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Perinatal outcome of 12 021 singleton and 3108 twin births after non-IVF-assisted reproduction: a cohort study

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Perinatal outcome of pregnancies caused by assisted reproduction technique (ART) is substantially worse when compared with pregnancies following natural conception. We investigated the possible risks of non-IVF ART on perinatal health. We conducted a retrospective cohort study with two exposure groups: a study group of pregnancies after controlled ovarian stimulation (COS), with or without artificial insemination (AI), and a naturally conceived comparison group. We used the data from the regional registry of all hospital deliveries in the Dutch-speaking part of Belgium during the period from January 1993 until December 2003 to investigate differences in perinatal outcome of singleton and twin pregnancies. 12 021 singleton and 3108 twin births could be selected. Naturally conceived subjects were matched for maternal age, parity, fetal sex and year of birth. The main outcome measures were duration of pregnancy, birth weight, perinatal morbidity and perinatal mortality. Our overall results showed a significantly higher incidence of prematurity (<32 and <37 weeks), low and very low birth weight, transfer to the neonatal intensive care unit and most neonatal morbidity parameters for COS/AI singletons. Twin pregnancies resulting from COS/AI showed an increased rate of neonatal mortality, assisted ventilation and respiratory distress syndrome. After excluding same-sex twin sets, COS/AI twin pregnancies were at increased risk for extreme prematurity and very low birth weight. In conclusion, COS/AI singleton and twin pregnancies are significantly disadvantaged compared to naturally conceived children.

Key words: insemination/matched control study/perinatal outcome/singletons/twin pregnancies

Introduction

Controlled ovarian stimulation (COS), with or without AI (artificial insemination), is frequently used and generally accepted as a valuable first-line treatment in case of subfertility due to ovulatory disorders, unexplained infertility and moderate male factor subfertility (Peterson *et al*., 1994; Ombelet *et al*., 1995, 1997, 2003a,b; Van Voorhis *et al*., 1997, 1998; Zayed *et al*., 1997; Guzick *et al*., 1998; Karande *et al*., 1999; Cohlen *et al*., 2000; Daya, 2000; Goverde *et al*., 2000; Philips *et al*., 2000; Van Voorhis and Syrop, 2000; Homburg and Insler, 2002; Hughes, 2003; Cohlen, 2005).

Today, there is a widespread belief that the perinatal outcome of pregnancies caused by assisted reproduction technique (ART) is substantially worse when compared with pregnancies following natural conception. This is mainly attributed to a higher rate of multiple birth, which in turn is associated with a higher rate of perinatal mortality and morbidity (Luke and Keith, 1992; Gissler *et al*., 1995; ESHRE Capri Workshop Group, 2000, 2003; Blickstein, 2003).

Because of the widespread use of gonadotrophins, induction of ovulation and COS are nowadays the most important cause of multiple pregnancies related to infertility treatment in the United States (Evans *et al*., 1995; Gleicher *et al*., 2000; Tur *et al*., 2001). In COS, the prediction of multiple gestation is highly uncertain especially when gonadotrophins are used (Gleicher *et al*., 2000). A few reports suggest that non-IVF ovarian stimulation is responsible for at least one-third of multiple pregnancies (Bergh *et al*., 1999; Tur *et al*., 2001).

Helmerhorst *et al*. (2004) reported a significantly worse perinatal outcome for singleton pregnancies following ART compared to pregnancies after natural conception. For twin pregnancies, the difference was less clear, and perinatal mortality was significantly lower for ART twins. This can be explained by the fact that monochorionic twins carry the highest risk of a poor outcome (Sebire *et al*., 1997). About 20% of all twins are monochorionic, but the proportion is higher in spontaneous twins (30%) compared to ART twins (3.7–7%) (Chow *et al*., 2001; Derom *et al*., 2001; Lambalk and van Hooff, 2001).

The reason why perinatal health problems occur more frequently in non-IVF pregnancies is still unknown, but can be explained by the procedures (intrauterine insemination), the medication used or the reason for infertility as such (Lambert, 2003). It also seems that spontaneous reduction of multiples pregnancies causes a higher risk for adverse obstetric and perinatal outcome compared to pregnancies without spontaneous reduction (Dickey *et al*., 2004; Pinborg *et al*., 2005). Because the increased risk for multiple pregnancies after non-IVF hormonal treatment is comparable with IVF (especially when gonadotrophins are used), this may also be an important factor influencing the worse perinatal outcome of non-IVF singleton and twin pregnancies after COS/AI.

