

Article

Impact of infertility characteristics and treatment modalities on singleton pregnancies after assisted reproduction



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Abstract

Obstetric and neonatal outcomes of assisted reproduction and control singletons were evaluated after taking into account treatment characteristics and infertility background. The elective single embryo transfer (eSET) group ($n = 45$) was compared with the compulsory single embryo transfer (cSET; $n = 52$), double embryo transfer (DET; $n = 227$) and control ($n = 304$) groups. Infertility-related prognostic factors for neonatal outcomes were also analysed. Data were collected with structured questionnaires at gestational week 20 and 8 weeks after delivery. Spontaneous onset of delivery was more typical of the eSET group than of cSET and DET groups (68.9 versus 52.0%, $P = 0.02$). Mean (\pm SD) gestation at birth (39.3 ± 1.6 weeks) and mean birth weight (3470 ± 505 g) of eSET singletons were comparable with other assisted reproduction groups, but gestational duration was lower than in the eSET group than in the control group (39.9 ± 1.4 ; $P < 0.05$). However, numbers of preterm births and low birth weight infants were similar between groups. History of induced abortion increased risk of preterm birth (OR 4.5 and 95% CI 1.2–17.1) in assisted reproduction singletons. A small though clinically unimportant difference in gestational age at birth and birth weight between assisted reproduction and control singletons was found regardless of the number of embryos transferred.

Keywords: assisted reproduction treatment, elective single embryo transfer, infertility characteristics, IVF, obstetric and neonatal outcome

Introduction

The term delivery of a healthy singleton can be considered the optimal outcome of assisted reproduction treatment. Still, in Europe, the proportion of multiple deliveries after assisted reproduction has remained quite stable at 25.5%, and close to 40% of all delivered assisted reproduction babies are twins (Nyboe Andersen *et al.*, 2005). The most efficient way to decrease the twinning rate is to restrict the number of transferred embryos to one (Tiitinen and Gissler, 2004; Levi Setti *et al.*, 2005). Elective single embryo transfer (eSET) results in twinning rate equal to the rate of spontaneous

twinning with acceptable clinical pregnancy and delivery rates (Martikainen *et al.*, 2001; Tiitinen *et al.*, 2003; Thurin *et al.*, 2004). Although the decline in number of twins will significantly reduce the total neonatal morbidity of assisted reproduction pregnancies (Källen *et al.*, 2005a), all adverse obstetric and neonatal outcomes in assisted reproduction singletons are not overcome.

Previous controlled studies have documented shorter gestational duration and lower birth weight (LBW) in assisted reproduction singleton pregnancies (Helmerhorst *et al.*, 2004; Jackson *et al.*, 2004; Schieve *et al.*, 2004). Identification

of prognostic factors of adverse obstetric and neonatal outcome from assisted reproduction patient characteristics is important and would help clinicians to plan optimal treatment. The assisted reproduction live-birth rates decrease with increasing female age, overweight, longer duration of infertility and many previous IVF attempts (Templeton *et al.*, 1996; Stolwijk *et al.*, 2000; Lintsen *et al.*, 2005). Whether these factors have also an impact on obstetric and neonatal outcome has not been studied. The aetiology of infertility and treatment type, on the other hand, do not seem to play an important role in neonatal outcome according to majority of studies (Wennerholm *et al.*, 1997; Bonduelle *et al.*, 2002; Schieve *et al.*, 2002, 2004; Hourvitz *et al.* 2005; Källen *et al.*, 2005b; Wang *et al.*, 2005).

The reported poorer neonatal outcome of assisted reproduction singletons in the controlled studies may also relate to the number of transferred embryos. According to a recent register study, 10% of assisted reproduction singletons originate from a twin pregnancy (Pinborg *et al.*, 2005). Vanishing twin survivors have been at an increased risk of preterm birth and low birth weight (LBW, i.e. <2500 g) as compared with other assisted reproduction singletons and could have contributed significantly to total adverse neonatal outcomes in IVF singletons observed previously (Dickey *et al.*, 2002; Pinborg *et al.*, 2005). As eSET pregnancies practically lack vanishing twins, their outcome is not biased in this respect. On the other hand, transferring the only embryo available [compulsory single embryo transfer (cSET)] associates with lower clinical pregnancy rates (Elsner *et al.*, 1997; Vilska *et al.*, 1999), and may relate also to poorer obstetric and neonatal outcomes.

This prospective and longitudinal study was run to evaluate both the somatic and the mental health of assisted reproduction and spontaneously conceived couples during the pregnancy and the child's first year (Repokari *et al.*, 2005). This paper evaluates the obstetric (pregnancy complications, hospitalization, the onset and the mode of delivery) and neonatal outcome (gestational age at birth, birth weight, Apgar scores, neonatal intensive care unit admissions and perinatal mortality) of singletons in the assisted reproduction and the control groups. Furthermore, the pregnancy outcome of eSET singletons was compared with the cSET, double embryo transfer (DET) and control singleton groups, and lastly, the impact of previous pregnancies and infertility characteristics (aetiology, duration and treatment history) on

neonatal outcome of the assisted reproduction pregnancies was analysed.

