Placental weight in singleton pregnancies with and without assisted reproductive technology: a population study of 536 567 pregnancies

C. Haavaldsen1,2,*, T. Tanbo3, and A. Eskild1,2,4

1Department of Gynecology and Obstetrics, Akershus University Hospital, 1478 Lørenskog, Norway 2Institute of Clinical Medicine, Akershus University Hospital, University of Oslo, Lørenskog, Norway 3Department of Gynecology, Oslo University Hospital, Rikshospitalet, University of Oslo, 0424 Oslo, Norway 4Division of Mental Health, Norwegian Institute of Public Health, 0304 Oslo, Norway

*Correspondence address. Tel: +47-67-96-47-72; E-mail: marit.camilla.haavaldsen@ahu.no

Submitted on August 2, 2011; resubmitted on October 18, 2011; accepted on November 17, 2011

BACKGROUND: Pregnancies conceived by assisted reproductive technology (ART) are at increased risk of adverse outcomes. Previous studies have suggested increased placental weight and increased placental weight/birthweight ratio in pregnancies associated with adverse outcomes. We therefore studied the association of ART with placental weight and placental weight/birthweight ratio.

METHODS: We included all singleton births in the Medical Birth Registry of Norway during the period 1999–2008 (n = 536 567, including 8259 after ART). We divided placental weight and placental weight/birthweight ratio into quartiles, and calculated the proportions of ART and spontaneous pregnancies in the lowest and the highest quartile by length of gestation. Thereafter, we estimated crude and adjusted odds ratios (ORs) for being in each quartile of placental weight for ART pregnancies with spontaneous pregnancies as the reference. The analyses were repeated with ART pregnancies subgrouped into IVF or ICSI.

RESULTS: Mean placental weight was 678.9 g in pregnancies conceived by ART, and 673.0 g in pregnancies after spontaneous conception. ART pregnancies were overrepresented in the highest quartile of placental weight and underrepresented in the highest quartile of birthweight, independent of length of gestation at delivery. Thus, placental weight/birthweight ratio was higher in ART pregnancies. For ART pregnancies, the OR for being in the highest quartile of placental weight was 1.37 (95% confidence interval 1.30–1.45) after adjustment for length of gestation, offspring birthweight, parity, fetal sex, maternal age, pre-eclampsia and diabetes. There was no difference in placental weight/birthweight ratio between IVF and ICSI pregnancies.

CONCLUSIONS: We found larger placentas and a higher placental weight/birthweight ratio among pregnancies conceived by ART compared with spontaneous pregnancies, and the difference was independent of length of gestation at delivery and ART method.

Key words: ART / ICSI / IVF / placental weight / placental weight/birthweight ratio

Introduction

The prevalence of infertility is increasing (Lutz et al., 2003; Nyboe Andersen and Erb, 2006; Skakkebaek et al., 2006), and part of this increase has been explained by a higher maternal age at pregnancy attempt, higher prevalence of obesity and reduced semen quality. Consequently, the number of couples undergoing assisted reproductive technology treatment (ART) is rising (Nygren et al., 2011). Pregnancies conceived by ART seem to have a higher risk of pre-eclampsia (Chen et al., 2009), placenta praevia (Romundstad et al., 2006), perinatal mortality, preterm delivery and low birthweight (Helmerhorst et al., 2004; Jackson et al., 2004). It has, however, been questioned whether the increased risk of adverse outcomes in ART pregnancies can be explained by the treatment itself or by characteristics of the infertile couple (Ghazi et al., 1991; Romundstad et al., 2008).

The placenta is essential for the maintenance of pregnancy and fetal growth. Placental weight may be an indicator of placental function, and small placentas are more likely to be dysfunctional (Thame et al., 2004; Salafia et al., 2006). Placental weight is closely correlated to birthweight (Salafia et al., 2008). Since infants conceived by ART have lower birthweight, we would expect these pregnancies also to have lower placental weight compared with spontaneously conceived pregnancies. However, in other complicated pregnancies associated with
low birthweight, such as pregnancies with pre-eclampsia (Eskild et al., 2009) or fetal death, a relative enlargement of the placenta when compared with fetal size has been seen. Since ART pregnancies are at increased risk of complications, disproportions between placental weight and birthweight may be more common in these pregnancies.

Our aim was to compare placental weight and placental weight/birthweight ratios in pregnancies obtained by ART with that of spontaneous pregnancies. The two most common ART methods are IVF and ICSI. IVF is mainly performed in cases of female infertility, whereas ICSI is mostly performed in couples with male infertility and a presumably fertile female spouse. Whether birthweight or placental weight differs by ART method is not known. Such knowledge could give insight into possible differential roles of male and female infertility on offspring growth. Therefore, in separate analyses, we subgrouped the ART pregnancies into IVF and ICSI. All comparisons were made across gestational length at delivery.