To investigate the possible risks of non-IVF ART on perinatal health, we conducted a retrospective cohort study of 12 021 singleton and 3108 twin births in the Dutch-speaking part of Belgium (Flanders) during the period from January 1993 until December 2003. To investigate the impact of twin pregnancies on perinatal health outcome, we also compared outcome parameters between singletons and twins obtained after non-IVF hormonal treatment.

Materials and methods

We performed this study by analysing the SPE (Study Centre for Perinatal Epidemiology of Flanders) data from the 'Studiecentrum voor Perinatale Epidemiologie'. The SPE collects data on the medical and obstetric history, and on perinatal events of each hospital delivery in Flanders of more than 21 weeks of gestational age and ≥500 g at birth. Full co-operation of all 80 departments of Obstetrics in Flanders has been established since 1993. The data are based on questionnaires completed by midwifes, obstetricians and paediatricians in the early neonatal period. The obstetric and perinatal file registers 33 items of data per child. If the newborn is transferred to the neonatology unit, another 20 items of neonatal data are registered. All data are sent to a data coordinator, who carries out a review for errors and omissions. Quality of the data gathering is controlled on a full-time basis through checking of the incoming records for internal inconsistencies, exactness and completeness. Correction and completion is assured by telephone calls, additional questionnaires and, if necessary, visits to the local departments. Subsequently, the files are stored in a computer database. Each year, a complete analysis of the data is performed. This results in a yearly global report and a unique report per obstetric unit.

COS/AI pregnancies (cases)

Of 619 065 pregnancies and 661 065 births between 1 January 1993 and 31 December 2003, we found 12 021 singleton and 3108 twin births of pregnancies obtained with COS and timed coitus or AI. It was not possible to make a distinction between insemination with donor and partner sperm. Because of their small numbers and the difficulty of finding appropriate control subjects, higher-order gestations were excluded from the study. According to a questionnaire filled out by most Flemish gynaecologists working in the field of human reproduction, in 10% of all AIs donor semen was used (Ombelet *et al*., 2003a,b, questionnaire organized by the Flemish Society of Obstetrics & Gynaecology).

Pregnancies after natural conception (naturally conceived comparison group)

Comparison pregnancies of the naturally conceived comparison group were computer selected from the SPE registry according to the following criteria: natural conception, multiplicity of birth, maternal age no more than 2 years apart from the study case, same parity, date of delivery no more than 1 year apart from the case and the same fetal sex. For each COS/AI pregnancy, and after adjusting for parity, fetal sex and year of birth, the best possible match for maternal age was selected. All pregnancies of the naturally conceived comparison group were unique. For twin pregnancies, we studied the results before and after excluding the like-sex twins.

Main outcome measures and definitions

The main outcome measures for this study were gestational age, birth weight, admission to the neonatal intensive care unit (NICU), perinatal mortality and perinatal morbidity including intracranial bleeding, assisted ventilation and respiratory distress syndrome (RDS). A distinction was made between normal birth weight (≥2500 g), low birth weight (<2500 g) and very low birth weight (<1500 g). Concerning gestational age, a distinction was made between term birth (≥37 weeks), preterm (<37 weeks) and extreme preterm (<32 weeks). Stillbirth was defined as the birth of a lifeless child of ≥500 g and neonatal death is the death of a live born child ≥500 g within 7 days after birth. The perinatal mortality rate is the sum of stillbirths and neonatal deaths divided by the total number of live and stillbirths. All minor and major congenital malformations, recognized during pregnancy or during hospitalisation in the neonatal period, were reported. Minor and major malformations were not differentiated. Because a lot of malformations, especially minor ones, are only detected after the first week after delivery and therefore adequate estimation of the exact malformation rate was not possible, this parameter was not used as a major outcome measure.