Materials and methods

Formation of the study groups

All Finnish-speaking voluntary couples with confirmed viable pregnancy following either fresh or frozen IVF or intracytoplasmic sperm injection (ICSI) cycle with own gametes were recruited by the couple's IVF doctor to this study from the infertility clinics of Helsinki University Central Hospital, the Family Federation of Finland (Helsinki, Oulu and Turku) and the Deaconess Institute (Helsinki) in 1999. The Finnish-speaking, spontaneously conceiving control couples were recruited by the research nurse by consecutive sampling aside their appointment for screening ultrasound scans at gestational weeks 16–18 at Helsinki University Central Hospital the same year. The exclusion criteria for control couples were previous infertility and infertility treatment and maternal age under 25 years.

Collection of the data

Collection of the data is reported previously (Repokari *et al.*, 2005). The recruiting infertility doctor collected detailed information of the duration and the aetiology of infertility and of the assisted reproduction history from clinics' patient registries, and the research nurse documented the medical and the obstetric histories of the participants in structured questions. The participants filled in a set of questionnaires at the 20th (\pm 3.2) gestational week (time point one = T1) and 8 weeks (\pm 3.4) after the delivery (time point two = T2). The first questionnaire was given at recruitment. The second questionnaire was mailed to participants after their willingness to continue in this study was confirmed with a telephone call. In addition, the T2 non-respondents' pregnancy duration at birth and newborns' birth weight and Apgar scores were retrospectively collected from the clinic patient registries for the non-respondent analysis. In total, 460 assisted reproduction conceived (367 singletons, 91 twins and two triplets) and 400 spontaneously conceived (379 singletons, 20 twins and one triplet) married or co-habiting women participated in this study at T1. For this paper, 324 assisted reproduction and 304 control women with singleton pregnancies who returned both questionnaires (88 and 80% of

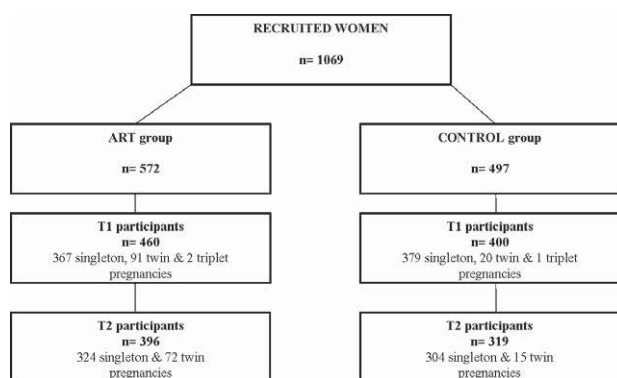


Figure 1. Formation of the study groups and participation at the first (T1) and at the second (T2) assessment.

initial respondents respectively, $P = 0.03$) were included. The formation of the assisted reproduction and the control group is summarized in **Figure 1**. All participants received oral and written information of the study and gave their informed consent voluntarily. The Ethics Committees of the clinics approved this study.

Infertility characteristics of the participants

The aetiology of infertility was classified as female factor in 107 (33%), male factor in 88 (27%), combined in 61 (19%) and unexplained in 68 (21%) of the assisted reproduction participants. The frequencies of different aetiological subgroups were comparable between the eSET, the cSET and the DET groups. Median duration of infertility was 3.4 years in the eSET group, 4.7 years in the cSET group and 4.0 years in the DET group. The studied treatment cycle was the first one in 67% of the eSET group, in 13% of the cSET group and in 26% of the DET group respectively ($P < 0.001$). However, the number of previous assisted reproduction pregnancies or previous assisted reproduction live births did not differ between the groups. The treatment was IVF in 128 (40%), ICSI in 59 (18%) and frozen embryo transfer (FET) in 137 (42%) cycles. The proportion of FET cycles varied between the groups as follows: 0% (eSET), 73.1% (cSET) and 43.6% (DET) ($P < 0.001$).

Measures

Women's age and body mass index (BMI; kg/m²) were reported at the recruitment. Women's general health (presence or absence of chronic illness and need of continuous medication) was assessed at T1. Tobacco smoking (0, <5, 5–10, >10 cigarettes per day) and alcohol consumption [0, <5, ≥5 units per week (one unit equals 12 g of pure alcohol)] were analysed in categories. Pregnancy complications and related hospitalisation after gestational week 20 were assessed with dichotomous questions at T2. The complications were defined as follows. Preterm contractions: uterine contractions before gestational week 37 needing specialized care; hypertension: blood pressure ≥140/90; pre-eclampsia: simultaneous hypertension and proteinuria; gestational diabetes: pathological 2 h oral glucose tolerance test and cholestasis in pregnancy: elevated hepatic transaminases and/or elevated serum biliary acids.

