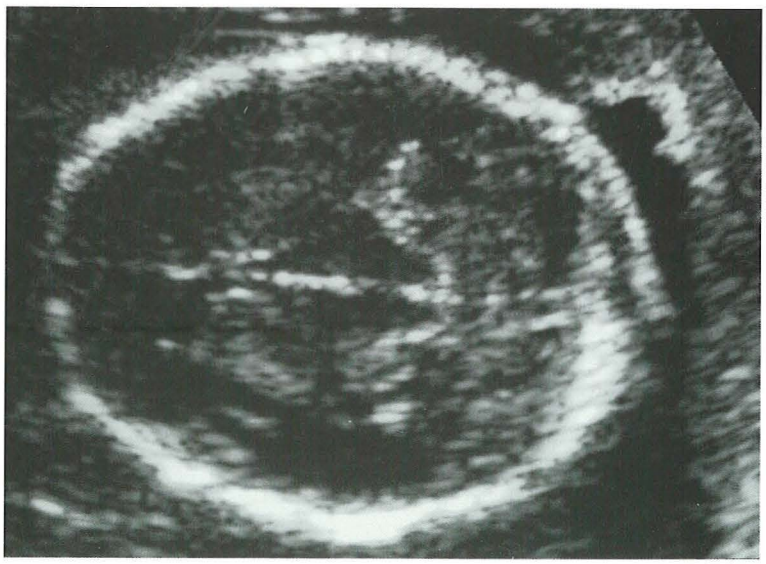
Katarina Tunón

ULTRASOUND AND PREDICTION OF GESTATIONAL AGE



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SUMMARY

Background: Reliable information about gestational age is necessary for optimal obstetric management of pregnancies and is the basis for calculation of fetal growth. Most pregnant women in developed countries participate in routine fetal examination programs that include fetal biometry for estimation of the gestational age. Nevertheless, there is still an ongoing debate regarding the accuracy of the ultrasound method compared to the accuracy of the last menstrual period method for the estimation of gestational age and thus the estimated day of delivery.

Aims: The aims of this study were to evaluate the accuracy of the ultrasound method and the last menstrual period method as the basis for estimation of the day of delivery (Paper I) and to evaluate the impact of fetal, maternal and external factors on the prediction of day of delivery (Paper II). Further aims were to evaluate the possibility of an increased risk for adverse fetal outcome when the predicted day of delivery as estimated by ultrasound is more than 14 days later than the predicted day of delivery as estimated by the last menstrual period (Paper III) and in pregnancies defined as post-term according to the last menstrual period estimate but not according to the ultrasound estimate (Paper IV). The final aim was to compare gestational age according to the time of oocyte retrieval with the gestational age calculated by the ultrasonic measurement of the crown-rump length (CRL) and the biparietal diameter (BPD) in pregnancies conceived after in vitro fertilization (Paper V).

Material and methods: The total population for the complete study was 15 241 pregnant women. An evaluation was performed of the ultrasonic measurement of the biparietal diameter (BPD) in pregnancy week 15–22 compared with a reliable last menstrual period (LMP) as the basis for estimation of the day of delivery (Papers I–IV). The clinical management of the pregnancy was based on gestational age estimated by ultrasound.

In the comparison between the ultrasound and LMP methods to predict day of delivery 10 478 women who had reliable LMP, singleton pregnancies and spontaneous onset of labor were included in the study. Women with regular and irregular cycles were compared (Paper I).

To evaluate the impact of various factors on the day of delivery, the study population consisted of 7824 women with reliable LMP and LMP and ultrasound estimates within 14 days of each other, singleton pregnancies and spontaneous onset of labor after 37 weeks. Multiple linear regression was used to assess the impact of parity, maternal age, smoking, gender and experience of the operator on the prediction of day of delivery (Paper II).

The impact of changing the day of delivery was studied in 12 436 women with singleton pregnancies and reliable LMP. The impact on fetal outcome was evaluated when the day of delivery as estimated by ultrasound was changed to a date more than 14 days later than the date that was in accordance with the LMP. A study group (the ultrasound estimate of day of delivery was more than fourteen days later than the estimate based on the last menstrual period) (n=787) and a control group (the two estimates were within seven days of each other) (n=9252) were compared regarding various parameters concerning fetal outcome (Paper III).

The possibility of an increased risk of adverse fetal outcome in fetuses that were post-term according to the last menstrual period estimate but not according to the ultrasound

estimate was evaluated. The study population consisted of 11 510 women with reliable LMP, singleton pregnancies and spontaneous onset of labor after 37 weeks. They were divided into four groups: Group one comprised the women who delivered at term (259–295 days), according to both the ultrasound and the last menstrual period. Group two comprised the women who delivered post-term according to the last menstrual period estimate but not according to the ultrasound estimate. Group three included those who delivered post-term according to the ultrasound estimate but not according to the last menstrual period estimate. Group four were those who delivered post-term according to both the ultrasound and the last menstrual period estimates (Paper IV).

A comparison of gestational age assessed from the time of oocyte retrieval (time of IVF) with gestational age from measurement of CRL in the first trimester and BPD in the second trimester was done.The study population consisted of 208 singleton pregnancies and 72 twins without malformations conceived after in vitro fertilization (Paper V).

Results: The comparison of the ultrasound and the LMP methods of estimating the day of delivery showed that the percentages of women who delivered within ± 7 days of the predicted day were 61% for the ultrasound method and 56% for the LMP method. The percentage of post-term births was 9% using the LMP method and 2% using the ultrasound method. In 52% of the women the ultrasound estimate was the better predictor of the day of delivery and in 46% the LMP estimate was the better predictor ($p < 0.001$). The ultrasound method was significantly better than the LMP method in predicting day of delivery when there was a difference of one week or more between the methods. When the difference was less than a week, the number of post-term births was higher when the LMP was used ($p < 0.05$) (Paper I).

There were variations in the size of the BPD measurements of the 18-week fetus. The variations were related to gender, maternal age, parity and experience of the operator. Because of these variations there was a total difference of ± 1 day in the day of delivery as determined by ultrasound (Paper II).

Using an ultrasound evaluation to change the estimated day of delivery to a date more than fourteen days later than the day of delivery as estimated in accordance with the last menstrual period, did not influence the risk of spontaneous abortion, perinatal death, Apgar score < 7 after 5 minutes or transfer to the neonatal intensive care unit. There was a difference of three days in the prediction of day of delivery between the two groups groups, i.e. the infants in the study group were born 3 days earlier than estimated. There was a greater number of infants with a birth weight below 2 500 g in the study group, but no difference between the groups in the number of infants with a birth weight < 2 SD below the mean according to the ultrasound estimate (Paper III).

The risk for perinatal death, Apgar score < 7 after 5 minutes or transfer to the neonatal intensive care unit was not increased for pregnancies post-term according to the last menstrual period estimate but not according to the ultrasound estimate (Paper IV).

In singleton pregnancies there was a high correlation in the gestational age at birth assessed from the time of IVF and that assessed from CRL ($R=0.992$ $p < 0.001$), or BPD ($R=0.975$ $p < 0.001$). The mean difference in gestational age was 0.9 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 gestational age 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 was not found for any of the estimates (Paper V).

Conclusions: In comparison with the last menstrual period, the ultrasonic measurement of the biparietal diameter is the superior method for the estimation of the day of delivery. The accuracy of the method is influenced by gender, parity, maternal age, and the experience of the operator, but these differences are small and of no clinical importance. There is no indication of any adverse consequence of the routine scan and change of estimated day of delivery. There is no indication of any increase in adverse fetal outcome for fetuses defined as post-term according to the last menstrual period estimate but not according to the ultrasound estimate. Assessment of gestational age, from the time of IVF, and from measurements of CRL or BPD in pregnancies conceived after in vitro fertilization shows high agreement between the three methods. This supports the use of ultrasound as a reliable method for estimation of gestational age. The ultrasound method can therefore be recommended as the method of choice for dating pregnancies.

LIST OF PAPERS

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals:

I Tunón K, Eik-Nes SH, Grøttum P. A comparison between ultrasound and a reliable last menstrual period as predictors of the day of delivery in 15 000 examinations. Ultrasound Obstet Gynecol 1996;8:178–185

II Tunón K, Eik-Nes SH, Grøttum P. The impact of fetal, maternal and external factors on prediction of the day of delivery by the use of ultrasound. Ultrasound Obstet Gynecol 1998;11:99–103

III Tunón K, Eik-Nes SH, Grøttum P. Fetal outcome when the ultrasound estimate of the day of delivery is more than 14 days later than the last menstrual period estimate. Ultrasound Obstet Gynecol 1999;14:17–22

IV Tunón K, Eik-Nes SH, Grøttum P. Fetal outcome in pregnancies defined as post-term according to the last menstrual period estimate, but not according to the ultrasound estimate. Ultrasound Obstet Gynecol 1999;14:12–16

V Tunón K, Eik-Nes SH, Grøttum P, V v Düring, J A Kahn. Gestational age in pregnancies conceived after in vitro fertilization; a comparison between age assessed from oocyte retrieval, CRL and BPD. Ultrasound Obstet Gynecol (In press)

ABBREVIATIONS

BPD	biparietal diameter
CI	confidence interval
CRL	crown-rump length
hCG	human chorionic gonadotrophin
IVF	in vitro fertilization
LH	luteinizing hormone
LMP	last menstrual period
MHz	Megahertz
SD	standard deviation
US	ultrasound
WHO	World Health Organization

INTRODUCTION

Historical background

The duration of the human pregnancy and the expected day of confinement has at all times been a matter of considerable social and medical importance. Both ancient Hindu and Roman cultures assumed the duration of pregnancy to be approximately 9 lunar months.

Reliable information about gestational age is a prerequisite for optimal obstetric management of the pregnancy. For example, the correct management of preterm and post-term pregnancies is dependent on such information. Information about gestational age is also necessary as age is the basis for calculation of fetal growth (Campbell and Wilkin, 1975; Eik-Nes, 1980). Information about fetal growth is essential in pregnancy management since we know that intrauterine growth retardation is associated with perinatal morbidity and mortality (Yerushalmy, 1970; Fitzhardinge and Stevens, 1972; Commey and Fitzhardinge, 1979; Holmqvist *et al.*, 1986; Laurin *et al.*, 1987; Taylor and Howie, 1989).

Various methods for estimation of gestational age have been used. The pregnant woman has always recognized quickening or movement of the fetus. This movement is noticed from about the end of week 20 in primiparas and from the end of week 18 or even earlier at 16–17 weeks in multiparas and gives an approximation of the length of pregnancy (Pschyrembel, 1973). Assessment of uterine size by pelvic examination in the first trimester of pregnancy and by measurements of the uterine fundus height are used but have been proven as imprecise methods for estimation of gestational age (Beazly and Underhill, 1970). Results of X-ray of lower femoral or upper tibial epiphyses in late pregnancy were used but found to be very variable and of no clinical value (Hall, 1990). Biochemical methods with maternal serum assays of placental proteins have been used (Westergaard *et al.*, 1983; Ahmed and Klopper, 1986). Ideally the duration of pregnancy would be calculated from fertilization, but that date is rarely known. Therefore, the calculation of gestational age is often done from the first day of the last menstrual period (assuming ovulation/fertilization on day 14).

In modern times obstetric ultrasound is frequently used and most pregnant women in developed countries participate in routine fetal examination programs that include fetal biometry for estimation of the gestational age. Despite the fact that obstetric ultrasound has been in clinical use for measurement and dating of the fetus since the late seventies there is still a debate about whether the last menstrual period method or the ultrasound method is more accurate for the estimation of gestational age.

The last menstrual period (LMP) method

An estimated day of delivery is often calculated according to «Nägele's rule» (Nägele FC. Lehrbuch der Geburtshülfe für Hebammen. Heidelberg: Akademische Buchhandlung von JEB Mohr, 1833) (Geirsson, 1997). This is done by adding 9 months and 7 days to the date of the first day of the last menstrual period. Whichever date in the year is taken, the interval between the last menstrual period and estimated day of delivery will be approximately 280 days (280–283). Franz Carl Nägele (1778–1851) was professor of medicine of Heidelberg and aware of the uncertainties associated with this method and that it could only be used as an approximation. This formula credited to Nägele was originally proposed by Hermann Boerhaave, professor of medicine and botany of Leyden (1709) and merely quoted to Nägele (Speert, 1996). Nägele neither formulated nor made any claim to the 'rule' that bears his name. He clearly presented it, rather, in the form of a direct quotation from Boerhaave, properly annotated and indeed in Boerhaaves original latin.

Cycle length and cycle regularity

Several studies have addressed the issue of the length and regularity of the menstrual cycle (Gunn *et al.*, 1937; Arey, 1939; Goldzieher *et al.*, 1947; Treolar *et al.*, 1967b; Chiazze *et al.*, 1968). These studies show that the majority of women do not have menstrual cycles with a constant length. In 1939 Arey summarized 50 years of studies on the degree of menstrual irregularity from 1500 individuals and 20 000 calendar records. He found great variation in cycle lengths both between women and from one cycle to the next in the same woman (Arey, 1939). The maximum departures of individuals from their mean extended from 1–69 days in adults and from 6–211 in pubertal girls. The individual cycle variation in each woman was more than 2–3 days from her own mean cycle length in at least 1/3 of the cycles and there was a skewness towards cycles longer than the mean. This was also found by Goldzieher (Goldzieher *et*

al., 1947). In 1995, Harlow and Ephross reviewed the variation of the menstrual cycle from menarche to menopause (Harlow and Ephross, 1995). The greatest variability in cycle length was seen in young women, whose cycles often were longer than cycles later in life. In a Danish study a maximum menstrual cycle variation of more than 14 days was found in one-third of regularly menstruating teenagers and in approximately 10% of regularly menstruating women aged ≥ 30 years (Münster *et al.*, 1992). Over time there will always be variations in the regularity of the menstrual cycle for any one woman, or as Arey expressed it in 1939; «Certainly, not the slightest evidence pointing toward perfect regularity has so far been produced for even a single exeptional individual. Should such a person be found at some future time, she will constitute a true medical curiosity».

LMP and time of intercourse

There are a few studies on women with regular menstrual cycles and where the time of intercourse is known. In 1916, Pryll studied cases with conception after a single act of intercourse and compared day of conception in relation to the first day of the last menstrual period (Pryll, 1916). He found that conception could occur at any time during a 42-day period counting from the first day of the last menstrual period. Jaeger summarized his own study with two previous studies and found that in 34% of pregnancies intercourse had taken place during 15–28 days after the first day of the last menstrual period (Jaeger, 1917). In a study on 416 women who claimed that a single act of intercourse had resulted in pregnancy, Weinstock found that in 61% of the pregnancies intercourse had taken place during the period from day 1 to day 14 (Weinstock, 1934). In the remaining 39% of women, intercourse had taken place during the period from day 15 to day 35 in the menstrual cycle. He concluded that women could become pregnant on any day of the menstrual cycle including the first with a skew towards later dates. A similar skew towards longer intervals has been shown by Treolar (Treolar *et al.*, 1967a).

LMP and time of ovulation

In modern times, information about the time of ovulation is gained from studies on basal body temperature rise and the LH surge (Saito *et al.*, 1972; Boyse *et al.*, 1976; McIntosh *et al.*, 1980; Walker *et al.*, 1988). Long menstrual cycles are often explained by an increase in the length of the follicular phase calculated from the first day of the menstrual

flow to the midcycle LH surge (McIntosh *et al.*, 1980). In a study on 75 ovulatory cycles with daily measurement of LH and hCG, the mean time from LMP until ovulation was 16.4 days, with a range of 8–35 days (Walker *et al.*, 1988). Ovulation on or after day 18 occurred in 21 cycles and in only 11 of these would late ovulation have been suspected on the basis of the menstrual history. In a study of 110 women, the time was calculated between the first day of the last menstrual period and delivery and between the day on which ovulation had probably taken place (estimated by basal body temperature rise) and delivery (Saito *et al.*, 1972). The results showed that delay of ovulation was the major cause of apparent prolongation of pregnancy. Similar results were found in a study of 317 conceptual cycles (Boyse *et al.*, 1976). In the study by Boyse gestational length was calculated both from the last menstrual period and from the time of ovulation (estimated by rise in basal body temperature). When gestational length was calculated from the LMP 11% of the cases were classified as postmature compared with 5% when gestational length was calculated from time of ovulation. The results from all these studies show that ovulation and thereby fertilization in many cases occur later than 14 days after the first day of the last menstrual period, even in women with otherwise 'regular' cycles.

LMP and time of fertilization

In the Carnegie staging system for dating and staging of human embryos, the first eight postovulatory weeks are divided into 23 stages based on the external and internal morphological status of the embryos (O'Rahilly and Müller, 1987). Embryonic life commences with fertilization (Carnegie stage 1) and is the procession of events that begins when a spermatozoon makes contact with an oocyte and ends with the intermingling of maternal and paternal chromosomes at metaphase of the first mitotic division of the zygote (Brackett *et al.*, 1972). In human oocytes fertlized in vitro, 11 hours were required for formation of pronuclei from human oocytes after insemination (Edwards, 1972).

It is likely that no more than one day intervenes between ovulation and fertilization (O'Rahilly and Müller, 1987). In a study on 221 women intending to get pregnant it was found that conception occurred only when intercourse took place during a six-day period that ended on the day of ovulation as estimated by hormonal methods (Wilcox *et al.*, 1995). These findings suggest a short survival time for the oocyte, or maybe a change in the cervical mucus post-ovulatory that obstructs the entry of sperm (Wilcox *et al.*, 1995).

The survival time for spermatozoa in vivo in cervical mucus is 5 days after insemination or intercourse, and occasionally up to 7 days (Perloff and Steinberger, 1964). Sperm retain the capacity to fertilize human oocytes in vitro for 5 days at room temperature (Cohen *et al.*, 1985). Fertilization, then can apparently take place no later than one day after ovulation but up to 7 days after the time of intercourse. This may explain some of the errors that occur when calculating gestational age from the day of intercourse. It may also shed light on the apparent discrepancy between gestational age of the fetuses of women who know they have had one intercourse only and where the ultrasound examination suggests the fetus is one week younger than assumed according to the time of intercourse.

Implantation

The implantation (Carnegie stage 4) takes place approximately 5–6 days after ovulation (O'Rahilly and Müller, 1987). It is the process that leads to the formation of a specialized intimate cellular contact between the trophoblast and the endometrium.

Delayed implantation i.e. the embryonic development being temporarily arrested prior to implantation at the blastocyst stage, is a well described phenomenon in several species of mammals and marsupials (Mead, 1993). 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 (Ertzeid *et al.*, 1993). In humans, a few cases of delayed implantation have been described after ovulation induction or in-vitro fertilization, most ending as spontaneous abortions (Naaktgeboren *et al.*, 1986; Grinsted and Avery, 1996). A recent ultrasound study of pregnancies conceived after assisted reproductive techniques have shown variability in size and development of human embryos before the tenth post-insemination week indicating delays in implantation and/or delays in embryonic development (Dickey and Gasser, 1993).

Early growth of the embryo

Embryological studies have implied a uniform development of the human embryo with small differences in size and age at the different developmental stages: In the Carnegie staging system for embryonic development (O'Rahilly and Müller, 1987), the time range for the stages 16–18 (37–44 postovulatory days) is approximately ± 1.5–2 days, and for stage 19 (47 postovulatory days) ± 1.5 days.

Delayed development i.e. the embryonic development being retarded after implantation, is only known to occur physiologically in bats and may be temperature dependent or temperature independent (Mead, 1993). Studies in mice have indicated that treatment with gonadotropin as it is used in in-vitro fertilization may impair embryonic/fetal development (Ertzeid *et al.*, 1993).

LMP and time of delivery

The 'correct' day of delivery for a given fetus is not known, so it is not possible to apply a gold standard for the time of birth. Calculation of the expected day of delivery is most often done by adding 280 days to the first day of the last menstrual period assuming ovulation/fertilization on day 14. This is a slight modification of Nägele's rule. The duration of pregnancy from ovulation/fertilization is then believed to be 266 days. The average length of pregnancy from ovulation (measured by rise in basal body temperature) has been calculated as 264 days (Saito *et al.*, 1972) and 267 days (Döring, 1962), respectively. According to the definitions by the World Health Organisation (WHO), the baby is considered to be born at term between 259–293 days, preterm < 259 days and post-term > 293 days ((WHO), 1977).

