

Paper V

Gestational age in pregnancies conceived after in vitro fertilization, a comparison between age assessed from oocyte-retrieval, CRL and BPD

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Short title

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ABSTRACT

Objective: To compare gestational age (GA) and day of delivery estimated from the time of in vitro fertilization (IVF) (oocyte retrieval + 14 days), the ultrasonic measurement of the crown-rump length (CRL) and the biparietal diameter (BPD) in pregnancies conceived in an IVF setting.

Design: Included were 208 singletons and 72 twin pregnancies conceived after IVF. GA estimated from the time of IVF was compared with the GA estimated from the ultrasonic measurement of the CRL in the first trimester and the BPD in the second trimester.

Results: In singletons there was a high correlation in the gestational age at birth assessed from the time of IVF and from CRL ($R=0.992$ $p<0.001$), from the time of IVF and from BPD ($R=0.975$ $p<0.001$). The mean difference in gestational age was 1.2 days between IVF and CRL estimates and 2.1 days between IVF and BPD estimates. The gestational age as estimated from CRL or BPD was shorter than the GA estimated from IVF. In 3 pregnancies there was a difference of more than 7 days between the gestational age estimated from IVF and CRL and in 22 pregnancies between gestational age estimated from IVF and BPD. A difference of more than 14 days for any of the estimates was not found in any case.

Conclusion: Assessment of gestational age from the time of IVF, CRL and BPD in pregnancies conceived after in vitro fertilization shows equally high agreement between the three methods, this supports the use of ultrasound as a reliable method for estimation of gestational age.

INTRODUCTION

Accurate dating of the pregnancy is the basis for optimal obstetric management. Ultrasonic measurement of the biparietal diameter (BPD) is better than the last menstrual period in predicting the day of delivery¹⁻⁵ and is the method of choice for estimation of day of delivery in many countries. Most formulae for ultrasound dating have been derived from studies using the last menstrual period as reference in series where the women included were selected for their regular menstrual cycles.

There are a few studies on pregnancies conceived with assisted reproductive techniques where the gestational age according to oocyte retrieval or embryo transfer is compared with the gestational age calculated from the ultrasonic measurement of the biparietal diameter⁶⁻⁹. To gain more knowledge about the accuracy of ultrasound measurement for estimation of gestational age and day of delivery it would be of interest to have information from pregnancies resulting from assisted reproductive programs; such information would include measurements of both the crown-rump length (CRL) and the BPD in the same pregnancies.

The aim of this study was to compare gestational age assessed from the time of in vitro fertilization with the gestational age calculated for the ultrasonic measurement of the CRL and the BPD in pregnancies conceived after in vitro fertilization.

SUBJECTS AND METHODS

Included were singleton and twin pregnancies without malformations that were conceived with the aid of artificial reproductive techniques at the University Hospital of Trondheim, and that were later delivered at the hospital. Further inclusion criteria were measurement of the crown-rump length (CRL) in the first trimester and measurement of the biparietal diameter (BPD) in the second trimester. Two hundred and eighty pregnancies fulfilled the inclusion criteria, 208 were singletons and 72 were twins (144 infants). Standard in vitro fertilisation (IVF) was used in 185 of the singleton pregnancies and 65 of the twin pregnancies, intracytoplasmic sperm injection (ICSI) was used in 5 singleton pregnancies and frozen embryo replacement was done in 18 of the singleton pregnancies and 7 of the twin pregnancies.

An additional comparison was made between the estimated gestational age at birth of the pregnancies conceived after in vitro fertilization and the estimated gestational age at birth of the pregnancies conceived spontaneously; the estimates were based on BPD measurements. Included were singletons without malformations with spontaneous onset of labor and delivery at the University Hospital of Trondheim. The subjects included 147 births after in vitro fertilization and 12 589 after spontaneous conception.

