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Comparison of the pregnancy outcomes of subfertile women after infertility treatment and in naturally conceived pregnancies

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BACKGROUND: Adverse obstetric outcomes in pregnancies achieved through assisted reproductive technology (ART) could either be due to the technology or to the underlying subfertility or to both. To address this issue, we compared the pregnancy outcomes of singletons conceived naturally after a long time to pregnancy (TTP) with those of ART pregnancies.

METHODS: We analysed an existing birth database. Altogether 428 ART pregnancies were compared with 928 spontaneously conceived pregnancies with TTP of 2 years or more, during the period 1989–2007 at Kuopio University Hospital, Finland. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for pregnancy outcomes.

RESULTS: Between treated and untreated subfertile women no significant differences were found in the rates of Caesarean sections (OR 1.21, 95% CI 0.89–1.64), preterm births (OR 1.28, 95% CI 0.81–2.03), small for gestational age (SGA) birthweight (OR 0.95, 95% CI 0.65–1.39), need of neonatal intensive care (OR 1.28, 95% CI 0.88–1.88) or low Apgar scores (OR 1.19, 95% CI 0.47–3.04). However, compared with pregnancies of women with TTP 0–6 months, ART pregnancies had significantly increased risks of preterm or very preterm birth, low birthweight and need of neonatal intensive care.

CONCLUSIONS: The risks of preterm birth, SGA, need for neonatal intensive care and low Apgar scores were not significantly different between subfertile women who conceived spontaneously and those who conceived through ART indicating that maternal factors relating to subfertility and not only infertility treatment are associated with adverse pregnancy outcomes.

Key words: subfertility / ART / IVF / time to pregnancy / pregnancy outcome

Introduction

The role of assisted reproductive technology (ART) increased from the 1990s so that now, in developed countries, 1.7–4.0% of all children are born after ART (Klemetti *et al*., 2002; Williams and Sutcliffe, 2009). Most fertile couples conceive within 3–6 months (Juul *et al*., 1999; Committee on Gynecologic Practice of American College of Obstetricians and Gynecologists and Practice Committee of American Society for Reproductive Medicine, 2008). Fecundability is the probability of achieving a pregnancy within a single cycle. Biologic fertility can be measured using time to pregnancy (TTP); referring to the time it takes for a couple takes to conceive (Joffe *et al*., 2005). In a clinical setting medical assessment is usually recommended if pregnancy does not begin within 1 year (Olsen *et al*., 1998). On the other hand, not all such couples need or desire treatment and a number of spontaneous pregnancies occur even after a long TTP.

Infertility has a major impact on the quality of life and the health experienced by affected couples (Eugster and Vingerhoets, 1999). Psychological stress during treatment may also worsen the results of infertility treatment (Ebbesen *et al*., 2009). Thus, the information provided to the patients on the risks of pregnancy outcomes and children's health should be accurate, to avoid adding unnecessary concerns to already stressed individuals. It is well documented that ART pregnancies, both higher order births but also singletons, are at an increased risk of low birthweight, fetal growth restriction and preterm birth (Klemetti *et al*., 2002; Allen *et al*., 2006; De Geyter *et al*., 2006; Reddy *et al*., 2007; Sutcliffe and Ludwig, 2007).

It has been proposed that the risks of ART may be due to underlying maternal factors associated with infertility, rather than the infertility treatment or technology (Saunders *et al.*, 1988; Henriksen *et al.*, 1997; Draper *et al.*, 1999; Basso and Baird, 2003; Lambert, 2003; Sutcliffe and Ludwig, 2007). This hypothesis has been tested by comparing siblings born spontaneously and after ART (Romundstad *et al.*, 2008), ART pregnancies with ovulation induction or insemination pregnancies (Nuojua-Huttunen *et al.*, 1999; De Sutter *et al.*, 2005) and spontaneous pregnancies of subfertile women with ART pregnancies (Basso *et al.*, 2003; De Geyter *et al.*, 2006; Kapiteijn *et al.*, 2006; Zhu *et al.*, 2006, 2007, 2009).