Materials and Methods

The Medical Birth Registry of Norway has registered all births in Norway since 1967. The notification is compulsory and the registration forms have remained almost unchanged. Since 1988, voluntary notification to the Medical Birth Registry of all diagnosed pregnancies after ART has been performed, and in 2001 the notification of all ART pregnancies conceived in Norway was made compulsory. Placental weight has been reported to the Medical Birth Registry since 1999. Our study population included all singleton births in Norway during 1999–2008, a total of 567 176 births. We excluded 3262 births with gestational length <22 weeks. Pregnancies with gestational length above 43 weeks, placental weight <25 g or above 2500 g, and birthweight <250 g or above 6500 g, a total of 2227 pregnancies were considered as having outlying values and were also excluded from our sample. Placental weight, offspring birthweight and gestational length at delivery were not registered for 25 110 of the remaining pregnancies, thus 536 567 pregnancies could be included in the study.

Placental weight, measured in grams, was the main outcome variable. The placentas were weighed by a midwife shortly after delivery with membranes and umbilical cord attached. Offspring birthweight was also measured in grams. Placental weight/birthweight ratios were calculated by dividing placental weight by birthweight in grams. Placental weight, offspring birthweight and placental weight/birthweight ratio were divided into quartiles based on the population as a whole. Hence, if there is no difference, 25% of both ART and spontaneous pregnancies are expected to be in each quartile. The quartiles were calculated separately within categories of gestational length at delivery.

ART treatment was coded yes or no and included IVF, ICSI, the combination of both or other and unspecified methods of ART. We also made separate analyses with pregnancies after IVF and ICSI.

Gestational length at delivery was based on the estimated date of term at routine fetal ultrasonographic examination in gestational weeks 17–19. If fetal ultrasonographic examination was not performed, date of term was based on last menstrual period. In ART pregnancies, date of embryo transfer is known but not reported to the Medical Birth Registry. Thus, the length of gestation could be estimated by the same means, independent of method of conception. Gestational length at delivery was grouped into 2 weeks’ intervals from 28 weeks of gestation. Deliveries at Weeks 22–27 were merged into one group because of the limited number of deliveries in ART pregnancies before Week 28.

We calculated mean placental weight, mean birthweight and mean placental weight/birthweight ratio in pregnancies after ART and in pregnancies with spontaneous conception by gestational length at delivery. Differences in mean placental weight and birthweight were assessed by Student’s t-test. We also assessed differences in placental weight and birthweight between the methods of conception after adjustment for length of gestation by applying linear regression analyses. Pearson’s correlation between placental weight and birthweight in ART and spontaneously conceived pregnancies was estimated. We also compared the proportions of pregnancies, spontaneously conceived or conceived by ART, in the lowest and the highest quartile of placental weight, birthweight and placental weight/birthweight ratio by length of gestation, and differences in proportions were tested by χ² tests. These analyses were repeated with ART pregnancies subgrouped as IVF or ICSI.

By applying logistic regression analyses, we estimated crude and adjusted odds ratios (ORs) for being in each quartile of placental weight for ART pregnancies, with spontaneous pregnancies as the reference. Adjustments were made for gestational length at delivery, birthweight, parity, offspring sex, maternal age, pre-eclampsia and diabetes mellitus, as reported to the Medical Birth Registry (Salafia et al., 2008; Eskild et al., 2009; Haavaldsen et al., 2011).

In the logistic regression analyses, birthweight was divided into categories of 500 g. Maternal age at delivery was divided into intervals of 5 years. Parity was defined as the number of previous deliveries after 16 weeks of gestation, and categorized as 0 or ≥1. Pre-eclampsia was defined as blood pressure ≥140/90 mmHg and proteinuria with dipstick ≥1 after 20 weeks of gestation. Diabetes included types I and II diabetes mellitus, unspecified diabetes, gestational diabetes or the use of antidiabetic medication during pregnancy.

We used the Statistical Package for the Social Sciences (SPSS, version 16.0) for all statistical analyses. The study was approved by the Advisory Committee for the Medical Birth Registry of Norway and the Norwegian Data Inspectorate.

Results

In our study sample of 536 567 singleton pregnancies, 8259 pregnancies (1.5%) were conceived by ART. Of the ART pregnancies, 4557 pregnancies were conceived by IVF (55.2%), 3192 pregnancies were conceived by ICSI (38.6%), 88 pregnancies were conceived by the combination of IVF and ICSI or other methods of ART (1.1%) and for 422 ART pregnancies the method was not specified (5.1%).