In a large Swedish study of more than 383 000 singleton pregnancies with reliable menstrual dates, the average duration from the last menstrual period to vaginal birth was 281 days (mean), 282 days (median), and 283 days (mode) (Bergsjø *et al.*, 1990). Similar results were found in a study on 24 275 deliveries where the length of gestation according to the last menstrual period (for women who went into spontaneous labor) was 280 days (mean), 281 days (median), and 283 days (mode), respectively (Gardosi *et al.*, 1997).

The distribution curve of gestational age at delivery according to any method is influenced by preterm births. Due to the negative skewness of the distribution curve of births it is not correct to use parametric statistics such as the mean and the standard deviation to derive the 'true' length of pregnancy. The median and the mode are the more robust estimates. The median tells us that 50% give birth before and 50% give birth after that day. With the physiology of pregnancy with abortions and preterm deliveries occurring continuously from conception, the median may not be the 'correct' day to determine the length of pregnancy. The mode, which is the most common value

observed, might be better, but large samples are needed as the fluctuations of small frequences are apt to produce spurious modes (Armitage, 1971).

The percentage of women with optimal menstrual history delivering spontaneously at 40 ± 2 weeks is 82–92% (Treolar *et al.*, 1967a; Campbell *et al.*, 1985; Waldenström *et al.*, 1990; Kieler *et al.*, 1993; Backe and Nakling, 1994), the corresponding percentage for women with unreliable menstrual history is 70–79% (Campbell *et al.*, 1985; Backe and Nakling, 1994). There is always a skewness towards longer gestations which is explained mostly by a long follicular phase and fertilization later than 14 days after the LMP. About 6 to 14% of women with a reliable menstrual history deliver later than 42 weeks after their LMP (Grennert *et al.*, 1978; Saari-Kempainen *et al.*, 1990; Backe and Nakling, 1994; Mongelli *et al.*, 1996).

Gestational age can also be underestimated using the last menstrual period method. This is illustrated by the results of a Norwegian study where the 97.5 percentile for birth weight at 28 weeks was > 4000g (Bjerkedal and Skjærven, 1980). Such a birth weight is unrealistically high for that particular age and is most likely result of misinterpretation of gestational age based on the last menstrual period. Underestimation of gestational age when calculating from the first day of the last menstrual period may probably be explained by bleeding in early pregnancy that has been mistaken for the last menstrual period. In the study by Bjerkedal several pregnancies lasted up to 46 weeks, further indicating the possibility of a misinterpretation of gestational age when using the last menstrual period.

Reliability of the LMP

In 1 to 9% of pregnancies, no date at all can be given for the first day of the last menstrual period due to factors such as no period since previous abortion/birth, prolonged amenorrhoea, continuous bleeding throughout pregnancy or no information available (Campbell *et al.*, 1985; Hall *et al.*, 1985). The information from women who provide the date of the LMP is unreliable in 10–45% of the cases due to irregular cycles or unreliable date of the LMP (Grennert *et al.*, 1978; Campbell *et al.*, 1985; Hall *et al.*, 1985; Bergsjø *et al.*, 1990). In a detailed study on 315 women coming to an antenatal booking clinic, 24% of the women were unsure of their LMP (Geirsson and Busby-Earle, 1991). Among the 76% with 'certain' dates, 6% had noted the last instead of the first day of bleeding, 10% counted back from the day they had expected the next

menstruation to start, and 18% used memory aids such as birthdays or holidays to remember. In 46%, the menstrual cycles were regular, although some of these women had an abnormal LMP, or had used oral contraceptives within 3 months of the LMP. In the end, only 32% were considered to have certain dates.

The use of oral contraceptives within 6 months of pregnancy often skews the ovulation to a date later than 14 days after the LMP. This results in a higher rate of pregnancies being classified as post-term (Ratten, 1981; Sviggum and Eik-Nes, 1988). All of the studies mentioned above demonstrate the uncertainty of using the last menstrual period for estimation of gestational age, and the importance of at least labelling the dates as reliable or unreliable.

The ultrasound method

The introduction of ultrasound into obstetrics and gynecology was made by Ian Donald in 1958 with his paper «Investigation of abdominal masses by pulsed ultrasound» (Donald *et al.*, 1958). In the early 1960s, Donald and Brown (Donald and Brown, 1961) and Willocks (Willocks, 1962; Willocks *et al.*, 1964) measured the fetal biparietal diameter (BPD) using an unidimensional A-scan method. Correlation between the BPD and fetal weight was suggested in 1964 (Willocks *et al.*, 1964). In the late 1960s Campbell (Campbell, 1968; Campbell, 1969; Campbell, 1970) improved the method and made the systematic association between early fetal measurement of the biparietal diameter and fetal age. Ultrasonography is now the method of choice in predicting the day of delivery in many countries.

In 1967 Kratochwil and Eisenhut showed that transvaginal ultrasound was possible and detected embryonic heart activity early in the first trimester (Kratochwil and Eisenhut, 1967), but it was not until the late 1980s that transvaginal ultrasound became available for clinical use.

Fetal biometry

Early in pregnancy, measurement of the crown-rump length (CRL) by abdominal or transvaginal ultrasound is widely used for the estimation of embryonic/fetal age. During recent years, the use of high frequency transvaginal scanning has made more thorough

evaluation of the embryo/fetus possible, and reference ranges for the BPD size by gestational age (Kustermann *et al.*, 1992) and BPD growth charts (Blaas *et al.*, 1998) for the first trimester have been developed. Ultrasonic fetal biometry up to 22–24 weeks can be used for estimating gestational age. Later in pregnancy the variation in fetal weight gain leads to wider confidence intervals of the biometric measurements and inaccuracies in predicting gestational age (Sabbagha and Hughey, 1978; Persson and Weldner, 1986; Kurz and Goldberg, 1988). Fetal measurements obtained later in pregnancy is most commonly BPD and femur length, but also head circumference (mostly based on BPD and occipito-frontal diameter), measurements of other long bones and of the cerebellum have been used for estimating gestational age.

Charts of fetal measurements

Many authors have published charts (reference standards) of fetal size (Deter *et al.*, 1986; Kurz and Goldberg, 1988). Nevertheless, a working group of the British Medical Society (BMUS 1990) had difficulties in identifying any one study with appropriate methodology for some fetal measurements; they found weaknesses in design and/or statistical analysis (Altman and Chitty, 1993). It is important to distinguish between cross-sectional charts of fetal size, and longitudinal charts of growth. There are three different main uses of charts of fetal measurements: 1 to compare the size of a fetus of known gestational age on a single occasion with reference data (cross-sectional); 2 to estimate gestational age from fetal size (cross-sectional); 3 to compare the growth of a fetus between two occasions with reference data (longitudinal) (Altman and Chitty, 1993). Charts for prediction of gestational age are based on regression of gestational age (dependent variable) on fetal size (independent variable) compared to size charts that are based on regression of fetal size (dependent variable) on gestational age (independent variable) (Altman and Chitty, 1993; Altman and Chitty, 1994).

Reference standards for ultrasound dating of the pregnancy are based on gestational age calculated from the last menstrual period, the time of ovulation or fertilization (assisted reproductive techniques). It is argued that ultrasound reference standards based on the last menstrual period could not possibly be more accurate than the last menstrual period method (Hall, 1990). However, ultrasound dating formulae are derived from relatively few pregnancies with carefully checked menstrual dates and regular 28 day cycles. In such populations irregularity of ovulation most likely also will be found, but the discrepancies are minimized by regression of the data.

Individual variation in size due to maternal age, parity, fetal sex or race may affect the measurements, but this seems to have a relatively small effect. The accuracy of the dating formulae derived from menstrual dates are also confirmed in studies based on pregnancies conceived by assissted reproductive techniques (Geirsson and Have, 1993; Mul *et al.*, 1996; Wennerholm *et al.*, 1998). The longitudinal variability in the second trimester is ± 5–6 days (± 2 SD) (Persson and Weldner, 1986). Ultrasound measurements in these reference standards have approximately a Gaussian distribution, and therefore the 'true' age for a fetus with a given value of the ultrasound measurement is most likely close to the mean value for that specific gestational age (Geirsson, 1991). This variation about the mean due to variation in growth velocities and measurement errors (Persson *et al.*, 1978a) is less than the variations in the follicular phase (Saito *et al.*, 1972; Boyse *et al.*, 1976; McIntosh *et al.*, 1980; Walker *et al.*, 1988).

BPD alone or a combination of BPD and femur length measurements?

There has been a discussion about wether assessment of gestational age is more accurate when dating formulae are based on BPD or on a combination of BPD and femur length (Ott, 1985; Persson and Weldner, 1986; Mul *et al.*, 1996). In a study by Ott, both BPD and femur length had identical low systematic errors, but femur length had a greater random error than BPD (Ott, 1985). In a study where gestational age was calculated from date of conception (basal body temperature rise), gestational age was estimated by BPD with a standard deviation of 3.2 days and by the combination of BPD and femur length with a standard deviation of 2.7 days (Persson and Weldner, 1986). Using BPD or femur length as individual variables, BPD gave the best precision. This was in agreement with a recent report where biparietal diameter measurements had a smaller variation than femur length measurements (Mul *et al.*, 1996).

Measurement of the crown-rump length (CRL)

In 1973, Robinson measured embryonic size with transabdominal ultrasound and he used the term 'crown-rump length' (Robinson, 1973). In 1975, a study on the correlation between gestational age and measurements of the CRL for dating of the pregnancy was published (Robinson and Fleming, 1975). This dating chart is still widely used and the measurements that were obtained by abdominal ultrasound differ very little from those in recent studies, where high frequency transvaginal scanning was

used (Blaas *et al.*, 1998). The ultrasonic measurement of the embryonic length although called the 'crown-rump length' is actually the 'greatest length' as used by Streeter (Streeter, 1920) and O'Rahilly and Müller (O'Rahilly and Müller, 1984) and not the 'crown-rump length' as defined by Mall (Mall, 1907). The greatest length is measured in a straight line from the cranial to the caudal end of the embryonic body. Mall described the CRL extending from 'a point just over the mid-brain' to 'the lowest point of the breech'. In smaller embryos (6 to 9 weeks) the CRL is less than the greatest length due to the natural curvature of the embryonic body and the anterior position of the mid-brain.

Measurement of the biparietal diameter (BPD)

The early cephalometric studies were done using the A-scan technique (Donald and Brown, 1961; Willocks, 1962; Willocks *et al.*, 1964). The amplitudes of the walls of the fetal skull and the falx, were reproduced and the markers were placed at the beginning of the rising amplitudes.

Using the B-scan technique, Campbell and Thoms described the measurement of the biparietal diameter in the second and third trimester (Campbell and Thoms, 1977). Longitudinal scans were made to determine the angle of inclination of the fetal head to the vertical axis. Subsequently, transverse scans were made so that a horizontal section of the fetal head was obtained; this was recognized by the appearance of the midline echo and the widest fetal head diameter at right angles to the midline echo was the biparietal diameter.

Outer-outer, outer-inner measurement of the BPD

Sound has different velocities in various tissues. We are able to measure the time it takes for an echo to travel from the transducer and back again. By specifying a sound velocity it is possible to measure distance. Distance (m) = sound velocity (m/s) x travelling time (s). Empirically it was established that when the ultrasound machine was calibrated to a sound velocity of 1600 m/s a measurement from the rising echo to the rising echo corresponding to the outer to the inner contour of the parietal bone the measurement obtained was equal to the true diameter of the fetal head. Later, the industry agreed to standardize the ultrasound machine to a sound velocity of 1540 m/s as an average of true ultrasound velocity in human tissue. When the calibration was set to 1540 m/s we received a diameter which is smaller than the true diameter. By measuring from the outer

to the outer contour of the parietal bone echo when the machine is calibrated to 1540 m/s we obtain a diameter which is 3.7% larger (3–4 mm) and now corresponds to the true diameter of the fetal head. However, when measuring the BPD from the outer to outer contour care must be taken so that medium amplification settings are used since the calvarial echos widen artifactually with increased amplification (Eik-Nes, 1980; Kurz and Goldberg, 1988); using modern equipment this problem has decreased. With the increasing use of transvaginal ultrasound, the fetal head is measured even in the first trimester. In the embryonic period, the term 'biparietal diameter' is not adequate and it would be more correct to use the term 'width of the head' (Blaas *et al.*, 1998). Accordingly, for measurements in the first trimester the calipers are placed at the outer borders of the largest width of the embryonic head.

Reproducibility of CRL and BPD measurements

The reproducibility of CRL and BPD measurements is of importance for the accuracy of the ultrasound dating method.

For CRL measurements between 9 and 54 mm, an intra-observer variation of ± 1.3 mm (± 2 SD) has been reported (Blaas *et al.*, 1998).

For BPD measurements, the smallest error described was in a study by Campbell, with a difference of ± 0.25 mm (SD) between scans of the same subjects (Campbell, 1970). Lunt found an average error of 1.53 mm in readings 15 minutes apart (Lunt and Chard, 1974). Cooperberg showed an error of ± 0.69 to ± 0.91 mm (SD) (Cooperberg *et al.*, 1976). A difference between examiners < 1 mm (SD) and a difference between examinations of < 1 mm (SD) was found by Persson (Persson *et al.*, 1978a). Conclusively, it is fair to assume that the average intra- and interobserver variation seems to be about 1 mm. With an increase in the size of the BPD of 0.44 mm per day (Persson *et al.*, 1978a), a measurement error of 1 mm corresponds to a difference of 2.3 days in gestational age.

Fetal sex differences

At birth, male infants are on average 180 g heavier than female infants (Persson *et al.*, 1978c; Moore *et al.*, 1988). In studies based on the last menstrual period it has been shown that BPD values are greater in male than in female fetuses from the second

trimester. A difference of less than 1 mm between the mean BPD for male and female fetuses at 18 weeks was found by Moore (Moore *et al.*, 1988). Persson et al. (Persson *et al.*, 1978c) found that from the 20th week, the BPD values for male fetuses were 1.7% larger than for females. Pedersen found BPD values on average 1.4 mm larger for males than females (Pedersen, 1980). Estimation of gestational age and day of delivery by ultrasound regards all fetuses with the same size as being the same gestational age. Thus, a difference in the BPD between the sexes might introduce a systematic error in the calculation of gestational age.

Race difference

A comparison of BPD measurements in pregnant Asian (n=142) and European (n=220) women did not show any significant difference up to 20 weeks of gestation (Parker *et al.*, 1982). In a study on 552 Nigerian women there was no significant difference in the BPD measurements of Nigerian versus European fetuses except towards term (Okupe *et al.*, 1984). An American study with BPD measurements obtained from 107 white and 91 black pregnant women did not show any differences in the second trimester (Sabbagha *et al.*, 1976). BPD measurements from 206 Aboriginal fetuses compared with BPD measurements reported by Sabbagha (Sabbagha and Hughey, 1978) showed differences from about 32 weeks and the deficit for the Aboriginal fetus became more obvious towards term (Watson, 1986). Conclusively, the same BPD reference charts can most likely be used in the second trimester regardless of race.

Pathology

Various pathological fetal conditions are associated with a decreased size of the fetal head. The size of the BPD may be smaller than expected for the 'true' age of the fetus, possibly already in the second trimester. Such pathological conditions can introduce error in the assessment of fetal age.

Early 'symmetric' intrauterine growth retardation is a common manifestation of major chromosomal abnormalities, particularly trisomies 13 and 18, and triploidy (Reisman, 1970; Golbus *et al.*, 1976; Benacerraf, 1988).

Infection of the fetus may result in early intrauterine growth retardation and infants who are small for their gestational age. This is reported for rubella, cytomegalovirus infection and toxoplasmosis (Remington and Klein, 1990).

Controversies

Dating of the pregnancy by ultrasound in the second trimester is now part of the clinical care of obstetrical patients in many countries. In spite of several studies demonstrating ultrasound to be a better method than the last menstrual period for estimating the day of delivery (Geirsson, 1997; Gardosi and Geirsson, 1998; SBU, 1998), there is still an ongoing scientific debate about the reliability of ultrasound versus the reliability of the last menstrual period for estimating the day of delivery.

One example of this controversy appeared in a recent commentary in British Journal of Obstetrics and Gynecology where it was argued that ultrasound dating has not been shown to be more accurate than the calendar method (Olsen and Clausen, 1997). Olsen and Clausen suggest that the differences between ultrasound and the last menstrual period can be resolved by adding 283 days (instead of 280) to the date of the last menstrual period and by subtracting two days from the ultrasound estimate. They further suggest that this way of calculation in combination with a more thorough menstrual history with information about cycle length, day of ovulation and day of sexual intercourse may well prove to be more accurate than the ultrasound method. Based on the knowledge of the variations in the length and regularity of the menstrual cycle and the time relationship between intercourse and fertilization already presented in this thesis one may be suprised to find such a statement in 1997. Nevertheless, the controversy seems to continue despite the scientific data available.

Another area of controversy is on the choice of policy. As of today, there is no uniform policy on how ultrasound should be used for dating of the pregnancy. The last menstrual period is still widely used. Although dates are usually 'confirmed' by scan, they are often not adjusted unless the discrepancy with the scan is at least 7, 10 or 14 days (Waldenström *et al.*, 1990; Mongelli *et al.*, 1996). Finally, it has been hypothesized in the Scandinavian literature that because the ultrasound method considers all fetuses of the same size as being of the same gestational age, a misinterpretation of gestational age could be a consequence of using the ultrasound method (SPRI, 1990; Bakketeig, 1991;

Berg, 1992; Bergsjø, 1992; Henriksen *et al.*, 1995).The fetus is thought to be younger instead of smaller in size or even growth retarded. This misinterpretation of gestational age could lead to suboptimal obstetric management and adverse fetal outcome.

AIMS OF THE STUDIES

The overall purpose of these studies from a large scale dataset was to evaluate if the ultrasound method could be recommended for the estimation of the day of delivery to be used in all pregnancies as routine procedure

The specific aims of the studies were:

to compare the ultrasonic measurement of the biparietal diameter with the last menstrual period as the basis for estimation of the day of delivery, and to evaluate the precision of these methods.

to evaluate the impact of gender, smoking, parity, maternal age and the experience of the operators on the accuracy of the prediction of day of delivery.

to evaluate the possibility of an increased risk of adverse fetal outcome and impaired fetal growth when the predicted day of delivery as estimated by ultrasound was more than 14 days later than the predicted day of delivery as estimated by the last menstrual period.

to evaluate if the risk of adverse fetal outcome was greater for fetuses that were post-term according to the last menstrual period estimate but not according to the ultrasound estimate.

to compare gestational age according to the time of oocyte retrieval with the gestational age calculated by the ultrasonic measurement of the CRL and the BPD in pregnancies conceived after in vitro fertilization.

MATERIAL AND METHODS

Population and study design

The pregnant women entered into the study all resided in a geographically well-defined area consisting of nine municipalities surrounding and including the city of Trondheim, Norway. The National Center for Fetal Medicine at the University Hospital of Trondheim is the only ultrasound unit in the area. According to the Norwegian Medical Birth Registry, 98% of the pregnant women living in the area who gave birth during the study period (1987–92) were delivered at the University Hospital. During the study period, 98% of these women underwent a routine fetal examination with ultrasound. The population of the present study thus consisted of the pregnant women living in one of the nine municipalities, and who had a routine fetal ultrasound examination and later delivered at the University Hospital, in total 15 241 women.

The routine fetal examination was scheduled to take place at 18 completed weeks as determined by the last menstrual period. When the routine ultrasound examination showed a pregnancy of less then 15 weeks, the woman received a new appointment; women with a pregnancy length of more than 22 weeks at the ultrasound examination were not included into the study (n=202 (1.3%)). The ultrasound examination was performed by specially trained midwives. A personal interview was carried out with the pregnant woman to obtain data about the maternal status and information about the menstrual history. At the ultrasound examination, the number of fetuses, the fetal anatomy, and the placenta location were assessed, and the biparietal diameter, the mean abdominal diameter and the femur length were measured. The information was registered in a computer data base. After the delivery, additional data about pre- and postnatal development were registered.

Paper I

Ultrasound versus the last menstrual period as predictors of day of delivery

Exclusions from the original population of 15 241 pregnant women are shown in Fig 1.

