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## ARTICLE

# Is the birthweight of singletons born after IVF reduced by ovarian stimulation or by IVF laboratory procedures?


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**Abstract** Singletons born after IVF are at risk of adverse pregnancy outcome, the cause of which is unknown. The present study investigated the influence of ovarian stimulation and IVF laboratory procedure on birthweight. Birthweight of singleton pregnancies resulting from IVF treatment with ( $n = 161$ ) and without ovarian stimulation (using a modified natural cycle (MNC) protocol;  $n = 158$ ), and spontaneous conceptions in subfertile patients ( $n = 132$ ) were compared. Mean  $\pm$  SD birthweight of singletons after conventional IVF with ovarian stimulation, MNC-IVF and natural conception were  $3271 \pm 655$ ,  $3472 \pm 548$  and  $3527 \pm 582$  g ( $P = 0.001$ ). After adjustment for biological and social confounders, the difference in birthweight between conventional IVF and MNC-IVF was reduced to 88 g and the differences between conventional IVF and MNC-IVF versus spontaneous conceptions to 123 and 23 g, respectively. The results lead to three conclusions. First, a major part of the crude differences in birthweight between the three groups is related to patient and pregnancy characteristics. Second, the IVF laboratory procedure has no influence on birthweight. Third, although a trend towards lower birthweight after ovarian stimulation was found, an adverse effect of ovarian stimulation on birthweight was not substantiated. 

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**KEYWORDS:** IVF, natural cycle, ovarian stimulation, perinatal outcome, pregnancy outcome, single embryo transfer

## Introduction

Compared with natural conceptions, singletons conceived by assisted reproduction techniques are at increased risk of adverse perinatal outcome (Helmerhorst et al., 2004; Jackson et al., 2004; Kalra and Molinaro, 2008; Romundstad et al., 2008; Schieve et al., 2004; Sutcliffe and Ludwig, 2007). This increased risk may be related to the treatment procedure, with the ovarian stimulation and laboratory procedure as possible contributing factors (Jackson et al., 2004). However, the observation that assisted reproduction pregnancies have adverse perinatal outcome may be confounded by factors influencing both fertility potential and perinatal outcome, as is suggested by studies on the outcome of natural conceptions in subfertile patients (Pandian et al., 2001; Romundstad et al., 2008; Thomson et al., 2005). Further, singleton pregnancies after stimulated IVF often occur after transfer of two embryos and in a number of cases are twin pregnancies spontaneously reduced to singletons. These so-called vanishing twins are associated with preterm delivery and low birthweight and their rather frequent occurrence may also contribute to adverse perinatal outcome of assisted reproduction pregnancies (Dickey et al., 2002; Pinborg et al., 2005).

The present study attempted to determine the effect of ovarian stimulation and IVF laboratory procedures on birthweight and to distinguish between the possible contributing factors by comparing three groups of singleton pregnancies in subfertile patients. The first group consisted of singleton pregnancies resulting from conventional IVF with ovarian stimulation and multifollicular growth. The second group consisted of singleton pregnancies conceived after modified natural cycle (MNC)-IVF, in which treatment was aimed at the use of the monofollicular cycle, without ovarian stimulation and with physiological oestradiol concentrations during the follicular phase (Nargund et al., 2007; Pelinck et al., 2005), serving as a control group for the influence of ovarian stimulation on perinatal outcome. The third group consisted of singleton pregnancies after natural conception in subfertile patients, occurring during infertility work-up, while on the waiting list for treatment or between treatment cycles, to control for the influence of the subfertility.

The present study is an extension of an earlier study, in which perinatal outcome of pregnancies resulting from MNC-IVF ( $n = 84$ ) and conventional IVF with ovarian stimulation ( $n = 106$ ) were compared (Pelinck et al., 2010). The group of spontaneous conceptions was added to serve as a control group for the influence of the subfertility, thus allowing for the assessment of the effect of the IVF laboratory procedures.