This study compares pregnancy outcomes in couples who conceived after at least 2 years of infertility with the outcomes of ART pregnancies.

Materials and Methods

Kuopio University Hospital is a tertiary level obstetric referral centre, but it also serves as the only general obstetric hospital in our district. Thus, it is possible to investigate patients from across the whole socio-economic spectrum.

Data were collected from primary health care maternity case notes that the pregnant women carry with them, since their first visit at maternity centres usually before the 10th week of pregnancy. The pregnant women also answered 75-item questionnaires at 20 weeks of pregnancy. Where data were missing from either of the data sources a nurse on the delivery ward interviewed the woman. Information on morbidity during pregnancy, delivery, pregnancy outcome and the neonatal period was collected and entered into the database in real-time as part of the clinical work. The definitions of background and outcome variables, as well as primary outcomes, are listed in Table I.

Since our data are based on an obstetric database, a rationale for the selection of the ART methods is not available. The patients have been treated in several infertility clinics, with different protocols, and the patient self-reported, whether the index pregnancy was of ART-origin.

A total of 42 890 infants were born at Kuopio University Hospital between 1989 and 2007. Multiple pregnancies ($n = 1681$ infants) and major fetal structural anomalies ($n = 354$) were excluded from our data, resulting in a sample consisting of 40 787 births.

When the information was available, TTP was assessed on the basis of the number of months that women reported they were attempting to get pregnant ($n = 19\,204$). Otherwise, TTP was calculated from the date of stopping birth control to the date of the last menstrual period (LMP), adding 7211 pregnancies. Using these two assessment methods, information on TTP was missing in 16 003 cases. Another 406 pregnancies were excluded because the time since the mother's last delivery and the length of time she said she had been trying to get pregnant were incompatible.

Of the study population, 428 pregnancies started after ART, either IVF or ICSI. Spontaneously conceived pregnancies with a TTP of 2 years or more ($n = 928$) were chosen as the reference. A comparative group of women having a TTP of 0–6 months consisted of 18 984 pregnancies. The data were processed anonymously. The ethical committee and the institutional review board accepted the study and gave permission for the results to be published.

Statistical analyses were performed using SPSS 14.0 for Windows (Release 14.0.1). Statistical significance was assessed by χ^2 analyses using cross tabulation. A value of $P < 0.05$ was considered statistically significant. Continuous variables were analysed using two-tailed, pooled *t*-tests and standard deviations ($\pm$SD) were calculated. The outcomes of the logistic regression analyses were adjusted for confounding factors, such as primiparity, prior miscarriages, prior induced abortions, pre-pregnancy BMI (continuous), surgically scarred uterus, smoking before pregnancy and drinking alcohol before pregnancy. Previous spontaneous and induced abortions were included as confounders, since they may affect both fertility and pregnancy outcome: they may be seen as lower numbers of ongoing pregnancies of fertile women, as well as cause complications that affect the pregnancy outcomes (Swingle *et al.*, 2009). Parity and maternal age correlated strongly and were thus not included in the models simultaneously. Confidence intervals (CIs) were evaluated at 95%.

Table I Definitions of background variables and outcomes.