The onset and the type of delivery were asked in multiple-choice questions. The questions addressing to the newborns' health depicted birth weight and height, apgar scores, health at birth, need and length of neonatal intensive care unit (NICU) treatment and length of hospitalization. The perinatal mortality rate (PNMR) refers to stillbirths (a birth of a dead child after 22 completed gestational weeks) and neonatal deaths (newborn's death up to the age of 6 days).

Statistics

Statistical analysis was run with Statistics Package for Social Sciences version 12.0.1. Categorical variables were analysed with Fisher's exact test and continuous variables with Student's *t*-test, Mann-Whitney *U*-test and analysis of variance (ANOVA) where applicable. $P < 0.05$ was regarded statistically significant. Logistic regression analysis was run to identify the prognostic factors for adverse obstetric and neonatal outcomes. First,

the risks of medical induction of delivery, Caesarean section, preterm birth, LBW and NICU admissions associated with assisted reproduction were assessed. Secondly, the contribution of previous non-viable pregnancies (none, miscarriage, induced abortion or ectopic pregnancy), duration (<2, 2–5, >5 years) and aetiology of infertility (female, male, combined, unknown), number of previous assisted reproduction treatments (0–2, 3–4, ≥5) and the current treatment type (IVF, ICSI and FET) to increased risks of preterm birth and LBW in the assisted reproduction singletons were studied. These logistic regression analyses were adjusted for woman's age (<30, 30–34, 35–44 years), BMI (<20, 20–24, ≥25 kg/m²), and parity.

Results

The mean age of women was comparable between the assisted reproduction and the control groups, while the eSET mothers were the youngest in subgroup analysis (**Table 1**). The presence of chronic illness was rare in all groups. The proportion of non-smokers was similar across the groups but the number of heavy (>10 cigarettes per day) smokers was highest in the control group. The control mothers used alcohol more frequently than the assisted reproduction mothers. Sixty-eight per cent of all couples were married and the rest co-habited. Significantly more women in the control group than in the assisted reproduction group had been pregnant or given birth previously, whereas previous ectopic pregnancies were characteristic to the assisted reproduction group (both $P < 0.001$).

The prevalence of self-reported pregnancy complications (preterm contractions, hypertension, pre-eclampsia, gestational diabetes and cholestasis in pregnancy) was similar in the assisted reproduction group and in the control group: 43% of the respondents reported at least one pregnancy complication. However, in the eSET group the prevalence of preterm contractions (35.6%) and vaginal bleeding (13.3%) were higher than in the cSET (15.4 and 1.9% respectively), DET (20.7 and 4.5% respectively) and control groups (22.4 and 2.6% respectively) ($P < 0.05$). Twelve to 20% of participants needed hospital treatment related to any of the predefined pregnancy complications and no difference between the groups existed. Assisted reproduction mothers were hospitalized before the delivery more often than the controls (18.8 versus 11.2%, $P = 0.006$). The most frequent indications for pre-delivery hospitalization in the assisted reproduction group were hypertensive disorder (59%), followed by cholestasis in pregnancy (20%) and suspected abnormal fetal growth or fetal distress (21%).

Preterm spontaneous delivery, medical induction of delivery, and operative deliveries were more common in the assisted reproduction pregnancies than in the control pregnancies (**Table 2**). However, medical induction of delivery was less frequent in the eSET group than in the cSET and DET groups. No difference in the type of spontaneous term delivery between the eSET and the control group existed.

The assisted reproduction singletons were born in earlier gestational weeks than the controls, but the proportion of prematurely born babies did not differ (**Table 3**). In the eSET group, the mean gestational age at birth was in accordance with the cSET and DET singletons, but lower than the

Table 1. Background characteristics of the assisted reproduction and control groups. Values are numbers with percentages in parentheses unless otherwise indicated.