## Materials and methods

### Patient selection

The treatments from which the pregnancies in this study resulted were performed at the Reproductive Medicine department of the University Medical Centre Groningen, The Netherlands between February 2001 and April 2006.

The first group consisted of singleton pregnancies arising from conventional IVF with ovarian stimulation. Only pregnancies resulting from fresh embryo transfer were included.

The second group consisted of singleton pregnancies arising from MNC-IVF. Pregnancies resulting from multifollicular cycles (more than three dominant follicles at ovulation triggering) were excluded from the analysis since these were considered to be the result of ovarian stimulation.

The third group consisted of naturally conceived singleton pregnancies in subfertile patients, occurring during infertility work-up, while on the waiting list for assisted reproduction techniques treatment or between treatment cycles.

The aim of this study was to investigate the possible influence of the IVF laboratory procedure and ovarian stimulation on birthweight. Therefore, for all three groups, pregnancies in women in-utero exposed to diethylstilbestrol (DES) and vanishing twin pregnancies were excluded, since these are at risk for low birthweight irrespective of the mode of conception. Only pregnancies with duration of  $\geq 24$  weeks were included. In the study clinic, the maximum female age for MNC-IVF treatment is 36 years. For the other two groups, patients with the same age range were included.

Details on patient demographics, lifestyle habits and pregnancy outcome were collected by chart review and patient questionnaires. For the IVF pregnancies, gestational age was calculated as duration between oocyte retrieval and delivery plus 14 days. For the natural conceptions, gestational age was calculated based on first-trimester ultrasound or last menstrual period.

Low birthweight and very low birthweight were defined as birthweight  $< 2500$  g and  $< 1500$  g, respectively. Preterm and very preterm delivery were defined as delivery before 37 and 32 completed gestational weeks, respectively.

### IVF treatment protocols

In conventional IVF with ovarian stimulation, a flare-up or down-regulation protocol was used with triptorelin (Decapeptyl; Ferring Nederland, Hoofddorp, The Netherlands) or leuproreline (Lucrin; Abbott, Hoofddorp, The Netherlands) and recombinant follicle-stimulating hormone (rFSH; Puregon; Organon, The Netherlands). Cycles were monitored with ultrasound. Ovulation was triggered by 10,000 units of human chorionic gonadotrophin (HCG) when at least half of the dominant follicles were  $> 18$  mm. Follicular aspiration was performed 36 h later under conscious sedation with fentanyl. IVF or intracytoplasmic sperm injection (ICSI) was performed according to standard procedures. Transfer of a maximum of three embryos was performed on day 2 or 3 after oocyte retrieval. Luteal support consisted of progesterone vaginal suppositories (200 mg, three times daily, started on the day of oocyte retrieval and continued until the day of pregnancy test) or HCG 1500 IU, days 5, 7 and 9 after oocyte retrieval.

MNC-IVF was performed as described previously (Pelinck et al., 2005). In short, cycles were monitored with ultrasound and serum oestradiol and LH measurements. Cetrorelix (0.25 mg/day; Cetrotide; Serono, The Hague, The Netherlands) together with rFSH (150 IU/day; Gonal-F; Serono Benelux, The Netherlands) was started after follicular

dominance had developed. Follicular aspiration was performed 34 h after ovulation triggering by 10,000 IU of HCG (Pregnyl; Organon) at a follicle size of at least 18 mm and/or plasma oestradiol concentrations of  $\geq 1.06$  nmol/l. IVF or ICSI was performed according to standard procedures. Embryo transfer was performed on day 3 after oocyte retrieval. Luteal support consisted of 1500 IU HCG days 5, 8 and 11 after oocyte retrieval. In a small number of patients ( $n = 3$ ), menotrofine (Menopur; Ferring Nederland) was given for substitution instead of rFSH, with a further identical protocol.