Mean placental weight and mean placental weight/birthweight ratio were higher, while mean birthweight was lower in ART pregnancies when compared with pregnancies after spontaneous conception (Table I). Mean gestational length was 276.6 days (SD 16.3) in ART pregnancies and it was 278.6 days (SD 13.7) in spontaneous pregnancies (Student’s t-test P < 0.001). The differences in placental weight and birthweight in ART and spontaneous pregnancies remained after adjustment for length of gestation at delivery. The adjusted regression coefficient for ART was 12.5 (P < 0.001) with placental weight as the dependent variable, and it was −55.9 (P < 0.001) with birthweight as the dependent variable. The estimated correlations between placental weight and birthweight were higher in ART pregnancies compared with spontaneous pregnancies at almost any length of gestation at delivery (Table II).

Pregnancies conceived by ART and spontaneously conceived pregnancies were similarly distributed in the lowest quartile of placental weight independent of length of gestation at delivery (Fig. 1A). In the highest quartile of placental weight, however, ART pregnancies were overrepresented throughout pregnancy (Fig. 1B). In gestational weeks 40–41, 28.3% of the pregnancies conceived by ART were in
the highest quartile of placental weight. The corresponding figure for spontaneously conceived pregnancies was 24.9% (test P = 0.005).

The distribution of placental weight in ART pregnancies differed from the distribution in spontaneously conceived pregnancies. ART pregnancies were overrepresented in the lowest quartile and underrepresented in the highest quartile of placental weight across gestational length. In deliveries in gestational weeks 40–41, 15% were in the highest quartile of placental weight, whereas 21% were in the lowest quartile. Similarly, 30.2% of pregnancies conceived by ART were in the lowest quartile of birthweight (Fig.2A), whereas 21.0% were in the highest quartile (Fig.2B). Thus, in pregnancies conceived by ART, the proportion of pregnancies with a large placenta relative to birthweight was increased throughout pregnancy. In deliveries in gestational weeks 40–41, 32.1% were in the highest quartile and only 19.5% were in the lowest quartile of placental weight/birthweight ratio (Fig.3). The corresponding figures for pregnancies with spontaneous conception were 24.9 and 25.1% (test P = 0.001).

Comparing ART pregnancies with spontaneous pregnancies, the OR for being in the highest quartile of placental weight was 1.12 [95% confidence interval (CI) 1.07–1.18] (Table III). The association increased after adjustment for length of gestation, offspring birthweight, parity, sex, maternal age, pre-eclampsia and diabetes (OR 1.37, 95% CI 1.30–1.45). The adjusted OR associated with ART for having a placenta in the lowest quartile was 0.73 (95% CI 0.69–0.79).

We also examined possible differences between IVF and ICSI pregnancies (27.6% days in IVF versus 27.7% days in ICSI) and found a difference in both mean placental weight and birthweight, but not in placental weight/birthweight ratio. The association between IVF and ICSI pregnancies (27.6% days in IVF versus 27.7% days in ICSI) and placental weight was 678.9 g in IVF and 673.0 g in ICSI. However, there was also a difference in mean placental weight and birthweight between IVF and ICSI pregnancies (27.6% days in IVF versus 27.7% days in ICSI). The adjusted OR for being in the highest quartile of placental weight was 1.12 (95% CI 1.30–1.45). The adjusted OR associated with ART for having a placenta in the lowest quartile was 0.73 (95% CI 0.69–0.79).

We also examined possible differences between IVF and ICSI pregnancies (27.6% days in IVF versus 27.7% days in ICSI) and found a difference in both mean placental weight and birthweight, but not in placental weight/birthweight ratio. The association between IVF and ICSI pregnancies (27.6% days in IVF versus 27.7% days in ICSI) and placental weight was 678.9 g in IVF and 673.0 g in ICSI. However, there was also a difference in mean placental weight and birthweight between IVF and ICSI pregnancies (27.6% days in IVF versus 27.7% days in ICSI). The adjusted OR for being in the highest quartile of placental weight was 1.12 (95% CI 1.30–1.45). The adjusted OR associated with ART for having a placenta in the lowest quartile was 0.73 (95% CI 0.69–0.79).