Unmarried	Civilian status other than marriage: cohabiting, single, widowed or divorced
Parity	Primiparous or parous, number of prior births
Prior induced abortion	Induced abortion of a viable fetus, separated from miscarriage
Prior stillbirth	Intrauterine death of a fetus over 22 weeks of gestational age or over 500 g
Overweight	Pre-pregnancy BMI was over 25 kg/m^2
Smoking	Self-reported smoking yes/no
Drinking alcohol	Self-reported alcohol use yes/no
Chronic illness	Conditions requiring regular medication that has possible effects on pregnancy: thyroid disease, arthritis, epilepsy, cardio-vascular and kidney diseases
Low haemoglobin	Hb under 100 g/l
Pre-eclampsia	Repeated blood pressure measurement exceeding 140/90 mmHg with proteinuria exceeding 0.5 g/day
Primary outcomes	
Preterm birth	Delivery before 37 weeks of gestation
Very preterm birth	Delivery before 32 weeks of gestation
SAG	Age- and sex-adjusted birthweight below the 10th percentile according to the normal tables for our population (Heinonen *et al.*, 2001)
Low birthweight	Birthweight <2500 g
Very low birthweight	Birthweight <1500 g
Extremely low birthweight	Birthweight <1000 g
Mode of delivery	Spontaneous, instrumental or Caesarean section
Apgar scores	Low when the scores were <7
Fetal acidosis	pH 7.15 at birth in the umbilical vein
Neonatal intensive care	Infants requiring more than 24 h surveillance

Results

In the study sample, 1.0% of births occurred after ART, whereas 2.2% started naturally after a TTP of over 2 years. Among subjects who conceived spontaneously after trying for >2 years TTP was self-reported in 743 pregnancies (79.6%), and calculated from the date of stopping birth control to the date of LMP in 185 (20.4%). The mean maternal age was 31.8 years in ART pregnancies and 31.6

years in pregnancies with a long TTP; the difference was not statistically significant. The maternal BMI (Mean ± SD) was 23 ± 4 kg/m^2 for women who had ART pregnancies and 24 ± 5 kg/m^2 for women who had natural pregnancies after a long TTP; the difference was significant ($P = 0.001$). No statistically significant differences were observed in the duration of pregnancies (39.1 versus 39.3 weeks) or birthweights (3470 versus 3440 g).

Table II summarizes maternal pre-pregnancy characteristics and the related statistical differences between the reference and study groups. Statistically significant differences were observed in obstetric history. Specifically, the women who conceived spontaneously with long TTP were more likely to be primiparous (62.5 versus 54.4%) and more likely to have had a miscarriage (15.9 versus 9.8%) or an induced abortion (9.2 versus 4.4%) than women in the ART group. Women who had spontaneous pregnancies after long TTP were significantly more likely to be overweight (27.4 versus 29.6%), to have smoked before pregnancy (29.4 versus 20.6%) and to have drunk alcohol before pregnancy (48.1 versus 37.4%) than women who conceived with ART.

Table IV shows that overall morbidity during pregnancy and pregnancy outcome were statistically similar in the study groups of ART pregnancies compared with pregnancies after >2 years TTP on the basis of both univariate and multivariate logistic regression analyses and controlling for the confounding effects of the most important factors related to adverse obstetric outcomes (listed in Table III). However, in a subgroup analysis that was performed on the women who reported TTP (743 pregnancies with long TTP, 79.6%), excluding those from whom it was estimated on the basis of time since stopping birth control, risk of very preterm birth in the ART pregnancies compared with the study group of long TTP,

Table II Maternal pre-pregnancy characteristics in women who conceived through ART and in those who conceived spontaneously with a TTP >2 years.

	ART pregnancy (n = 428)		Spontaneous conception after ≥2 years (n = 928)		Statistical significance
	n	%	n	%	P
Primiparous	233	54.4	580	62.5	0.005
Prior miscarriage	42	9.8	148	15.9	0.002
Prior stillborn	5	1.2	11	1.2	0.98
Prior induced abortion	19	4.4	85	9.2	0.002
Surgically scarred uterus	30	7.0	82	8.8	0.26
Age ≥ 30 years	172	40.2	621	66.9	<0.001
Age > 35 years	107	25.0	229	24.7	0.90
Not married	125	29.2	270	29.1	0.97
BMI ≥ 25	84	19.6	254	27.4	0.002
BMI ≥ 30	20	4.7	110	11.9	<0.001
BMI < 20	38	8.9	133	14.3	0.005
Smoked before pregnancy	88	20.6	273	29.4	0.001
Smoked during pregnancy	59	13.8	176	19.0	0.019
Drank alcohol before pregnancy	160	37.4	446	48.1	<0.001
Drank alcohol during pregnancy	8	1.9	30	3.2	0.16
Infertility	271	63.3	404	43.5	<0.001
Chronic illness	45	10.5	116	12.5	0.29
Hypertonia arterialis	4	0.9	22	2.4	0.073
Morbidity					
Third trimester anaemia	5	1.2	12	1.3	0.85
Elevated blood pressure	2	0.5	12	1.3	0.25[a]
Gestational diabetes	39	9.1	91	9.8	0.69
Pre-eclampsia	16	3.7	47	5.1	0.28
Gestational hepatosis	1	0.2	6	0.6	0.44[a]
Placenta praevia	11	2.6	14	1.5	0.18
Chorioamnionitis	7	1.6	22	2.4	0.38
Placental abruption	1	0.2	12	1.3	0.074[a]