### Statistical analysis

Univariate analyses were performed first, using the chi-squared test for categorical outcome variables and Student's *t*-test for continuous outcome variables. A *P*-value  $< 0.05$  was considered statistically significant. Linear regression was applied for the analysis of birthweight, with

adjustment for confounders. Factors with *P*-value  $< 0.10$  in univariate analysis were retained for further analysis by linear regression. Additionally, the a-priori decision was made to enter factors in the model with a known strong influence on birthweight (parity, gestational age, infant gender and smoking) regardless of the *P*-value found in univariate analyses. For the analyses, Statistical Package for Social Sciences version 14.0 (SPSS, Chicago, IL, USA) was used.

### Results

From February 2001 to April 2006, 161 and 158 singleton pregnancies resulting from conventional IVF and MNC-IVF were included. In addition, 132 natural conceptions were identified. Of the natural conceptions, five (3.8%) occurred in between IVF treatments. In the group of pregnancies resulting from conventional IVF, 37 (23.0%) occurred in patients in whom MNC-IVF had not been successful.

**Table 1** Patient characteristics according to treatment modality.

Characteristic	Conventional IVF	n <sup>a</sup>	Modified natural cycle IVF	n <sup>a</sup>	Natural conception	n <sup>a</sup>
Maternal age (years)	32.9 $\pm$ 2.9 <sup>b</sup>	161	32.4 $\pm$ 3.0 <sup>c</sup>	158	31.5 $\pm$ 3.9 <sup>c,b</sup>	132
Maternal height (cm)	170.2 $\pm$ 7.0	143	171.5 $\pm$ 6.1	147	171.1 $\pm$ 6.3	102
BMI (kg/m <sup>2</sup> )	23.6 $\pm$ 3.6	141	23.3 $\pm$ 3.2	144	26.0 $\pm$ 17.1	102
Maternal ethnicity						
Caucasian	129 (89.6) <sup>d</sup>	144	140 (95.9) <sup>d</sup>	146	97 (91.5)	106
Other	15 (10.4)		6 (4.1)		9 (8.5)	
Maternal level of education						
High	40 (26.8) <sup>b,d</sup>	149	52 (35.9) <sup>d</sup>	145	50 (42.4) <sup>b</sup>	118
Moderate/low	109 (73.2)		93 (64.1)		68 (57.6)	
Parity						
Nulliparous	114 (70.8) <sup>c</sup>	161	105 (66.5)	158	79 (59.8) <sup>c</sup>	132
Parous	47 (29.2)		53 (33.5)		53 (40.2)	
Cause of subfertility						
Tubal	40 (24.8)	161	34 (21.5)	158	9 (7.4)	122
Male factor	54 (33.5)		58 (36.7)		30 (24.6)	
Unexplained	31 (19.3)		46 (29.1)		62 (50.8)	
Endometriosis	15 (9.3)		11 (7.0)		6 (4.9)	
Cervix	6 (3.7)		4 (2.5)		3 (2.5)	
Failed donor inseminations	6 (3.7)		5 (3.2)		0 (0.0)	
Hormonal	9 (5.6)		0 (0.0)		12 (9.8)	
Laboratory procedure						
IVF	116 (72.0)	161	117 (74.1)	158	—	—
ICSI	45 (28.0)		41 (25.9)			
Duration subfertility (years)	4.3 $\pm$ 2.1 <sup>c,e</sup>	159	3.7 $\pm$ 2.1 <sup>c,e</sup>	155	2.5 $\pm$ 1.8 <sup>e</sup>	131
Paternal height (cm)	183.0 $\pm$ 7.6 <sup>c</sup>	136	184.8 $\pm$ 7.2 <sup>c,d</sup>	140	183.1 $\pm$ 6.5 <sup>d</sup>	102
Paternal ethnicity						
Caucasian	125 (92.6) <sup>d</sup>	135	136 (97.1) <sup>d,e</sup>	140	84 (84.8) <sup>d,e</sup>	99
Other	10 (7.4)		4 (2.9)		15 (15.2)	

Values are mean  $\pm$  SD or number (%). Chi-squared test and Student's *t*-test were used for categorical and continuous variables, respectively.

