

Increased risk of placenta previa in pregnancies following IVF/ICSI; a comparison of ART and non-ART pregnancies in the same mother

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BACKGROUND: The risk of placenta previa may be increased in pregnancies conceived by assisted reproduction technology (ART). Whether the increased risk is due to factors related to the reproductive technology, or associated with maternal factors, is not known. **METHODS:** In a nationwide population-based study, we included 845 384 pregnancies reported to the Medical Birth Registry of Norway between 1988 and 2002 and compared the risk of placenta previa in 7568 pregnancies conceived after assisted fertilization, with the risk in naturally conceived pregnancies. To study the influence of ART more directly, we compared the risk of placenta previa between consecutive pregnancies among 1349 women who had conceived both naturally and after assisted fertilization. Odds ratios (OR), adjusted for maternal age, parity, previous Caesarean section and time interval between pregnancies were estimated using logistic regression. **RESULTS:** There was a six-fold higher risk of placenta previa in singleton pregnancies conceived by assisted fertilization compared with naturally conceived pregnancies [adjusted OR 5.6, 95% confidence interval (CI) 4.4–7.0]. Among mothers who had conceived both naturally and after assisted fertilization, the risk of placenta previa was nearly three-fold higher in the pregnancy following assisted fertilization (adjusted OR 2.9, 95% CI 1.4–6.1), compared with that in the naturally conceived pregnancy. **CONCLUSIONS:** The use of ART is associated with an increased risk of placenta previa. Our findings suggest that the increased risk may be caused by factors related to the reproductive technology.

Key words: assisted reproduction technology/placenta previa/population study/sibling comparisons

Introduction

Placenta previa, placentation in the lower segment of the uterine cavity, is associated with serious maternal and adverse fetal outcomes, including haemorrhage, prematurity and increased perinatal morbidity and mortality (McShane *et al.*, 1985; Ananth *et al.*, 1989). Its aetiology remains unclear, but several studies have reported higher frequencies of placenta previa in pregnancies of women with advanced maternal age, multiparity and previous Caesarean delivery and abortion (Faiz and Ananth, 2003). Lifestyle factors such as smoking and cocaine abuse during pregnancy have also been related to the increased risk of placenta previa (Handler *et al.*, 1994; Ananth *et al.*, 1996). In a meta-analysis of complications related to assisted reproduction, the investigators reported three-fold higher risk of placenta previa associated with the treatment (Jackson *et al.*, 2004). The result was, however, based on six small studies, with only 39 cases of placenta previa in 1610 pregnancies conceived by assisted fertilization.

The comparison group in the studies included in the meta-analysis has been women with naturally conceived pregnancies from the general population. However, these studies have not been able to separate effects of unfavourable maternal factors from factors that may be related to the reproduction technology. Worldwide, an increasing proportion of pregnancies are conceived by assisted fertilization, and therefore, possible iatrogenic side effects of the treatment should be clarified.

In this study, we first contrasted the prevalence of placenta previa in pregnancies following assisted fertilization with the prevalence in naturally conceived pregnancies. Second, we attempted to separate the influence of maternal factors from that of the assisted reproduction technology (ART) by studying women who had conceived both naturally and after assisted fertilization. Among these women, we compared the risk of placenta previa between consecutive pregnancies, where one sibling was conceived spontaneously and the other after

assisted fertilization. We hypothesized that if a pregnancy following assisted fertilization was more likely to result in placenta previa, the increased risk could be attributed to the ART and not only to maternal factors.

Materials and methods

Data were derived from the Medical Birth Registry of Norway. This nationwide registry was established in 1967 and comprises records from more than 2×10^6 deliveries (Irgens, 2000). Information on each pregnancy is based on standardized forms completed by midwives within 1 week of delivery. The reporting is mandatory and covers virtually all births in Norway. The form gives information related to the mother's health before and during pregnancy, complications during pregnancy and at delivery and perinatal data of the child.