	Assisted reproduction	Control	P-value 1	eSET	cSET	DET	P-value 2
Total (n)	324	304		45	52	227	
Age [years; mean (SD)]	33.0 (4.1)	33.3 (3.0)	NS	31.3 (3.9)	33.9 (4.0) ^a	33.2 (4.2) ^a	0.006
BMI [mean (SD)]	22.6 (3.3)	23.1 (3.2)	NS	22.3 (3.2)	23.3 (3.6)	22.6 (3.3)	NS
Chronic illness	4 (1.2)	4 (1.4)	NS	0	2 (3.8)	1 (0.4)	NS
<i>Smoking while pregnant (cigarettes per day)</i>							
0	277 (85.5)	267 (87.8)	NS	39 (86.7)	43 (82.7)	195 (85.9)	NS
<5	4 (1.2)	13 (4.3)	0.03	1 (2.2)	1 (1.9)	2 (0.9)	NS
5–10	7 (2.2)	6 (2.0)	NS	1 (2.2)	2 (3.8)	4 (1.8)	NS
10–20	2 (0.6)	10 (3.3)	0.02	0	0	2 (0.9)	NS
<i>Alcohol use while pregnant (units^b per week)</i>							
0	275 (84.9)	239 (78.6)	NS	38 (84.4)	45 (86.5)	192 (84.6)	NS
<5	19 (5.9)	55 (18.1)	<0.001	3 (6.7)	2 (3.8)	14 (6.2)	NS
5–10	0	1 (0.3)	NS	0	0	0	-
Nulliparous	227 (70.1)	104 (34.2)	<0.001	31 (68.9)	22 (42.3) ^a	166 (73.1)	NS
<i>Previous pregnancies</i>							
Miscarriages	62 (19.1)	66 (21.7)	NS	4 (8.9)	8 (15.4)	50 (22.0) ^a	NS
Legal abortions	29 (9.0)	26 (8.6)	NS	7 (15.6)	7 (13.5)	15 (6.6)	NS
Ectopic pregnancies	27 (8.3)	4 (1.3)	<0.001	3 (6.7)	3 (5.8)	21 (9.3)	NS

P-value 1 refers to the comparison between the assisted reproduction treatment group and the control group; P-value 2 refers to the comparison between the eSET, DET and cSET groups.

BMI = body mass index; cSET = compulsory embryo transfer; DET = double embryo transfer; eSET = elective single embryo transfer; NS = not statistically significant.

^aP < 0.05 when compared with the eSET group.

^bUnit of alcohol = 12 g of pure alcohol (i.e. 12 cl of wine).

Table 2. Delivery characteristics for the assisted reproduction groups and controls. Values are numbers with percentages in parentheses unless otherwise indicated.

	Assisted reproduction	Control	P-value 1	eSET	cSET	DET	P-value 2
Total	324	304		45	52	227	
<i>Spontaneous onset</i>							
≥37 gestational weeks	176 (54.3)	214 (70.4)	<0.001	31 (68.9)	27 (51.9) ^a	118 (52.0) ^a	0.02
<37 gestational weeks	16 (4.9)	5 (1.6)	0.003	4 (8.9)	2 (3.8)	10 (4.4)	NS
<i>Medical induction</i>							
≥37 gestational weeks	85 (26.2)	53 (17.4)	0.01	4 (8.9)	14 (26.9) ^a	66 (29.1) ^b	0.02
<37 gestational weeks	5 (1.5)	4 (1.3)	NS	1 (2.2)	1 (1.9)	3 (1.3)	NS
<i>Type of delivery</i>							
Caesarean section: all	85 (26.2)	58 (19.1)	0.02	11 (24.4)	16 (30.7)	59 (26.0)	NS
Elective	34 (10.5)	25 (8.2)	NS	5 (11.1)	6 (11.5)	23 (10.1)	NS
Emergency	52 (16.0)	33 (10.9)	NS	6 (13.3)	10 (19.2)	36 (15.9)	NS
Vacuum extraction	33 (10.2)	15 (4.9)	0.02	1 (2.2)	6 (11.5)	26 (11.5)	NS
Vaginal	199 (61.4)	229 (75.3)	0.001	32 (71.1)	30 (57.7)	137 (60.4)	NS

P-value 1 refers to the comparison between the assisted reproduction treatment group and the control group; P-value 2 refers to the comparison between the eSET, DET and cSET groups.

cSET = compulsory embryo transfer; DET = double embryo transfer; eSET = elective single embryo transfer; NS = not statistically significant.

^{a,b}P < 0.05 or 0.001 respectively when compared with the eSET group.

Table 3. Neonatal outcome in the assisted reproduction groups and controls. Values are numbers with percentages in parentheses unless otherwise indicated.

	Assisted reproduction	Control	P-value	eSET ^b	cSET ^b	DET ^b
Pregnancies/infants (n)	324/324	304/304		45/45	52/52	227/227
<i>Gestational duration in weeks</i>						
Mean (SD)	39.6 (1.7)	39.9 (1.4)	0.01	39.3 (1.6) ^a	39.5 (1.6)	39.7 (1.8)
Range	26.3–42.6	32.4–42.4		34.4–41.7	35.6–42.3	26.3–42.6
>37	296 (91.4)	292 (96.1)	NS	40 (88.9) ^a	47 (90.4)	210 (92.5)
32–36	23 (7.1)	12 (3.9)	NS	5 (11.1) ^a	5 (9.6)	13 (5.7)
<32	1 (0.3)	0	NS	0	0	1 (0.4)
<i>Birth weight</i>						
Mean [g (SD)]	3490 (554)	3630 (500)	0.001	3470 (505)	3611 (523)	3466 (569)
Range	975–4820	1635–5965		2275–4770	2040–4440	975–4820
>2500 g	310 (95.7)	299 (98.4)	NS	44 (97.8)	50 (96.2)	216 (95.2)
1500–2499 g	12 (3.7)	4 (1.3)	NS	1 (2.2)	2 (3.8)	9 (4.0)
<1500 g	1 (0.3)	0	NS	0	0	1 (0.4)
<i>Apgar scores</i>						
1” <7	19 (5.9)	12 (3.9)	NS	1 (2.2)	2 (3.8)	16 (7.0)
NICU admission	12 (3.7)	5 (1.6)	NS	0	2 (3.8)	10 (4.4)
Healthy at birth	296 (91.4)	288 (94.7)	NS	40 (88.9)	49 (94.2)	207 (91.2)
Perinatal mortality n/total ^c	3/369 (0.8)	1/379 (0.3)	NS			