Ultrasonic measurement of the crown rump length (CRL) was done by transvaginal ultrasound in the first trimester. The CRL, which actually was the greatest length, was measured in a straight line from the cranial to the caudal end of the embryonic body. Measurement of the biparietal diameter

from the outer to the outer contour of the parietal bone echo was done at the fetal examination that took place at approximately 18 completed weeks. Data from the examinations were prospectively registered. After the delivery, additional pre- and postnatal data concerning the pregnancy, birth, and neonatal development were added.

Gestational age according to IVF for standard IVF and ICSI was calculated from the day of oocyte retrieval, which was converted into menstrual age by adding 14 days. Frozen embryo replacement was performed 3 days after ovulation and actual gestational age was then calculated by adding 14 days to the ovulation date. Gestational age according to CRL was calculated by the equation developed by Wisser derived from pregnancies conceived after assisted reproductive techniques, $t=35.72 + 1.082L^{1/2} + 1.472L - 0.09749L^{3/2}$ where L is the greatest embryonic length¹⁰. Gestational age according to the BPD was calculated according to the laboratory's own standard¹¹.

The calculation of the estimated day of delivery was made when the biparietal diameter was ≥ 35 and ≤ 60 mm; this measurement corresponded to 15–22 completed weeks of pregnancy. In twin pregnancies, the calculation of the estimated day of delivery was based on the ultrasound measurement from the largest twin.

The clinical management of the pregnancy was based on the ultrasound dating by BPD. Term was assumed to be at 282 completed gestational days¹² for both ultrasound and the last menstrual period; the infant was considered preterm when delivery occurred before 259 completed days¹³

and post-term when the gestation lasted ≥ 296 days. Smoking was defined as the self-reported smoking of one cigarette or more per day at the time of the ultrasound examination in the second trimester.

Statistical evaluation was done with the BMDP statistical package (BMDP Statistical Software Inc., Los Angeles, CA). Pair- and groupwise comparisons were performed using the Wilcoxon signed-rank test and the Mann Whitney rank-sum test. Parametric analysis of variance with linear analysis of covariates was employed to assess differences in gestational age and birth weight between IVF pregnancies and normally conceived pregnancies. Statistical significance was assigned at a level of $p < 0.05$.

RESULTS

The difference in mean gestational age between the day estimated from the time of IVF and the gestational age as estimated from ultrasound by measurement of the CRL or the BPD and between the two ultrasound estimates are shown in Table 1. In singletons, the mean gestational age calculated from the CRL and the BPD measurements was shorter than the gestational age estimated from IVF. The mean gestational age at the routine fetal examination where BPD was measured by ultrasound was 130.5 days (range 110–157) as estimated from IVF. In the present study no significant difference in gestational age was seen between fetuses conceived with the standard IVF technique, ICSI or the replacement of frozen-thawed embryos, this was in accordance with previous findings⁹ thus the different groups were analyzed together in this study.

In 3 pregnancies there was a difference of more than 7 days between the gestational age estimated from the IVF and from the CRL and in 27 pregnancies between the gestational age estimated from the IVF and the BPD; in the latter group there were 5 twin pregnancies (10 infants). In 13 pregnancies there was a difference of more than 7 days between gestational age estimated from the CRL and from the BPD; among those were 2 twin pregnancies. All infants with a difference of more than 7 days between the different estimates were born healthy.

There was a significant correlation between gestational age at birth assessed from the time of IVF and from CRL ($R=0.992$ $p<0.001$) (Fig 1), between gestational age at birth assessed from IVF and from BPD ($R=0.975$

$p < 0.001$) (Fig 2) and between gestational age at birth assessed from CRL and from BPD ($R = 0.975$ $p < 0.001$).

The onset of labor was spontaneous in 147 (71%) of the singletons and 22 (31%) of the twins. The day of delivery for spontaneous births is shown in Table 2. The mean birth weight for singletons was 3 340 g and 2 752 g for twins.