From all fertility clinics in Norway, the Medical Birth Registry also receives separate notification of pregnancies conceived after assisted fertilization. This reporting is also mandatory and includes information related to the use of ART, notably IVF, ICSI and cryopreservation of embryos. In all these methods, fertilization occurs *in vitro*, and the resulting embryos are transferred to the uterus. Information on the date of embryo transfer, the number of embryos transferred and the number of fetuses with ongoing heart activity confirmed by ultrasound at gestational weeks 7–8 is also recorded. In this study, we did not include the induction of ovulation or insemination as methods of ART. Norwegian ART clinics have since mid-1990s almost exclusively replaced a maximum of two embryos. Fetal reduction is virtually never performed in Norway.

We used data for the period 1988–2002, comprising 882 040 pregnancies. According to recommendations from the WHO, we restricted the analyses to pregnancies where the length of gestation was 22 weeks or more and offspring birthweight was at least 500 g, resulting in 3607 excluded pregnancies. There were no pregnancies after assisted fertilization among mothers younger than 20 years of age or with parity of five or higher. Therefore, we excluded all pregnancies among mothers below 20 years of age ($n = 29\ 998$) and parity of five or more ($n = 1802$). We also excluded 335 triplet pregnancies (137 after assisted fertilization), 19 quadruplet pregnancies (six after assisted fertilization) and 895 pregnancies with missing data on the length of gestation and birthweight. This left 845 384 deliveries among 502 840 women; 832 490 were singletons, and 5581 (0.7%) of the singleton pregnancies were conceived after assisted fertilization. Among 12 894 twin pregnancies, 1987 (15.4%) were conceived after treatment with ART.

Consecutive pregnancies in the same mother

In the study population of 502 840 women, 1349 women were registered with two consecutive singleton pregnancies, where one sibling was delivered after spontaneous conception and the other was delivered after ART. If the mothers had given birth to more than two singletons, we used the two first consecutive births eligible for the sibling comparison. Thus, among 2698 deliveries, 1349 children were conceived spontaneously and 1349 after ART. Among the pregnancies, 762 (56%) of those conceived by ART preceded the naturally conceived pregnancy.

Placenta previa

Ultrasound screening is routinely offered to all pregnant women in Norway around week 18 of gestation. Approximately 98% of all pregnant women attend this ultrasound examination (Backe, 1997), and depending on the findings, some of these women are followed up throughout pregnancy with repeated ultrasound examinations. When

placenta previa is detected at the routine screening, the condition has to be verified at the follow-up examination around week 32 and subsequently confirmed at birth to be reported to the Medical Birth Registry. In births before the follow-up scan at week 32, the diagnosis is based on verification at birth. The standardized form sent to the Medical Birth Registry does not differentiate between placenta previa *marginalis* and placenta previa *totalis*.

Statistical analysis

First, we used information from the general population of pregnant women and compared the risk of placenta previa between naturally conceived pregnancies and pregnancies conceived after assisted fertilization. Second, we restricted the analysis to consecutive pregnancies of singletons among mothers who had delivered both after spontaneous conception and after the use of assisted reproductive technology.

To account for the dependencies of pregnancies delivered by the same mother, we adjusted the SE for intra-group dependencies (Williams, 2000). We also used generalized estimating equation (GEE) and conditional logistic regression (Carlin *et al.*, 2005). The three techniques produced similar results, and we only present the results from the logistic regression analyses.

In the analyses, we evaluated possible confounding by other factors and adjusted for maternal age (20–29, 30–34, 35 years and older), parity (0, 1, 2 or higher), time interval between births (<3 years, ≥ 3 years), period of birth (5-year categories), previous Caesarean sections, sex of offspring and marital status. Stratified analyses were performed for combinations of period, maternal age and parity. In supplementary subanalyses, we adjusted for maternal smoking (before and during pregnancy) and the level of education. For the analyses, we used SPSS for Windows (Version 13, Chicago, IL, USA) and Stata (Version 9, College Station, TX, USA).

Results

Placenta previa in the general population of pregnant women

Women who gave birth after the use of ART were older and had fewer previous births than women who delivered after spontaneous conception (Table I). They also smoked less, but the level of education did not differ between the groups. Among 845 384 pregnancies, 1949 (0.23%) were diagnosed with placenta previa; 1910 in singleton pregnancies and 39 in twin pregnancies. The overall prevalence of placenta previa was fairly stable from 1988 to 2002, but in pregnancies following assisted fertilization, the prevalence was consistently higher throughout the period compared with spontaneously conceived pregnancies. Before any adjustments were made, the crude prevalence of placenta previa in naturally conceived singleton pregnancies was 0.22% as compared with 1.59% in singleton pregnancies conceived after assisted fertilization (Table I). In twin pregnancies, the corresponding proportions were 0.21 and 0.81%.