ART, assisted reproductive technology; BMI, body mass index kg/m^2.
[a]Fisher's exact test.

Table III Mode of delivery and adverse pregnancy outcomes in pregnancies conceived by ART compared with those conceived spontaneously with a TTP >2 years, or 0–6 months.

	ART pregnancy (n = 428)		Spontaneous pregnancies TTP > 2 years (n = 928)		ART versus TTP > 2 years pregnancies	Spontaneous pregnancy TTP 0–6 months (n = 18 984)		ART versus TTP 0–6 months pregnancies
	n	%	*n*	%	*P*	*n*	%	*P*
Caesarean section	105	24.5	22	24.7	0.91	3.84	16.2	<0.001
Vacuum delivery	35	8.2	100	10.8	0.14	1173	6.2	0.091
Abnormal CTG	67	15.7	147	15.8	0.93	2577	13.6	0.22
Umbilical vein pH under 7.15 at birth	5	1.2	17	1.8	0.37	250	1.3	0.79
1 min Apgar score under 7	29	6.8	58	6.3	0.71	921	4.9	0.068
5 min Apgar score under 7	7	1.6	17	1.8	0.80	275	1.4	0.75
Preterm birth < 37 pregnancy weeks	34	8.3	64	7.0	0.44	978	5.2	0.006
Preterm birth 32–36 pregnancy weeks	24	6.0	54	6.0	0.99	793	4.3	0.09
Very preterm birth < 32 pregnancy weeks	10	2.4	10	1.1	0.064	185	1.0	0.004
Low birthweight < 2500 g	31	7.2	53	5.7	0.28	721	3.8	<0.001
Low birthweight < 2500–1500 g	20	4.8	44	0.99	4.8	532	2.8	0.017
Very low birthweight < 1500–1000 g	5	1.2	3	0.3	0.06	100	0.5	0.06
Extremely low birthweight < 1000 g	6	1.4	7	0.8	0.25	92	0.5	0.008
SGA	47	11.0	113	12.2	0.53	1729	9.1	0.18
Neonatal intensive care	56	13.1	104	11.2	0.32	1443	7.6	<0.001
Poor neonatal health[a]	61	14.3	120	12.9	0.51	1793	9.4	0.001
Male sex of the newborn	245	57.2	480	51.7	0.058	9325	51.0	0.033

CTG, cardiotocogram; ART, assisted reproductive technology; SGA, small for gestational age.
[a]One or more: Apgar ≤ 7 at the age of 5 min, acidosis at birth, neonatal intensive care.

Table IV Results of logistic regression analyses: adjusted ORs and unadjusted ORs of adverse obstetric outcomes in pregnancies conceived by ART (n = 428) compared with those conceived spontaneously with a TTP of >2 years months (n = 928), or with women with a TTP of 0–6 months (n = 18 984).