The characteristics of the singleton pregnancies conceived after IVF and those conceived spontaneously are shown in Table 3. An analysis of variance with gestational age at delivery (estimated from the BPD) as dependent variable and maternal age, parity, smoking and sex of the fetus as covariates was performed. Deliveries before day 259 were excluded. The contribution of each factor to gestational age at delivery is shown in Table 4. The adjusted cell means for gestational age at delivery was 278.4 days for IVF and 280.6 for the other pregnancies ($p < 0.01$).

An analysis of variance with birth weight as dependent variable and maternal age, parity, smoking and sex of the fetus as covariates was performed. The contribution of each factor to the birth weight is shown in Table 5. The adjusted cell means for birth weight was 3510 g for IVF and 3610 g for the other pregnancies ($p = 0.01$).

DISCUSSION

In the present study there was a high correlation in the gestational age at birth between the estimates by IVF, CRL and the BPD measurements; this is in accordance with previous studies on BPD^{6, 7}.

Several studies have compared gestational age calculated from mid-trimester biometry with gestational age estimated from the last menstrual period¹⁻⁵ and a few studies have compared gestational age as estimated from biometry with gestational age in pregnancies achieved with assisted reproductive techniques where day of conception was known⁶⁻⁹. All these studies indicate that the the ultrasound method predicts gestational age with sufficient accuracy. In spite of the consistency of the data there is still an ongoing debate about the reliability of ultrasound for estimation of gestational age.

In the present study, the mean difference in gestational age at scanning was 1.2 days between the IVF and CRL estimates and 2.1 days between the IVF and BPD estimates. The mean ultrasound estimates gave a shorter gestational age. This has also been shown in a previous study where a mean difference of 2.1 days between IVF and BPD estimated gestational age has been found⁹. In both these studies the gestational age was calculated by adding 14 days to the day of oocyte retrieval. In a study where gestational age was estimated from the day after oocyte retrieval which shortens the gestation by 1 day compared to our calculations, the gestational age was 0.86 days shorter by the BPD estimate⁶. Results from other studies where estimation of gestational age was based on the day of fertilization (or frozen embryo replacement)^{7, 8} have shown a difference of less than one day

between age calculated from conception and the BPD measurement. When the differences in ways of calculating gestational age from the IVF are taken into consideration the results from the various studies are similar. There seems to be a difference of approximately 1–2 days between the estimates of gestational age from IVF and from ultrasound. However in the individual embryo/fetus the difference between the gestational age estimated by IVF and BPD could be as much as 14 days; this has been observed both in the present and a previous study⁹. We looked at the cases with a difference of more than 7 days between any two of the three different estimates and in the majority of cases a difference of more than 7 days was found between the IVF and the BPD estimates and were not present or were very small at the time of the CRL measurement.

In pregnancies where gestational age has been calculated from both the last menstrual period and the BPD measurement, differences of more than 14 days between the two estimates have been observed in 6 %⁵. In 83% of these pregnancies the gestational age was shorter according to the ultrasound method. It is of interest to note that in the present and a previous study⁹ on pregnancies conceived by in vitro fertilization no case with a difference of more than 14 days between the IVF estimate and the BPD estimate was found. A difference of more than 7 days between IVF and CRL estimates was found in only three fetuses. This supports the assumption that large differences between gestational age estimated by the last menstrual period and ultrasound are caused by unreliability in the last menstrual period estimate and not by pathology in the fetus¹⁴.

There are several possible explanations for a difference between the estimates by IVF, CRL and BPD. We still lack exact information about fertilization and implantation. The time span from ovulation to fertilization and nidation in pregnancies conceived in natural cycles might not be equal to that in in vitro fertilized pregnancies. It has been shown that CRL dating curves based on the last menstrual period underestimate the gestational age compared to dating curves based on known ovulation date¹⁵. The CRL curve in the present study is derived from women who had undergone assisted reproductive techniques, and the BPD curve based on menstrually timed pregnancies.