Statistical methodology

The Mann–Whitney *U*-test was used to test group differences in parity, duration of pregnancy, birth weight and maternal age. This test is a non-parametric analogue of the unpaired Student's *t*-test and uses the ranks of the observations to derive the test statistic. Dichotomous data (such as gestational age <37 weeks) were summarized in contingency tables, and the resulting log-odds ratio, together with the corresponding 95% confidence limits were used to make inferences. We used the odds ratio (OR) and relative risk (RR) module of the MEDCALC program, its 95% confidence interval (CI) and the corresponding *P*-values (Sheskin, 2004). A difference at the 5% level of significance was considered the threshold of significance.

Results

Of 619 065 pregnancies and 661 065 births between 1 January 1993 and 31 December 2003, a total of 12 021 singleton (1.82%) and 3108 twin births (0.47%) of pregnancies obtained with COS/AI were analysed and compared with the same number of matched pregnancies following natural conception.

Singleton pregnancies

Data on perinatal outcome of 12 021 COS/AI and 12 021 naturally conceived singleton pregnancies are summarized in Table I. Parity and maternal age were similar in both the study and the naturally conceived comparison group. Mean gestational age was significantly lower in the COS/AI study group (38.8 versus 39.2 weeks, $P < 0.01$). Study subjects had a mean birth weight of 3271 g versus 3350 g in the naturally conceived comparison group (difference 79 g, $P < 0.01$). Premature and very premature babies were seen more often in the study group (<32 weeks: 1.3 versus 0.4%, OR 3.26, CI 2.32–4.59; <37 weeks: 7.8 versus 4.2%, OR 1.89, CI 1.69–2.12). Low birth weight and very low birth weight were also observed

Table I. Comparison of obstetric and perinatal data of 12 021 COS/AI and 12 021 spontaneously conceived singleton births, matched for parity, maternal age, date of birth and fetal sex

	COS/AI	Controls			
Births	*n* = 12 021 Mean ± SD	*n* = 12 021 Mean ± SD			
General data					
Gestational age	38.8 ± 2.0	39.2 ± 1.7		$P < 0.01$*	
Parity	1.5 ± 0.82	1.5 ± 0.82		NS	
Birth weight	3271 ± 556	3350 ± 492		$P < 0.01$*	
Maternal age	29.7 ± 4.1	29.6 ± 4.1		NS	
Perinatal data	*n* (%)	*n* (%)	OR (95% CI)	*P*-value	RR (95% CI)
GA <32 weeks	152 (1.3)	47 (0.4)	3.26 (2.32–4.59)	<0.001*	3.23 (2.33–4.48)
GA <37 weeks	938 (7.8)	514 (4.2)	1.89 (1.69–2.12)	<0.001*	1.28 (1.64–2.03)
Birth weight <1500 g	159 (1.3)	50 (0.4)	3.21 (2.31–4.47)	<0.001*	3.18 (2.31–4.26)
Birth weight <2500 g	794 (6.6)	441 (3.7)	1.86 (1.65–2.10)	<0.001*	1.80 (1.61–2.02)
Transfer to NICU	2194 (18.3)	1536 (12.8)	1.52 (1.42–1.64)	<0.001*	1.43 (1.35–1.52)
Perinatal death	91 (0.76)	70 (0.58)	1.30 (0.94–1.80)	0.11	1.30 (0.95–1.77)
Stillbirth	59 (0.49)	45 (0.37)	1.31 (0.88–1.97)	0.20	1.31 (0.89–1.93)
Neonatal death	32 (0.27)	25 (0.21)	1.28 (0.74–2.23)	0.42	1.28 (0.76–2.16)
Assisted ventilation	183 (1.5)	85 (0.7)	2.17 (1.66–2.84)	<0.001*	2.15 (1.67–2.78)
IC bleeding	46 (0.4)	14 (0.1)	3.29 (1.76–6.28)	<0.001*	3.28 (1.81–5.97)
RDS	102 (0.8)	40 (0.3)	2.56 (1.75–3.76)	<0.001*	2.55 (1.77–3.67)

OR, odds ratio; CI, 95% confidence interval; NS, not significant; RR, relative risk; GA, gestational age; NICU, neonatal intensive care unit; IC bleeding, intracranial bleeding; RDS, respiratory distress syndrome.
*$P < 0.05$ = significant.

more often in the study group (<1500 g: 1.3 versus 0.4%, OR 3.21, CI 2.31–4.47; <2500 g: 6.6 versus 3.7%, OR 1.86, CI 1.65–2.10). Admission to the NICU was found more frequently in the study group (18.3 versus 12.8%, OR 1.52, CI 1.42–1.64). COS/AI pregnancies were also at increased risk for assisted ventilation, intracranial bleeding and RDS (Table I).