	ART pregnancies versus TTP > 2 years adjusted OR			ART pregnancies versus TTP > 2 years adjusted OR			ART pregnancies versus TTP > 2 years unadjusted OR			ART pregnancies versus TTP 0–6 months adjusted OR		
	Analysis 1	Lower	Higher	Analysis 2	Lower	Higher		Lower	Higher	Analysis 1	Lower	Higher
Caesarean section	1.21	0.89	1.64	1.15	0.85	1.55	1.012	0.78	1.33	1.56	1.22	2.00
Preterm birth < 37 weeks[a]	1.28	0.81	2.03	1.23	0.78	1.93	1.20	0.78	1.85	1.57	1.08	2.27
Preterm birth 32–36 weeks[a]	1.06	0.63	1.80	1.01	0.60	1.70	1.00	0.61	1.65	1.32	0.85	2.04
Very preterm birth < 32 weeks[a]	2.43	0.97	6.06	2.35	0.95	5.83	2.26	0.93	5.46	2.67	1.39	5.08
SGA	0.95	0.65	1.39	0.94	0.65	1.37	0.89	0.62	1.28	1.19	0.86	1.64
Low birthweight < 2500 g[a]	1.31	0.84	2.18	1.32	0.82	2.13	1.29	0.82	2.04	1.92	1.31	2.81
NICU	1.28	0.88	1.88	1.26	0.86	1.84	1.19	0.84	1.69	1.59	1.17	2.17
Acidosis	0.74	0.27	2.05	0.75	0.27	2.07	0.63	0.23	1.73	0.90	0.37	2.20
Low 5 min Apgar score	1.19	0.47	3.04	1.15	0.46	2.92	0.81	0.37	2.17	0.87	0.38	1.99
Poor neonatal health[b]	1.25	0.87	1.78	1.21	0.85	1.75	1.12	0.80	1.56	1.38	1.02	1.87

Analysis 1: adjusted for primiparity, prior miscarriages, prior induced abortions, pre-pregnancy BMI (continuous), pregnancy duration (continuous), surgically scarred uterus, smoking before pregnancy, drinking alcohol before pregnancy.
Analysis 2: adjusted for primiparity, pre-pregnancy BMI (continuous), pregnancy duration (continuous), surgically scarred uterus, smoking before pregnancy, drinking alcohol before pregnancy.
ART, assisted reproductive technology; NICU, neonatal intensive care.
[a]Not adjusted for pregnancy duration.
[b]One or more: Apgar ≤ 7 at the age of 5 min, acidosis at birth, neonatal intensive care.

was statistically significantly increased at an odds ratio (OR) of 2.72 (95% CI 1.02–7.22).

The incidence of adverse obstetric outcome was higher for both ART pregnancies and pregnancies after a long TTP, compared with the fertile obstetric population with a TTP of 0–6 months (Table III). To enable comparison of our data with previously published, the statistical comparison of ART pregnancies and pregnancies with a TTP of 0–6 months is presented (Table IV): the risks of Caesarean section were 1.56-fold, for preterm birth 1.54-fold, for very preterm birth 2.67-fold, for low birthweight 1.92-fold, for need of neonatal intensive care 1.59-fold and having one or more of the following markers of poor neonatal heath: low Apgar score, acidosis at birth and neonatal intensive care 1.38-fold increased.

Discussion

At present, nearly one child in every school class has been born after ART treatment and a similar number have been born as a result of natural conception after 2 years TTP. The main finding of the current study was that the incidence of morbid pregnancy outcomes was similar in pregnancies conceived by ART-treated and those conceived naturally after a TTP of 2 years or more. In accordance with the previously reported increased pregnancy risks of ART pregnancies over pregnancies in fertile women (Klemetti *et al*., 2002; Allen *et al*., 2006; De Geyter *et al*., 2006; Reddy *et al*., 2007; Sutcliffe and Ludwig, 2007): we observed a 1.6-fold risk of Caesarean section as the mode of delivery, a 1.5-fold risk of preterm birth, a 1.9-fold risk of low birthweight and 1.6-fold risk of need for neonatal intensive care. Our results together with previously published results indicate that the adverse obstetric outcomes of ART pregnancies may be related partly to infertility itself, not to the treatment only (Saunders *et al*., 1988; Henriksen *et al*., 1997; Draper *et al*., 1999; Klemetti *et al*., 2002; Basso and Baird, 2003; Lambert, 2003; De Sutter *et al*., 2005; Allen *et al*., 2006; Sutcliffe and Ludwig, 2007; Zhu *et al*., 2007; Romundstad *et al*., 2008).