P-value 1 refers to the comparison between the assisted reproduction treatment group and the control group; P-value 2 refers to the comparison between the eSET, DET and cSET groups.

cSET = compulsory embryo transfer; DET = double embryo transfer; eSET = elective single embryo transfer; NICU = neonatal intensive care unit; NS = not statistically significant.

^aP < 0.05 when compared with controls.

^bThere were no statistically significant differences between the three assisted reproduction groups.

^cTotal refers to the participants at the first assessment (T1).

controls. Furthermore, preterm births were more numerous in the eSET group than in the control group. The majority (21 of 24; 87.5%) of the preterm assisted reproduction singleton deliveries took place after gestational week 35. One assisted reproduction singleton of all (0.3%) was born very preterm (<32 weeks gestation). In spontaneous deliveries only (i.e. not including those following induction), the mean (SD) duration of pregnancy was lower in the assisted reproduction than in the control group: 39.5 (1.8) versus 39.9 (1.3) respectively ($P = 0.003$). The assisted reproduction singletons' mean birth weight was lower than in the controls, but the difference was not statistically significant. Eleven out of 13 (84.6%) LBW infants were born preterm and two (15.4%) at term in the assisted reproduction group. The proportion of low Apgar scores and NICU admissions were similar across the groups.

In the assisted reproduction group, two stillbirths (at gestational weeks 34 and 37; reason unknown) and one neonatal death (due to left ventricular hypoplasia of the heart) were reported. In the control group, one singleton stillbirth occurred at gestational week 30 (reason unknown). Perinatal mortality rates (PNMR) did not differ between the assisted reproduction and the control groups (a subgroup analysis was not run).

were originally twin pregnancies. In six of them, the co-twin had spontaneously aborted (diagnosed with vaginal ultrasound in gestational weeks 8–10). In two, the co-twin was selectively reduced (one fragile X syndrome, one Down's syndrome). The mean gestational weeks at birth in these eight cases were 40 (± 1.0 ; range 38.3–41.1) and the mean birth weight was 3358 g (± 513 g; range 2710–4400 g). None of the vanishing twin survivors was admitted to NICU. The number of vanishing twins in the control group is not known.

Because there was no control for parity at enrolment, parity adjusted multiple logistic regression analysis was run to identify risks of adverse obstetric and neonatal outcomes associated independently with assisted reproduction (**Table 4**). Assisted reproduction did not affect the risk of studied outcomes, whereas nulliparity increased the risks of medical induction of delivery [odds ratio (OR) 1.6 and 95% CI 1.0–2.5], all Caesarean sections (OR 2.8 and 95% CI 1.8–4.5), low Apgar scores (OR 5.6 and 95% CI 2.0–15.8) and NICU admission (OR 4.8 and 95% CI 1.2–18.6). BMI ≥ 25 kg/m² was also associated with the increased risk of Caesarean section (OR 3.2 and 95% CI 1.7–6.0). In the above logistic regression analysis, no interaction between variables existed.

Eight of the studied assisted reproduction singleton pregnancies

Secondly, the impact of previous pregnancies and infertility

Table 4. Multiple logistic regression. Odds ratios (OR) and 95% confidence intervals (CI) for adverse obstetric and neonatal outcomes.