A comparison was made between the ultrasonic measurement of the biparietal diameter and a reliable last menstrual period as the basis for estimation of the day of delivery. Women with regular and irregular cycles were compared. The method which predicted closest to the actual day of delivery was the 'best' predictor of the day of delivery.

Paper II

Impact of various factors on the ultrasound prediction of day of delivery

Included from the original population of 15 241 pregnant women, were those who had a reliable last menstrual period, regular cycles and where the difference between the ultrasound method and the last menstrual period method in predicting the day of delivery was < 14 days. All women included had singleton pregnancies, spontaneous delivery after 37 weeks and were examined by experienced operators who had performed > 100 examinations following the completion of their ultrasound training. The study population thus consisted of 7824 women.

The impact of maternal age, parity, smoking, sex of the fetus and experience of the operator on the ultrasonic measurement of the biparietal diameter and the accuracy of the day of delivery was evaluated.

Paper III

Day of delivery > 14 days later by ultrasound than by last menstrual period - fetal outcome

Excluded from the original population of 15 241 women were: multiple pregnancies and women with an unreliable date or missing information about their last menstrual period (n=2805). The remaining number of women was 12 436.

A study group (based on the ultrasound estimate, the day of delivery was changed to more than fourteen days later than the estimate based on the last menstrual period) (n=787) and a control group (the ultrasound estimate and the LMP estimate were within seven days of each other) (n=9252) were compared regarding various parameters concerning fetal outcome.

Paper IV

Post-term according to last menstrual period but not according to ultrasound

Excluded from the original population of 15 241 women were: multiple pregnancies, abortions and women with an unreliable date or missing information about the last menstrual period (n=2851). Women who delivered preterm (< 259 days) according to ultrasound (n=880) were also excluded. The remaining number of women (n=11 510) were divided into four groups: 1) women who delivered at term, i.e. within 259 to 295 days according to both the ultrasound and the last menstrual period estimate. 2) women who delivered post-term according to the last menstrual period estimate. 3) women who delivered post-term according to the ultrasound estimate but not according to the last menstrual period estimate. 4) women who delivered post-term according to both the ultrasound and the last menstrual period estimates. The four groups were compared regarding perinatal death, Apgar score < 7 after 5 min and transfer to the neonatal intensive care unit.

Paper V

Gestational age estimated from the time of oocyte retrieval, CRL and BPD

This was a study on pregnancies conceived after in vitro fertilization at the University Hospital of Trondheim 1989–1996. Included were singleton and twin pregnancies without malformations conceived after in vitro fertilization at the University Hospital of Trondheim, and that were later delivered at the hospital. Further inclusion criteria were measurement of the CRL in the first trimester, and BPD in the second trimester. Two hundred and eighty pregnancies fulfilled the inclusion criteria, 208 were singletons and 72 were twins (144 infants).

A comparison of gestational age and day of delivery estimated from the time of oocyte retrieval (+ 14 days) and from gestational age estimated from the ultrasonic mesurement of CRL and BPD was done.

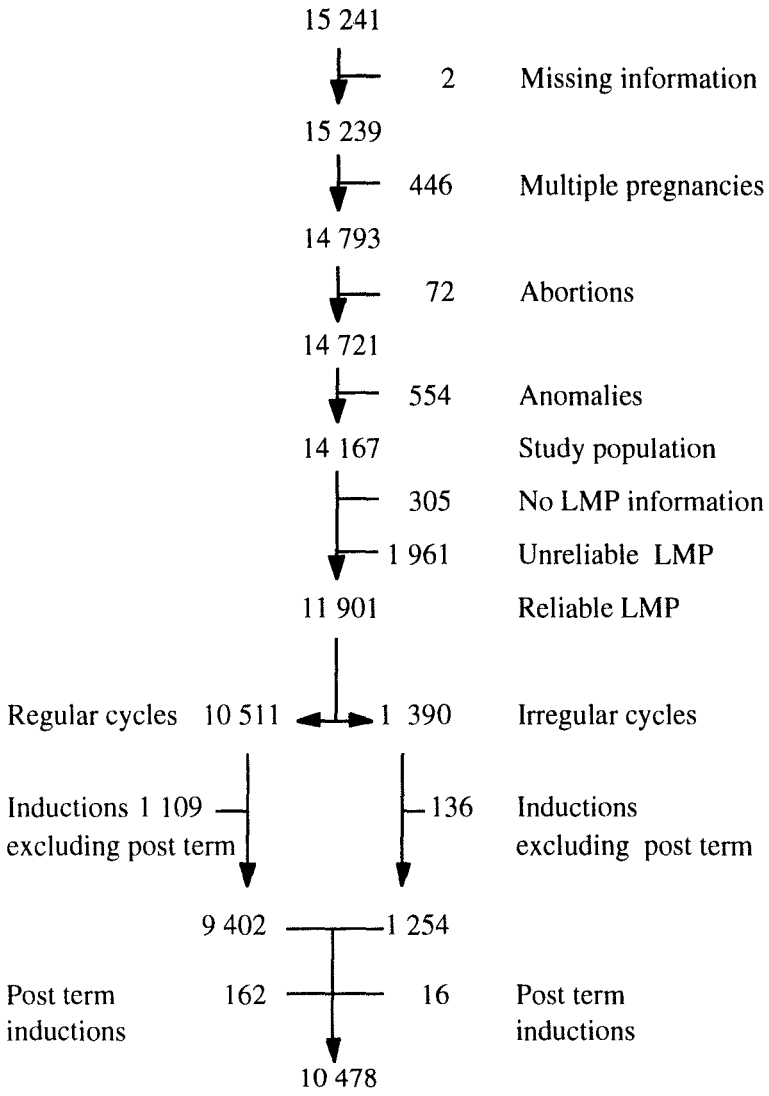

Figure 1 Pregnant women entered into the study, women excluded for various reasons, and numbers of inductions and spontaneous births, as indicated. LMP, last menstrual period.

Methods

Ultrasound equipment

A Hitachi EUB-415 ultrasound scanner (Hitachi, Tokyo, Japan) with a 6.5-MHz transvaginal transducer was used for examinations in the first trimester (Paper V). Hitachi EUB-410 and EUB-415 ultrasound scanners (Hitachi, Tokyo, Japan) with 5-MHz curvilinear transducers were used for examinations in the second trimester (Papers I–V). Sound velocity was calibrated to 1540 m/s.

Reliability and regularity of the last menstrual period

The last menstrual period was considered unreliable when no specific date for the last menstrual period could be recalled. The menstrual cycle was considered regular when the women reported intervals of 28 ± 4 days.

Gestational age

Gestational age was estimated from the first day of the last menstrual period (Papers I–IV), the CRL (Paper V), the BPD (Papers I–V), or the day of oocyte retrieval, which was converted into menstrual age by adding 14 days (Paper V). Gestational age according to CRL was calculated by the equation $t=35.72 + 1.082L^{1/2} + 1.472L - 0.09749L^{3/2}$ developed by Wisser (Wisser *et al.*, 1994) where L is the greatest embryonic length and in practice correlated to the CRL. Gestational age according to the BPD was calculated on the basis of the laboratory's own standard (Eik-Nes *et al.*, 1983). The estimated day of delivery was calculated providing the BPD fell in the range of 35–60 mm, corresponding to 15–22 weeks of pregnancy. Term was assumed to be at 282 completed gestational days; when delivery occurred before 259 completed days, the infant was considered preterm, and when the gestation lasted ≥ 296 days the infant was considered post-term. The clinical management of the pregnancy was based on gestational age estimated by ultrasound.

CRL and BPD measurements

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 (Paper V).

The BPD was measured from the outer to the outer contour of the parietal bone echo at the level of the thalami and the cavi septi pellucidi just above the cerebellum (Papers I–V).

Statistical analysis

Statistical evaluation was done with the BMDP statistical package (BMDP Statistical Software Inc. Los Angeles, CA) and the SAS statistical package (SAS Institute Inc. Cary, NC).

Paper I

Ultrasound versus the last menstrual period as predictors of day of delivery

Equality of proportions between rows or columns in 2 x 2 tables was tested by Yates' corrected χ^2 -test or Fisher's exact test. Marginal probabilities were assessed by the test for marginal homogeneity in the 4 F program in the BMDP statistical package. Matched variables were tested by the separate variance *t* -test (mean), the sign test (median) or the Wilcoxon signed rank-test. Two-sample comparisons were performed using the Mann-Whitney rank-sum test. Statistical significance was assigned at a level of $p < 0.05$.

Paper II

Impact of various factors on the ultrasound prediction of day of delivery

In a previous study, the relationship between BPD and the gestational age according to the last menstrual period was established (Eik-Nes *et al.*, 1983). From these data an equation was derived for estimating the expected day of delivery from the BPD measurement. In the present study the same data were used to estimate an expected BPD from the observed gestational age according to the last menstrual period. The difference (dBPD) between the observed BPD and the expected BPD was used in the statistical analysis for assessing the influence of operator, fetal and maternal factors on the BPD.

Stepwise multiple linear regression (program 2 R of the BMDP package) was performed. Assumptions of linearity were checked by visual inspection of bivariate plots and plots of residuals. The dependent variables were: the day of delivery as determined

by the LMP, the dBPD, and the day of delivery as determined by ultrasound. The independent variables were: sex of the fetus, parity, maternal age, smoking, gestational age at the ultrasound scan and the number of examinations performed by each operator. The categorical variables of sex, parity and smoking were assigned the following values in these analyses: male=1, female=0; multipara=1, nullipara=0; smoking=1, non-smoking=0. Statistical significance was assigned at a level of $p < 0.01$.

Paper III

Day of delivery > 14 days later by ultrasound than by last menstrual period - fetal outcome

Equality of proportions between rows or columns in 2 x 2 tables was tested by Yates' corrected χ^2 -test or Fisher's exact test. Adverse fetal outcomes were assessed by estimates of relative risk. Two-sample comparisons were performed using the Mann-Whitney rank-sum test. Statistical significance was assigned at a level of $p < 0.05$.

Paper IV

Post-term according to last menstrual period but not according to ultrasound

Equality of proportions between rows or columns in 2 x 2 tables was tested by Fisher's exact test. Statistical significance was assigned at a level of $p < 0.05$. Stepwise logistic regression using the LR program was performed to test the relationship between adverse fetal outcome and selected maternal and fetal parameters. The explanatory variables were entered in a stepwise manner based on their contribution to the maximized likelihood function. Forward stepping was used and was terminated when no variable had a tail probability of more than 0.10 of the improvement chi-square test. Design variables for categorical variables were entered simultaneously as a set. The design variables for the post-term categorization were chosen so that the term group served as a control.

Paper V

Gestational age estimated from the time of oocyte retrieval, CRL and BPD

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 in vitro fertilized pregnancies and normally fertilized pregnancies. Statistical significance was assigned at a level of $p < 0.05$.

RESULTS AND COMMENTS

Paper I

Ultrasound versus the last menstrual period as predictors of day of delivery

The reliability of the menstrual history in women with singleton pregnancies without malformations is shown in Table 1. In the women with reliable last menstrual period, regular menstrual cycles and spontaneous onset of labor, the mean pregnancy length calculated from ultrasound was 279.1 days, the median and mode both 281 days. The mean pregnancy length calculated from the last menstrual period was 282 days, the median 283 days and the mode 284 days. The percentages of women who delivered within ± 7 days of the predicted day were 61% according to the ultrasound estimate and 56% according to the last menstrual period estimate. The proportion of post-term births was 2% using the ultrasound method and 9% using the last menstrual period method ($p < 0.001$). The ultrasound estimate was the superior predictor in 52% of the cases, and the last menstrual period estimate was the better predictor in 46% ($p < 0.001$). The greater the difference between the two estimates, the further away the actual day of delivery moved from the last menstrual period estimated day. When the difference between the two estimates was less than a week the methods were equally good but the number of post-term births was higher when the last menstrual period was used to estimate delivery day ($p < 0.05$).

Table 1 The reliability of the menstrual history in women with singleton pregnancies without fetal malformations

Menstrual history	N	%
Reliable LMP		
Regular cycles	10 511	74
Irregular cycles	1 390	10
Unreliable LMP	1 961	14
LMP missing	305	2
Total	14 167	100

Comments:
According to previous reports the menstrual history is inadequate in 10–45% of women (Grennert *et al.*, 1978; Campbell *et al.*, 1985; Hall *et al.*, 1985; Bergsjø *et al.*, 1990). This is confirmed by the findings in the present study.

The pregnancy length was shorter when calculated from the BPD than when it was calculated according to the last menstrual period. This is in consistence with previous findings (Backe and Nakling, 1994; Kieler *et al.*, 1995; Mongelli *et al.*, 1996; Gardosi *et al.*, 1997). Even in pregnancies with 'reliable menstrual history', the distribution of births was much wider with a skewness towards an over-estimation of gestational age when estimated based on the last menstrual period than estimated based on ultrasound. There are several explanations for the apparently more advanced gestational age according to the last menstrual period estimate. For example, in a cycle that leads to a pregnancy, the intervals may be delayed between the last menstrual period and ovulation (Saito *et al.*, 1972; Walker *et al.*, 1988), possibly between ovulation and fertilization, and between fertilization and implantation, even in women with otherwise regular cycles.

In the present study, the number of pregnancies classified as post-term was higher for the last menstrual period method than for the ultrasound method. This is in accordance with previous studies, where the percentage of pregnancies classified as post-term according to the last menstrual period method varied from 5.5 to 13.9% compared to 2.9 to 3.0% classified as post-term according to the ultrasound method (Grennert *et al.*, 1978; Persson and Kullander, 1983; Kramer *et al.*, 1988; Saari-Kempainen *et al.*, 1990; Waldenström *et al.*, 1990; Backe and Nakling, 1994; Mongelli *et al.*, 1996). In a large study on 34 249 singleton pregnancies with 'certain' menstrual dates ultrasonographic dating led to a 70% reduction in the number of pregnancies considered post-term compared with use of certain menstrual dates (Mongelli *et al.*, 1996).

A recent commentary (Olsen and Clausen, 1997) questioned the accuracy of ultrasound and argued for the use of menstrual history, suggesting that the number of post-term pregnancies could be reduced by using 283 days (instead of 280) as the length of pregnancy. However, conclusions about the length of pregnancy cannot be derived from the last menstrual period as the length of the follicular phase before fertilization is not known and shows great variation both between women and in the same woman, even in women with otherwise 'regular' cycles and there is always a skewness towards long cycles (Saito *et al.*, 1972; Boyse *et al.*, 1976; McIntosh *et al.*, 1980; Walker *et al.*,

1988). A change from 280 to 283 days for the estimated day of delivery by the last menstrual period will therefore not have a great effect on the proportion of post-term pregnancies lasting up to 44–46 weeks according to the last menstrual period.

In a study by Mongelli et al., the estimated date of delivery was calculated by five different methods: menstrual dates alone, ultrasound alone, or a combination of both; menstrual dates being used if the discrepancy with the ultrasound dates was within 7, 10 or 14 days, respectively (Mongelli *et al.*, 1996). In the study by Mongelli, taking menstrual dates into consideration gave no advantages. This is confirmed in the present study where ultrasound gave fewer pregnancies estimated as post-term even when there was a discrepancy of less than 7 days between the ultrasound and the LMP method. In this study, the distribution of births according to the ultrasound estimate was significantly narrower in comparison with the distribution according to the last menstrual period estimate. The number of post-term deliveries was reduced using the ultrasound method. The ultrasound method was superior to the last menstrual period for predicting the day of delivery; the greater the difference between the two methods, the better the ultrasound method turned out to be. Even when the difference in gestational age between mehods was small, the ultrasound method had significant advantages regarding the post-term deliveries.

Paper II

Impact of various factors on the ultrasound prediction of day of delivery

Table 2 Impact of various factors on the BPD measurement
The regression coefficient expresses, in millimeters, the contribution of each factor to the difference in BPD

	Regression coefficient	p value	Comments
Sex of the fetus	1.1	<0.001	Males 1.1 mm larger BPD than females
Parity	–0.5	<0.001	Nullipara 0.5 mm larger BPD than multipara
Maternal age (years)	0.08	<0.001	For every year of maternal age there is an 0.08 mm increase in BPD
Smoking		N.S.	
Operators	0.0001	<0.001	For 1000 examinations performed by each operator there is an 0.1 mm increase in measured BPD

Table 3 Impact of various factors on the day of delivery as determined by ultrasound
The regression coefficient expresses, in days, the contribution of each factor to the difference in day of delivery

	Regression coefficient	p value	Comments
Sex of the fetus	0.9	<0.001	Males born 0.9 days later than females
Parity	–0.8	<0.001	Nullipara give birth 0.8 days later than multipara
Maternal age (years)	0.1	<0.001	Every year of maternal age postponed the birth by 0.1 day
Smoking		N.S.	
Operators	0.0003	<0.001	1000 examinations performed by each operator gave a 0.3 day's earlier birth

Table 4 Impact of various factors on the day of delivery as determined by the reliable LMP

The regression coefficient expresses, in days, the contribution of each factor to the difference in day of delivery

	Regression coefficient	p value	Comments
Sex of the fetus	−1.4	<0.001	Males born 1.4 days earlier than females
Parity		N.S.	
Maternal age (years)		N.S.	
Smoking		N.S.	

Comments:

The effect of the various factors, except for the sex of the fetus, on the day of delivery can be explained by the differences in the size of the BPD. The normal growth of the width of the fetal skull is 0.44 mm a day at eighteen weeks (Persson *et al.*, 1978a). At the time of the ultrasound scan the BPD value for male fetuses was 1.1 mm larger than for female fetuses and should therefore cause a difference in day of delivery of 2.5 days between males and females. The ultrasound method implies that all fetuses of the same BPD size are of the same gestational age. Actually, at the same BPD, males are younger than females and should therefore be expected to be born later than females according to ultrasound. This assumption requires equal gestational length in both sexes and fertilization at the same time in the menstrual cycle for males and females. A previous study did not show any association between timing of intercourse in relation to ovulation and sex of the fetus (Wilcox *et al.*, 1995). The observed difference in the day of delivery between the sexes was 0.9 days (Table 3). The discrepancy of 1.6 days (2.5–0.9) between the observed and the expected difference in day of delivery indicates a true difference in the gestational length between the sexes with females having a longer gestation. That assumption is supported in this study (Table 4) and partly compensates for the difference in the BPD.

A previous study on fetal growth did not show any difference in the BPD from 20 weeks of pregnancy for groups with different maternal age or between nullipara and multipara (Persson *et al.*, 1978c). The reason for the discrepancy between the previous and the present study might be explained by different statistical approaches - bivariate versus multivariate analyses.

In this study, no difference in the BPD value between smokers and non-smokers in gestational week 15–22 was found. A difference in the BPD value between smokers and non-smokers from gestational week 22 with an increase through pregnancy has been demonstrated in a previous study (Persson *et al.*, 1978b). A possible explanation for the difference is that the fetuses in the present study were examined prior to week 22 when the prediction of the day of delivery does not seem to be affected by smoking. Later on in pregnancy the influence of smoking increases, resulting in differences in birthweight between infants from smoking and non-smoking mothers. A shorter mean gestational length in smoking mothers 26–35 years of age has been found in an earlier study (Wen *et al.*, 1990); this differs from the results found in the present study. In the earlier study however, gestational length was calculated from the best estimate, i.e. LMP, ultrasound, physical examination, quickening and auscultation of the fetal heart. A higher rate of preterm deliveries in smokers was also found in the same study. In contrast to the present study, the preterm deliveries in Wen's study were included in the calculation of mean gestational length and might thus explain the shorter period of gestation.

In a Norwegian study, the performance of 14 individual ultrasound operators could be analyzed in 1217 pregnancies (Backe and Nakling, 1994). The range of ultrasound exminations per operator was 12-171. No significant difference in predicting the day of delivery was found between the operators, which is also consistent with findings in the present study. The operators in the present study had more experience than the operators in the study by Backe, supporting that the ultrasound method is a reliable method whether applied at university centers or in remote daily practices.

The accuracy of prediction of the day of delivery by ultrasound is influenced by the gender of the fetus, by parity, by maternal age and by the experience of the operator. The difference in day of delivey according to ultrasound for the various factors was in the range of 1 day which must be considered to be of negligible clinical importance.