Adjustment for potentially confounding factors did not substantially alter the association between the use of ART and the occurrence of placenta previa (Table II). Thus, the odds ratio (OR) for singleton pregnancies was 5.6 [95% confidence interval (CI) 4.4–7.0] after adjustment for maternal age, parity, interval between deliveries, the year of delivery, the history of Caesarean section, offspring sex and marital status. In a separate subgroup analysis, we could also adjust for maternal smoking and the level of education, but the results were not

Table I. Maternal characteristics of pregnancies conceived by assisted fertilization and spontaneously conceived pregnancies in Norway, 1988–2002^a

	Singleton pregnancies, <i>n</i> (%)		Twin pregnancies, <i>n</i> (%)	
	Assisted fertilization	Spontaneous conception	Assisted fertilization	Spontaneous conception
Maternal age (years)				
20–29	1036 (18.6)	493 403 (59.7)	428 (21.5)	5501 (50.4)
30–34	2601 (46.6)	235 609 (28.5)	999 (50.3)	3692 (33.8)
35–39	1883 (33.7)	97 897 (11.8)	560 (28.2)	1714 (15.7)
40+	61 (1.1)	7715 (0.9)	7 (0.4)	90 (0.8)
Parity				
0	3962 (71.0)	341 917 (41.3)	1388 (69.8)	4297 (39.4)
1	1457 (26.1)	301 642 (36.5)	543 (27.3)	4025 (36.9)
≥2	162 (2.9)	183 350 (22.2)	56 (2.8)	2656 (23.6)
Previous Caesarean section				
No	5319 (95.3)	765 050 (92.5)	1889 (95.1)	10 083 (92.4)
Yes	262 (4.7)	61 859 (7.5)	98 (4.9)	824 (7.6)
Smoking during pregnancy ^b				
Yes	261 (10.3)	30 834 (14.2)	83 (8.8)	447 (14.0)
No	1782 (70.0)	137 986 (63.6)	647 (68.9)	2008 (62.7)
Unknown	502 (19.7)	48 052 (22.2)	209 (22.3)	746 (23.3)
Method				
IVF ^c	4033 (72.3)	–	1533 (77.2)	–
ICSI ^c	981 (17.6)	–	305 (15.3)	–
Unknown	567 (10.2)	–	149 (7.5)	–
Placenta previa	89 (1.59)	1821 (0.22)	16 (0.81)	23 (0.21)

^aRestricted to pregnancies among mothers 20 years or older with five or less previous births.^bSmoking data restricted to pregnancies after November 1998.^cIncluding thawed embryo replacements.**Table II.** Odds ratio (OR) of placenta previa in pregnancies after assisted fertilization versus spontaneous conception adjusted for maternal age at birth, parity, duration between pregnancies, calendar period of birth and previous Caesarean section by plurality^a

	Singletons					Twins				
	<i>N</i>	Cases	Crude OR	Adjusted OR	95% confidence interval (CI)	<i>n</i>	Cases	Crude OR	Adjusted OR	95% CI
Spontaneous conception	826 909	1821	1.0	1.0	Reference	10 907	23	1.0	1.0	Reference
Assisted fertilization	5581	89	7.3	5.6	4.4–7.0	1987	16	3.8	2.9	1.5–5.8
Maternal age										
20–29	494 439	711	1.0	1.0	Reference	5929	6	1.0	1.0	Reference
30–34	238 210	692	2.0	1.8	1.6–2.0	4691	21	4.4	3.4	1.3–8.9
35+	99 841	507	3.5	2.9	2.6–3.3	2274	12	5.2	3.7	1.3–10.8
Parity										
Para 0	345 879	591	1.0	1.0	Reference	5685	16	1.0	1.0	Reference
Para 1	303 099	750	1.4	1.2	1.0–1.3	4568	16	1.2	0.9	0.3–2.7
Para 2+	183 512	569	1.8	1.1	1.0–1.3	2641	7	0.9	0.7	0.2–2.0
Time between births										
Para 0 ^b	345 879	591	–	–	–	5685	16	–	–	–
<3 years	213 974	485	1.0	1.0	Reference	2827	6	1.0	1.0	Reference
>3 years	272 637	834	1.4	1.1	1.0–1.3	4382	17	1.8	1.5	0.6–3.9
Year of birth										
1988–1992	278 813	588	1.0	1.0	Reference	3548	8	1.0	1.0	Reference
1993–1997	282 386	617	1.0	1.0	0.9–1.1	4347	15	1.5	1.3	0.5–3.0
1998–2002	271 291	705	1.1	1.0	0.9–1.2	2641	16	4	1.0	0.4–2.2
Previous Caesarean section										
No	770 369	1670	1.0	1.0	Reference	11 927	6	1.0	1.0	Reference
Yes	62 121	240	1.8	1.4	1.2–1.6	922	33	2.4	2.2	0.8–5.9