Twin pregnancies

As shown in Table II, 3108 COS/AI twin births could be selected and compared with an identical number of matched controls. Parity and maternal age were similar in both study and comparison group. Gestational age was significantly lower in the COS/AI study group (35.6 versus 35.9 weeks, $P < 0.01$). The mean birth weight of the first baby and second baby was respectively 2368 and 2311 g for the COS/AI babies compared to 2410 (difference 42 g, $P < 0.01$) and 2350 g (difference 39 g, $P < 0.01$) for the naturally conceived comparison group. Prematurity and low birth weight were observed more often in the study group, but the differences were not statistically significant. Although perinatal mortality was not significantly different

Table II. Comparison of obstetric and perinatal data of 3108 COS/AI and 3108 spontaneously conceived twin births, matched for parity, maternal age, date of birth and fetal sex

	COS/AI	Controls			
Births	*n* = 3108 Mean ± SD	*n* = 3108 Mean ± SD			
General data					
Gestational age	35.6 ± 2.9	35.9 ± 2.7		$P < 0.01$*	
Parity	1.5 ± 0.8	1.5 ± 0.8		NS	
Birth weight A	2368 ± 572	2410 ± 554		$P < 0.01$*	
Birth weight B	2311 ± 581	2350 ± 554		$P < 0.01$*	
Maternal age	29.7 ± 3.7	29.7 ± 3.7		NS	
Perinatal data	*n* (%)	*n* (%)	OR (95% CI)	*P*-value	RR (95% CI)
GA <32 weeks	244 (7.9)	208 (6.7)	1.19 (0.98–1.45)	0.09	1.17 (0.98–1.40)
GA <37 weeks	1669 (53.7)	1602 (51.5)	1.09 (0.99–1.21)	0.09	1.04 (0.99–1.09)
Birth weight <1500 g	265 (8.5)	235 (7.6)	1.14 (0.94–1.37)	0.18	1.13 (0.95–1.34)
Birth weight <2500 g	1762 (56.7)	1719 (55.3)	1.06 (0.96–1.17)	0.28	1.03 (0.98–1.07)
Transfer to NICU	2111 (67.9)	2119 (68.2)	0.99 (0.89–1.10)	0.85	0.99 (0.96–1.03)
Perinatal death	98 (3.15)	76 (2.45)	1.30 (0.95–1.78)	0.11	1.29 (0.96–1.73)
Stillbirth	45 (1.45)	48 (1.54)	0.94 (0.61–1.44)	0.83	0.94 (0.62–1.40)
Neonatal death	53 (1.73)	28 (0.92)	1.91 (1.18–3.20)	0.007*	1.89 (1.20–2.98)
Assisted ventilation	244 (7.9)	203 (6.5)	1.22 (1.00–1.49)	0.05	1.20 (1.01–1.44)
IC bleeding	61 (1.9)	46 (1.5)	1.33 (0.89–2.00)	0.17	1.33 (0.91–1.94)
RDS	191 (6.1)	155 (5.0)	1.25 (1.00–1.56)	0.05	1.23 (1.00–1.51)

OR, odds ratio; CI, 95% confidence interval; NS, not significant; RR, relative risk; GA, gestational age; NICU, neonatal intensive care unit; IC bleeding, intracranial bleeding; RDS, respiratory distress syndrome.
*$P < 0.05$ = significant.