	<i>Medical induction of delivery</i>			<i>Caesarean section: all</i>			<i>Preterm birth (<37 weeks)</i>			<i>Low birth weight (<2500 g)</i>			<i>NICU admission</i>		
	n	OR	95% CI	n	OR	95% CI	n	OR	95% CI	n	OR	95% CI	n	OR	95% CI
Total	611			614			628			628			613		
<i>Age</i>															
20–29 ^a	69	1	–	70	1	–	70	1	–	70	1	–	69	1	–
30–34	333	1.0	0.5–2.0	332	0.9	0.5–1.8	336	1.0	0.4–3.1	336	0.5	0.2–2.5	331	1.3	0.3–6.8
35–44	209	1.7	0.9–3.2	212	1.6	0.8–3.1	213	1.2	0.4–3.5	213	1.0	0.2–4.1	213	2.0	0.4–10.0
<i>BMI</i>															
<20 ^a	101	1	–	103	1	–	104	1	–	104	1	–	102	1	–
20–24	390	1.4	0.8–2.4	390	1.2	0.7–2.1	393	1.2	0.4–3.3	393	1.0	0.3–3.9	390	2.9	0.4–23.2
≥25	120	1.5	0.8–2.8	121	3.2	1.7–6.0	122	1.8	0.6–5.5	122	0.6	0.1–3.7	121	6.9	0.8–60.0
<i>Parity</i>															
Parous ^a	287	1	–	289	1	–	292	1	–	292	1	–	288	1	–
Nulliparous	324	1.6	1.0–2.5	325	2.8	1.8–4.5	327	1.5	0.7–3.3	327	0.8	0.3–2.7	325	4.8	1.2–18.6
<i>Group</i>															
Control ^a	299	1	–	300	1	–	301	1	–	301	1	–	299	1	–
Assisted reproduction	312	1.5	0.9–2.3	314	1.0	0.7–1.6	318	1.9	0.8–4.2	318	3.5	0.9–14.1	316	1.5	0.5–4.7

BMI = body mass index; NICU = neonatal intensive care unit.

^aReference group.

characteristics on the risks of preterm birth and LBW in the assisted reproduction group was studied in separate adjusted multiple logistic regressions (**Table 5**). BMI, aetiology, duration or treatment of infertility did not affect these risks. History of induced abortion, on the other hand, was associated with a 4-fold risk of preterm birth (OR 4.5 and 95% CI 1.2–17.1). In this logistic regression analysis, ‘duration of infertility’ and ‘number of treatments’ were related (correlation coefficient 0.7). When interaction term ‘duration of infertility’ × ‘number of treatments’ was included instead of independent variables ‘duration of infertility’ and ‘number of treatments’, the OR (95% CI) increased to 1.0 (0.8–1.2) compared with the lower OR of the separate variables (**Table 5**). Nevertheless, even the interaction variable did not reach statistical significance.

Comparison of fresh and frozen embryo transfer (FET) cycles

The pregnancy outcome following fresh and FET was compared in a sub analysis (results not shown). The only significant finding was the greater mean (SD) birth weight after FET than after fresh embryo transfer: 3579 g (586) and 3424 g (522) respectively ($P = 0.01$). Number of parous women was higher in the FET group than in the fresh group: 51 (37.2%) versus 46 (24.6%) respectively ($P = 0.02$).

Neonatal outcome of non-respondents at second assessment (T2)

The gestational weeks at birth, birth weights and low Apgar scores were analysed in the non-respondents. The mean gestational weeks at birth in the non-responding assisted

reproduction singletons ($n = 43$) was lower than in the participating assisted reproduction singletons (38.9, range 31–42 versus 39.6, range 26–43; $P = 0.02$). In the controls, gestational weeks did not differ between the non-respondents and the participants. Birth weights and Apgar scores were similar between the non-respondents and the participants both in the assisted reproduction and in the control groups.

Discussion

This study analysed the obstetric and neonatal outcome of assisted reproduction singleton pregnancies and their controls with prospective and multidimensional material (Repokari *et al.*, 2005). An attempt was made to identify potential infertility related prognostic factors of obstetric and neonatal outcome, which would help to plan optimal treatment of infertility and correct pregnancy monitoring after successful assisted reproduction. In this study, infertility and treatment characteristics were not associated with the risk of preterm birth and LBW. However, a small, though clinically not important, difference was found in gestational age at birth and birth weight between the assisted reproduction and the control singletons regardless of the number of embryos transferred.

It was particularly desired to assess the obstetric and neonatal outcome in the eSET subgroup. The proportion of eSET has increased substantially in Finland and the need for correct patient counselling has grown. In Finland, eSET policy was implemented in 1997 by clinicians’ initiative and has been well adopted without a law or reimbursement system in contrary to other countries (Gordts *et al.*, 2005). In 2004, over 50% of embryo transfers were performed as SET in Finland. Still, it

Table 5. Age-adjusted multiple logistic regression: Odds ratio (OR) and 95% confidence intervals (CI) for preterm birth and low birth weight in the assisted reproduction singletons.