We also examined possible differences between IVF and ICSI pregnancies (27.6% days in IVF versus 27.7% days in ICSI) and found a difference in both mean placental weight and birthweight, but not in placental weight/birthweight ratio. The association between IVF and ICSI pregnancies (27.6% days in IVF versus 27.7% days in ICSI) and placental weight was 678.9 g in IVF and 673.0 g in ICSI. However, there was also a difference in mean placental weight and birthweight between IVF and ICSI pregnancies (27.6% days in IVF versus 27.7% days in ICSI). The adjusted OR for being in the highest quartile of placental weight was 1.12 (95% CI 1.30–1.45). The adjusted OR associated with ART for having a placenta in the lowest quartile was 0.73 (95% CI 0.69–0.79).
0.17) with birthweight as the dependent variable. In both IVF and ICSI pregnancies, we found similar distributions of placental weight/birthweight ratios across delivery weeks as for ART pregnancies as a whole, with underrepresentation in the lowest and overrepresentation in the highest quartile (Fig. 4A and B).

**Discussion**

In this study, comparing 8259 pregnancies after ART with more than half a million spontaneous pregnancies, we found significantly increased placental weights and increased placental weight/birthweight ratios in ART pregnancies. These differences were observed independent of length of gestation at delivery. In pregnancies conceived by IVF or ICSI, we found the same patterns as for ART pregnancies as a whole.

We have no reason to believe that the methods of placental weighing have differed by mode of conception. However, mode of delivery may influence placental weighing procedures, and mothers after ART are more often delivered by Caesarean section than mothers with spontaneous pregnancies (Helmerhorst et al., 2004), accounting for 21.9 and 14.6%, respectively of the deliveries in our study. In supplementary data analyses, we included Caesarean delivery in multivariable analyses; however, the association of ART with placental weight remained unchanged.

Also, differences in the prevalence of placenta praevia between ART pregnancies and spontaneously conceived pregnancies may have confounded our results (Tanbo et al., 1995; Romundstad et al., 2006). A low placentation in the uterine cavity has been associated with intrauterine growth restriction (Newton et al., 1984), however, data are conflicting (Ananth et al., 2001; Harper et al., 2010) and the association with placental weight is not known. Inclusion of adjustment for placenta praevia in multivariable analyses did not alter the association of ART with high placental weight.

High maternal age and pre-eclampsia have been related to a high placental weight/birthweight ratio, while low parity and female offspring have been associated with low placental weight (Naeye, 1987; Dombrowski et al., 1994; Thompson et al., 2007; Eskild et al., 2009; Dean et al., 2010; Haavaldsen et al., 2011). When we made adjustments for these factors, the association between ART and a large placenta was strengthened, and our findings were thus supported.

![Figure 1](image1.png) **Figure 1** The proportion of pregnancies in the lowest (A) and highest (B) quartile of placental weight in pregnancies with ART or spontaneous conception by length of gestation at delivery. All singleton pregnancies in Norway during 1999–2008 (n = 536 567).

![Figure 2](image2.png) **Figure 2** The proportion of pregnancies in the lowest (A) and highest (B) quartile of birthweight in pregnancies with ART or spontaneous conception by length of gestation at delivery. All singleton pregnancies in Norway during 1999–2008 (n = 536 567).
Previous studies on placental weight in ART pregnancies are scarce. One study, including 45 singleton ART pregnancies and 45 spontaneously conceived pregnancies, reported higher placental weight and placental weight/birthweight ratio in pregnancies conceived by ART (Daniel et al., 1999). Two other studies including 50 and 70 ART pregnancies respectively, found no significant difference in placental weight between ART and non-ART pregnancies (Jauniaux et al., 1990; Gavril et al., 1993). Previous comparisons of obstetric outcomes between IVF and ICSI have shown virtually similar results by the two methods, however, only a limited number of pregnancies were included (Hourvitz et al., 2005; Ombelet et al., 2005; Buckett et al., 2007).

Pregnancies after ART differ from natural conception in many ways. First of all, infertile couples have an increased risk of adverse pregnancy outcome independent of the ART treatment itself (Ghazi et al., 1991; Romundstad et al., 2008). Hence, factors associated with the infertility may explain our findings.

ART treatment, both IVF and ICSI, includes stimulation with exogenous FSH for development of multiple follicles. Such stimulation results in supraphysiological levels of pre-ovulatory estradiol and elevated levels of estadiol and progesterone from multiple corpora lutea during the luteal phase. Endometrium exposed to such high levels is less receptive to implantation of the embryo than the endometrium in natural cycles (Bourgain and Devroey, 2003). An indication of sub-optimal endometrial receptivity after multifollicular development is the higher birthweight in offspring after ART with transfer of cryopreserved/thawed embryos. In such pregnancies, the women are not treated with FSH for induction of multifollicular growth (Pelkonen et al., 2010; Henningsen et al., 2011). Survival of an implanting embryo in a non-optimal endometrium may necessitate a compensatory growth of the placenta. Both IVF and ICSI pregnancies in our study had higher placental weight/birthweight ratios than spontaneous pregnancies. This finding suggests common factors associated with both male and female infertility to be associated with placental growth. Changes in the endometrium, as a consequence of multifollicular development in response to FSH treatment, may be one such common factor. The stable difference between ART and spontaneous pregnancies independent of gestational length at delivery in our study, suggests that the differences in growth may be caused very early in pregnancy and not by conditions that occur in the later part of pregnancy.