In a study on 107 pregnancies from an assisted fertilization program, differences in the CRL were found in pregnancies of the same age¹⁶. At post-insemination day 41, the CRL in 10 embryos varied from 7–15 mm. Other CRL studies based on populations derived from assisted reproductive treatment programs analyzed the accuracy of age assessment by measuring the embryonic length, and found relatively wide 95 % prediction intervals of 12.8 days¹⁵, 9.8 days¹⁷, and 9.3 days¹⁰. In a subfertile population intervention is necessary to achieve pregnancy, and these pregnancies may not meet the criterion 'normal' though they develop uneventfully in most cases. Studies in mice have indicated that treatment with gonadotropin as it is used in in-vitro fertilization may have adverse effects such as delayed implantation and impaired embryonic/fetal development¹⁸. However, one must be cautious about applying such findings to humans.

Embryological studies have implied uniform development in the human embryo with small differences in size and age at the different development

stages¹⁹. In a recent study on embryonic growth with age based on the last menstrual period the CRL measurements showed large variations between embryos of the same age²⁰. However, the growth curves from 7 weeks to 12 weeks were parallel, indicating that the embryos followed the same growth curve, which implied that first trimester embryos of identical size had approximately the same 'true' age. The biological variation in fetal size increases as the pregnancy continues and the variation of the BPD in the second trimester is in the range of 5–7 days^{21, 6, 7}. In the present study this may be illustrated by a greater number of fetuses with a difference of seven days or more between the IVF and BPD estimates than between the IVF and CRL estimates.

Previous studies have shown a shorter gestational age at birth²² and a higher rate of preterm infants^{23, 24, 22} in IVF pregnancies compared to spontaneously conceived pregnancies. The IVF pregnancies also differed in several other aspects such as a higher maternal age^{23, 24} higher rate of primiparas^{23, 24} lower rate of smokers²⁴ and a lower mean birth weight^{23, 24}. In the present study we had similar results and we therefore compared the gestational age estimated from BPD in IVF pregnancies with spontaneously conceived singleton pregnancies from the same area with correction for maternal age, parity, smoking and sex of the fetus by analysis of variance. After exclusion of preterm deliveries there was a difference of 2.2 days in gestational age at birth between the two groups with the shorter gestation for IVF pregnancies. The difference in birth weight after correction for the covariates was 100 g between the two groups with the lower birth weight for IVF pregnancies. Whether the IVF pregnancies have

a shorter gestational age at birth and therefore a lower birth weight or if they are smaller at the same gestational age and therefore have the gestational age overestimated by ultrasound can not be answered.

In previous studies, the difference in gestational age between the IVF and the BPD estimates did not show any significant difference between singletons and twins^{8, 9}. In the present study there was a difference of 2.8 days. The explanation for this discrepancy might be that in the present study the largest BPD measurement in each pair of twins was used for the calculation of gestational age.

In spite of the fact that IVF pregnancies are achieved through intervention, the high agreement between the gestational age calculated from the time of IVF and from the early CRL measurements in the same pregnancies, the high agreement between gestational age calculated from the time of IVF and BPD supports the use of ultrasound as a reliable method for estimation of gestational age.

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LEGENDS

Figure 1

Correlation between gestational age at birth assessed from IVF and from CRL in singletons (n=208).