	<i>Preterm birth (<37 weeks)</i>			<i>Low birth weight (<2500 g)</i>		
	n	OR	95% CI	n	OR	95% CI
Total	309			310		
<i>BMI</i>						
<20 ^a	62	1	–	62	1	–
20–24	185	3.2	0.5–10.4	186	2.9	0.3–26.0
≥ 25	62	5.7	0.5–17.3	62	1.0	0.1–18.9
<i>Previous non-viable pregnancies</i>						
None ^a	193	1	–	193	1	–
Miscarriage	61	2.8	0.9–8.9	61	1.7	0.3–8.8
Induced abortion	29	4.5	1.2–17.1	29	3.3	0.6–19.2
Ectopic pregnancy	26	2.7	0.6–11.2	26	2.7	0.4–16.8
Nulliparity	218	0.9	0.3–2.3	219	1.4	0.3–6.2
<i>Aetiology of infertility</i>						
Female ^a	91	1	–	91	1	–
Male	84	0.3	0.1–1.5	84	1.0	0.1–7.3
Combined	60	0.8	0.2–3.0	60	2.1	0.3–12.3
Unexplained	74	0.8	0.2–3.0	75	1.2	0.2–7.9
<i>Duration of infertility (years)</i>						
<2 ^a	143	1	–	143	1	–
2–5	55	0.0	0.0–	56	0.0	–
>5	111	0.7	0.2–2.0	111	1.4	0.4–5.4
<i>Number of treatments</i>						
1–2 ^a	161	1	–	162	1	–
3–4	83	0.5	0.1–1.6	83	0.2	0.0–1.7
≥ 5	65	1.1	0.3–3.0	56	0.6	0.1–3.7
<i>Treatment type</i>						
IVF ^a	120	1	–	121	1	–
ICSI	56	1.6	0.4–5.7	56	0.6	0.1–7.2
FET	133	0.5	0.2–1.6	133	1.6	0.4–7.1

BMI = body mass index; FET = frozen embryo transfer; ICSI = intracytoplasmic sperm injection.

^aReference group.

must be kept in mind that in the study year, 23% of all embryo transfers were performed as SET in Finland and the major indication for eSET was patient's suspected susceptibility to obstetric complications (Vilksa *et al.*, 1999; Stakes, 2001). Therefore, the patient selection may reflect the inferior neonatal outcome of the eSET group to the controls in this study. Further, data on embryo morphology were not included in this study, and therefore only the number but not the quality of transferred embryos can be discussed. Lastly, the number of eSET patients in this study was quite low, and the results need to be evaluated against larger groups in the future. Still, it was possible to evaluate the impact of these first eSET cycles to overall obstetric and neonatal outcome in this study.

The assessed 324 assisted reproduction singleton deliveries constitute 73.8% of the participating clinics' singleton deliveries and 32.3% of all assisted reproduction singleton deliveries in Finland in 1999. Although the results on obstetric and neonatal outcome are more limited than those of controlled register based studies with higher statistical power (Bergh *et al.*, 1999; Klemetti *et al.*, 2002; Koivurova *et al.*, 2002; Schieve *et al.*, 2004), only the chosen study design allows us to consider the dynamics of infertility characteristics and pregnancy history on obstetric and neonatal outcome. Nevertheless, the overall pregnancy outcome of assisted reproduction singletons in this study was very similar to the Finnish cohort study on all Finnish assisted reproduction pregnancies in 1998–1999 (Klemetti *et al.*, 2002). Therefore, a noteworthy selection bias is unlikely to have happened. The control women, on the other hand, were older, more often married and smoked less frequently than the average Finnish parturient (Stakes, 2004). A tendency towards a better pregnancy outcome as measured in the rate of preterm births, LBW and PNMR was noticed in the control mothers as compared with the Finnish cohort study (Klemetti *et al.*, 2002).

The response rate in this study is relatively high, which strengthens the representativeness of the study. In the non-respondent analysis, no specific factor in female characteristics (age, socio-economic status or parity) was associated with an increased likelihood to interrupt the study (Repokari *et al.*, 2005). However, the duration of the assisted reproduction singleton non-respondents' pregnancies was shorter than that of those who responded to both assessments. This could explain the comparable rates of preterm births, LBW babies and NICU admissions among singletons in the study sample.

In this study, the proportion of women who reported at least one pregnancy complication was similar between the whole assisted reproduction and the control singletons. In addition, the frequencies of specific pregnancy complications in the assisted reproduction group were comparable with those of the control group contradictory to the observations of other investigators (Koudstaal *et al.*, 2000; Koivurova *et al.*, 2002). Because the findings are based on self-reporting, some inconsistency may exist in understanding the presence and the severity of a pregnancy complication and comparison to other studies with different methodologies is difficult. According to preliminary results, the highest rates of vaginal bleeding and preterm contractions were reported in the eSET group. Previously only more frequent hypertension in the SET pregnancies than in the spontaneous pregnancies has been suggested (De Neubourg *et al.*, 2005). The assisted reproduction group was more frequently

hospitalized before delivery. Whether this implies more serious complications in the assisted reproduction group or more cautious obstetric monitoring of these 'precious' pregnancies cannot be answered.