### Table III

<table>
<thead>
<tr>
<th>Quartiles</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First quartile</td>
<td>0.96 (0.91–1.01)</td>
<td>0.73 (0.69–0.78)</td>
</tr>
<tr>
<td>Second quartile</td>
<td>0.96 (0.91–1.01)</td>
<td>0.96 (0.92–1.02)</td>
</tr>
<tr>
<td>Third quartile</td>
<td>0.96 (0.91–1.01)</td>
<td>1.03 (0.98–1.09)</td>
</tr>
<tr>
<td>Fourth quartile</td>
<td>1.12 (1.07–1.18)</td>
<td>1.37 (1.30–1.45)</td>
</tr>
</tbody>
</table>

Spontaneously conceived pregnancies were used as the reference.

*Adjusted for length of gestation, offspring birthweight, parity, fetal sex, maternal age, pre-edampsia and diabetes.

### Figure 3

The proportion of pregnancies in the lowest and highest quartile of placental weight/birthweight ratio in pregnancies with ART (n = 8259).

### Figure 4

The proportion of pregnancies in the lowest (A) and highest (B) quartile of placental weight/birthweight ratio in pregnancies with IVF, ICSI or spontaneous conception. All singleton pregnancies in Norway during 1999–2008 (n = 536567).
An alternative explanation is that only ‘the best fit’ embryos result in a viable pregnancy after ART. It is possible that mainly pregnancies with a high correlation between placental and birthweight are successful in ART pregnancies, whereas in spontaneously conceived pregnancies also sub-optimal endometrial or placental function may result in a live born offspring. Also in pregnancies of women with high age, a high correlation between placental and birthweight has been reported (Haavaldsen et al., 2011). In these pregnancies, as in ART pregnancies, there is a high miscarriage rate and thereby a stronger selection of embryos to a successful pregnancy.

The means of oocyte fertilization and culturing the preimplantation embryo in vitro may also affect pregnancy outcome. Stimulation of multiple follicles with FSH, embryo culture in vitro and the culture media used have all been shown to alter methylation of imprinted genes in the oocytes, spermatozoa and embryos (Lucifero et al., 2004; Fauque et al., 2007; Sato et al., 2007; Market-Velker et al., 2010), and different media for culturing preimplantation embryos result in different birthweights (Dumoulin et al., 2010). Therefore, epigenetic changes caused by ART resulting in differential growth of the fetus and the placenta are plausible (Tilghman, 1999; Tycko and Morison, 2002).

Transfer of multiple embryos may result in a singleton pregnancy with an early vanishing twin. In singleton births with a vanishing twin, the birthweight is lower than in singletons with no vanishing twin (Pinborg et al., 2005). Whether the placental anlage from the vanishing twin undergoes early necrosis or is present during the remaining pregnancy is unknown. We studied singleton pregnancies only and had no information on the number of transferred embryos. The frequency of twins following double embryo transfer varies between 10 and 47% (Pinborg et al., 2005). During the study period, there has been a change in recommended treatment from double to elective single embryo transfer. Nevertheless, a significant proportion of the singleton pregnancies in our study may have been the result of double embryo transfer.

Conclusions
We found larger placentas and higher placental weight/birthweight ratios in pregnancies conceived by ART when compared with spontaneously conceived pregnancies. When IVF and ICSI pregnancies were studied separately, the same pattern was seen as for ART pregnancies in general.

Authors’ roles
C.H. analysed the data and wrote the manuscript. T.T. contributed to the interpretation of the results and writing of the manuscript. A.E. had the original idea for the study. She contributed to the statistical analysis and the writing of the manuscript.

Funding
We have received no external funding for this study.

Conflict of interest
None declared.

References
Houriavitz A, Pri-Paz S, Dor J, Seidman DS. Neonatal and obstetric outcome of pregnancies conceived by ICSI or IVF. Reprod Biomed Online 2005; 11: 469–475.


Naeye RL. Do placental weights have clinical significance? Hum Pathol 1987;18:387–391.