Paper III

Day of delivery > 14 days later by ultrasound than by last menstrual period - fetal outcome

In fetuses without anomalies, changing the estimated day of delivery, based on ultrasound evaluation, to a date more than fourteen days later than the day of delivery as estimated according to the last menstrual period, did not influence the risk of abortion,

perinatal death, infants with Apgar score < 7 after 5 minutes or infants transferred to the neonatal intensive care unit (Table 5). There was a greater number of infants with a birth weight below 2 500 g in the study group, but no difference between the groups in the number of infants with a birth weight < 2 SD below the mean according to the ultrasound estimate. Between the two groups there was a difference of three days in the prediction of day of delivery with ultrasound i.e. the infants in the study group were born 3 days earlier than estimated.

Table 5 Obstetrical complications for women in the study group and the control group.

	Study group N=760		Control group N=8992		
	n	%	n	%	Relative risk (95 % CI)
Spontaneous abortions	1	0.1	15	0.2	0.79 (0.10–5.96)
Perinatal deaths	7	0.9	40	0.4	2.07 (0.93–4.61)
Apgar 5 min <7	2	0.1	77	0.2	0.31 (0.08–1.25)
Neonatal intensive care unit	68	9.0	733	8.2	1.10 (0.87–1.39)

Spontaneous abortions and intrauterine deaths are excluded in the analysis of Apgar and neonatal intensive care unit.

Comments:
No difference in fetal outcome between the study group and the control group as measured by the number of abortions, perinatal deaths, infants with Apgar score < 7 after 5 minutes or infants transferred to the neonatal intensive care unit was found. However, the total number of perinatal deaths was quite small, and the wide confidence interval of the relative risk of perinatal death indicates a low test power. As perinatal death is a rare event this is to be expected. Therefore, all the seven perinatal deaths in the study group were scrutinized, but there was nothing to indicate that any fetus could have been saved had the estimated day of delivery according to the last menstrual period been used instead. The findings in the present study are supported by a Swedish case control study of possible reasons for late fetal death (Walles *et al.*, 1994). The Swedish study showed no relationship between fetal death and differences between ultrasound and the last menstrual period in prediction of the day of delivery.
Despite the lack of distinctive pathological findings in the deaths of the study group, the estimated relative risk of perinatal death of 2.07 with a confidence interval of 0.93–4.61

should lead to further investigations of the frequency and causes of perinatal mortality in patients where day of delivery estimated by ultrasound is more than 14 day later than estimate by the last menstrual period. It is possible that the extensive difference in gestational age between the two estimates is a marker for fetuses that might benefit from closer monitoring including Doppler.

The hypothesis that a misinterpretation of gestational age by ultrasound could lead to adverse fetal outcome could not be supported in the present study.

Paper IV

Post-term according to last menstrual period but not according to ultrasound

Fisher's exact test showed no significant difference in mortality between the term group and the three study groups. Stepwise logistic regression was used to test if the risk of Apgar score < 7 after 5 minutes and transfer to the neonatal intensive care unit was greater for any of the post-term groups. The possible contribution of other maternal and fetal factors was also included (Table 6). The number of deaths was too small to permit a similar regression analysis for this variable. The risk for Apgar score < 7 after 5 minutes was significantly greater for the group of post-term pregnancy by the ultrasound estimate but not by the last menstrual period estimate. The risk for transfer to the neonatal intensive care unit was significantly greater if the woman was nulliparous, older, delivered a male infant and if she was in the group of pregnancies assessed as post-term by both the ultrasound and the last menstrual period estimates.

Table 6 Impact of various factors on the risk of Apgar score < 7 after 5 minutes and transfer to the neonatal intensive care unit (N=11 218) evaluated by stepwise logistic regression.

	Apgar < 7 after 5 minutes		NICU	
	Odds ratio	95% CI	Odds ratio	95% CI
Parity	0.77	0.48–1.22	0.57 *	0.47–0.68
Maternal age	1.00	0.96–1.05	1.03 *	1.01–1.05
Smoking	1.16	0.70–1.91	1.01	0.84–1.22
Fetal sex	1.27	0.80–2.02	1.28 *	1.09–1.51
Post-term LMP and term US	0.46	0.15–1.47	0.95	0.71–1.28
Post-term US and term LMP	4.96 *	1.97–12.5	1.29	0.69–2.39
Post-term LMP and post-term US	1.96	0.61–6.29	2.05 *	1.35–3.12

The p-value for the log-ratio test during forward stepping was 0.10 and significant variables are marked by *. Adjusted odds ratios and 95% confidence intervals are given for the significant variables. Unadjusted odds ratios and 95% confidence intervals are given for the non-significant variables. Last menstrual period (LMP). Ultrasound (US). Neonatal intensive care unit (NICU). The categorical variables of parity, smoking, sex of the fetus were assigned the following values: multipara = 1, nullipara = 0; smoking = 1, non-smoking = 0; male = 1, female = 0.

Comments:

Post-term pregnancy is considered to be a risk factor for adverse fetal outcome (Clifford, 1954; Evans *et al.*, 1963; Naeye, 1978; Bakketeig and Bergsjø, 1989). Changing the day of delivery as estimated by ultrasound to a later date than to the day estimated in accordance with the last menstrual period might lead to a risk of the fetus reaching the post-term pregnancy period. In the Scandinavian literature (SPRI, 1990; Bratlid, 1991) it has been hypothesized that a consequence of this change of the estimated day of delivery could lead to suboptimal obstetric management for fetuses that are truly post-term, but falsely not characterized as such.

In the present study analysis was performed to calculate the possible impact of various factors on perinatal death, Apgar score < 7 after 5 minutes, and transfer to the neonatal intensive care unit. The evaluation did not show any correlation between post-term pregnancy as estimated by the last menstrual period but not by ultrasound, and adverse

fetal outcome. However, as there were few perinatal deaths, the statistical power to detect any difference in mortality was small. A previous case control study on possible reasons for late fetal death did not find any correlation between fetal demise and pregnancy post-term by the ultrasound estimate or pregnancy post-term by the last menstrual period estimate but not by the ultrasound estimate (Walles *et al.*, 1994).

Paper V

Gestational age estimated from the time of oocyte retrieval, CRL and BPD

In singleton pregnancies there was a high correlation between the gestational age at birth assessed from the time of IVF and that assessed from CRL ($R=0.992$ $p < 0.001$), or BPD ($R=0.975$ $p < 0.001$). The mean difference in gestational age was 0.9 days between IVF and CRL estimates, and 2.1 days between IVF and BPD estimates. The gestational age as estimated from the CRL or from the BPD was shorter than the gestational age estimated from IVF. In three pregnancies there was a difference of more than 7 days between the gestational age estimated from IVF and CRL and in 22 pregnancies there was a difference between gestational age estimated from IVF and BPD. A difference of more than 14 days was not found for any of the estimates.

Comments:

The high correlation between gestational age at birth between the estimates from the time of IVF, and from the measurements of the CRL and the BPD found in the present study is in accordance with previous studies (Geirsson and Have, 1993; Mul *et al.*, 1996). A mean difference in gestational age at scanning of up to 2.1 days between the IVF and BPD estimates has been found by others (Geirsson and Have, 1993; Wennerholm *et al.*, 1998), which is in accordance with the findings in the present study.

In the individual embryo/fetus the difference between the gestational age estimated by IVF and by BPD may be as much as 14 days; this has been observed both in the present study and in a previous one (Wennerholm *et al.*, 1998). In pregnancies where gestational age was calculated from both the last menstrual period and the BPD measurement, differences of more than 14 days between the two estimates were observed in 6% (Tunón *et al.*, 1996). A difference of more than 14 days between the IVF estimate and the BPD estimate was not found in the present study or in a previous one (Wennerholm *et al.*, 1998). 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 (Tunón *et al.*, 1999).

There are several possible explanations for a difference between the estimates by IVF, CRL and BPD. In a subfertile population intervention is necessary to achieve pregnancy, and though they develop uneventfully in most cases, these pregnancies do not meet the criterion 'normal'. We still lack exact information about fertilization and implantation. The time span from ovulation to fertilization and implantation in pregnancies conceived in natural cycles might not be equal to that in in vitro fertilized pregnancies. In a study on 107 pregnancies from an assisted fertilization program, differences in the CRL in pregnancies with the same age were found (Dickey and Gasser, 1993). At post-insemination day 41, the CRL in 10 embryos varied from 7–15 mm. Previous studies on assessment of gestational age from the CRL measurement based on populations derived from assisted reproductive programs have shown relatively wide 95% prediction intervals of 12.8 days (MacGregor *et al.*, 1987) 9.8 days (Daya, 1993), and 9.3 days (Wisser *et al.*, 1994), respectively.

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

CONCLUSIONS

Based on a non-selected population of over 15 000 consecutive pregnancies equal to 1/4 of the total number of pregnancies in Norway per year it can be concluded that:

Ultrasonic measurement of the bipariteal diameter between 15–22 weeks of pregnancy is superior to the last menstrual period method for estimating the day of delivery also when the last menstrual period is classified as reliable.

The accuracy of prediction of the day of delivery by ultrasound is influenced by the gender, parity, maternal age and the experience of the operator, but these differences are small and of no clinical importance.

There is no indication of any effect on fetal outcome by changing the dates on the basis of ultrasound fetometry at a routine second trimester scan

There is no indication of any increase in adverse fetal outcome for fetuses defined as post-term according to the last menstrual period estimate but not according to the ultrasound estimate.

Assessment of gestational age from the time of in vitro fertilization compared with measurements of CRL or BPD in pregnancies conceived after in vitro fertilization shows agreement between the three methods, supporting the use of ultrasound as a reliable method for estimation of gestational age.

In conclusion, the utrasound method for predicting day of delivery can therefore be recommended as the method of choice to be used in all pregnancies.

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CORRECTIONS

Paper II There are numbers missing in the paper that were present on the print proof. In the printed version of this thesis these has been corrected as follows:

Table 1 Intercept **2.6287**

Table 2 Intercept **9.7087**, Regression coefficients Sex of the fetus **1.0736**, Maternal age **0.0760**

Table 3 Intercept **2.5310,** Regression coefficients Sex of the fetus **0.9386**, Maternal age **0.1195**, Number of examinations **0.0003**.

Paper I

Ultrasound Obstet. Gynecol. 8 (1996) 178–185

A comparison between ultrasound and a reliable last menstrual period as predictors of the day of delivery in 15 000 examinations

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Key words: ROUTINE ULTRASOUND, GESTATIONAL AGE, LAST MENSTRUAL PERIOD, PREGNANCY

ABSTRACT

In a non-selected population comprising 15 241 women, an evaluation was performed of the ultrasonic measurement of the biparietal diameter compared with a reliable last menstrual period as the basis for estimation of the day of delivery. In women with a reliable menstrual history and spontaneous onset of labor, the ultrasound estimate was the significantly better predictor of the day of delivery in 52% of cases, and the last menstrual period estimate was the better predictor in 46% of cases. The percentages of women who delivered within 7 days of the predicted day were 61 and 56% for the ultrasound and the last menstrual period estimations, respectively. There was a significantly narrower distribution of births according to the ultrasound estimate ($p < 0.001$). *The proportion of estimated post-term births was 4% using the ultrasound method and 10% using the last menstrual period method* ($p < 0.001$). *Even when the difference between the methods in predicting the day of delivery was less than 7 days, the ultrasound method was better than the last menstrual period method. It is concluded that ultrasonic measurement of the biparietal diameter between 15 and 22 weeks of pregnancy is the best method for the estimation of the day of delivery and should be used as a routine procedure.*

INTRODUCTION

Reliable information about gestational age is necessary for optimal obstetric management of pregnancies. Perinatal morbidity and mortality are associated with preterm delivery and intrauterine growth retardation. Reliable information about gestational age is the basis for calculation of fetal growth[1,2]. The correct management of preterm and post-term pregnancies is also dependent on such information.

The first day of the last menstrual period has been the accepted basis for calculation of the day of delivery. The unreliability of this method has been demonstrated by various authors[3–5], who found that 10–45% of women did not have useful information about the last menstrual period due to inability to remember the exact date, or because of amenorrhea, irregular menstrual cycles, use of oral contraceptive pills, or bleeding during pregnancy. Additionally, the rate of post-term pregnancy has been described as very high (5–14%) when the last menstrual period method has been used[6–8].

The first reliable method for predicting gestational age based on ultrasonic measurement of the biparietal diameter was described in 1969 by Campbell[9]. The reliability of this method in predicting the day of delivery has been demonstrated in several later studies[3,6,10–12].

Several studies have indicated that ultrasonic measurement of the biparietal diameter is better than the first day of the last menstrual period for predicting the day of delivery[3,6,8]. However, better results with the last menstrual period method compared to the ultrasound method have also been reported[13], and an apparent increase in the number of preterm deliveries when the ultrasound method was used has been shown[14]. There has been a continuous discussion about the reliability of the ultrasound method[5], and disagreement about which method to use when the difference in gestational age as determined by the two methods is less than a week[15,16].

Ultrasonography is now the method of choice in predicting the day of delivery in many countries. In Europe, fetal examination programs are officially available to all pregnant women in Germany, Norway, Iceland, Austria and Switzerland. Since ultrasound today is used extensively, it is important to examine whether it can be used as the method of choice in a large non-selected pregnant

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population. The purpose of this study was to compare the ultrasonic measurement of the biparietal diameter with the last menstrual period as the basis for estimation of the day of delivery, and to evaluate the precision of these methods as routine procedures.

SUBJECTS AND METHODS

The subjects comprised women residing in a geographically well-defined area consisting of nine municipalities surrounding and including Trondheim. The National Center for Fetal Medicine at the University Hospital in Trondheim is the only ultrasound unit in the area. According to the Norwegian Medical Birth Registry, 97% of the pregnant women living in this area who gave birth during the study period (1987–92) were delivered at the University Hospital. We found that, during the study period, 97% of these women had a routine fetal examination with ultrasound.

Routine fetal examination has been offered in Norway since 1986. In the Trondheim area, the women were referred for examination by their general practitioner, by the obstetricians in private practice or by the high-risk clinic at the University Hospital in Trondheim. The fetal examination was scheduled to take place at 18 completed weeks as determined by the last menstrual period or the best clinical assessment of gestational age. The ultrasound examinations were performed by specially trained midwives. A personal interview was carried out with the pregnant woman, to obtain data about the maternal status and information about the menstrual history. At the ultrasound examination, the number of fetuses, the fetal anatomy, the placental location, and the amount of amniotic fluid were assessed, and the biparietal diameter, the mean abdominal diameter and the femur length were measured. The information was registered in a computer database. After the delivery, additional pre- and postnatal data concerning the pregnancy, birth and neonatal development were registered.

The gestational age and the day of delivery were estimated by ultrasound for all the women, and those with a reliable last menstrual period date also had the day of delivery estimated on this basis. The biparietal diameter was measured from the outer to the outer contour of the parietal bone echo, and gestational age was calculated according to the laboratory's own standard. The mean of three measurements was used for the calculation. The estimated day of delivery was calculated when the biparietal diameter was in the range 35–60 mm; this range corresponds to 15–22 completed weeks of pregnancy. Hitachi EUB-410 and EUB-415 ultrasound scanners (Hitachi, Tokyo, Japan) with 5-MHz curvilinear transducers were used, with the sound velocity calibrated to 1540 m/s.

A total of 15 443 women attended the routine fetal examination. Of these, 202 (1.3%) showed a biparietal diameter > 60 mm and were not entered in the study. The exclusion criteria for the remaining women are shown in Figure 1. After various exclusions, the study population was 14 167 women. The last menstrual period was considered unreliable when no specific date for the last menstrual period could be recalled. The menstrual cycle was considered regular when the interval was 28 ± 4 days. The estimated day of delivery based on the last menstrual period was corrected for the cycle length. For clinical management of the pregnancy, the following standards were used. Term was assumed to be at 282 completed gestational days[5]; the infant was considered preterm when delivery occurred before 259 completed days[17], and post-term when the gestation lasted ≥ 296 days. The data were also calculated according to World Health Organization (WHO) standards, i.e. preterm before 259 days, term at 280 days and post-term at or later than 294 completed days.

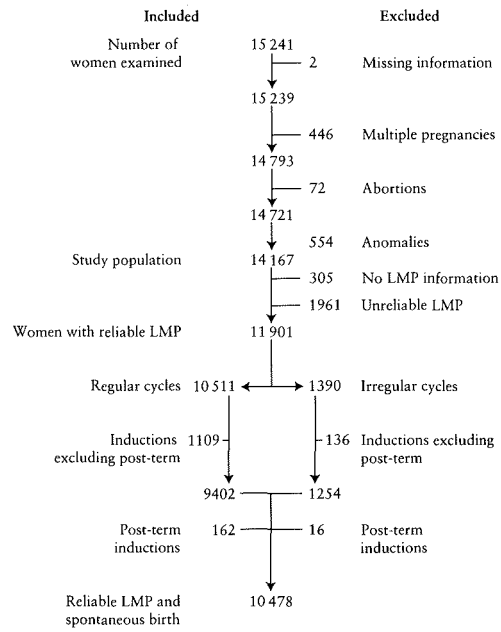

Figure 1 Patients entered into the study, patients excluded for various reasons, and numbers of inductions and spontaneous births, as indicated. LMP, last menstrual period

The clinical management of the pregnancy was based on ultrasound dating. In some patients who received the clinical diagnosis of post-term pregnancy, labor was induced, so that the number of spontaneous post-term deliveries according to ultrasound dating was consequently reduced. The total number of post-term births according to ultrasound dating was estimated as the number of spontaneous deliveries at or after 296 completed days, plus the number of inductions for supposed post-term pregnancy before, at or after 296 days. This ensured that none of the possible post-term deliveries were excluded from the group of estimated post-term deliveries. The total number of post-term deliveries according to the last menstrual period was estimated as the number of post-term deliveries, plus the number of inductions for supposed post-term pregnancy at or after 296 days.

Statistical evaluation was performed with the BMDP statistical package (BMDP Statistical Software Inc., Los Angeles, CA, USA). Equality of proportions between rows or columns in 2×2 tables was tested by Yates' corrected χ^2-test. Marginal probabilities were assessed by the test for marginal homogeneity in the 4 F program in the BMDP statistical package. Matched variables were tested by the separate variance *t*-test (mean), the sign test (median) or the Wilcoxon signed-rank test. Two-sample comparisons were performed using the Mann–Whitney rank-sum test.

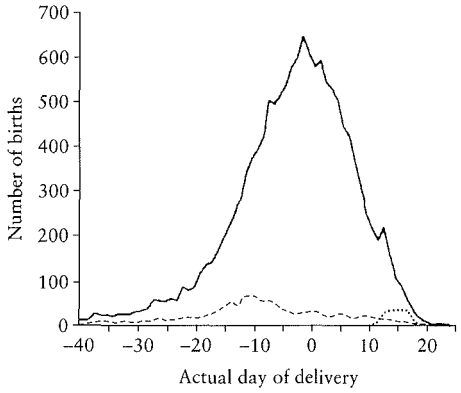

Figure 2 Distribution of births according to the estimated day of delivery (day 0) calculated from ultrasound for the study population of 14 167 women (all births, solid line). The general inductions (dashed line) and the inductions for the clinical diagnosis of post-term pregnancy (dotted line) are also shown

RESULTS

The estimated day of delivery was calculated from ultrasound measurements in 14 167 women. Of the 12 502 women with spontaneous onset of labor, 7635 (61.1%) gave birth within 7 days of the estimated day, while 10 966 (87.7%) gave birth within 14 days of the estimated day. In 559 cases (4.5%), the deliveries were preterm and, in 281 cases (2.2%), the deliveries were in the post-term period. The median day of delivery was 281 days, the mean 278.8 days and the mode 281 days. The distribution of delivery days is shown in Figure 2.

Labor was induced in 1665 (11.7%) of the 14 167 women. The reasons for induction are listed in Table 1. The clinical diagnosis of post-term pregnancy was made in 201 (12.1%) of the inductions. Of these, 50 were induced before 296 completed days and 151 at or after day 296 measured according to the ultrasound estimation.