The groups differed significantly in the onset and the type of the delivery. In the assisted reproduction group deliveries were more often medically induced or operative, which supports previous studies (Koudstaal *et al.*, 2000; Koivurova *et al.*, 2002; Helmerhorst *et al.*, 2004). However, the results suggest that the obstetric outcome might improve with eSET, as in the eSET group the onset and the type of delivery were comparable to controls. A higher rate of obstetric interventions in the whole assisted reproduction group was attributable to nulliparity according to the adjusted logistic regression analysis, whereas assisted reproduction women's good reported health, less frequent smoking, less common alcohol use and similar complication rates to controls do not give an explanation. The quite low rate of smokers and alcohol users in the assisted reproduction group shows high commitment to current pregnancy and to the well-being of the child.

Similarly to previous research (Helmerhorst *et al.*, 2004; Jackson *et al.*, 2004; Schieve *et al.*, 2004), the results showed slightly poorer neonatal outcome in the assisted reproduction singletons than control singletons, regardless of the number of transferred embryos. The assisted reproduction singletons were born approximately 2–4 days earlier than the control singletons both in deliveries following spontaneous and induced onset. Although the whole assisted reproduction group had similar rate of preterm births to the control group, more preterm births occurred in the eSET group than in the control group. The latter is probably associated with the higher frequency of preterm contractions and vaginal bleeding in the eSET group as discussed before, and it can reflect the patient selection for performing eSET in 1999. The spontaneous preterm onset of delivery was more typical in the assisted reproduction group than in the control group. The identification of factors associated with spontaneous preterm assisted reproduction deliveries would be useful, and should be investigated in future studies. The majority of the preterm assisted reproduction singletons were delivered after gestational week 35. Because the most severe neonatal problems are associated with very preterm infants (Kramer *et al.*, 2000), the slight prematurity observed in this study does not necessarily have clinical significance regarding the later development of the children.

In this study, the mean birth weights were comparable between the eSET, cSET and DET groups. Higher mean birth weight after eSET than after DET has been reported before (De Sutter *et al.*, 2003). However, the observed mean birth weights of eSET singletons were higher than reported before (De Sutter *et al.*, 2003; De Neubourg *et al.*, 2005). Overall, the lower observed mean birth weight of the assisted reproduction singletons is explained by the shorter gestational duration of pregnancy at birth. Ideally, only gestational age adjusted birth weights should be compared.

The detected NICU admissions were lower than reported in the previous studies (Schieve *et al.*, 2002; Helmerhorst *et al.*, 2004) whereas PNMR was similar to national (Klemetti *et al.*, 2002) and international (Bergh *et al.*, 1999) studies. In this study, all vanishing twin survivors ended in term delivery with normal

birth weight contradictory to results from the bigger studies (Dickey *et al.*, 2002; Pinborg *et al.*, 2005).

The next study objective was to identify possible infertility related prognostic factors of adverse neonatal outcomes in the assisted reproduction singleton mothers. The history of induced abortion increased the risk of preterm birth to 4-fold. Unfortunately, it is now known whether a woman had had more than one induced abortion in the past. However, increased risk of preterm birth in women with previous induced abortion has previously been reported in a larger sample and is not attributable to infertility itself (Ancel *et al.*, 2004). In this study, the aetiology, duration or treatment of infertility did not affect the risks of preterm birth or LBW. Tubal factor infertility was associated with increased risk of preterm birth and LBW compared with unexplained infertility in a retrospective cohort study (Omeland *et al.*, 2005), but in a larger register based study the cause of infertility did not matter (Schieve *et al.*, 2004). However, frozen embryo transfer (FET) was associated with decreased risk of preterm birth, LBW and low Apgar scores compared with fresh IVF in large register studies from Sweden and Australia (Källen *et al.*, 2005b; Wang *et al.*, 2005). This may associate with different patient characteristics between fresh and FET groups. The improved neonatal outcome after FET could not be verified in this study, perhaps due to quite rare cases of preterm births and LBW infants in this sample. In a subanalysis of the data, FET was associated only with higher mean birth weight than the fresh embryo transfer group probably reflecting the higher proportion of multiparous women in the FET group. In addition, a comparable neonatal outcome of ICSI singletons to controls has been reported (Ombelet *et al.*, 2005). However, in this study, the neonatal outcomes were compared as regards to the treatment types only within the assisted reproduction group and not against the control group.

In conclusion, a small, though clinically not important, difference was found in gestational age at birth and birth weight between the assisted reproduction and the control group regardless of the number of embryos transferred. The observed differences of obstetric and neonatal outcomes between the assisted reproduction and the control singletons were attributable to nulliparity. Yet, in the future, women seeking assisted reproduction will be of older age with few previous deliveries. Therefore, all adverse outcomes after assisted reproduction cannot be completely overcome and recognition of other possible risk factors among infertile couples needs to be considered. Among the studied assisted reproduction singletons, none of the infertility related factors increased the risk of preterm birth or LBW suggesting that no special risk group in the infertility treated population exists.

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