BMI = body mass index; ICSI = intracytoplasmic sperm injection.

<sup>a</sup>Number of cases of which information was available.

<sup>b</sup>*P*  $< 0.01$ .

<sup>c</sup>*P*  $< 0.05$ .

<sup>d</sup>*P*  $< 0.10$ .

<sup>e</sup>*P*  $< 0.001$ .

Of the pregnancies resulting from conventional IVF, 29 occurred after single-embryo transfer (SET), 131 after double-embryo transfer (DET) and one after the transfer of three embryos. Of the MNC pregnancies, 154 resulted from SET and four from DET.

Baseline characteristics of all patients are shown in **Table 1**. Pregnancy characteristics according to treatment modality are reported in **Table 2**. Mean birthweights were 3271, 3472 and 3527 g after conventional IVF, MNC-IVF and natural conception, respectively (**Table 3**).

## Results of regression analysis

Results of the linear regression analyses are reported in **Tables 4 and 5**. Between conventional IVF and MNC-IVF pregnancies, the crude difference in birthweight was 201 g in favour of MNC-IVF ( $P = 0.003$ ; **Table 4**). After correction for pregnancy factors and duration of subfertility, the difference remaining was 117 g ( $P = 0.02$ ). After correction for smoking and maternal and paternal characteristics in a next step, the difference remaining was no longer significant (88 g).

**Table 2** Pregnancy characteristics according to treatment modality.

Pregnancy characteristic	Conventional IVF	n <sup>a</sup>	Modified natural cycle IVF	n <sup>a</sup>	Natural conception	n <sup>a</sup>
Smoking during pregnancy						
Yes	21 (14.0)	150	13 (8.7)	149	13 (10.7)	122
No	129 (86.0)		136 (91.3)		109 (89.3)	
Alcohol use during pregnancy						
Yes	5 (3.3)	150	3 (2.0)	149	4 (3.4)	119
No	145 (96.7)		146 (98.0)		115 (96.6)	
Diabetes						
Yes	0 (0.0)	154	3 (2.0)	152	2 (1.5)	131
No	154 (100)		149 (98.0)		129 (98.5)	
Hypertension						
Yes	12 (7.7) <sup>c</sup>	155	13 (8.6) <sup>b</sup>	152	21 (16.0) <sup>b,c</sup>	131
No	143 (92.3)		139 (91.4)		110 (84.0)	
Pregnancy duration (days)	274.8 ± 14.3 <sup>b</sup>	161	277.1 ± 12.0	158	277.7 ± 14.5 <sup>b</sup>	132
Pregnancy duration (weeks)						
>37	146 (90.7)	161	146 (92.4)	158	122 (92.4)	132
32–37	13 (8.1)		12 (7.6)		8 (6.1)	
24–32	2 (1.2)		0 (0.0)		2 (1.5)	
Mode of delivery						
Vaginal	126 (78.3)	161	126 (79.7)	158	105 (79.5)	132
Caesarean section	35 (21.7)		32 (20.3)		27 (20.5)	

Values are number (%) or mean ± SD. Chi-squared test and Student's *t*-test were used for categorical and continuous variables, respectively.

<sup>a</sup>Number of cases of which information was available.

<sup>b</sup> $P < 0.10$ .

<sup>c</sup> $P < 0.05$ .