Table 1 Induction of birth for the 14 167 women in the study population

Reason for induction	*n*	*% of inductions*	*% of study population*
Pre-eclampsia	320	19	2.3
Post-term	201	12	1.4
Fetopelvic disproportion	310	19	2.3
Intrauterine growth retardation	90	5	0.6
Previous Cesarean section	89	5	0.6
Poor obstetric history	75	5	0.5
Asphyxia	75	5	0.5
Miscellaneous	505	30	3.6
Total	1665	100	11.8

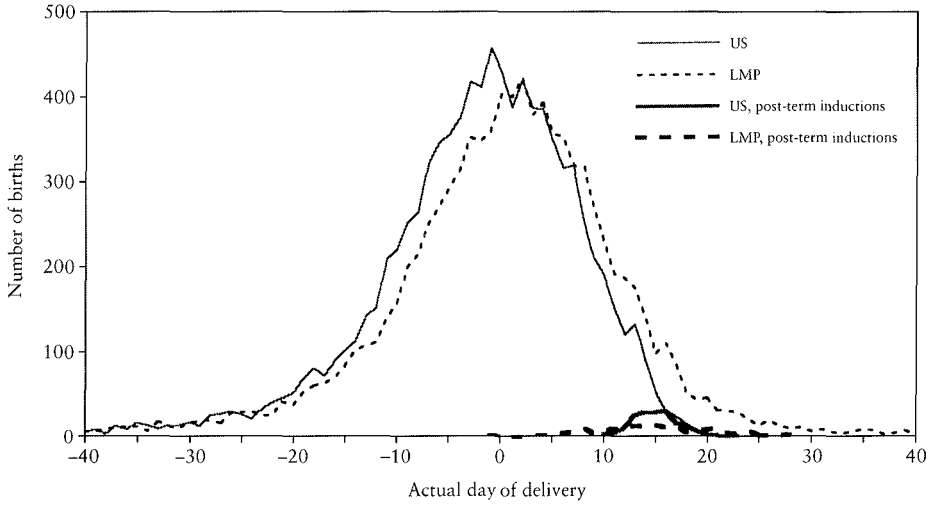

Figure 3 Distribution of spontaneous births according to the estimated day of delivery (day 0) calculated from ultrasound (US) and the last menstrual period (LMP) for 9240 women with regular menstrual cycles, including 162 deliveries induced due to the clinical diagnosis of post-term pregnancy

Table 2 Distribution of spontaneous births for women with regular menstrual cycles (n = 9402) and irregular menstrual cycles (n = 1254) according to the estimated day of delivery (282 days) based on the ultrasound and the last menstrual period (LMP) estimates. Inductions due to clinical diagnosis of post-term pregnancy are included

	Regular cycles			*Irregular cycles*		
	Ultrasound	*LMP*	*p*	*Ultrasound*	*LMP*	*p*
Median (days)	281	283	< 0.001	280	286	< 0.001
Mean (days)	279.1	281.8	< 0.001	278.1	286.2	< 0.001
Mode (days)	281	284		—	281	

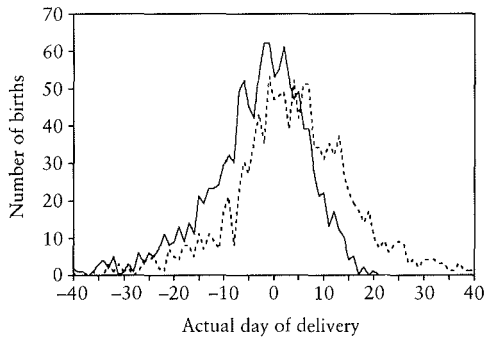

Figure 4 Distribution of spontaneous births according to the estimated day of delivery (day 0) calculated from ultrasound (solid line) and the last menstrual period (dotted line) for 1238 women with reliable last menstrual period, but irregular menstrual cycles

Excluding inductions for reasons other than the clinical diagnosis of post-term pregnancy there were 9402 women with a reliable date of the last menstrual period and with regular menstrual cycles. The distribution of births according to the ultrasound and last menstrual period estimates of the day of delivery is shown in Figure 3 and Table 2. For these 9402 women, the number of estimated post-term births was 918 (9.8%) according to the last menstrual period method and 387 (4.1%) according to the ultrasound method ($p < 0.001$). The onset of labor was spontaneous in 9240 of these women; in 162 women labor was induced due to a clinical diagnosis of post-term pregnancy. The distribution of spontaneous births for the women with regular cycles is shown in Table 3.

Excluding inductions for reasons other than clinical diagnosis of post-term pregnancy, there were 1254 women with a reliable date of the last menstrual period and with irregular menstrual cycles. The distribution of births according to the ultrasound and last menstrual period estimates is shown in Figure 4 and Table 2. For these 1254 women, the estimated number of post-term births was 251 (20.0%) according to the last menstrual period method and 38 (3.0%) according to the ultrasound method ($p < 0.001$). The onset of labor was spontaneous in 1238 of these women; in 16 women labor was induced due to a clinical diagnosis of post-term pregnancy.

The four medians for the births according to the last menstrual period and ultrasound estimates for women who had regular and irregular cycles were different ($p < 0.001$)

Table 3 Distribution of spontaneous births for women with regular menstrual cycles (n = 9240) according to the estimated day of delivery based on the ultrasound and the last menstrual period (LMP) estimates

	Ultrasound		*LMP*	
Delivery	n	%	n	%
± 7 days	5663	61	5202	56
± 14 days	8151	88	7729	84
< 259 days	380	4	376	4
≥ 296 days	225	2	821	9

from the estimated day of delivery (282 days) (see Table 2). To test for equality of variability between these last menstrual period and ultrasound estimates, the median in each group was calibrated to 282 days, and a matched-variable Wilcoxon signed-rank test was performed on the absolute value of the prediction error. The distribution of births according to the ultrasound estimate was significantly narrower, both for women with regular and with irregular menstrual cycles ($p < 0.001$). There was also a narrower distribution of births for the 9240 women with regular cycles compared to the 1238 women with irregular cycles according to the last menstrual period estimate ($p < 0.001$). There was no difference in the variability of the distribution of births for the ultrasound estimate according to whether the menstrual cycle was regular or not.

For the women with a reliable last menstrual period date and regular cycles, the ultrasound estimate of the day of delivery was later than the last menstrual period estimate for 5611 women (59.7%), and earlier for 3110 women (33.1%). In 681 cases (7.2%), there was no difference between the estimates. When there was a difference between the two methods in predicting the day of delivery, ultrasound was a better predictor than the last menstrual period. In 4514 of these cases (51.8%), ultrasound was the best method, and the last menstrual period was best in 4043 cases (46.4%) ($p < 0.001$). They were equally good in 164 cases (1.8%). As the difference in gestational age between the two methods increased, ultrasound gave a progressively better estimate, as shown in Figure 5. In the group (n = 7210) in which the difference in gestational age between the two estimates was ≤ 7 days, the number of estimated post-term births was 355 (4.9%) when the last menstrual period method was used and 320 (4.4%) when ultrasound was used ($p < 0.05$).

The distribution curves of spontaneous births for which the predicted day of delivery was different for each method

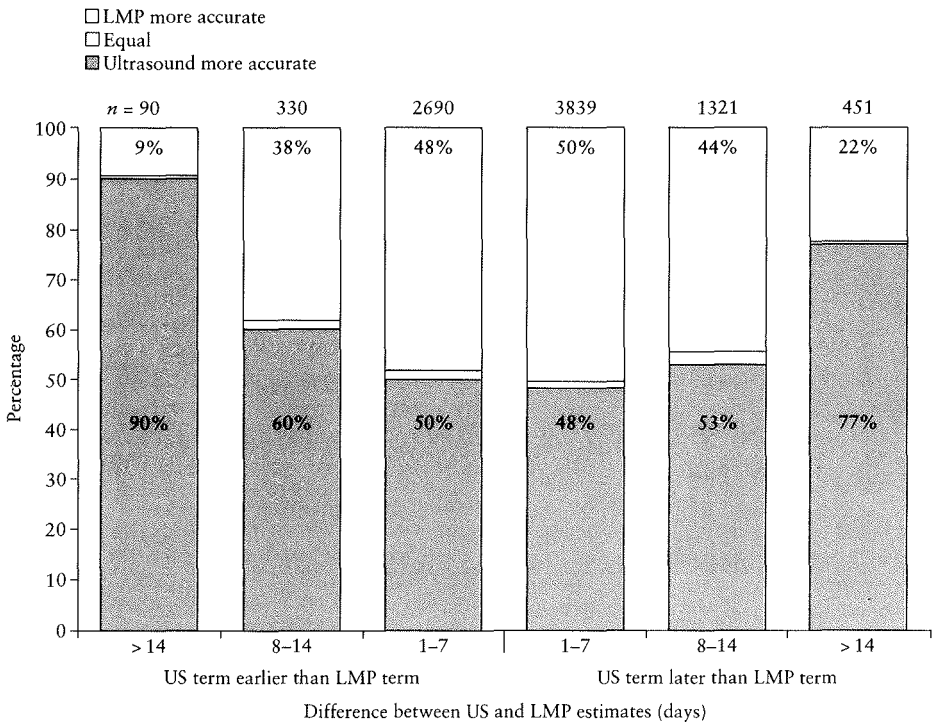

Figure 5 Comparison between the ultrasound- and last menstrual period (LMP)-based estimate of the day of delivery. The columns represent groups of women whose estimated day of delivery based on ultrasound was later or earlier than the LMP estimate

can be seen in Figure 6. The greater the difference between the estimates, the further away the actual day of delivery moved from the last menstrual period estimated day.

By the standard definition of the WHO, the normal length of human gestation is 280 days. Applying this gestational length to our population, the estimated frequency of post-term births at or after 294 days was 14% in the women with regular cycles and 26% in the women with irregular cycles, calculated from the last menstrual period date.

DISCUSSION

In this prospective study based on a large non-selected population, it was found that ultrasonic measurement of the biparietal diameter between 15 and 22 weeks of pregnancy was significantly better than the last menstrual period method for predicting the day of delivery.

The 'correct' day of delivery for any given fetus is not known, so it is not possible to apply a gold standard for the time of birth. In a Swedish study of more than 383 000 singleton pregnancies with reliable menstrual dates, the median duration of pregnancy according to the last menstrual period was 282 days, the mean 280.9 days and the mode 283 days[5]. It is not possible to tell which of these estimates was most representative for the normal pregnancy, because they were influenced by preterm births and births falsely registered as post-term. The median and the mode are, however, the most robust estimates. Both median and mean pregnancy durations according to last menstrual period were 1 day longer in the present study than in the Swedish study (see Table 2), indicating a small difference in the population samples. A possible explanation is the difference in the registration of the menstrual history; in the Swedish study the population was grouped as either certain or uncertain, without any further indication of regularity. In the present study, the median and mean pregnancy durations according to ultrasound were shorter than both the matched last menstrual period estimates and those of the Swedish study. However, they corresponded to the median and the mean days of delivery for the ultrasound estimate in women with regular menstrual cycles in another Norwegian study[8]. There are several explanations for the apparently more advanced gestational age according to the last menstrual period estimate. For example, in a cycle that leads to a pregnancy, the intervals may be delayed between last menstrual period and ovulation[18,19], possibly between ovulation and fertilization, and between fertilization and nidation, even in women with otherwise regular cycles.

The distribution of births according to the ultrasound method was negatively skewed, ending with a steep fall and

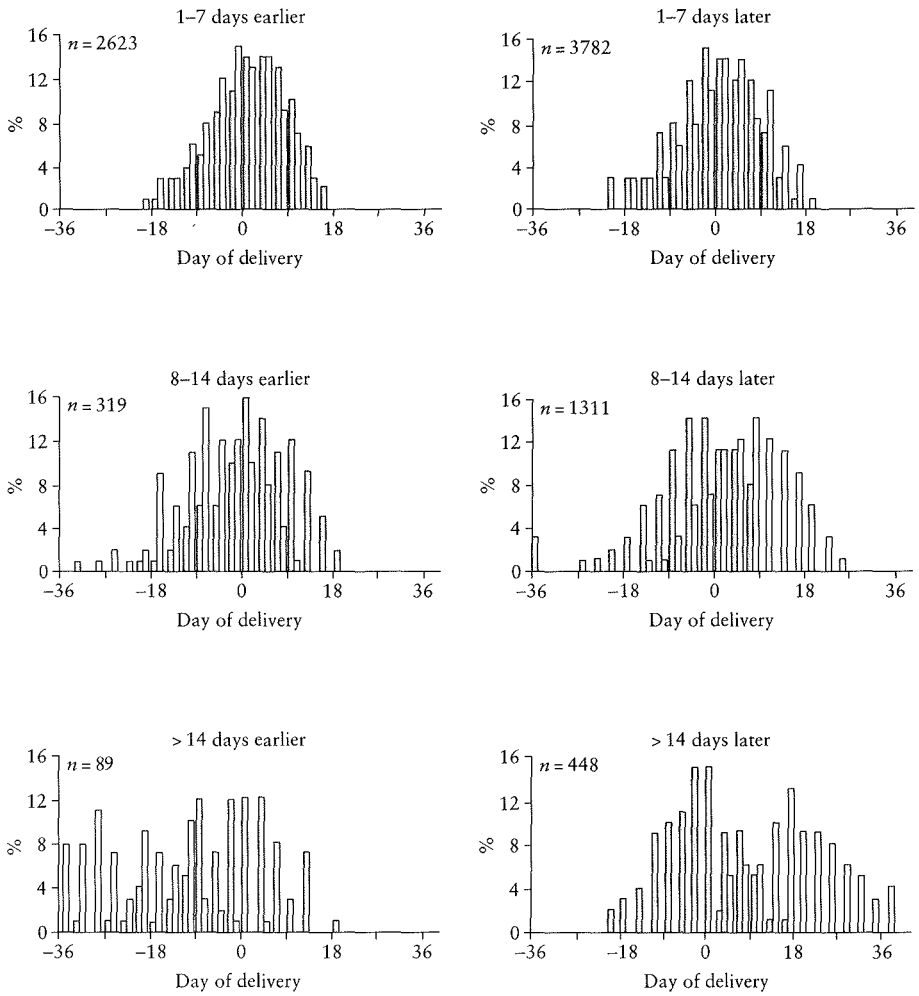

Figure 6 Group-wise distribution of spontaneous births according to the estimates based on ultrasound (gray columns) and last menstrual period (hollow columns) in women whose estimated day of delivery based on ultrasound was a later date or earlier date than the estimate of last menstrual period

only a few post-term births. According to the last menstrual period method, the distribution of births was closer to Gaussian. The most prominent difference in the distributions of births was the absence of the tail of post-term births for the ultrasound-dated pregnancies. The upper part of the distribution of the ultrasound-estimated births was to some extent curtailed by the inductions for post-term pregnancy, which could influence the comparison of the two methods. Therefore an estimated number of post-term births according to ultrasound was calculated as the sum of spontaneous post-term deliveries and the number of pregnancies where labor was induced due to the clinical diagnosis of post-term pregnancy, whether these inductions were done before, at or after 296 days. This reason for induction is dependent on the gestational age. Thus, a 'worst case' situation is created for ultrasound as 25% of the women classified as post-term on a clinical basis had an ultrasound-estimated gestational length of less than 296 days. According to the last menstrual period estimate, some women had a gestational length of less than 296 days at the time of induction for post-term pregnancy. If the induction had not been carried out, some of these women might have continued their pregnancy past 295 days and become post-term according to the last menstrual period estimate. They were, however, not included in the number of estimated post-term births according to last menstrual period. Thus a 'best case' situation is created for the last menstrual period method. In spite of this, the number of pregnancies classified as post-term was higher for the last menstrual period method, emphasizing the

significant difference between methods concerning post-term pregnancy.

The corresponding numbers of post-term deliveries for the spontaneous births only were also significantly higher for the last menstrual period estimate. This is in accordance with other reports[6–8] in which the number of post-term spontaneous births was 2.9–3.0% for the ultrasound method and 5.5–13.9 for the last menstrual period method.

As previously mentioned, the gestational length at term was assumed to be 282 completed days for both ultrasound and last menstrual period methods. When, in accordance with the WHO standards, a gestational length of 280 days for the last menstrual period estimate was used, the number of births at or after 294 days was 14% for the women with regular menstruations and 26% for the women with irregular menstruations. The results concerning the mean duration of gestation in this study (Table 2) and a Swedish study[5] indicate that the common assumption of a gestational length of 280 days based on the last menstrual period should be revised.

This study, comprising over 9000 women with spontaneous births and regular menstrual cycles in a non-selected population, did not show any difference in the rate of preterm delivery between the ultrasound and the last menstrual period methods. Our results therefore differ from those of a study in Alabama, USA[14], where the rate of preterm births rose from 12% to 17% after the introduction of ultrasound. Both rates are very high and might indicate a selection bias in the Alabama population rather than a true difference between the ultrasound and last menstrual period methods.

It is in the interest of the obstetrician to estimate a day which is as close as possible to the actual day of delivery, for as many women as possible. In this study we have shown that the variation of the births around the estimated day of delivery is significantly smaller for the ultrasound method than for the last menstrual period method. This has also been indicated in previous studies[3,8,15]. It has been alleged that the reduction in the number of post-term pregnancies is caused by a systematic left-shift of the births instead of a narrowing of the distribution curve[5]. The present study does not support this assertion.

When the routine ultrasound examination at 18 weeks showed a discrepancy between the last menstrual period estimate and the ultrasound estimate in predicting the day of delivery, the day estimated by ultrasound was later in 59.7% of the women. This corresponds to a Swedish study in which the day of delivery estimated by ultrasound was later in 64% of the women[15].

For those with a discrepancy between the last menstrual period estimate and the ultrasound estimate, the ultrasound estimate was a better predictor of the day of delivery for most of the deliveries. Similar results are also seen in a Swedish study[15,16]. In that study it was stated that the two methods were equally good when the difference in predicting day of delivery between methods was ≤ 7 days. This was supported in the present study with an equal number of births closest to the predicted day regardless of which of the methods was used; however, since the number of post-term pregnancies was significantly higher when the last menstrual period estimate was used, a positive effect of ultrasound was demonstrated even when the difference was ≤ 7 days.

Several authors have discussed the use of the last menstrual period or the ultrasound estimate to predict the day of delivery when the difference between the methods is small. Waldenström and colleagues[15] and Kieler and associates[16] argue that either method could be used if the difference is ≤ 7 days. However, to determine the cases in which last menstrual period estimates can be used, we use ultrasound, and since the last menstrual period method has not been proven to be better, we may as well use ultrasound for those cases too. The method which is best overall ought to be used in calculating the estimated day of delivery[20]. A significant discrepancy between the two methods, i.e. more than 14 days, should receive special attention. In these cases, a thorough anatomical evaluation of the fetus might be necessary to exclude malformations as a cause for the discrepancy.

It has been argued that the ultrasound method could not be better than the last menstrual period method since the biparietal diameter growth charts are based on the last menstrual period[4,5]. However, the biparietal diameter charts are usually derived from women with less cycle variability than is found in average women[3]. In addition, the ultrasound prediction is based on the regression of the data, further eliminating the effects of random cycle variations. On the negative side, the biological variation in the size of fetuses of the same age will produce different estimates of gestational age. However, there is reason to believe that this variation is small[21].

Previous studies[3–5] have shown that 10–45% of women have an unreliable menstrual history. These results are in accordance with ours.

In this study, the ultrasound and the last menstrual period methods have been evaluated prospectively in a large non-selected population. When the ultrasound method was used, the distribution of births was narrower and the number of post-term births was reduced in comparison with the last menstrual period method. Any shift in the distribution of births according to the ultrasound method, causing an increased rate of preterm delivery, could not be verified. The ultrasound method was better than the last menstrual period method for predicting the day of delivery; the greater the difference between the two methods, the better the ultrasound method turned out to be. Even when the difference in gestational age between methods was small, the ultrasound method had significant advantages regarding the post-term deliveries. The ultrasound method for predicting day of delivery can therefore be recommended as the method of choice.