^aAnalysis restricted to pregnancies among mothers giving birth at age 20 or older and with five or less previous births. SE corrected for intra-group dependencies.^bDropped because of collinearity with parity.

substantially different from the main results (data not shown). In twin pregnancies, the adjusted OR was 2.9 (95% CI 1.5–5.8).

We analysed different methods of assisted reproduction separately and found that the increased risk of placenta previa was fairly similar for IVF and ICSI. Compared with the spontaneously conceived pregnancies, the prevalence was six-fold

higher in IVF pregnancies (adjusted OR 6.3, 95% CI 4.9–8.1) and four-fold higher in ICSI pregnancies (adjusted OR 4.4, 95% CI 2.5–7.8). In pregnancies after the replacement of thawed embryos, the numbers were too small to study any effects (three cases of placenta previa among 227 singleton pregnancies).

Table III. Characteristics of pregnancies complicated by placenta previa after assisted fertilization and spontaneous conception in Norway from 1988 to 2002 by plurality^a

	Singletons		Twins	
	Assisted fertilization (<i>N</i> = 89)	Spontaneous conception (<i>N</i> = 1821)	Assisted fertilization (<i>N</i> = 16)	Spontaneous conception (<i>N</i> = 23)
Mean gestation in days (SD)	259.0 (20.2)	258.4 (23.3)	245.0 (16.0)	238 (23.0)
Mean birthweight in kg (SD)	2838 (638)	2904 (777)	2370 (716)	2507 (661)
Caesarean section (%)	96.6	85.1	100	87.0

^aRestricted to pregnancies among mothers giving birth at age 20 or older and with five or less previous births.

In cases of placenta previa, mean gestational age and mean birthweight were fairly similar in pregnancies after naturally conceived and after assisted fertilization, whereas Caesarean delivery was more frequent if the pregnancy was conceived after assisted fertilization (Table III). Thus, the proportion of Caesarean section was 96.6% in singleton pregnancies with placenta previa as compared with 85.1% in spontaneously conceived pregnancies. To avoid the possibility that placenta previa was reported more often in pregnancies after assisted fertilization (potential surveillance bias), we restricted the diagnosis of placenta previa to pregnancies with Caesarean delivery. However, the results were similar to those of the main analysis, showing six-fold higher prevalence (OR 6.3, 95% CI 4.9–7.9) of placenta previa associated with assisted fertilization.

We also stratified the analysis according to the calendar period of birth (1988–1992, 1993–1997 and 1998–2002), parity and maternal age, but the results did not substantially differ across strata of these variables.

Comparison of consecutive sibling pregnancies

In the study population, 1349 women had delivered singletons both after natural conception and after assisted fertilization (Table IV). In pregnancies following assisted reproduction, women were slightly older but had fewer previous births and previous Caesarean sections than when the same women delivered after spontaneous conception. The crude prevalence of placenta previa was 2.0% in pregnancies conceived by ART as compared with 0.7% in pregnancies following natural conception, suggesting approximately three-fold higher prevalence. After adjustment for maternal age, parity and previous Caesarean section, placenta previa was nearly three times more likely to occur in pregnancies following assisted fertilization (OR = 2.9, 95% CI 1.4–6.1) compared with spontaneously conceived sibling pregnancies (Table V).