**Table 3** Neonatal outcome according to treatment modality.

Neonatal outcome	Conventional IVF	n <sup>a</sup>	Modified natural cycle IVF	n <sup>a</sup>	Natural conception	n <sup>a</sup>
Infant sex						
Male	78 (48.4)	161	72 (45.6) <sup>b</sup>	158	74 (56.1) <sup>b</sup>	132
Birthweight (g)	3271 ± 655 <sup>c,d</sup>	161	3472 ± 548 <sup>c</sup>	158	3527 ± 582 <sup>d</sup>	132
Birthweight (g)						
>2500	147 (91.3)	161	151 (95.6)	158	126 (95.5)	132
1500–2500	11 (6.8)		7 (4.4)		5 (3.8)	
<1500	3 (1.9)		0 (0.0)		1 (0.8)	

Values are mean ± SD or number (%). Chi-squared test and Student's *t*-test were used for categorical and continuous variables, respectively.

<sup>a</sup>Number of cases of which information was available.

<sup>b</sup> $P < 0.10$ .

<sup>c</sup> $P < 0.01$ .

<sup>d</sup> $P < 0.001$ .

**Table 4** Linear regression analysis of the relationship between conception mode (modified natural cycle IVF versus conventional IVF) and birthweight.

<i>Factors in the model</i>	<i>Difference in birthweight (g)<sup>a</sup></i>	<i>P-value</i>	<i>n<sup>b</sup></i>
None	201 (67–334)	0.003	319
Pregnancy factors (pregnancy duration, parity, infant gender)	123 (27–219)	0.01	319
Pregnancy factors and duration of subfertility	117 (19–214)	0.02	314
Pregnancy factors, duration of subfertility and smoking, maternal ethnicity (Caucasian versus other), maternal level of education (high versus other), paternal height and paternal ethnicity (Caucasian versus other)	88 (–14–190)	NS	260

NS = not statistically significant.

<sup>a</sup>Values are mean (95% CI).<sup>b</sup>Number of cases of which information was available.**Table 5** Linear regression analysis of the relationship between conception mode and birthweight.

<i>Factors in the model</i>	<i>Difference in birthweight (g)<sup>a</sup></i>	<i>P-value</i>	<i>n<sup>b</sup></i>
Natural conception versus conventional IVF			
None	256 (111–340)	0.001	293
Pregnancy factors (pregnancy duration, parity, infant gender)	139 (37–242)	0.008	293
Pregnancy factors and duration of subfertility	103 (–8–214)	NS	290
Pregnancy factors, duration of subfertility and smoking, maternal age, maternal level of education, paternal ethnicity (Caucasian versus other), hypertension	123 (–9–255)	NS	223
Natural conception versus modified natural cycle-IVF			
None	55 (–76–186)	NS	290
Pregnancy factors (pregnancy duration, parity, infant gender)	7 (–43–56)	NS	290
Pregnancy factors and duration of subfertility	–6 (–58–45)	NS	286
Pregnancy factors, duration of subfertility and smoking, maternal age, paternal height, paternal ethnicity (Caucasian versus other), hypertension	23 (–35–82)	NS	220

NS = not statistically significant.

<sup>a</sup>Values are mean (95% CI).<sup>b</sup>Number of cases of which information was available.

Between natural conceptions and conventional IVF or MNC-IVF pregnancies, the crude differences in birthweight were 256 and 55 g, respectively ( $P = 0.001$  and not statistically significant; **Table 5**). After correction for pregnancy factors and duration of subfertility, the differences remaining were 103 and –6 g. After correction for smoking and maternal and paternal characteristics in a next step, the differences remaining were 123 and 23 g.

## Discussion

This explorative study found a trend towards lower birthweight in singletons conceived by conventional IVF compared with MNC-IVF singletons and to naturally conceived singletons in a subfertile population. Multivariate analysis of the data indicated that the major part of the lower birthweight found after conventional IVF is attributable to patient and pregnancy characteristics.

It should be noted that the power of this study is relatively low due to the rather small numbers of cases. In addition,

the regression analysis was hampered by missing data, in particular for social background variables. Therefore, a small but real difference in birthweight between conventional IVF compared with MNC-IVF and natural conceptions cannot be excluded with certainty.