Table III. Comparison of obstetric and perinatal data of 1320 COS/AI and 1320 spontaneously conceived unlike-sex twin births, matched for parity, maternal age, date of birth and fetal sex

	COS/AI	Controls			
Births	*n* = 1320 Mean ± SD	*n* = 1320 Mean ± SD			
General data					
Gestational age	35.5 ± 3.0	36.0 ± 2.7		$P < 0.01$*	
Parity	1.5 ± 0.8	1.5 ± 0.8		NS	
Birth weight A	2362 ± 587	2468 ± 556		$P < 0.01$*	
Birth weight B	2295 ± 581	2396 ± 575		$P < 0.01$*	
Maternal age	29.6 ± 3.7	29.6 ± 3.6		NS	
Perinatal data	*n* (%)	*n* (%)	OR (95% CI)	*P*-value	RR (95% CI)
GA <32 weeks	114 (8.6)	85 (6.4)	1.37 (1.02–1.86)	0.033*	1.34 (1.02–1.76)
GA <37 weeks	719 (54.5)	615 (46.6)	1.96 (1.67–2.31)	<0.001*	1.17 (1.08–1.26)
Birth weight <1500 g	119 (9.0)	90 (6.8)	1.61 (1.21–2.14)	0.037*	1.32 (1.02–1.72)
Birth weight <2500 g	764 (57.8)	669 (50.7)	1.14 (1.34–1.56)	<0.001*	1.14 (1.06–1.23)
Transfer to NICU	894 (67.7)	885 (67.0)	1.03 (0.87–1.22)	0.71	1.01 (0.96–1.07)
Perinatal death	45 (3.41)	29 (2.19)	1.57 (0.96–2.59)	0.06	1.55 (0.98–2.46)
Stillbirth	21 (1.59)	12 (0.90)	1.76 (0.82–3.82)	0.11	1.75 (0.86–3.54)
Neonatal death	24 (1.85)	17 (1.28)	1.42 (0.73–2.77)	0.26	1.41 (0.76–2.62)
Assisted ventilation	98 (7.4)	93 (7.0)	1.06 (0.78–1.44)	0.71	1.05 (0.80–1.38)
IC bleeding	25 (1.9)	26 (1.9)	1.04 (0.58–1.87)	0.89	0.96 (0.56–1.66)
RDS	82 (6.2)	73 (5.5)	1.13 (0.81–1.59)	0.46	1.12 (0.83–1.53)

OR, odds ratio; CI, 95% confidence interval; NS, not significant; RR, relative risk; GA, gestational age; NICU, neonatal intensive care unit; IC bleeding, intracranial bleeding; RDS, respiratory distress syndrome.
*$P < 0.05$ = significant.

between both groups, early neonatal mortality was significantly increased in the study group (OR 1.91, CI 1.18–3.20). This was also reflected in a higher incidence of assisted ventilation and RDS in the COS/AI pregnancies.

Since we may expect an overrepresentation of monozygotic twins in the naturally conceived comparison group compared to the study group, data were reanalysed after excluding all same-sex twin pairs. Consequently, 1320 unlike-sex COS/AI twin babies could be compared with 1320 unlike-sex babies of the comparison group. In this selected group of unlike-sex twins, we observed a significantly higher rate of very low birth weight (9.0 versus 6.8%, OR 1.61, CI 1.21–2.14) and extreme prematurity (8.6 versus 6.4%, OR 1.37, CI 1.02–1.86) for the COS/AI group compared to naturally conceived controls (Table III). Stillbirth, neonatal death and perinatal mortality were seen more frequently in the study group, although the differences were not statistically significant.

Singleton versus twin pregnancies

Comparison between obstetric and perinatal data of 12 021 singleton and 3108 twin births after COS/AI showed a highly significant worse outcome for twin pregnancies compared to singletons for all studied parameters (Table IV). There was a highly significant difference in gestational age (39.0 weeks for singletons, 35.6 weeks for twins, $P < 0.001$). Parity and maternal age were comparable in both groups. The mean birth weight was significantly higher in singletons (3315 g for singletons, 2348 g for twins, $P < 0.001$).

Discussion

Ovarian stimulation, with or without AI, is a widely used treatment option for many subfertile couples in case of ovulatory dysfunction, mild endometriosis, mild and moderate male subfertility and unexplained infertility. Because it is a successful, easier, less invasive and cheaper first-line treatment compared with IVF, it is nowadays the most frequent used treatment option of ART worldwide.