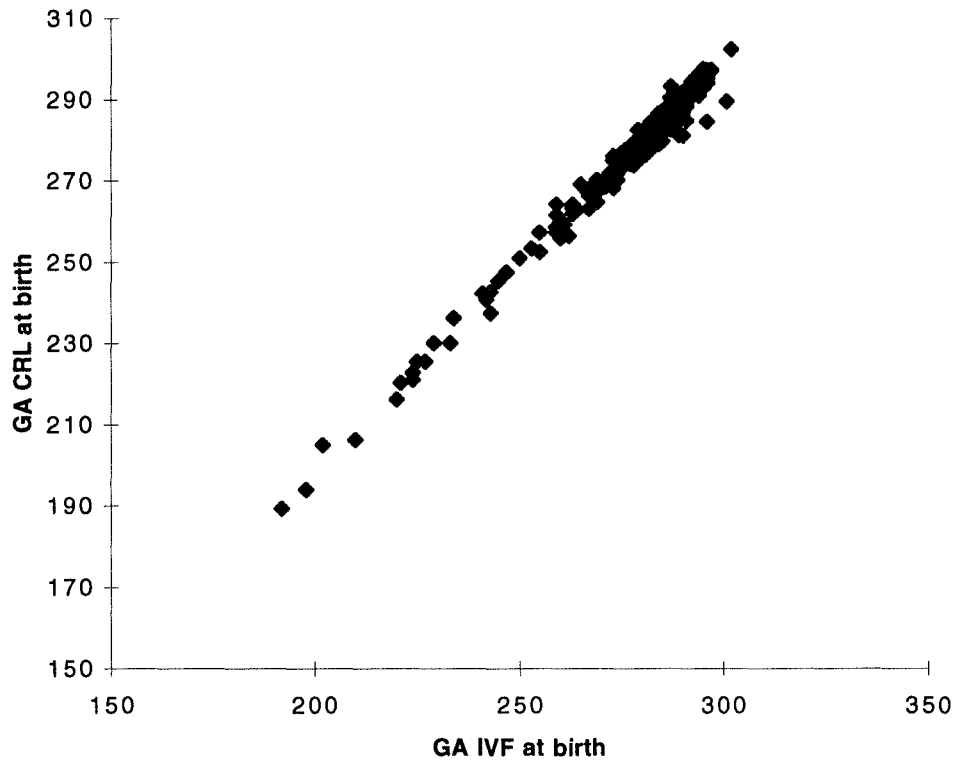


Figure 2

Correlation between gestational age at birth assessed from IVF and from BPD in singletons (n=208).