In additional analyses, we studied the association with placenta previa in pregnancies where the first child was conceived spontaneously and in pregnancies where the first child was conceived by assisted fertilization. After adjustment for maternal age and previous Caesarean section, the results showed a positive association with placenta previa regardless of whether the first (OR 2.5, 95% CI 0.5–12.5) or the second pregnancy (OR 2.6, 95% CI 0.4–16.8) was conceived by the use of ART.

Table IV. Maternal characteristics of consecutive singleton pregnancies among women who have given birth both after assisted fertilization and after spontaneous conception

	Assisted fertilization (<i>N</i> = 1349), <i>n</i> (%)	Spontaneous conception (<i>N</i> = 1349), <i>n</i> (%)
Maternal age at birth (years)		
20–29	254 (18.8)	461 (34.2)
30–34	676 (50.1)	489 (36.3)
35+	419 (31.1)	399 (29.6)
Parity		
0	675 (50.0)	537 (39.8)
1	617 (45.7)	704 (52.2)
≥2	57 (4.2)	108 (8.1)
Previous Caesarean section		
No	1225 (90.8)	1138 (84.4)
Yes	124 (9.2)	211 (15.6)
Method		
IVF	961 (71.2)	–
ICSI	194 (14.4)	–
Unknown	194 (14.4)	–
Smoking during pregnancy ^a		
Yes	57 (9.9)	51 (11.5)
No	402 (69.4)	302 (68.0)
Unknown	120 (20.7)	91 (20.5)
Placenta previa	27 (2.0)	10 (0.7)

^aSmoking data restricted to pregnancies after November 1998.

Discussion

By comparing consecutive pregnancies, where the mother conceived spontaneously in one pregnancy and after assisted fertilization in the other, it seems reasonable to attribute differences in pregnancy complications to the reproduction technology rather than to maternal factors. Consequently, the nearly three-fold higher risk of placenta previa that we observed in the pregnancy following assisted fertilization may largely be attributed to factors related to the reproduction technology.

Within the large, unselected population, we found that placenta previa occurred six times more often in singleton pregnancies after assisted reproduction compared with naturally conceived pregnancies. In this setting, the higher prevalence of placenta previa is most likely due to a combination of maternal factors and factors related to the ART.

Previously, a few small studies have examined the association between assisted fertilization and the risk of placenta previa (Howe *et al.*, 1990; Tan *et al.*, 1992; Tanbo *et al.*, 1995; Verlaenen *et al.*, 1995; Reubinoff *et al.*, 1997; Koudstaal *et al.*, 2000; Shevell *et al.*, 2005). Most studies found that placenta previa is more common after assisted reproduction. Six of

Table V. Odds ratio (OR) of placenta previa in consecutive singleton pregnancies among women who have given birth both after assisted fertilization and after spontaneous conception

	Women	Placenta previa	Crude OR	AdjustedOR ^a	95% confidence interval
Spontaneous conception	1349	10	1.0	1.0	Reference
Assisted fertilization	1349	27	2.7	2.9	1.4–6.1
Order of mode of conception					
Spontaneous first					
Spontaneous conception	587	3	1.0	1.0	Reference
Assisted fertilization	587	17	5.8	2.6	0.4–16.8
Assisted fertilization first					
Spontaneous conception	762	7	1.0	1.0	Reference
Assisted fertilization	762	10	1.4	2.5	0.5–12.5

^aAdjusted for maternal age at birth, parity and previous Caesarean section.

these studies were included in a meta-analysis of complications after assisted fertilization (Jackson *et al.*, 2004). The joint results indicated three-fold higher risk of placenta previa in pregnancies after assisted fertilization compared with naturally conceived pregnancies. However, the analysis was only based on 39 cases of placenta previa in 1610 pregnancies following assisted fertilization. However, no study could distinguish between the impact of maternal factors and factors related to the reproduction technology.

Our study includes an unselected nationwide population with compulsory reporting of all births to the Medical Birth Registry of Norway. The unique identification number of every citizen in the country enables pregnancies conceived after assisted fertilization to be identified and linked to pregnancy outcome. Information on potentially confounding factors, such as parity, maternal age and previous Caesarean section, allows us to adjust for these factors in the statistical analysis, and in a subset of the population, the information on the level of education and smoking could also be taken into account.