Multiple pregnancy is the most important adverse outcome with current methods of infertility treatment. Neonatal complications as a result of extreme prematurity and their long-term sequelae, maternal complications and social problems are seen more often after multiple birth (Elster, 2000; Denton and Bryan, 2002; Finnstroem, 2002; Ozturk and Templeton, 2002; Bryan, 2003; Ombelet *et al*., 2005). For IVF and ICSI, transferring multiple embryos into the uterus maximizes pregnancy rates, at the expense, however, of an unacceptably high multiple pregnancy rate. Because of the widespread use of gonadotrophins, induction of ovulation and COS have become the main cause of multiple pregnancies related to infertility treatment in the USA (Evans *et al*., 1995; Gleicher *et al*., 2000; Tur *et al*., 2001).

Although information concerning the obstetric and perinatal outcome of pregnancies following infertility treatment is essential, only data of IVF and ICSI pregnancies are registered worldwide. US and European results are published on an annual basis (ASRM/SART Registry, 2000, 2002a,b; Nygren and Andersen, 2001a,b, 2002; Andersen *et al*., 2004). For non-IVF, registration is almost non-existent. Until now, only three studies reported on the obstetric and perinatal outcome after intrauterine insemination (IUI), with contradictory results (Nuojua-Huttunen *et al*., 1999; Wang *et al*., 2002; Gaudoin *et al*., 2003). In the first study, 111 IUI pregnancies were compared with 333 spontaneous and 333 IVF pregnancies. They used data obtained from the Finnish Medical Birth Register (MBR). Obstetric and perinatal outcome was similar in all

Table IV. Comparison of obstetric and perinatal outcome measures between 12 021 COS/AI singleton and 3108 COS/AI twin births

	Twins	Singletons			
Births	*n* = 3108 Mean ± SD	*n* = 12 021 Mean ± SD			
General data					
Gestational age	35.6 ± 2.9	38.8 ± 2.0		$P < 0.001$*	
Parity	1.5 ± 0.8	1.5 ± 0.82		NS	
Birth weight	2348 ± 570	3271 ± 556		$P < 0.001$*	
Maternal age	29.7 ± 3.7	29.7 ± 4.1		NS	
Perinatal data	*n* (%)	*n* (%)	OR (95% CI)	*P*-value	RR (95% CI)
GA <32 weeks	244 (7.9)	152 (1.3)	6.65 (5.41–8.18)	<0.001*	6.21 (5.09–7.57)
GA <37 weeks	1669 (53.7)	938 (7.8)	13.70 (12.43–15.10)	<0.001*	6.88 (6.42–7.38)
Birth weight <1500 g	265 (8.5)	159 (1.3)	6.95 (5.69–8.50)	<0.001*	7.29 (6.02–8.84)
Birth weight <2500 g	1762 (56.7)	794 (6.6)	18.51 (16.73–20.48)	<0.001*	8.58 (7.97–9.24)
Transfer to NICU	2111 (67.9)	2194 (18.3)	9.84 (8.68–10.36)	<0.001*	3.72 (3.56–3.89)
Perinatal death	98 (3.15)	91 (0.76)	4.27 (3.20–5.69)	<0.001*	4.17 (3.14–5.53)
Stillbirth	45 (1.45)	59 (0.49)	2.98 (2.02–4.40)	<0.001*	2.95 (2.01–4.34)
Neonatal death	53 (1.73)	32 (0.27)	6.50 (4.18–10.10)	<0.001*	6.41 (4.14–9.92)
Assisted ventilation	244 (7.9)	183 (1.5)	5.51 (4.53–6.70)	<0.001*	5.16 (4.28–6.22)
IC bleeding	61 (1.9)	46 (0.4)	5.21 (3.55–7.66)	<0.001*	5.13 (3.51–7.51)
RDS	191 (6.1)	102 (0.8)	7.22 (5.66–9.22)	<0.001*	7.24 (5.71–9.18)

OR, odds ratio; CI, 95% confidence interval; NS, not significant; RR, relative risk; GA, gestational age; NICU, neonatal intensive care unit; IC bleeding, intracranial bleeding; RDS, respiratory distress syndrome.
*$P < 0.05$ = significant.