Assuming an existing difference in birthweight, the difference cannot be attributed to the IVF and ICSI laboratory procedures, since these were the same in both IVF-pregnancy groups. No difference in birthweight was found between MNC-IVF pregnancies and natural conceptions, which also disqualifies the laboratory procedure as a cause for lower birthweight.

Since the trend for lower birthweight was found in the conventional IVF group only, a potential difference in birthweight may be attributed to the ovarian stimulation. It is unclear by what mechanisms ovarian stimulation would influence birthweight, but high oestradiol concentrations associated with ovarian stimulation may play a role, as they may modulate growth factors, cell-adhesion molecules, steroid receptors, angiogenetic factors and the expression of pinopodes in the endometrium, influencing endometrial



receptivity (Devroey et al., 2004; Macklon and Fauser, 2000). In one study, a negative correlation between oestradiol concentrations and birthweight in conventional IVF with ovarian stimulation was found (Mitwally et al., 2004). Also, ovarian hyperstimulation syndrome, which is associated with high oestradiol concentrations, is reported to be associated with adverse outcome in pregnancies achieved through assisted reproduction techniques (Abramov et al., 1998; Chung et al., 2006). On the other hand, in another study, no correlation was found between birthweight and duration of stimulation, amount of gonadotrophins used or numbers of oocytes retrieved (Griesinger et al., 2008).

Whether an effect of ovarian stimulation would be through an effect on the endometrium, leading to diminished quality of the implantation environment or through an effect on oocyte or embryo or both, is unknown and difficult to distinguish. Invasion of the endometrium by the trophoblast during placentation is regulated by many factors produced within the trophoblast-endometrial microenvironment and deficiencies herein can result in early miscarriage or pre-eclampsia and intrauterine growth restriction (Paiva et al., 2007). Many endocrine, immunological and genetic factors have been identified that are involved in the process of embryo implantation (Edwards, 2006).

Subfertility as such has been proposed as the predominant cause for lower birthweight in IVF children (Romundstad et al., 2008). This further complicates the interpretation of the present study's data, since those patients conceiving after conventional IVF have the most severely diminished fertility potential, as illustrated by the longer duration of subfertility in this group. Of the conventional IVF pregnancies, 23% occurred after MNC-IVF had been unsuccessful. Although MNC-IVF failures in some cases may be coincidental, this suggests that the fertility potential of these patients was more strongly diminished as compared with the patients who did conceive with MNC-IVF. Also, the majority of conventional IVF pregnancies resulted from DET, while in MNC-IVF in most cases a single embryo was transferred. Patients conceiving a singleton after DET may have more strongly diminished fertility than those conceiving twins. In studies comparing pregnancy outcome after SET and DET, higher birthweight and longer pregnancy duration was found by some, but not others (Poikkeus and Tiitinen, 2008).

The difference in birthweight found in this study is small and not statistically significant. Despite this, and despite the methodological limitations of the study, the trend for lower birthweights in children born after conventional IVF compared with MNC-IVF and naturally conceived singletons is potentially interesting since, in general, birthweight reflects the health of newborns. The relationship between low birthweight and development of cardiovascular and metabolic disease later in life has been well established in many studies (Barker, 2002; Ceelen et al., 2008; de Boo and Harding, 2006; Eriksson et al., 2002; Gluckman and Hanson, 2004; Khan et al., 2003; McMillen and Robinson, 2005).

In conclusion, the major part of the crude differences in birthweight between conventional IVF, MNC-IVF and natural conceptions found in this study are related to patient and pregnancy characteristics. The IVF laboratory procedure has no influence on birthweight. A trend towards lower birthweight after ovarian stimulation was found, but since so many factors influence birthweight, the present study

lacks power to substantiate such an effect, if present. Larger studies are necessary to accurately assess the effect of ovarian stimulation on birthweight.

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