Outcomes of ART pregnancies have been previously compared with naturally conceived pregnancies of infertility clinic patients who had a TTP over 1 year (De Geyter *et al*., 2006) and in population-based cohorts (Basso and Baird, 2003; Kapiteijn *et al*., 2006; Zhu *et al*., 2006, 2007). Similarly to our results, no difference between treated and untreated subfertile women has been reported for pregnancy duration and birthweight of primiparous women (Basso and Baird, 2003) and for estimates of small for gestational age (SGA) (Zhu *et al*., 2007). In contrast with our study a 4–5 day shorter mean pregnancy duration and a 160–188 g lower mean birthweight for infants born after ART were reported by Geyter *et al*. (2006). In that study, no multivariable analyses were performed to control for confounding factors, which possibly explains the difference between the results compared with those from the current study (De Geyter *et al*., 2006). An analysis of multiparous women only showed a 1.7-fold increased risk of preterm birth and 2.5-fold increased risk of very preterm birth or low birthweight (Basso and Baird, 2003). Furthermore, a 1.1-fold risk of congenital malformations has been published (Zhu *et al*., 2006). In the study of Kapitejn *et al*., the rates of low and very low birthweights, and preterm and very preterm infants born after natural pregnancies to subfertile women, were compared with the corresponding rates among women conceived after ovarian hyperstimulation, IVF and hyperstimulation or frozen embryo transfer in a natural cycle, concluded that both the method and subfertility partly explained the observed impaired pregnancy outcomes, not solely subfertility (Kapiteijn *et al*., 2006).

During childhood, also, psychomotor development and behavioural problems of these children has been compared, being very similar for both groups regardless of treatment (Zhu *et al*., 2009; Middelburg *et al*., 2010; Zhu *et al*., 2011).

Association between a long TTP and adverse pregnancy outcomes is available in the literature (Williams *et al*., 1991; Joffe and Li, 1994; Henriksen *et al*., 1997; Pandian *et al*., 2001; Basso and Baird, 2003; Basso *et al*., 2003; Thomson *et al*., 2005; Zhu *et al*., 2006, 2007; Raatikainen *et al*., 2009; Jaques *et al*., 2010). Specifically, a 1.5–1.6-fold risk of poor neonatal health (Raatikainen *et al*., 2009), a 1.2–2.7-fold risk of preterm birth (Joffe and Li, 1994; Henriksen *et al*., 1997; Basso and Baird, 2003; Jaques *et al*., 2010), a 1.2-fold risk of fetal growth restriction (Zhu *et al*., 2007) and a 1.4–2.3-fold risk of low birthweight (Williams *et al*., 1991; Jaques *et al*., 2010), a 1.3–5-fold risk of pre-eclampsia (Pandian *et al*., 2001; Basso *et al*., 2003; Jaques *et al*., 2010), a 1.2-fold risk of congenital malformations (Zhu *et al*., 2006) and a 1.5-fold risk of Caesarean section and induction of labour (Pandian *et al*., 2001; Jaques *et al*., 2010) have been reported.

Furthermore, after birth, it has also been reported associations with a 2.8-fold risk of neonatal mortality (Basso and Olsen, 2005), an increased risk of a modest psychomotor developmental delay (Middelburg *et al*., 2010) and even 1.9-fold risk of schizophrenia in the offspring (Opler *et al*., 2010). However, conflicting results showing no association between TTP and pregnancy outcome have also been published (Axmon and Hagmar, 2005; Cooney *et al*., 2006; Joffe *et al*., 2007) but different study design, incompletely reported TTPs and differences in populations planning pregnancies may have had a role herein.