groups (Nuojua-Huttunen *et al*., 1999). Wang *et al*. (2002) examined the preterm birth rate in 1015 IUI/DI (homologous/donor insemination) singleton births compared to 1019 IVF/ICSI and 1019 naturally conceived births. In this study, singleton IUI/DI births were about 1.5 times more likely to be born preterm than naturally conceived singletons, whereas the IVF/ICSI group were 2.4 times more likely to be born preterm than the naturally conceived group. They found no significant difference in the risk of preterm birth for IUI (partner semen) compared to DI (donor semen) within their 'low-technology' group (7.0 versus 7.5% respectively). Gaudoin *et al*. (2003) compared 133 COS/AI pregnancies with 109 443 pregnancies of the Scottish national cohort. They concluded that the perinatal outcome of singletons after COS/AI is poorer and associated with low birth weight, but only when IUI was done with partner semen and not with donor semen.

In our study, pregnancies following non-IVF hormonal treatment are compared to a matched group of naturally conceived pregnancies. Data were obtained from the SPE. The study group was matched to controls according to four important factors influencing obstetric and perinatal outcome, namely maternal age, parity, date of delivery and fetal sex. Because of the high difference in perinatal health outcome between singleton and twin pregnancies, we also matched for plurality. Our SPE registry data did not allow matching for other prominent confounders such as smoking, obesity, infection, insulin resistance, socioeconomic status, occupation exposures and pre-existing disease. Our SPE data did not allow differentiation between insemination with donor and partner sperm. Nevertheless, a questionnaire among Flemish infertility specialists showed that in approximately 10% of AIs in our series, donor semen was used. It is well known that pregnancies resulting from donor insemination carry no increased risk compared to spontaneous gestations (Hoy *et al*., 1999; Wang *et al*., 2002; Gaudoin *et al*., 2003).

Considering singletons, it is not possible from the present study to tease out which potential causal factor (insemination procedure, medication used, the influence of vanishing twins or the underlying infertility as such) is responsible for the difference in perinatal outcome between both groups. Our data of a large series of non-IVF pregnancies showed that even after matching for four different confounding factors, the frequency of perinatal health problems such as prematurity, low birth weight and perinatal mortality is higher in COS/AI babies when compared to naturally conceived babies. Neonatal morbidity parameters such as assisted ventilation, intracranial bleeding and RDS were also seen more often in the COS/AI study group. Our data on singleton pregnancies are similar to the results of other studies (Wang *et al*., 2002; Gaudoin *et al*., 2003; Helmerhorst *et al*., 2004).

The outcome of twin pregnancies after ART (IVF and non-IVF) has also been investigated in the structured review published by Helmerhorst *et al*. (2004). In matched studies of twin gestations, they observed no significant difference between ART and spontaneous gestations for very preterm birth, preterm birth, very low birth weight, low birth weight and for small gestational age. Perinatal mortality was about 40% lower after assisted compared with natural conception (relative risk 0.58, CI 0.44–0.77). It was suggested that the lower rate of monochorionic placentas is responsible for the lower risk for perinatal health problems in ART twins. In our series, early neonatal mortality (OR 1.91, CI 1.18–3.20), assisted ventilation (OR 1.22, CI 1.00–1.49) and RDS (OR 1.25, CI 1.00–1.56) were seen more often in the study (COS/AI) group. Contradictory to the study results of Helmerhorst, we observed a higher perinatal mortality in the study group (3.15 versus 2.45%), although this difference was not statistically significant. In the structured review of Helmerhorst *et al*. (2004), almost all studies on the outcome of pregnancies are dealing with IVF/ICSI, and this might be an explanation for the different results of our study examining a solely non-IVF population.

Because monochorionicity is highly associated with an increased perinatal mortality and morbidity, we also studied the data of unlike-sex twins only. In this selected group of dizygotic pregnancies (42.5% of all twin pregnancies after COS/AI treatment in this study), we found a significantly higher rate of very low birth weight (9.0 versus 6.8%, OR 1.61, CI 1.21–2.14) and extreme prematurity (8.7 versus 6.4%, OR 1.37, CI 1.02–1.86) for the COS/AI group compared to the naturally conceived comparison group. Stillbirth, neonatal death and perinatal mortality were seen more frequently in the study group, although the differences were not statistically significant (Table III). Our results indicate that, after excluding the perinatal problems associated with monozygotic pregnancies by using unlike-sex twins only, ART twins carry a higher perinatal risk compared to naturally conceived twins.

