0.31	52.2	42.2	0.04

[a] Completed weeks.

pregnancies. Mean gestational age was 38.7 weeks in both groups. Respectively, 8.4 and 10.5% of babies were born preterm. In twin pregnancies, mean gestational age was not significantly different (36.2 vs 36.3 weeks). However, the incidence of preterm delivery was significantly higher after assisted reproduction (52.2 vs. 42.2%; P = 0.04).

Neonatal outcome is summarized in Table III. There was no significant difference in mean birthweight and incidence of LBW and VLBW between babies born after ART and naturally conceived babies, either for singletons or for twins. Mean birth weight in singletons was 3159 and 3203 g, respectively. The incidence of VLBW and LBW babies was 1.6 and 7.7% in the study group and 2.9 and 11.3% in the control group. Birth weight in twins averaged 2360 and 2427 g, respectively. In both groups, more than half of twin neonates (55.3 vs. 54.8%) weighed less than 2500 g at birth.

ART singletons required no more intensive care than babies in the control group. This was not the case for ART twin neonates, who were significantly more often admitted to intensive neonatal care than naturally conceived twins (46.9 vs 26.1%). Hospitalization was not protracted, however. The reported incidence of congenital malformations did not differ significantly between the groups. Respectively, 14 (4.5%) of the 311 ART singletons and 17 (2.7%) of the 622 singletons in the control group were born with a malformation. All congenital anomalies seen are listed in Table IV, categorized according to the affected organ system. In twins, the incidence of a malformation was, respectively, 3.5% (8 of 223 children affected) in the ART group and 1.7% (4 of 230 children affected) in the control group (P = 0.23). Perinatal mortality was not significantly different between the groups.

DISCUSSION

It is generally accepted that IVF pregnancies carry an overall increased risk of complications ranging from ectopic pregnancy, miscarriage, bleeding, placenta previa, and high cesarean section rate to preterm birth.

Table III. Neonatal Outcome

	Singleton			Twin		
	ART (n = 311)	Control (n = 622)	P	ART (n = 115)	Control (n = 115)	P
Birth weight (g)[a]	3159 ± 560	3203 ± 656	0.31	2360 ± 557	2427 ± 498	0.19
Range	400–4600	470–4660		470–3680	1100–3750	
<1000 g (%)	1.0	1.4		2.6	0.0	
≥1000–<1500 g (%)	0.6	1.4		3.5	5.7	
≥1500–<2500 g (%)	6.1	8.4		49.1	49.1	
≥2500 g (%)	92.3	88.7		44.7	45.2	
Intensive care (%)[b]	9.6	9.8	0.91	46.9	26.1	S[c]
Mean stay (days)	14.4	11.53		17.9	20.5	
Malformations (%)	4.5	2.7	0.16	3.5	1.7	0.23
Perinatal mortality	2	10	0.22	0	3	0.08
Male/female (%)	49.2/50.8	54.3/45.7		51.3/48.7	43.9/56.1	

[a] Mean ± SD.
[b] Percentage admissions to neonatal intensive care unit.
[c] Significant.

Table IV. Congenital Malformations

	Singleton		Twin	
	ART (n = 311)	Control (n = 622)	ART (n = 115)	Control (n = 115)
Anencephaly	–	–	–	–
Spina bifida	–	1	–	–
Hydrocephaly	–	2	–	–
Cleft lip or palate	–	–	1	–
Anal imperforation	–	–	1	–
Limb reduction	–	–	–	–
Diaphragmatic hernia	–	–	–	–
Omphalocoele/gastroschisis	–	1	–	–
Nerve system/sensorium	–	1	–	–
Gastrointestinal tract	5	1	1	–
Urogenital tract	3	4	1	1
Heart/lung	4	3	–	1
Musculosceletal	1	–	4	–
Craniofacial complex	–	–	–	–
Multiple malformations	–	1	–	–
Chromosomal malformations	2	1	–	1
Other	–	2	–	1

In most large series, the ongoing pregnancy rate is approximately 75%, which seems to be significantly lower than in naturally conceived pregnancies. Some factors that may contribute to these complications have been identified and are related to the hyperstimulation of the endometrium, diseased tubes, the age and parity of the patient, and above all, the high incidence of multiple pregnancy. With incidences of up to 30% following IVF, multiple pregnancy is the major culprit of preterm birth and LBW, preeclampsia, increased perinatal morbidity, and mortality. It certainly is the single most important target for improving the outcome of IVF pregnancies. Unless a breakthrough occurs in the prediction of the viability of the individual embryo, allowing the transfer of a single embryo without affecting the efficiency of IVF a solution to this problem is not in the offing. Restricting the number of embryos transferred to two, as we ourselves have been practicing for the past 2 years, will eliminate multiple pregnancies of a higher order but will barely change the incidence of twin pregnancies.