ACKNOWLEDGEMENTS

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Paper II

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The impact of fetal, maternal and external factors on prediction of the day of delivery by the use of ultrasound

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Key words: ROUTINE ULTRASOUND, GESTATIONAL AGE, LAST MENSTRUAL PERIOD, PREGNANCY

ABSTRACT

In a non-selected population comprising 15 241 women, an evaluation was performed of the impact of fetal, maternal and external factors on the ultrasonic measurement of the biparietal diameter (BPD) and the day of delivery. The 7824 women who constituted the study population had singleton pregnancies and reliable menstrual histories, and they delivered spontaneously after 37 weeks. Multiple linear regression analysis was used. There was a difference in the size of the BPD at the ultrasound scan related to the gender, parity, maternal age, gestational age according to the last menstrual period and the experience of the operators. There was a total difference of ± 1 day in the day of delivery as determined by ultrasound and the factors above. The effect on the day of delivery is explained by the differences in the BPD. An effect of gender on gestational length was present as well, which partly compensated for the difference in the BPD. In conclusion the accuracy of prediction of the day of delivery by ultrasound is influenced by the gender, parity, maternal age and the experience of the operator, but these differences are small and of no clinical importance.

INTRODUCTION

Ultrasonic measurement of the biparietal diameter (BPD) as the basis for assessing the day of delivery is today the method of choice in many countries. Ultrasound has a high reliability in predicting the day of delivery[1–4] and is more accurate than the last menstrual period (LMP)[2,3,5]. However, for any method there is a risk of systematic error. The ultrasound method is based on the simplified assumption that all fetuses of the same BPD have the same gestational age. Thus factors affecting the increase in size of the BPD may influence the accuracy of the method. Earlier studies have shown differences in the size of the BPD in the second trimester related to the sex of the fetus[6–8] and to the smoking habits of the mother[9]. Birth weight as an indicator of growth is related to parity[10] and maternal age[11]. Differences in size between fetuses increase with advancing gestational age[1,12,13]; thus the precision of the prediction of the day of delivery might vary according to the time of the ultrasound examination, even if it is carried out as early as in the middle of the second trimester. Assessment of the influence of the experience of the operators in measuring the size of the BPD is also of importance in a routine program.

The aim of this study was to evaluate the impact of gender, smoking, parity, maternal age, time of the ultrasound scan and the experience of the operators on the accuracy of the prediction of the day of delivery in a routine setting.

SUBJECTS AND METHODS

The study population comprised women residing in a geographically well-defined area consisting of the city of Trondheim and eight surrounding municipalities. There is only one ultrasound unit in the area, and only one delivery ward. Of the women from this population, 97% had a routine fetal examination with ultrasound during the study period from 1987 to 1992 and later delivered at the hospital, thus forming a non-selected population.

The fetal examination was scheduled to take place at 18 completed weeks as determined by the LMP or the best clinical assessment of gestational age. Specially trained midwives performed the ultrasound examinations. To obtain key data about the maternal status and information about the menstrual history, a personal interview with the pregnant women was conducted by the midwives. The BPD, the mean abdominal diameter and the femur length were measured. The information was recorded in a computer database.

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The BPD was measured from the outer to the outer contour of the parietal bone echo and the mean of three measurements was used for calculation. Ultrasound scanners Hitatchi EUB-410 and EUB-415 (Hitachi, Tokyo, Japan) with 5-MHz curvilinear transducers were used, with a sound velocity calibrated to 1540 m/s. The estimated day of delivery was calculated when the BPD was ≥ 35 and ≤ 60 mm; this measurement corresponded to 15–22 completed weeks of pregnancy. The gestational age and day of delivery were estimated by ultrasound for all the women. Those with a reliable LMP also had the day of delivery estimated on the basis of the LMP. Term was assumed to be at 282 completed gestational days[14] for both ultrasound and the LMP.

A total of 15 241 pregnant women attended a routine fetal examination and had a BPD of ≥ 35 and ≤ 60 mm. Excluded were multiple pregnancies, abortions and anomalies (n = 1074). Women with induced labor, those who could not recall a specific day for the LMP and those with cycle lengths exceeding 28 ± 4 days were excluded (n = 5300). Further exclusions were women who delivered preterm (< 259 days[15] according to ultrasound), the pregnancies for which the difference between the ultrasound and the LMP methods in predicting the day of delivery was over 14 days, and the pregnancies examined by inexperienced operators who had performed fewer than 100 examinations following the completion of their ultrasound training (n = 1043). The study population thus consisted of 7824 women. Smoking was defined as the self-reported smoking of one cigarette or more per day at the time of the ultrasound scan. Gestational age at the time of the ultrasound examination was calculated by the LMP and varied between 103 and 170 days. In a previous sequential study of a highly selected population, the relationship between BPD and the gestational age according to LMP was established[16]. From these data an equation was derived for estimating the expected day of delivery from the BPD measurement. In the present study, the same data were used to estimate an expected BPD from the observed gestational age according to the LMP. The difference (dBPD) between the observed BPD and the expected BPD was used in the statistical analysis for assessing the influence of operator, fetal and maternal factors on the BPD.

Statistical evaluation was carried out with the BMDP statistical package (BMDP Statistical Software Inc. Los Angeles, CA). Stepwise multiple linear regression (program 2 R) was performed. Assumptions of linearity were checked by visual inspection of bivariate plots and plots of residuals. Possible interactions were evaluated in selected regressions. The dependent variables were: the day of delivery as determined by the LMP, the dBPD and the day of delivery as determined by ultrasound. The accuracy of prediction of the day of delivery was calculated as the actual day of delivery minus the predicted day of delivery. The independent variables were: sex of the fetus, parity, maternal age, smoking, gestational age at the ultrasound scan and the number of examinations performed by each operator. The categorical variables of sex, parity and smoking were assigned the following values: male = 1, female = 0; multipara = 1, nullipara = 0; smoking = 1, nonsmoking = 0. Statistical significance was assigned at a level of $p < 0.01$.

RESULTS

The sex of the fetus had a significant influence on the day of delivery and the gestational length as determined by the LMP (Table 1). Parity, maternal age, and smoking did not contribute significantly to the regression. There was a significant impact of the sex of the fetus, parity, maternal age, gestational age at the examination and the operator's experience on the dBPD values (Table 2). There was a significant influence of the same factors on the day of delivery as determined by ultrasound (Table 3). The effects of the individual explanatory variables on the multiple regression are discussed below.

Sex of the fetus

A total of 3949 (50.5%) male children and 3875 (49.5%) female children were born. Based on the LMP estimate, there was a difference between the sexes of 1.4 days in the day of delivery with the boys being born earlier than the girls (Table 1). The difference in the dBPD values between males and females at the time of the ultrasound scan was 1.1 mm (Table 2). The males had the larger size of the BPD. Based on the ultrasound estimate, there was a difference between the sexes of 0.9 days in the day of delivery with the boys being born later (Table 3).

Table 1 Impact of different factors on the day of delivery as determined by the reliable last menstrual period (n = 7824). The regression coefficient expresses, in days, the contribution of each factor to the difference in day of delivery

	Regression coefficient	*Standard error*	*p Value*
Intercept	**2.6287**		
Sex of the fetus	−1.3989	0.1949	< 0.001
Parity			NS
Maternal age (years)			NS
Smoking			NS

Table 2 Impact of different factors on the difference between the observed and expected biparietal diameter (dBPD) (n = 7824). The regression coefficient expresses, in millimeters, the contribution of each factor to the difference in dBPD

	Regression coefficient	*Standard error*	*p Value*
Intercept	**9.7087**		
Sex of the fetus	**1.0736**	0.052	< 0.001
Parity	−0.4848	0.058	< 0.001
Maternal age (years)	**0.0760**	0.006	< 0.001
Smoking			NS
Gestational age at examination (days)	−0.1015	0.005	< 0.001
Number of examinations/ operator (n)	0.0001	0.00003	< 0.001

Parity

The number of nulliparae was 3536 (45%) and the number of multiparae was 4288 (55%). Based on the LMP estimate, there was no difference between nullipara and multipara in the day of delivery (Table 1). The difference in the dBPD values of the fetuses between nulliparae and multiparae at the time of the ultrasound scan was 0.5 mm (Table 2). The nulliparae had the fetuses with the larger size of the BPD. Based on the ultrasound estimate, nulliparae gave birth, on average, 0.8 days later than multiparae (Table 3).

Maternal age

The mean age of the mothers at the time of the ultrasound scan was 27.6 years. Based on the LMP estimate, there was no difference due to different maternal age in the day of delivery (Table 1). There was a positive correlation between the dBPD and the age of the mother. The size of the BPD increased by 0.08 mm per year of maternal age (Table 2). Specifically, there was no significant interaction between either parity or maternal age and dBPD. Based on the ultrasound estimate, there was an increase of 0.12 days in the day of delivery per year of maternal age (Table 3).

Smoking

In the study period, 5676 (73%) women reported themselves to be non-smoking whereas 2148 (27%) reported to be smoking at least one cigarette daily at the time of the routine fetal examination. Based on the LMP estimate, there was no difference between non-smokers and smokers regarding the day of delivery (Table 1). There was no difference in the dBPD values between smokers and non-smokers (Table 2). Based on the ultrasound estimate, there was no difference between non-smokers and smokers in the day of delivery (Table 3).

Gestational age at the examination

The mean gestational age at the examination was 131 days (95% confidence interval 124–141 days). There was a negative correlation between the dBPD and the gestational age at the examination. An increase of 1 day in gestational age at the examination corresponded to an increase of 0.1 mm in the expected size of the BPD compared to the measured size (Table 2). An increase of 1 day in gestational age at the time of the examination corresponded to a decrease in the day of delivery of 0.06 days compared to the predicted day (Table 3).

Different operators

The total number of examinations per operator was between 173 and 3151. There was a positive correlation between the experience of the operators and the dBPD. There was an increase of 0.1 mm in the BPD measurement per 1000 examinations performed (Table 2). There was a 0.3 day increase in prediction related to actual day of delivery per 1000 examinations performed (Table 3). There was no significant effect of operators' experience on measurement variability. The day of delivery compared to the predicted day of delivery for fetuses examined by the five most experienced operators is shown in Table 4.

DISCUSSION

In this prospective study based on a large non-selected population, it was found that the accuracy of prediction of the day of delivery by ultrasound is negligibly influenced by the gender, parity, maternal age, gestational age at the examination and the experience of the operator.

To investigate the effect of these parameters on the BPD, the study relied on the LMP to establish the gestational age at the time of the ultrasound examination. Consequently, only women with regular menstrual cycles and known LMP were included. However, it has previously been shown that the LMP is an inaccurate predictor of the actual day of delivery when the discrepancy between the LMP and the ultrasound estimate becomes too great[17]. Pregnancies in which the difference between the two methods was over 14 days were therefore excluded.

A difference of 1–2 mm in the BPD value at 18 weeks between the sexes has been demonstrated in different studies[6–8] and is in accordance with the findings in this study. The larger BPD value of 1.1 mm at the time of the ultrasound scan for the male fetuses should correspond to a difference of 2.5 days between males and females at the day

Table 3 Impact of various factors on the day of delivery as determined by ultrasound ($n = 7824$). The regression coefficient expresses, in days, the contribution of each factor to the difference in day of delivery

	Regression coefficient	*Standard error*	*p Value*
Intercept	**2.5310**		
Sex of the fetus	**0.9386**	0.184	< 0.001
Parity	−0.8376	0.206	< 0.001
Maternal age (years)	**0.1195**	0.022	< 0.001
Smoking			NS
Gestational age at examination (days)	−0.0586	0.015	< 0.001
Number of examinations/ operator (n)	**0.0003**	0.0001	< 0.001

Table 4 The day of delivery related to the predicted day (the accuracy of the prediction of the day of delivery was the day of delivery minus the predicted day) for fetuses examined by operators ordered in decreasing level of experience

		Day of delivery	
Operator	*n*	*Mean*	*SD*
1	1461	−0.05	8.2
2	1448	−1.4	8.0
3	1341	−1.9	8.1
4	1258	−0.6	8.2
5	976	−0.6	8.0
Total	6484		

of delivery, as the growth of the fetal skull is 0.44 mm a day[18]. One should expect males to be born later than females according to ultrasound, as they are younger at the same BPD. This calculation assumes equal gestational length in both sexes. The actual difference in the day of delivery of 0.9 days indicates the presence of a true difference in the day of delivery between males and females of approximately 1.6 days, with females having a longer gestation. That assumption was supported in this study (Table 1) and in a Swedish study[14] in which gestational age also was based on the LMP. That study was based on approximately 383 000 cases and the data concerning the relationship between LMP and age at delivery were considered to be reliable, although other aspects of that study have been discussed[19]. The true difference in the gestational length between males and females partly compensates for the difference in the day of delivery according to ultrasound, owing to the difference in the BPD.

In this study, the size of the BPD for the fetuses of the nulliparae was significantly larger than for the multiparae at similar gestational age. In another study[9] no difference was found. In the present study, the nulliparae gave birth later than the multiparae according to ultrasound. For nulliparae and multiparae, there was no difference in the day of delivery according to the LMP. The observed difference in day of delivery according to ultrasound is probably caused, therefore, by the difference in the BPD. Here our findings differ from those of the Swedish study[14] in which a 1-day shorter gestation for multiparae than nulliparae was found. The reason for this discrepancy is not clear, but the Swedish study did not perform a multivariate analysis which could isolate the effects of the individual independent variables.

Maternal age did affect the BPD and therefore indirectly the day of delivery as determined by ultrasound. It did not have an effect by itself on gestational length. These results differ from those of other studies that found that maternal age did not affect BPD[10] but had an effect on gestational length[14]. Again, the use of different statistical approaches – bivariate vs. multivariate analysis – might contribute to the different results.

In this study, no difference in the BPD value between smokers and non-smokers in gestational weeks 15–22 was found. A difference in the BPD value between smokers and non-smokers from gestational week 22 with an increase through pregnancy has been demonstrated in a previous study[9]. A possible explanation for the difference is that the fetuses in this study were examined prior to week 22, when the prediction of the day of delivery does not seem to be affected by smoking. Later on in pregnancy, the influence of smoking increases, resulting in differences in birth weight between infants from smoking and non-smoking mothers. A shorter mean gestational length in smoking mothers of 26–35 years of age has been found in an earlier study[20]; this differs from the results of the present study. In the earlier study, however, gestational length was calculated from the best estimate, i.e. LMP, ultrasound, physical examination and quickening and auscultation of the fetal heart. A higher rate of preterm deliveries in smokers was also found in the same study. In contrast to the present study, the preterm deliveries were included in the calculation of mean gestational length and might thus explain the shorter period of gestation.

The gestational age at the ultrasound examination influenced the difference between the day of delivery and the predicted day. An ideal prediction method should not be influenced by the gestational age at the examination. The normal range curve underestimated the BPD in the lower part of the interval at 15–22 gestational weeks and overestimated the BPD in the upper part of the interval. The variance in the distribution cannot be examined, as the number of examinations, both in the lower and the upper part of the prediction interval, was too low to compare the influence of age on the method. It is most likely that the curve needs to be adjusted.

The reproducibility of the BPD measurements in the present study between different operators with varying experience in a routine setting must be considered high in this study. All operators in this study had a basic training. Similar results with an interobserver error at 18 weeks in the range of 1 mm have been shown in earlier studies[13,21]. This emphasizes the fact that the prediction of gestational age by ultrasound is a robust method if performed by experienced personnel. The importance of experienced personnel performing the ultrasound examination has also been pointed out by others[4,5].

There were differences in the BPD at the ultrasound scan that were related to the sex of the fetus, parity, maternal age, gestational age of the fetus at the ultrasound scan and the number of examinations performed by each operator. There was a difference in the day of delivery as determined by ultrasound influenced by the factors above. The effect on the day of delivery of the different factors can be explained by the differences in the BPD measurements, except for the sex of the fetus. For the sex of the fetus, there was also an effect on gestational length that partly compensated for the difference in the BPD. This effect on gestational length by gender was confirmed by a difference in the day of delivery when determined by the LMP.

It is concluded that the accuracy of prediction of the day of delivery by ultrasound is influenced by the gender, parity, maternal age and the experience of the operator, but that these differences are small. The difference in day of delivery according to ultrasound for the various factors was in the range of 1 day, which must be considered to be of negligible clinical importance. Based on previous evaluations of the method[2,3,17], the present evaluation supports the use of ultrasound as the method of choice for dating pregnancy at 16–18 weeks of gestation.

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Paper III

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Fetal outcome when the ultrasound estimate of the day of delivery is more than 14 days later than the last menstrual period estimate

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Key words: ROUTINE ULTRASOUND, GESTATIONAL AGE, LAST MENSTRUAL PERIOD, PREGNANCY

ABSTRACT

Objective *To evaluate the effect on fetal outcome of changing the estimated day of delivery as calculated according to ultrasound measurements more than 14 days later than the day estimated according to the last menstrual period.*

Design *A non-selected population comprising 15 241 women was evaluated. A study group (the day of delivery based on the ultrasound estimate being changed to more than 14 days later than the estimate based on the last menstrual period) and a control group (the two estimates being within 7 days of each other) were compared regarding various parameters concerning fetal outcome.*

Results *Changing the estimated day of delivery, based on the ultrasound evaluation, to a date 14 days later than the day of delivery as estimated according to the last menstrual period did not influence the risk of abortion, perinatal death or transferral to the neonatal intensive care unit. There was a difference of 3 days in the accuracy of the prediction of day of delivery between the two groups. There was a greater number of infants with a birth weight below 2500 g in the study group, but no difference was found between the groups in the number of infants with a birth weight < 2 SD from the mean according to the ultrasound estimate.*

Conclusion *There was no indication of any adverse consequence of the routine scan and change of estimated day of delivery among 15 000 pregnancies in a non-selected population.*

INTRODUCTION

Ultrasonic measurement of the biparietal diameter (BPD) in the second trimester is now the widespread method of choice in predicting the day of delivery. Several studies have indicated that ultrasonic measurement of the BPD is better than the last menstrual period (LMP) for predicting the day of delivery[1–4]. The ultrasound method regards all fetuses with the same BPD as being the same age. Early impairment of fetal growth might therefore influence the accuracy of the method. Impairment of fetal growth early in pregnancy may be caused by chromosomal aberrations, fetal malformations or infections, or it may be an isolated feature. Growth-restricted fetuses will have a smaller BPD than expected, not because they are younger but because they are growth-restricted. A consequence of this early growth restriction might be to change the day of delivery as estimated by ultrasound, to a later date than the day of delivery that is determined in accordance with the LMP. Such an extension of the estimated day of delivery might therefore lead to a falsely lower gestational age and a later detection or no detection at all of the growth restriction, with the possible consequence of adverse obstetric management of the pregnancy.

The purpose of this study was to evaluate the possibility of an increased risk of adverse fetal outcome and impaired fetal growth when the predicted day of delivery as estimated by ultrasound was more than 14 days later than the predicted day of delivery as estimated by the LMP.

SUBJECTS AND METHODS

The study population came from a geographically well-defined area consisting of the city of Trondheim and eight surrounding municipalities. In this area, there is only one ultrasound unit and one delivery department. A total of 97% of the women from this population had a routine fetal examination with ultrasound in the study period from 1987 to 1992 and later delivered at the hospital, thus forming a non-selected population.

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The fetal examination was scheduled to take place at 18 completed weeks. The gestational age for the initial examination was based on clinical assessment. The fetal examinations were performed by midwives specially trained in ultrasound. The women were scheduled for appointments at 30-min intervals which included a personal interview about the woman's basic obstetric history. The scan comprised measurements of the BPD, the mean abdominal diameter and the femur length. The number of fetuses was checked and a detailed anatomical survey was carried out. Data from the examinations were recorded in a computer database. Following the delivery, additional pre- and postnatal data concerning the pregnancy, birth and neonatal development were recorded.

The BPD was measured from the outer to the outer contour of the parietal bone echo, and the mean of three measurements was used for calculation of gestational age according to the laboratory's own standard[5]. Ultrasound scanners (Hitachi EUB-410 and EUB-415, Hitachi, Tokyo, Japan) with 5-MHz curvilinear transducers were used. Sound velocity was calibrated to 1540 m/s. Calculation of the estimated day of delivery was performed when the BPD was ≥ 35 and ≤ 60 mm; this measurement corresponded to 15–22 completed weeks of pregnancy. Gestational age and day of delivery were estimated by ultrasound for all the women. Those with a reliable LMP also had the day of delivery estimated on that basis. Term was assumed to be at 282 completed gestational days[6] for both ultrasound and the LMP.