Although complete previa (*'totalis'*) tends to be associated with more severe bleeding and an absolute indication for Caesarean section, a less severe degree of placenta previa (*'marginalis'*) may also cause life-threatening haemorrhage and may therefore be regarded as clinically important even though the site of placentation allows vaginal delivery (Ghourab, 2001). Thus, we included all cases of placenta previa regardless of the mode of delivery in the primary analysis. In a secondary analysis, we restricted the diagnosis of placenta previa to Caesarean section deliveries. This restriction provided a slightly stronger association between ART and the risk of placenta previa (OR = 6.3), and the adjusted OR of 5.6 obtained in the primary analysis may be considered as a more conservative estimate.

Except for one extra ultrasound examination in weeks 7–8 of pregnancy, women who conceive after assisted fertilization attend the standard programme for prenatal care in Norway. Specially trained midwives perform the routine ultrasound examination at 17–18 weeks of gestation, and virtually, all pregnant women in the country attend this examination (Backe, 1997). If prenatal surveillance was more rigorous for women who received assisted fertilization, one consequence could be that placenta previa would be diagnosed more often in the assisted fertilization group than among women who conceived spontaneously. To reduce a possible diagnostic bias, we restricted the diagnosis of placenta previa to cases that were

registered after Caesarean deliveries. However, this did not attenuate the strong positive association with assisted fertilization. Twins constitute another group that receives close surveillance, regardless of whether the pregnancy is conceived spontaneously or after assisted fertilization. However, the higher frequency of placenta previa in twin pregnancies conceived by reproduction technology strengthens the validity of our findings and suggests that placenta previa is not diagnosed systematically different between the groups.

Nonetheless, women who seek infertility treatment represent a selected group of women. By using naturally conceived pregnancies from the general population as comparison, one cannot readily distinguish the impact of maternal factors from factors related to ART. By comparing consecutive pregnancies among women who have delivered after both assisted fertilization and spontaneous conception, one may, at least partly, solve this problem because confounding by maternal and environmental factors is less likely. The results for consecutive siblings, showing three-fold higher risk of placenta previa associated with assisted fertilization, suggest that a substantial proportion of the increased risk may be attributed to ART.

The underlying mechanism for this effect is not clear. In assisted fertilization, drugs are utilized to induce multiple follicular development. Fertilization and embryo development take place outside the body, and embryos enter the uterine cavity through the cervix by mechanical means.

The stimulation protocol used in assisted reproduction frequently results in very high levels of gonadal steroids that induce morphological and structural changes and disturbed expression of relevant genes in the endometrium (Horcajadas *et al.*, 2005). These effects are thought to be global, and given the current knowledge, this effect on the endometrium is not likely to contribute to a higher risk of placenta previa.

It is well documented that fertilization and embryo culture *in vitro* can change key metabolic pathways in the embryo (Leese *et al.*, 1998). These effects may interfere with implantation and early embryo development, but it is difficult to explain how the changes could result in more frequent implantation in the lower segment of the uterus.

In ART, embryos are placed in the uterine cavity by the transcervical route using a catheter. This procedure may induce uterine contraction, possibly due to the release of prostaglandins after mechanical stimulation of the internal cervical os (Fraser, 1992; Fanchin *et al.*, 1998; Mansour, 2005). It has

been demonstrated that as much as 15% of replaced embryos may be totally expelled from the uterus (Poindexter *et al.*, 1986). It is conceivable that these mechanically induced uterine contractions could lead to higher frequencies of implantation in the lower uterine segment and thereby increase the risk of placenta previa. Another study reported that 80% of embryos were implanted in the area in which they were transferred (Baba *et al.*, 2000), suggesting that the site of replacement could be particularly important. Also, lower deposition in the uterine cavity may improve the rate of successful implantation (Waterstone *et al.*, 1991; Coroleu *et al.*, 2002), and preference now tends to be lower replacement of the embryo. To evaluate whether the risk of placenta previa may be attributed to the depth of embryo replacement, however, the transfer distance from both the internal cervical os and the uterine fundus should be monitored and systematically recorded.

In summary, the risk of placenta previa in pregnancies following assisted reproductive treatment is considerably higher than in pregnancies following natural conception. Our results suggest that factors directly related to the reproduction technology contribute to the increased risk.

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