A matter of debate, however, is whether IVF pregnancies still carry an increased risk of complications after all compounding factors have been taken into account. This question can be addressed only by case–control studies in which IVF pregnancies are matched very carefully with controls.

Overall, our data indicate that beyond the second half of pregnancy singleton pregnancies obtained by IVF or ICSI are not compounded by an increased risk of adverse outcome. For twin pregnancies, there is an increased incidence of preterm birth compared to naturally conceived dizygotic twin pregnancies, without affecting, however, perinatal mortality. The conclusions from these data, however, are limited by the scope of the data that could be collected. Follow-up of IVF pregnancies is difficult for several reasons. Large infertility centers and infertility specialists are not involved in the obstetric care of the patients they helped to get pregnant and have to rely on second-hand information for the obstetrical outcome. This problem is further aggravated by the fact that many patients do not deliver at the same institution where the infertility center is located. To perform a case–control study, a minimal set of identical obstetric data should be available for both the cases and the controls. Although more data were available on the cases, we had to limit the comparison to the data that were included in the regional register, which covers more than 95% of all deliveries performed in the Flemish-speaking part of Belgium. This registration is limited to simple but reliable facts and data. Outcome of pregnancies ending before the 24th week could not be investigated and a number of complications of the second and third trimester (e.g., preeclampsia, bleeding) were not recorded. On the other hand, the main outcome measures concerning perinatal morbidity and mortality are very reliable and allow a comparison with the study group.

Our data about the outcome of singleton pregnancies are at variance with those from a number of case–control studies, which have shown an increased risk

of preterm birth and LBW infants and a higher incidence of cesarean section (21–23). There is no straightforward explanation for the discordance between our data and those from other reports. Differences in sample size, matching criteria, obstetric policy or sheer odds can account for the discrepant results. For instance, part of the increased incidence of preterm birth in these studies was iatrogenic due to a higher rate of cesarean section (22,23) and induction of labor (21,22). The incidence of cesarean section in the case and control group is slightly higher than the overall incidence in the Dutch-speaking part of Belgium, which was, respectively, 13.5% in singleton pregnancies and 41.9% in multiple pregnancies in 1996. The higher incidence of cesarean section in both the control and the case groups can be explained by the shift in age and parity of the population studied. More important, however, is the fact that although the differences in these studies between the case and the control groups were statistically significant, they were in fact small and clinically not relevant because serious perinatal morbity and mortality were not affected.

In twin ART pregnancies, the rate of preterm birth and the incidence of intensive neonatal care were slightly higher than in the control group but eventually had no impact on the perinatal outcome. These findings are in agreement with a recent report by Bernasko *et al.* (24), who found that LBW occurred more frequently in twin ART pregnancies but that the perinatal outcome was comparable to that of spontaneously conceived twin pregnancies.

The data about congenital malformations are particularly reassuring, given the fact that more than half of the pregnancies were obtained by ICSI. Several reports have shown that IVF pregnancies carry no increased risk for congenital malformations (2,5,7). Initial doubts about the safety of ICSI with regard to congenital malformations have also been partially resolved, except for a slightly increased rate of sex chromosome anomalies (16). With respect to congenital anomalies that are manifest at birth, our data confirm the safety of both IVF and ICSI.

CONCLUSIONS

From a matched case–control study involving 311 singleton and 115 twin pregnancies obtained after IVF or ICSI, we can infer that the perinatal outcome of both singleton and twin pregnancies is in essence comparable to that of a control population. No increase in congenital malformations, assessed by clinical examination of the infant at birth, was observed in infants conceived by either IVF or ICSI.