It has also been shown in other reports that the increased incidence of premature birth reported for IVF singleton and twin births, compared to spontaneous pregnancies, is due in large part to the initial occurrence of triplet and higher-order gestations which will undergo spontaneous reduction in 47% of triplet and 45% of quadruplet gestations. These pregnancies continued as viable singleton and twin pregnancies, but they are increased risk for prematurity compared to IVF singleton and twins that began as singleton and twin gestation (Dickey *et al*., 2004; Dickey, 2005). Pinborg *et al*. (2005) recently showed that more than 10% of IVF/ICSI singletons are the result of a vanishing twin. They also observed that survivors of a vanishing co-twin have a higher risk for prematurity and low birth weight compared to singletons from single gestations. Since we may expect that the rate of spontaneous reduction is comparable for IVF and non-IVF ART, this phenomenon can explain, at least partly, the worse perinatal health outcome after COS/AI compared to natural conception singleton and twin pregnancies. A close follow-up of ART pregnancies from the early beginning is mandatory to detect spontaneous reduction of multiple pregnancies which might be very important for that particular pregnancy. In our study, there were no data available on spontaneous reduction, and therefore these important parameters could not be evaluated.

This large retrospective analysis also showed an overall increased perinatal risks of multiple pregnancies compared to singletons. Low birth weight and preterm delivery are the most important factors accounting for the excess in perinatal mortality and morbidity in multiple pregnancies. According to the literature, the incidence of early preterm delivery (<32 weeks) and very-low-birth-weight infants (<1500 g) is almost five times higher in ART twin pregnancies compared to ART singletons (Keith and Oleszczuk, 1999; Martin *et al*., 2002; Ombelet *et al*., 2005). In this study, twins were at increased risk for perinatal mortality and morbidity parameters, which could easily be explained by a six- to sevenfold increase in prematurity and low birth weight (Table IV). The prediction of multiple gestation is highly uncertain in COS with or without IUI, especially when gonadotrophins are used (Gleicher *et al*., 2000). Therefore, prevention of multiple pregnancy remains the cornerstone of success in non-IVF procedures using COS. When three or more follicles of a diameter ≥15 mm are present, reasonable options are (i) to cancel the insemination procedure, (ii) to prevent timed coitus during the following days, (iii) to perform rescue IVF with or without the use of GnRH antagonist and/or (iv) to do follicular aspiration (Lessing *et al*., 1991; Many *et al*., 1999; Fatemi *et al*., 2002). Trials with low-dosage gonadotrophin protocols resulted in a lower multiple birth rate without influencing the ongoing pregnancy rate significantly (Dhaliwal *et al*., 2002; Alsina *et al*., 2003). Clomiphene citrate remains a good first-line option with successful ovulation induction in about 50–70% of cases and a reasonable multiple pregnancy rate of 6–8% (Ombelet *et al*., 1996, 1997; Sovino *et al*., 2002).

According to the results of our study and the findings of many other reports, couples have to be informed about the risks of multiple pregnancies associated with infertility treatment. On the other hand, subfertile couples have to be aware of the higher perinatal morbidity and mortality rate even when a singleton pregnancy occurs after non-IVF hormonal treatment.

Conclusion

This retrospective cohort study examines the largest series of pregnancies following COS and/or AI ever published. This study shows a higher incidence of low birth weight, prematurity and perinatal mortality and morbidity for singletons in the infertile population. When all twin pregnancies were considered, only neonatal death was observed more often in the study group. However, when the comparison was restricted to unlike-sex twin pairs, COS/AI twins were significantly disadvantaged compared to naturally conceived unlike-sex twins with a higher incidence of very low birth weight and severe prematurity. Our results emphasize the need to inform couples undergoing treatment with COS, with or without AI, about the increased risk of perinatal mortality and morbidity in twins compared to singletons. Low-dose protocols of ovarian stimulation are mandatory for the prevention of multiple pregnancies in non-IVF hormonal stimulation. Couples should also be informed about an increased risk for perinatal health problems after non-IVF ART in singletons and twin pregnancies when compared to spontaneous pregnancies.

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