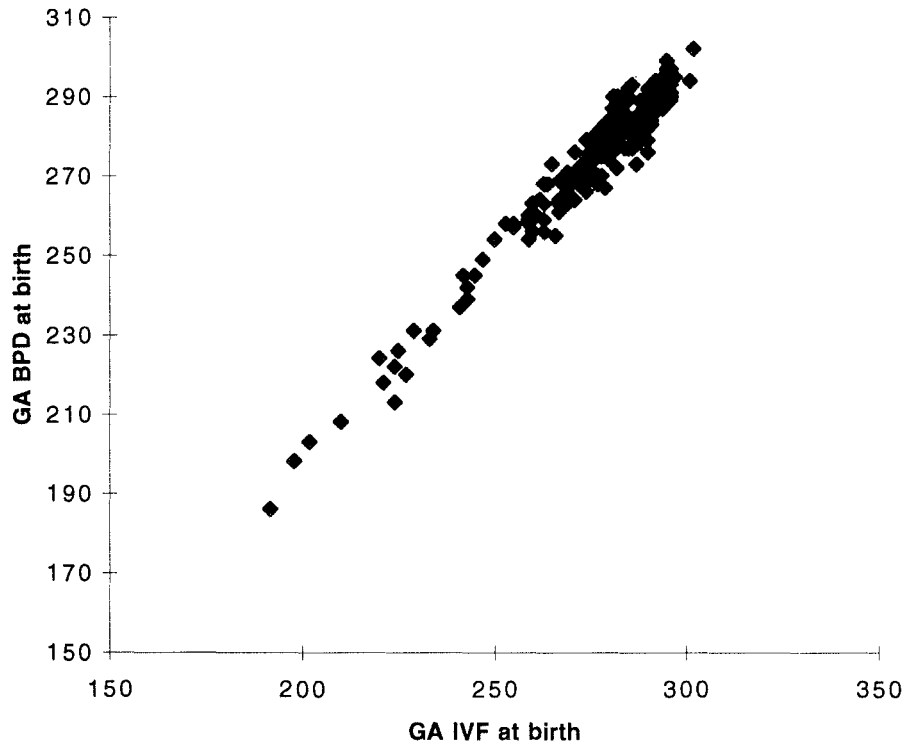


Table 1

Difference in gestational age (GA) between the IVF estimate and the ultrasound estimates.
 Negative sign; the gestation is shorter by the IVF estimate than by the ultrasound estimate.

	GA IVF – GA CRL	GA IVF – GA BPD	GA CRL – GA BPD
Singletons (n)	208	208	208
Mean (SD)	0.9 (2.5)	2.1 (4.2)	1.1 (4.3)
Range	-7 - 11	-9 - 14	-8 - 15
p value	<0.001	<0.001	<0.001
Twins (n)	72	72	72
Mean (SD)	0.7 (2.6)	-0.7 (4.2)	-1.4 (4.7)
Range	-6 -10	-9 - 9	-12 -11
p value	0.05	0.2	0.02

Table 2
Day of delivery for spontaneous births, for the IVF and ultrasound estimates respectively.

	n	Birth (days)			Birth distribution			
		mean	SD	median	±7 days %	±14 days %	<259 days %	≥296 days %
Singletons spontaneous								
IVF	147	277.8	15.2	280	58.5	89.1	8.2	3.1
CRL	147	276.9	15.4	279	58.5	83.6	9.5	2.1
BPD	147	275.6	15.3	279	57.8	83.7	8.8	0.7
Twins spontaneous								
IVF	22	251.9	11.6	255				
CRL	22	251.5	11.3	253				
BPD	22	253.0	12.6	253				

Table 3

Maternal and fetal characteristics of pregnancies conceived after IVF (n=147) and pregnancies conceived spontaneously (n=12589). All were singletons without malformations and had spontaneous onset of labor.

	IVF		Other births		p value
	n	%	n	%	
Primipara n (%)	104	71	5803	46	<0.001
Smoking n (%)	125	15	8871	30	<0.001
Males n (%)	74	50	6288	50	1.0
Preterm delivery (<259 days)	13	9	533	4	0.01
Maternal age, mean (years)	33.2		27.3		<0.001

Table 4

Impact of different factors on the gestational age at delivery as determined by the ultrasonic measurement of the biparietal diameter in IVF pregnancies compared with other pregnancies. The regression coefficient expresses, in days, the contribution of each factor to the gestational age at delivery. The categorical variables of parity, smoking and sex of the fetus were assigned the following values: male=1, female=0; multipara=1, primipara=0; smoking=1, non-smoking=0.

	Regression coefficient	Standard error	P
Maternal age (years)	0.1238	0.0177	<0.001
Parity	-0.7328	0.1652	<0.001
Smoking	-0.2363	0.1636	0.15
Sex of the fetus	1.1828	0.1472	<0.001
Mean birth weight (g)	0.0075	0.0001	<0.001
	IVF	Other	P
Adjusted cell means for gestational age at delivery (days)	278.4	280.6	<0.001

Table 5

Impact of different factors on the mean birth weight in IVF pregnancies compared with other pregnancies. The regression coefficient expresses, in grams, the contribution of each factor to mean birth weight. The categorical variables of parity, smoking and sex of the fetus were assigned the following values: male=1, female=0; multipara=1, primipara=0; smoking=1, non-smoking=0.

	Regression coefficient	Standard error	P
Maternal age (years)	0.7699	0.9747	0.43
Parity	142.9695	9.0986	<0.001
Smoking	-178.7702	9.0110	<0.001
Sex of the fetus	126.3620	8.1057	<0.001

	IVF	Other	P
Adjusted cell means for birth weight (g)	3510	3610	0.001