REFERENCES

1. Lancaster PAL, Australian In Vitro Fertilization Collaborative Group: High incidence of preterm births and early losses in pregnancy after IVF. BMJ 1985;291:1160–1163
2. Beral V, Doyle P, MRC Working Party on Children Conceived by In Vitro Fertilisation: Births in Great Britain resulting from assisted conception, 1978–87. BMJ 1990;300:1229–1233
3. Seoud MA, Toner JP, Kruithoff C, Muasher SJ: Outcome of twin, triplet, and quadruplet in vitro fertilization pregnancies: The Norfolk experience. Fertil Steril 1992;57:825–834
4. Doyle P, Beral V, Maconochie N: Preterm delivery, low birth weight and small-for-gestational-age in liveborn singleton babies resulting from in-vitro fertilization. Hum Reprod 1992;7:425–428
5. Tan SL, Doyle P, Campbell S, *et al.*: Obstetric outcome of in vitro fertilization pregnancies compared with normally conceived pregnancies. Am J Obstet Gynecol 1992;167:778–784
6. Olivennes F, Rufat P, André B, Pourade A, Quiros MC, Frydman R: The increased risk of complication observed in singleton pregnancies resulting from in-vitro fertilization (IVF) does not seem to be related to the IVF method itself. Hum Reprod 1993;8:1297–1300
7. Rufat P, Olivennes F, de Mouzon J, Dehan M, Frydman R: Task force report on the outcome of pregnancies and children conceived by in vitro fertilization, France 1987–1989. Fertil Steril 1994;61:324–33
8. Wang JX, Clark AM, Kirby CA, et al: The obstetric outcome of singleton pregnancies following in vitro fertilization/gamete intra-fallopian transfer. Hum Reprod 1994;9:141–146
9. Kessler L, Lancet M, Borenstein R, Steinmetz A: The problem of the older primipara. Obstet Gynecol 1980;56:165–169
10. Ghazi HA, Spielberger C, Kallen B: Delivery outcome after infertility—a registry study. Fertil Steril 1991;55:726–732
11. Williams MA, Goldman MB, Mittendorf R, Monson RR: Subfertility and the risk of low birth weight. Fertil Steril 1991; 56:668–671
12. Tuck SM, Yudkin PL, Turnbull AC: Pregnancy outcome in elderly primigravidae with an without a history of infertility. Br J Obstet Gynaecol 1988;95:230–237
13. Li TC, Macleod I, Singhal V, Duncan SLB: The obstetric and neonatal outcome of pregnancy in women with a previous history of infertility: A prospective study. Br J Obstet Gynaecol 1991;98:1087–1092
14. Petersen K, Hornnes PJ, Ellingsen S, Jensen F, Brocks V, Starup J, Ramsøe Jacobsen J, Nyboe Andersen A: Perinatal outcome after in vitro fertilization. Acta Obstet Gynecol Scand 1995; 74:129–131
15. Bonduelle M, Legein J, Buysse A, Van Assche E, Wisanto A, Devroey P, Van Steirteghem A, Liebaers I: Prospective follow-up study of 423 children born after intracytoplasmic sperm injection. Hum Reprod 1996;11:1558–1564
16. Bonduelle M, Wilikens A, Buysse A, Devroey P, Van Steirteghem A, Liebaers I: Een follow-up-studie van kinderen geboren na intracytoplasmatische sperma-injectie. Tijdschrift Fertiliteitsonderzoek 1997;11:13–19

17. In 't Veld P, Brandenburg H, Verhoeff A, Dhont M, Los F: Sex chromosomal abnormalities and intracytoplasmic sperm injection. Lancet 1995;346:773
18. Van Opstal D, Los FJ, Ramlakhan S, Van Hemel JO, Van Den Ouweland AMW, Brandenburg H, Pieters MHEC, Verhoeff A, Vermeer MCS, Dhont M, In 't Veld PA: Determination of the parent of origin in nine cases of prenatally detected chromosome aberrations found after intracytoplasmic sperm injection. Hum Reprod 1997;12:682–686
19. Bonduelle M, Legein J, Derde MP, Buysse A, Schietecatte J, Wisanto A, Devroey P, Van Steirteghem A, Liebaers I: Comparative follow-up study of 130 children born after intracytoplasmic sperm injection and 130 children born after in-vitro fertilization. Hum Reprod 1995;10:3327–3331
20. De Neubourg F, Van Mullem A, Van der Elst J, Defoort P, De Sutter P, Dhont M: Comparative study of the perinatal outcome of 325 children born after in-vitro fertilization and 429 children born after intracytoplasmic sperm injection. 13th Annual Meeting of the European Society of Human Reproduction and Embryology. Edinburgh, United Kingdom, 22–25 June 1997. Hum Reprod 12, Abstract Book 1, Abstract 0–125
21. Verlaenen H, Cammu H, Derde MP, Amy JJ: Singleton pregnancy after in-vitro fertilization: Expectations and outcome. Obstet Gynecol 1995;86:906–910
22. Tallo CP, Vohr B, Oh W, Rubin LP, Seifer DB, Haning RV Jr: Maternal and neonatal morbidity associated with in vitro fertilization. J Pediatr 1995;127:794–800
23. Tanbo T, Dale PO, Lunde O, Moe N, Abyholm T: Obstetric outcome in singleton pregnancies after assisted reproduction. Obstet Gynecol 1995;86:188–192
24. Bernasko J, Lynch L, Lapinski R, Berkowitz RL: Twin pregnancies conceived by assisted reproductive techniques: Maternal and neonatal outcomes. Obstet Gynecol 1997;89:368–372