Although the underlying mechanisms for adverse obstetric outcomes in pregnancies of subfertile women have not been resolved, possible explanations are the medical conditions that ultimately caused the subfertility, sperm factors and in ART pregnancies the ovarian stimulation, embryo culture and freezing (Romundstad *et al*., 2008).

The hypothesis of causality could be tested by, for example, comparing patients treated by ART with patients treated by ovulation induction or insemination (Sutcliffe and Ludwig, 2007). One such study reported similarly reduced birthweights for both insemination pregnancies and IVF pregnancies, compared with those for fertile controls (Nuojua-Huttunen *et al*., 1999). Another study comparing insemination- and IVF pregnancies showed similar pregnancy duration, birthweight, Caesarean section rate and need for neonatal intensive care in these groups (De Sutter *et al*., 2005). Recently, the question of causality has been studied by comparing subsequent pregnancies for the same women, one after assisted fertilization and another after spontaneous pregnancy. Interestingly, no differences were reported between these siblings. This result indicates that the adverse obstetric outcomes of ART pregnancies associate also with the underlying factors of subfertility, not only by the ART-technique (Romundstad *et al*., 2008). In earlier studies of pregnancy outcome after ART the comparative groups were a general obstetric population (Klemetti *et al*., 2002; Allen *et al*., 2006; Sutcliffe and Ludwig, 2007).

Based on the present study, subfertile women who conceive without ART appear to represent a more informative reference population when the effect of the ART treatments on pregnancy outcome is the focus.

Another important finding in the current study was that women who had ART pregnancies had substantially better health behaviour than women who conceived spontaneously after a long delay. Smoking, being overweight and drinking alcohol are all well-documented risk factors of subfertility (Augood *et al.*, 1998; Jensen *et al.*, 1998; Eggert *et al.*, 2004; Hassan and Killick, 2004; Gesink Law *et al.*, 2007; Homan *et al.*, 2007). Possibly, our data based on subfertile women in the general obstetric population is different from that for patients of infertility clinics (De Geyter *et al.*, 2006): these women with a long TTP may have had less knowledge of these effects and might benefit from preventive measures. On the other hand, better health-related behaviour might lead to less need for using ART and infertile couples might even be required to make lifestyle changes before active medical treatment.

Although our data are registry based on the impaired pregnancy outcomes of the ART pregnancies could be confirmed, even after wide adjustments for confounding factors (Reddy *et al.*, 2007). However, a weakness of our data is that no more information on the ART method can be given, due to the study method. Using calculated TTP data in one-fifth of all cases may also give a bit different information from the data retrieved from the self-reported time of attempting to get pregnant. The possibility that the risk of very preterm births is higher in ART pregnancies than in natural pregnancies of subfertile women needs to be confirmed in future studies.

One strength of this study was the birth database that made possible large-scale adjustments for confounding factors in obstetric history, maternal anthropometry and health-related behaviour. If a woman did not report either to the primary health care unit or at the hospital that the pregnancy was conceived by ART, the pregnancy may have been misclassified and placed in the spontaneous pregnancies category. Previous studies have found that the validity of self-reported TTP data is high though, particularly for current or recent pregnancies (Joffe *et al.*, 1993; Olsen *et al.*, 1998). We were only able to investigate pregnancies lasting more than 22 weeks, and no analysis could be made for the miscarriages. Neither was the health behaviour of women trying to get pregnant, with or without medical treatment, assessable.

Conclusion

Pregnancies of women with a long TTP were somewhat similar to IVF pregnancies. These results strongly support the hypothesis that the increased risks of impaired pregnancy outcomes of ART pregnancies are partly related to infertility itself, not only to the treatment. Evidently, when assessing the health impacts of ART, the choice of comparative study group is of importance.

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Authors' roles

K.R. and M.H. designed the study, K.R. performed the analyses, K.R., M.H., P.K.-P. and S.H. participated in drafting and critically discussing the manuscript.

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Conflict of interest

None declared.

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