A total of 15 241 women attended a routine fetal examination and had fetuses with a BPD of ≥ 35 and ≤ 60 mm. Exclusions were multiple pregnancies and women with an unreliable date or missing information about their LMP (n = 2805). A total of 12 436 women remained. A study group for whom the day of delivery was more than 14 days later by the ultrasound estimate than by the LMP estimate (n = 787) was compared with a control group that included women for whom the absolute value of the difference between the day of delivery estimated by the LMP and the ultrasound method was within 7 days (n = 9252). The anomalies among these were accounted for separately. Smoking was defined as the self-reported smoking of more than one cigarette per day at the time of the ultrasound scan. Perinatal death was defined as death during pregnancy after 28 weeks, or within 7 days postpartum for live-born infants. A birth weight < 2 SD from the mean using a Swedish normal range curve[7] for births after 153 days of gestation was considered as diagnostic of growth restriction. Male and female infants were analyzed separately.

Statistical evaluation was carried out with the BMDP statistical package (BMDP Statistical Software Inc., Los Angeles, CA, USA) and the SAS statistical package (SAS Institute Inc., Cary, NC, USA). Equality of proportions between rows or columns in 2×2 tables was tested by Yates' corrected χ^2 or Fisher's exact test. Adverse outcomes were assessed by estimates of relative risk. Two-sample comparisons were performed using the Mann–Whitney rank-sum test. Statistical significance was assigned at a level of $p < 0.05$.

RESULTS

Fetuses with anomalies

The number of anomalies was 27 (3.4%) in the study group (n = 787) and 260 (2.8%) in the control group (n = 9252); the difference was not significant; the relative risk was 1.22; the 95% confidence interval (CI) 0.83–1.80. The number of anomalies detected by ultrasound in the study group was 13 (48%) (Table 1) and in the control group 101 (39%); the difference was not significant; the relative risk was 1.51 (0.85–2.69).

Fetuses without anomalies

In the total population (n = 12 436), 12 060 women had fetuses without anomalies. The pregnancies of the 760 women in the study group for whom the day of delivery as estimated by ultrasound was more than 14 days later than the date estimated according to the LMP were compared with the pregnancies of 8992 women in the control group where the difference between the day of delivery estimated by the LMP and the ultrasound method was within 7 days. The number of mothers who smoked was 228 (30%) in the study group and 2398 (27%) in the control group (the difference was not significant). The number of nulliparous women was 370 (49%) in the study group and 4085 (45%) in the control group (the difference was not significant). The mean maternal age was 26.0 years in the study group

Table 1 Total number of anomalies in study group, detected (n = 13) and not detected (n = 14) by ultrasound

Type of anomaly	*Number of cases*	*Fetal outcome*
Detected		
Arthrogryposis	1	TOP
Trisomy 18	1	TOP
Complex heart defect	1	TOP
Dysmorphic syndrome	1	TOP
Hydrops, CMV	1	spontaneous abortion
CHD	1	
Mesoblastic nephroma	1	
Hydrocephalus	1	
Hydronephrosis	2	
Pes equinovarus	1	
Cleft lip/palate	1	
Scoliosis	1	
Not detected		
Syndrome anomalies: various organs	1	dead
Hydrocephalus	1	
CHD	5	
Cleft lip/palate	2	
Pes equinovarus	2	
Poly/syndactyly	2	
Hypospadias	1	

TOP, termination of pregnancy; CMV, cytomegalovirus; CHD, coronary heart disease

Table 2 Obstetric complications for women in the study group (n = 760) and the control group (n = 8992). Spontaneous abortions and intrauterine deaths are excluded in the analysis of Apgar scores and admissions to the neonatal intensive care unit (NICU). The 95% confidence intervals are in parentheses

	Study group		*Control group*		
	n	%	*n*	%	*Relative risk*
Spontaneous abortions	1	0.1	15	0.2	0.79 (0.10–5.96)
Perinatal deaths	7	0.9	40	0.4	2.07 (0.93–4.61)
Apgar score at 5 min < 7	2	0.1	77	0.2	0.31 (0.08–1.25)
NICU	68	9.0	733	8.2	1.10 (0.87–1.39)

Table 3 Detailed information about the study group fetuses (n = 7) without anomalies that died perinatally

Case number	*Age at birth, by ultrasound* (weeks + days)	*Difference in age at birth by LMP – ultrasound* (days)	*Reason for hospital admission*	*Onset of labor*	*Mode of delivery*	*Birth weight* (g)	*Fetal outcome*
1	23 + 2	24	contractions	spontaneous	vaginal	680	NICU, dead
2	25 + 2	16	PROM 11 days, placental abruption	spontaneous	Cesarean	835	NICU, dead
3	25 + 5	37	contractions, placental abruption	spontaneous	Cesarean	1015	NICU, dead
4	26 + 0	24	PROM 43 days	spontaneous	Cesarean	860	dead
5	33 + 3	18	no movement	induced	vaginal	1660	intrauterine death: toxoplasmosis
6	37 + 3	43	no movement	induced	vaginal	3560	intrauterine death
7	41 + 6	17	contractions	induced	vaginal	4600	intrauterine death

LMP, last menstrual period; NICU, neonatal intensive care unit; PROM, premature rupture of membranes

and 27.9 years in the control group ($p < 0.001$). There was no significant difference between the two groups regarding the proportion of abortions, perinatal deaths, infants with Apgar score of < 7 after 5 min, or infants transferred to the neonatal intensive care unit (NICU) (Table 2). However, the confidence interval of the relative risk of perinatal death was very wide. The only abortion in the study group was spontaneous and due to bleeding and preterm rupture of the membranes. Gestational age according to early ultrasound assessment in the 6th week of pregnancy was in agreement with gestational age according to routine ultrasound assessment in week 18. Detailed information about the infants in the study group who died perinatally is given in Table 3. The first four cases all had spontaneous onset of labor and the infants died immediately after birth or in the NICU. A knot on the umbilical cord was found at birth in Case 6. In Case 7 induction was tried twice, owing to the expectation of a heavy fetus, but without success. Cesarean section was not performed because the mother was adipose; she was also a drug and alcohol abuser.

The mean fetal weight at birth for live-born infants was 3495 g in the study group and 3560 g in the control group, the difference not being significant (p = 0.06). The number of infants weighing less than 2500 g was 36 (4.8%) in the study group and 276 (3.1%) in the control group (p = 0.02). The weight distribution can be seen in Figure 1. The number of fetuses with birth weight < 2 SD from the mean according to the ultrasound estimate was 14 (1.9%) in the study group (Table 4) and 173 (1.9%) in the control group. Only fetuses born after 153 days of gestation were included in the calculation: 754 in the study group and 8925 in the control group.

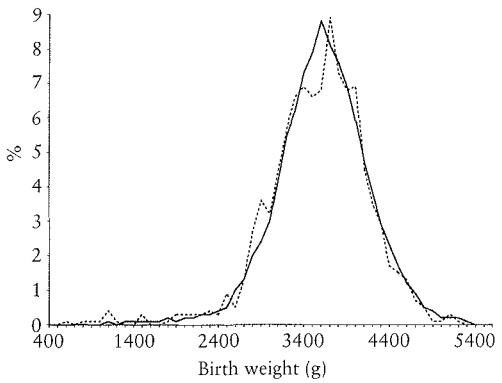

Figure 1 Birth weight for live-born infants without anomalies in the study group (dashed line) (n = 752) and the control group (unbroken line) (n = 8937)

The mean fetal length at birth for live-born infants was 50.1 cm in the study group and 50.4 cm in the control group (p = 0.03).

The distribution of live births according to the day of delivery as estimated by ultrasound and according to the LMP in the two groups can be seen in Figures 2, 3 and 4. The median day of delivery according to ultrasound was 278 days in the study group and 281 days in the control group ($p < 0.01$). The median day of delivery according to the LMP was 300 days in the study group and 282 days in the control group. The number of preterm deliveries was 56 (7%) in the study group and 458 (5%) in the control group according to the ultrasound estimate. The number of

Table 4 Detailed information about study group infants without anomalies weighing less than 2 SD from the mean at birth (n = 14)

Case number	*Age at birth, by ultrasound* (weeks ± days)	*Difference in age at birth by LMP – ultrasound* (days)	*Reason for hospital admission*	*Onset of labor*	*Mode of delivery*	*Birth weight* (g)	*Fetal outcome*
1	26 + 1	59	PROM 14 days, amnionitis	spontaneous	Cesarean	710	NICU, home
2	27 + 5	24	abdominal pain (affected CTG)	induced	Cesarean	820	NICU, home
3	29 + 6	16	contractions (affected CTG), IUGR known	spontaneous	Cesarean	550	NICU, home, cerebral palsy
4	34 + 4	16	bleeding (affected CTG)	spontaneous	Cesarean	1820	NICU, home
5	38 + 0	25	contractions, dystocia	spontaneous	Cesarean	2360	home
6	38 + 2	16	contractions, IUGR known	spontaneous	vaginal	2220	NICU, home
7	38 + 3	20	IUGR known	induced	Cesarean	2255	NICU, home
8	38 + 5	19	contractions	spontaneous	vaginal	2490	home
9	39 + 4	18	contractions	spontaneous	vaginal	2600	home
10	40 + 0	34	contractions	spontaneous	vaginal	2730	home
11	40 + 1	18	contractions	spontaneous	Cesarean	2750	home
12	40 + 2	16	IUGR known	induced	vaginal	2800	home
13	40 + 5	26	contractions, IUGR known	spontaneous	Cesarean	2800	home
14	41 + 0	15	IUGR known	induced	Cesarean	2790	home

LMP, last menstrual period; PROM, premature rupture of membranes; NICU, neonatal intensive care unit; IUGR known, intrauterine growth restriction detected prior to hospital admission; CTG, cardiotocography

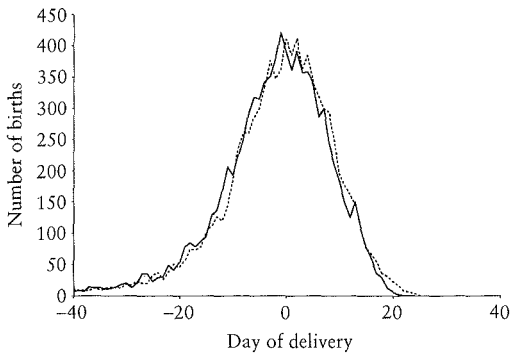

Figure 2 Distribution of live births in the control group (n = 8937) according to the estimated day of delivery (day 0) calculated from ultrasound (unbroken line) and the last menstrual period (dashed line)

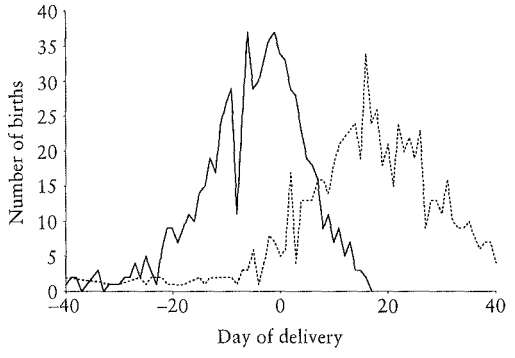

Figure 3 Distribution of births in the study group (n = 752) according to the estimated day of delivery (day 0) calculated from ultrasound (unbroken line) and the last menstrual period (dashed line)

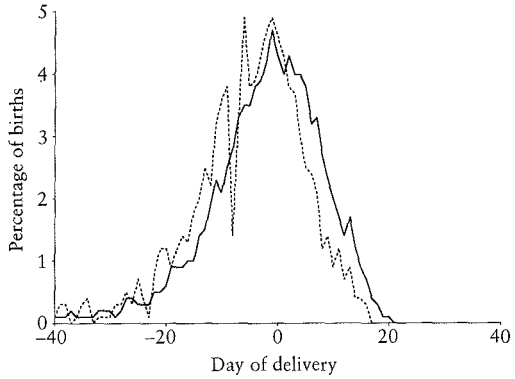

Figure 4 Distribution of births according to the estimated day of delivery (day 0) calculated from ultrasound in the control group (unbroken line) (n = 8937) and the study group (dashed line) (n = 752)

post-term deliveries was eight (1%) in the study group and 335 (4%) in the control group according to the ultrasound estimate. According to the LMP estimate the number of preterm deliveries was 20 (3%) and the number of post-term deliveries was 483 (64%) in the study group.

DISCUSSION

In this study, based on a large, primarily non-selected population of fetuses without anomalies, no indication of adverse fetal outcome was found that could be linked to changing the estimated day of delivery as determined by ultrasound to more than 14 days later than the day of delivery that was in accordance with the LMP.

Fetuses with anomalies

There was no difference in the total number of anomalies or in the number of anomalies detected by ultrasound

between the study group and the control group. As the presence of fetal anomalies might impair fetal growth, it is reasonable to have expected a higher number of anomalies in the study group. The wide confidence interval of the relative risk indicates a low test power to detect a possible difference between the two groups. If future studies with greater power are able to show an over-representation of anomalies when the day of delivery estimated by ultrasound is more than 14 days later than the LMP estimation, then this change might be used as a marker; such fetuses might then possibly benefit from an anomaly scan.

Fetuses without anomalies

It has been hypothesized in the Scandinavian literature[8,9] that, when the day of delivery as estimated by ultrasound is changed to a date that is later than the day estimated in accordance with the LMP, a growth-restricted fetus might be observed. The consequences of this could be a misinterpretation of gestational age, i.e. the fetus is thought to be younger instead of growth-restricted. This could lead to a later detection or no detection of the growth restriction; suboptimal obstetric management of the pregnancy might then lead to adverse fetal outcome.

To examine this hypothesis, we compared a study group (with the ultrasound estimate of the day of delivery more than 14 days later than the LMP estimate) and a control group (with the two estimates within 7 days of each other) regarding various parameters related to fetal outcome. The reason for choosing a difference of more than 14 days between the methods for the study group was that this discrepancy is sometimes used clinically as an indication for an anomaly scan. Any difference in fetal outcome between the study group and the control group, measured by the number of abortions, perinatal deaths or infants transferred to the NICU, could not be verified. However, the total number of perinatal deaths was small and the wide confidence interval of the relative risk of perinatal death indicates a low test power. As perinatal death is a rare event, this degree of uncertainty is to be expected. Therefore, all the seven perinatal deaths in the study group were scrutinized. However, there was nothing to indicate that any fetus could have been saved had the estimated day of delivery according to the LMP been used instead of ultrasound-assigned dates. The preterm infants that died in the perinatal period owing to preterm rupture of membranes or preterm contractions would have been managed in the same way regardless of which of the two gestational age estimates had been used. All these infants born alive were transferred to the NICU. The finding that prenatal death in the study group was no greater than in the control group in the present study is supported by a Swedish case–control study of possible reasons for late fetal death[10]. In that study, no difference between the day of delivery as estimated by ultrasound and as estimated by the LMP could be found between the infants who died in the perinatal period and their controls.

Despite the lack of distinctive pathological findings in the deaths of fetuses in the study group, the estimated relative risk of perinatal death of 2.07 with a confidence interval of 0.93–4.61 should lead to further investigations of the frequency and causes of perinatal mortality in this group of patients. It is possible that the extensive discrepancy in gestational age is a marker for fetuses that might benefit from closer monitoring.

Early growth restriction exists but seems to be very rare. In this study, there was no difference between the study and the control groups in the number of infants weighing less than 2 SD of the mean birth weight according to the ultrasound estimate. However, in the study group there was a greater number of infants weighing less than 2500 g. All fetuses in the study group weighing less than 2 SD of the mean birth weight according to ultrasound were scrutinized; one fetus that could clearly be categorized as early growth-restricted was found (Table 4, Case 3). In addition, five of the growth-restricted infants (Table 4, Cases 1, 2, 4, 6 and 7) were transferred to the NICU, but the other eight did not need any special care.

One might argue against using gestational age according to ultrasound to calculate the number of infants weighing less than 2 SD of the mean birth weight. However, at 18 weeks an early growth restriction that results in changing the estimated day of delivery to a date 2–3 weeks later in accordance with the ultrasound estimate means that the BPD is at least 6 mm smaller than it should be, i.e. the width of the BPD is already 14% less than expected for the age. This indicates an extensive restriction that is probably outside the physiological range, and cannot be considered compatible with continuous normal development. Such a severe and highly pathological growth restriction will be most likely to continue and make itself manifest later in pregnancy even if it is (mistakenly) corrected for at 18 weeks.

The difference between the LMP and ultrasound estimates always shows a negative skewness towards longer gestations according to the LMP[4,11–13]. There are several physiological explanations for the apparently more advanced gestational age according to the LMP estimate. For example, in a cycle that leads to a pregnancy, there might be delays in the intervals between the LMP and ovulation[14,15], possibly between ovulation and fertilization and between fertilization and nidation, even in women with otherwise regular cycles.

Between the two groups examined in this study, there was a difference of 3 days in the median day of delivery as estimated by ultrasound. The infants in the study group were born earlier than estimated. An ideal method for estimating day of delivery should not show any difference between the groups. However, in the estimation of the median day of delivery according to the LMP there was a difference of 18 days between the study and the control groups. This increased difference (18 days versus 3 days) indicated that the change by ultrasound was basically correct. The true variability of the BPD in the early second trimester (the range of 2 SD) has been found to correspond to ± 5–6 days[16]. Where data have been obtained from women with a known date of ovulation[16] or from pregnancies from *in vitro* fertilization[17], the variation

diminishes. Most probably there is an over-representation of genetically small fetuses in the study group that could explain the small shift in the median day of delivery. Such a shift of 3 days may be caused by the BPD being 1–2 mm smaller than the median. Consequently, small but genetically normal fetuses introduce only a small error in the prediction of gestational age; this error is clinically insignificant. The accuracy of prediction of the day of delivery by ultrasound is also influenced by the gender, parity, maternal age and the experience of the operator, but these differences are small and of no clinical importance[18].

In the present study, changing the estimated day of delivery to a later date did not increase the risk significantly for perinatal death, Apgar score of < 7 after 5 min or for transferral to the NICU. There was no difference between the study group and the control group in mean birth weight or the number of growth-restricted infants. There was a difference of 3 days in the accuracy of the prediction of day of delivery between the two groups and a higher number of infants with a birth weight below 2500 g in the study group.

In conclusion, there is no indication of any adverse consequence of the routine scan and change of estimated day of delivery among 15 000 pregnancies in a non-selected population. However, further studies are required to explore this phenomenon.

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Paper IV

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Fetal outcome in pregnancies defined as post-term according to the last menstrual period estimate, but not according to the ultrasound estimate

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Key words: ROUTINE ULTRASOUND, GESTATIONAL AGE, LAST MENSTRUAL PERIOD, POST-TERM PREGNANCY

ABSTRACT

Objective *To study the risk of adverse fetal outcome in fetuses that were post-term according to the last menstrual period estimate but not according to the ultrasound estimate.*

Design *A total of 11 510 women with singleton pregnancies, reliable last menstrual period and delivery after 37 weeks were divided into four groups: women who delivered at term, i.e. within 259–295 days according to both the ultrasound and the last menstrual period estimate; women who delivered post-term according to the last menstrual period estimate but not according to the ultrasound estimate; women who delivered post-term according to the ultrasound estimate but not according to the last menstrual period estimate; and women who delivered post-term according to both the ultrasound and the last menstrual period estimates. Stepwise logistic regression was used to test whether the risk of Apgar score of < 7 after 5 min and transfer to the neonatal intensive care unit increased in any of the post-term groups.*

Results *There was no significant difference in mortality between the term group and the three study groups. There was no significant increase in the risk for Apgar score of < 7 after 5 min or transfer to the neonatal intensive care unit for pregnancies that were defined as post-term according to the last menstrual period estimate but not according to the ultrasound estimate. There was, however, an increased risk for Apgar score of < 7 after 5 min in the group that was post-term according to the ultrasound estimate but not according to the last menstrual period estimate. There was also an increased risk for transfer to the neonatal intensive care unit in the group that was post-term according to both estimates.*

Conclusion *The effect of ultrasound in changing the estimated day of delivery to a later date leading to pregnancies becoming post-term according to the last menstrual period estimate but not according to the ultrasound estimate does not have any adverse consequences for the fetal outcome. However, there seems to be an increased risk for adverse consequences for pregnancies that are post-term according to the ultrasound estimate.*

INTRODUCTION

The accurate determination of the expected day of delivery is a key to optimal obstetric management. The method of choice for estimation of day of delivery in many countries is ultrasonic measurement of the biparietal diameter (BPD). Population-based data analysis has shown that ultrasonic measurement of the BPD is better than the last menstrual period in predicting the day of delivery[1–4]. The ultrasound method regards all fetuses with the same BPD as being of the same gestational age. If the day of delivery as estimated by ultrasound is later than the day of delivery that is in accordance with the last menstrual period, using the ultrasound-estimated day in predicting term could lead to a risk of the pregnancy becoming post-term. Post-term pregnancy is considered to be a risk factor for adverse fetal outcome[5–8]. It has been speculated that changing the estimated day of delivery to a later date could increase the risk for fetal compromise because fetuses that are actually post-term are not regarded and treated as such[9,10].

The purpose of this study was to determine whether the risk of adverse fetal outcome was greater for fetuses that were post-term according to the last menstrual period estimate but not according to the ultrasound estimate.

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SUBJECTS AND METHODS

The study population comprised pregnant women from the city of Trondheim and eight surrounding municipalities. There is only one ultrasound unit and one delivery department in the area. The percentage of women from this population who had a routine fetal examination with ultrasound in the study period from 1987 to 1992 and later delivered at the hospital was 97%. They formed a non-selected population.

The ultrasound examination of the fetus was scheduled to take place at 18 completed weeks, as assessed clinically. The ultrasound scans were performed by specially trained midwives. To obtain information about the basic obstetric history, a personal interview with each pregnant woman was carried out by a midwife. At the ultrasound examination, the BPD, the mean abdominal diameter and the femur length were measured. The number of fetuses and the fetal anatomy were assessed. Data from the examinations were recorded in a computer database. After the delivery, additional pre- and postnatal data concerning the pregnancy, birth and neonatal development were recorded. Hitachi EUB-410 and EUB-415 ultrasound machines (Hitachi, Tokyo, Japan) with 5-MHz curvilinear transducers were used. Sound velocity was calibrated to 1540 m/s. The estimated day of delivery was calculated when the BPD was ≥ 35 and ≤ 60 mm; this measurement corresponded to 15–22 completed weeks of pregnancy. An ultrasound estimation of the gestational age and day of delivery was made for all the women. The day of delivery was also estimated on the basis of the last menstrual period for those women who had a reliable last menstrual period. Term was assumed to be at 282 completed gestational days[11] for both ultrasound and the last menstrual period; the infant was considered preterm when delivery occurred before 259 completed days[12] and post-term when the gestation lasted ≥ 296 days.

A total of 15 241 women were included initially, but data from multiple pregnancies, abortions and women with an unreliable date or missing information about the last menstrual period ($n = 2851$) were subsequently excluded, as were women who delivered preterm according to ultrasound or the last menstrual period ($n = 880$). The remaining women ($n = 11\,510$) were divided into four groups. Women who delivered at term, i.e. within 259–295 days according to both the ultrasound and the last menstrual period estimates, formed one group. Those who delivered post-term according to the last menstrual period estimate but not according to the ultrasound estimate formed a second group. A third group consisted of those who delivered post-term according to the ultrasound estimate but not according to the last menstrual period estimate. The fourth group consisted of those who delivered post-term according to both the ultrasound and the last menstrual period estimates.

The clinical management of the pregnancy was based on gestational age estimated by ultrasound. In pregnancies lasting ≥ 296 days, the women were monitored by cardiotocography (CTG) and assessment of amniotic fluid volume every 2nd day. If obstetric complications developed or if the gestational age reached 303 days, labor was induced.

Smoking was defined as the self-reported smoking of more than one cigarette per day at the time of the ultrasound scan. Perinatal death was defined as death during pregnancy after 28 weeks or within 7 days postpartum for live-born infants.

Statistical evaluation was performed with the BMDP statistical package (BMDP Statistical Software Inc., Los Angeles, CA, USA). Equality of proportions between rows or columns in 2×2 tables was tested by Fisher's exact test. Statistical significance was assigned at a level of $p < 0.05$. Stepwise logistic regression using the LR program of the BMDP package was performed to test the relationship between adverse fetal outcome and selected maternal and fetal parameters. The explanatory variables were entered in a stepwise manner based on their contribution to the maximized likelihood function. Forward stepping was used and was terminated when no variable had a tail probability of more than 0.10 of the improvement by χ^2 test. Design variables for categorical variables were entered simultaneously as a set. The design variables for the post-term categorization were chosen so that the term group served as a control.

RESULTS

There was no difference between the four groups in the number of fetal anomalies ($p = 0.6$) (Table 1). The subsequent analysis was therefore confined to fetuses without anomalies.

The frequency of perinatal deaths, infants with Apgar score of < 7 after 5 min and infants transferred to the neonatal intensive care unit in the four different groups are shown in Table 2. Fisher's exact test showed no significant difference in mortality between the term group and the three study groups. Stepwise logistic regression was used to test whether the risk of Apgar score of < 7 after 5 min and transfer to the neonatal intensive care unit was greater for any of the post-term groups. The possible contribution of other maternal and fetal factors was also included (Table 3). The number of deaths was too small to permit a similar regression analysis for this variable. The risk for Apgar score of < 7 after 5 min was greater for the group of

Table 1 Number of women with fetal anomalies in the four different groups

	Anomalies		
	n	%	*Total*
Term US and term LMP	258	2.6	10 048
Post-term LMP and term US	26	2.5	1 048
Post-term US and term LMP	5	3.0	168
Post-term US and post-term LMP	3	1.2	246
Total	292	2.5	11 510

US, ultrasound; LMP, last menstrual period

post-term pregnancy according to the ultrasound estimate but not according to the last menstrual period estimate. The risk for transfer of the infant to the neonatal intensive care unit was greater if the woman was nulliparous, older, delivered a male infant and/or was in the group with pregnancies assessed as post-term by both the ultrasound and the last menstrual period estimates.

Detailed information about all the perinatal deaths is given in Table 4. Cases 1 and 11 were post-term according to the last menstrual period estimate but not according to the ultrasound estimate. A knot on the umbilical cord was found at birth in Case 1. In Case 11, induction for suspected macrosomia was tried twice, but without success. Cesarean section was not performed because of maternal adiposity (131 kg), drug and alcohol abuse. The woman was allowed to leave the hospital and returned 2 days later having suffered intrauterine death of the fetus.

The mean birth weights and lengths of the neonates are shown in Table 5. There was no significant difference between the mean birth weight of neonates of women in the group defined as post-term by the ultrasound estimate and the mean birth weight of those born to women in the group defined as post-term by both the ultrasound and the last menstrual period estimates.

The day of delivery for spontaneous births as estimated by ultrasound and the last menstrual period is shown in Table 6. In the group defined as post-term according to the last menstrual period but not according to ultrasound, the estimated mean gestational age at the time of the ultrasound scan was 18 days more for the last menstrual period estimate than for the ultrasound estimate.

Table 2 Percentage of spontaneous births and obstetric complications in the four different groups. Intrauterine deaths were excluded in the analysis of Apgar scores and admission to the neonatal intensive care unit (NICU)

	Spontaneous births		*Perinatal deaths*		*Apgar score of < 7 after 5 min*		*NICU*	
	n	%	*n*	%	*n*	%	*n*	%
Term US and term LMP	9790	91	9	0.1	62	0.6	521	5.3
Post-term LMP and term US	1022	92	2	0.2	3	0.3	52	5.1
Post-term US and term LMP	163	67	0	0	5	3.0	11	6.7
Post-term US and post-term LMP	243	58	0	0	3	1.2	26	10.7

US, ultrasound; LMP, last menstrual period

Table 3 Impact of various factors on the risk of Apgar score of < 7 after 5 min and transfer to the neonatal intensive care unit (NICU) (n = 11 218) evaluated by stepwise logistic regression

	Apgar score of < 7 after 5 min		*NICU*	
	Odds ratio	*95% CI*	*Odds ratio*	*95% CI*
Parity	0.77	0.48–1.22	0.57*	0.47–0.68
Maternal age	1.00	0.96–1.05	1.03*	1.01–1.05
Smoking	1.16	0.70–1.91	1.01	0.84–1.22
Fetal gender	1.27	0.80–2.02	1.28*	1.09–1.51
Post-term LMP and term US	0.46	0.15–1.47	0.95	0.71–1.28
Post-term US and term LMP	4.96*	1.97–12.5	1.29	0.69–2.39
Post-term LMP and post-term US	1.96	0.61–6.29	2.05*	1.35–3.12

LMP, last menstrual period; US, ultrasound.
The p value for the log-ratio test during forward stepping was 0.10 and significant variables are marked by asterisks. Adjusted odds ratios and 95% confidence intervals (CI) are given for the significant variables. Unadjusted odds ratios and 95% confidence intervals are given for the non-significant variables. The categorical variables of parity, smoking and fetal gender were assigned the following values: multipara = 1, nullipara = 0, smoking = 1, non-smoking = 0, male = 1, female = 0

Table 4 Information about the perinatal deaths (n = 11)

Case	*Age at birth by ultrasound* (weeks + days)	*Difference in age at birth by LMP – ultrasound* (days)	*Reason for hospital admission*	*Onset of labor*	*Mode of delivery*	*Birth weight* (g)	*Fetal outcome*
1	37 + 3	43	no movements	induced	vaginal	3560	intrauterine death
2	37 + 4	0	contractions	spontaneous	vaginal	2290	intrauterine death
3	37 + 5	4	vaginal bleeding	induced	vaginal	2510	intrauterine death
4	37 + 6	−4	no movements	induced	vaginal	2870	intrauterine death
5	37 + 6	7	no movements	induced	vaginal	2940	intrauterine death
6	37 + 6	11	no movements	induced	vaginal	2820	intrauterine death
7	38 + 0	−2	contractions	spontaneous	vaginal	2130	intrauterine death
8	38 + 2	7	contractions	spontaneous	vaginal	2700	intrauterine death
9	38 + 2	13	contractions	spontaneous	vaginal	3820	death at age 6 days
10	41 + 2	−2	contractions	spontaneous	vaginal	3670	intrauterine death
11	41 + 6	17	contractions	induced	vaginal	4600	intrauterine death

Table 5 Mean birth weight and length of the live-born neonates in the four groups

	n	*Weight* (g)	*Length* (cm)
Term US and term LMP	9782	3590	50.5
Post-term LMP and term US	1021	3760	51.2
Post-term US and term LMP	163	3990	52.5
Post-term US and post-term LMP	243	3900	52.1

US, ultrasound; LMP, last menstrual period

Table 6 Day of delivery (mean) as estimated by ultrasound (US) and the last menstrual period (LMP) for spontaneous onset of labor

		Days	
	n	*US*	*LMP*
Term US and term LMP	8869	280	282
Post-term LMP and term US	936	286	304
Post-term US and term LMP	110	297	291
Post-term US and post-term LMP	142	297	301

DISCUSSION

This study did not suggest that there is any increase in the risk of adverse fetal outcome for fetuses that were post-term according to the last menstrual period estimate but not according to the ultrasound estimate.

Post-term pregnancy is considered to be a risk factor for adverse fetal outcome[5–8]. Changing the day of delivery as estimated by ultrasound to a date later than the day calculated from the last menstrual period might lead to a risk of the fetus reaching the post-term pregnancy period. In the Scandinavian literature[9,10] and anecdotally[10] it has been hypothesized that this change of the estimated day of delivery could lead to suboptimal obstetric management for fetuses that are truly post-term, but falsely not characterized as such.

In the present study, analysis was performed to calculate the possible impact of various factors on perinatal death, Apgar score of < 7 after 5 min and transfer to the neonatal intensive care unit. There was no correlation between post-term pregnancy, as estimated by the last menstrual period but not by ultrasound, and adverse fetal outcome. As there were few perinatal deaths, the statistical power to detect any difference was small. However, a previous case–control study on possible reasons for late fetal death found no correlation between fetal demise and pregnancy post-term by the ultrasound estimate or pregnancy post-term by the last menstrual period estimate but not by the ultrasound estimate; this supports the findings in the present study[13]. The regression model used in the present study must be considered to be sensitive as it showed a correlation between transfer to the neonatal intensive care unit and factors that are known to have a correlation with adverse fetal outcome such as maternal age, parity and fetal gender[14,15].

Smoking is known to increase the rate of preterm delivery and low birth weight[15], but in the present study smoking did not contribute significantly to such risks. This lack of correlation between adverse fetal outcome and smoking was probably due to the exclusion of all preterm deliveries from the analysis.

The birth weight in the group defined as post-term according to the last menstrual period estimate was slightly higher than the term group (Table 5). This can be explained by the fact that the gestational age in these pregnancies was more advanced; the ultrasound estimate affirms this explanation (Table 6).

Ultrasound dates are more accurate than menstrual dates in predicting the day of delivery[3,4]. Ultrasound dating also reduces the number of post-term pregnancies[2,4,16–18]. These findings are consistent with the findings in the present study, where the estimated day of delivery according to ultrasound was 18 days (mean) later than the last menstrual period estimate, and the actual day of delivery was much closer to the ultrasound-estimated day in the group post-term according to the last menstrual period but not according to ultrasound. These results indicate that the ultrasound estimation is closer to the correct term.

Findings in a recent study suggest that, even if the discrepancy between menstrual dates and scan dates is less than a week, ignoring menstrual dates altogether and using scan dates alone to date pregnancy would reduce the induction rate substantially[19]. In that study, a reduction of induced pregnancies from 16.6% to 13.7% was estimated if the policy for calculation of expected day of delivery was changed in favor of the ultrasound method for all pregnancies. In the Trondheim population, where scan dates are the basis for clinical management of the pregnancy, the overall induction rate was 11.7%[4]. In the present study there was no difference in the number of inductions between the group that was post-term according to the last menstrual period estimate and the group that was term according to both the last menstrual period and the ultrasound estimates.

There was no indication of any increase in adverse fetal outcome for fetuses defined as post-term according to the last menstrual period estimate but not according to the ultrasound estimate. A slight increase, however, was shown in infants with Apgar score of < 7 after 5 min in the group that was post-term according to the ultrasound estimate but not according to the last menstrual period. There was also a higher number of transfers to the neonatal intensive care unit in the group that was post-term according to both the ultrasound and the last menstrual period estimates. These results are expected, as post-term pregnancy is known to be a risk factor for adverse fetal outcome[5–7]. The fact that post-term pregnancy increases the risk of stillbirth, neonatal and post-neonatal mortality has also been shown in a recent study in which mortality rates were calculated per 1000 ongoing pregnancies[20].

In conclusion, using ultrasound to correct dates and postpone the estimated day of delivery leads to some pregnancies being defined as post-term according to the last menstrual period estimate but not as post-term according to the ultrasound estimate. However, managing these pregnancies according to the ultrasound estimate does not have any adverse consequence on the fetal outcome.

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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

Gestational age in pregnancies after in vitro fertilization

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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 delivery[1-5] 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 diameter[6-9]. 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 artifical 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, intracytoplasmatic 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 reproducyive techniques, $t=35.72 + 1.082L^{1/2} + 1.472L - 0.09749L^{3/2}$ where L is the greatest embryonic length [10]. Gestational age according to the BPD was calculated according to the laboratory's own standard[11].

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 days[12] for both ultrasound and the last menstrual period; the infant was considered preterm when delivery occurred before 259 completed days[13]

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 findings[9] 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 period[1-5] 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 known[6-9]. 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 found[9]. 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 estimate[6]. 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 as much as 14 days; this has been observed both in the present and a previous study[9]. 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 study[9] 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 fetus[14].

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 date[15]. The CRL curve in the present study is derived from women who had undergone assissted reproductive techniques, and the BPD curved 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 age[16]. 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 days[15], 9.8 days[17], and 9.3 days[10]. 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 development[18]. 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

stages[19]. 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 age[20]. 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 birth[22] 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 smokers[24] 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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Figure 1

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

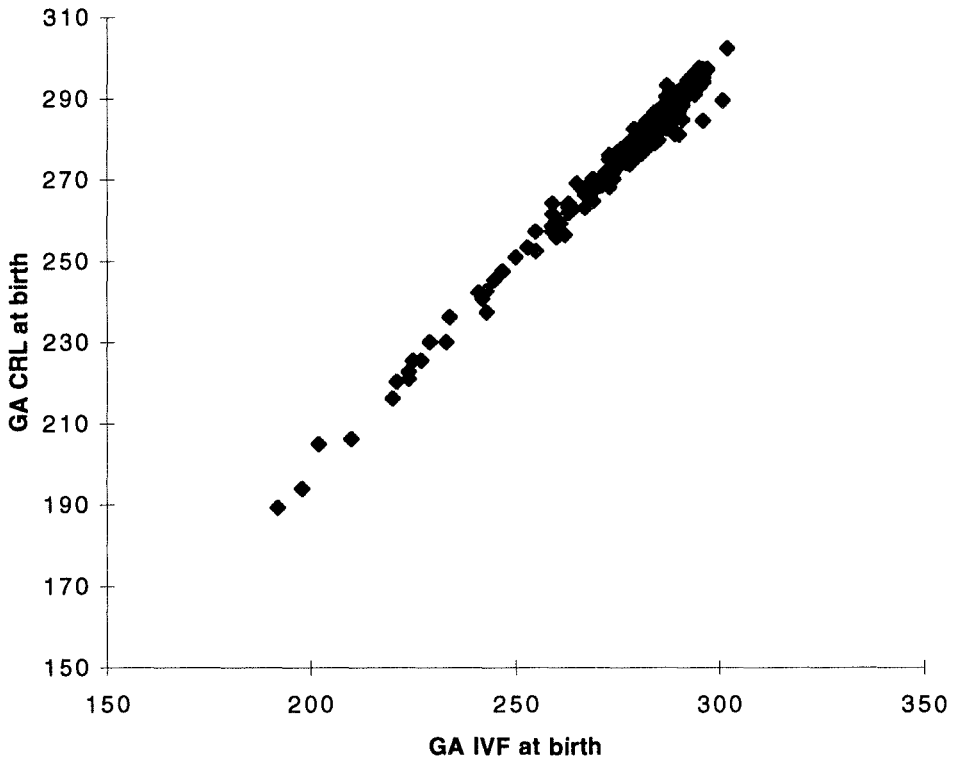

Figure 2

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

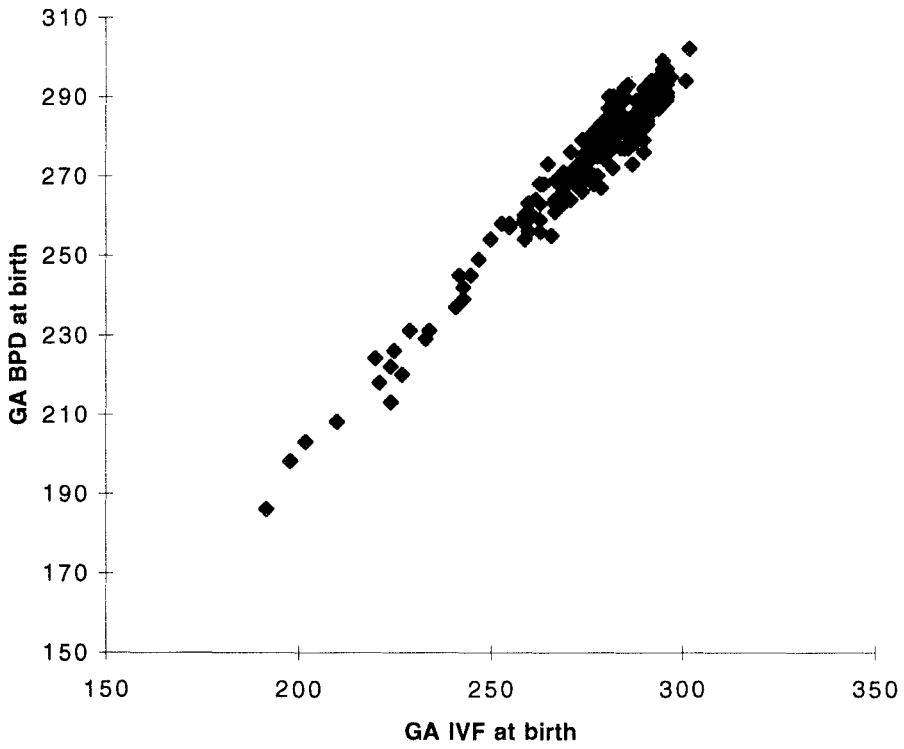

Table 1

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.

		Birth (days)			Birth distribution			
	n	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		
	n	%	n	%	p value
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

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