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Results and consequences of routine ultrasound screening in pregnancy
A geographic based population study

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Contents

Acknowledgements .............................................................................................................. 5
List of abbreviations ........................................................................................................... 7
1 Introduction .......................................................................................................................... 9
  1.1 Routine ultrasound examination in Norway ................................................................. 9
  1.2 Establishment of a perinatal database in Oppland ....................................................... 11
2. Aims of the study ............................................................................................................. 13
3. List of papers .................................................................................................................... 15
Erratum: ............................................................................................................................... 17
4. Material and methods ...................................................................................................... 19
  4.1 The study population ................................................................................................... 19
  4.2 The routine ultrasound examination ........................................................................... 19
  4.3 Definitions .................................................................................................................. 21
  4.5 Statistical methods ..................................................................................................... 21
  4.6 Paper I ......................................................................................................................... 22
  4.7 Paper II ......................................................................................................................... 22
  4.8 Paper III ....................................................................................................................... 23
  4.9 Paper IV ....................................................................................................................... 23
  4.10 Paper V ....................................................................................................................... 24
5. Main results .................................................................................................................... 25
6. Discussion .......................................................................................................................... 29
7. Conclusions ...................................................................................................................... 37
8. References ........................................................................................................................ 39

Papers I - V
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Jakob Nakling
List of abbreviations

AGA: Appropriate for Gestational Age
BPD: Biparietal Diameter
EDD: Estimated Date of Delivery
LMP: Last Menstrual Period
MHz: Mega Herz
NICU: Neonatal Intensive Care Unit
OC: Oral Contraceptives
OR: Odds Ratio
RR: Relative Risk
SD: Standard Deviation
SGA: Small for Gestational Age
TOP: Termination of pregnancy.
1 Introduction

1.1 Routine ultrasound examination in Norway

Routine ultrasound screening in pregnancy was introduced in Norway after a consensus conference on ultrasound in pregnancy in 1986 (1). A similar conference had been conducted in USA, 1984 (2). The conclusion from that conference was that ultrasound was a valuable examination in pregnancy, but that there were no basis for introducing routine use of ultrasound in all pregnancies. At that time, only West-Germany had established ultrasound screening in pregnancy. In most other European countries, the official recommendation was to use ultrasound on clinical indications only.

The consensus panel summarized the arguments for offering one ultrasound examination in Norway in this way(1):

- A total of 94% of the pregnant women were examined with ultrasound during their pregnancy. The mean number of examinations performed was 2.45(3).
- Many obstetrical departments practiced routine ultrasound, but considerable differences were shown between the regions. The proportion of the pregnant women that were offered routine ultrasound varied from 83 % in health region 1 to 61 % in region 3. The number of routine examinations varied, as well as the time in pregnancy, the purpose and the content of the examinations. Hence, it may be concluded that the quality of the examinations as well as the utility varied considerably. Also, there was no quality assessment of the technical apparatus and no systematic education of the personnel (3).
- The general opinion in Norway is that antenatal care should be similar throughout the country

The consensus panel stated that:

- Every pregnant women should be offered one routine ultrasound examination at approximately the 17th week of gestation
For the purposes of continuous quality control, registration of selected data from all ultrasound examinations in pregnancy should be established.

- The examinations must be conducted by personnel with specialized competence – preferably gynaecologists and midwives.
- Responsibility for organizing ultrasound examinations in a given geographical area must be clearly defined.
- Effective means must be employed to reduce the current over utilization.
- The examination should preferably be conducted at the maternity department where the woman is expected to deliver.
- Personnel conducting ultrasound examinations must have sufficient time for the women examined. Information should preferably be both written and oral. The written information must be given well in advance of the examination itself.

For the purpose of quality control, the consensus panel recommended that a systematic registration of selected data from all ultrasound examinations should be established (1).

Shortly after the consensus conference the consensus statement was approved by the Directorate of Health and submitted to doctors and midwives as a guideline for the use of ultrasound in pregnancy, replacing the recommendation not to screen from 1984 (4).

In the following years, the public debate became more focused on detection of fetal malformations. This aspect of routine ultrasound was not dealt with in detail in the 1986-conference, as the standard of the equipment at that time limited the examination of fetal anatomy. However, both the ultrasound technology and the skills of the ultrasound operators improved over the years. A broad ethical debate was raised and parliamentarians urged the Health Authorities to initiate a new consensus conference. As part of the program for medical technology assessment, the National Norwegian Research Council in 1995 organized the second Norwegian consensus conference on routine ultrasound in pregnancy (5). In the consensus statement, the recommendation...
from 1986 to offer one routine examination in gestational week 18 was repeated. The panel concluded that screening for fetal malformations was an integrated part of the routine ultrasound examination. The panel recommended research in the following areas:

- Pregnancies that are post-term pregnancies according to estimated day of delivery by ultrasound.
- Cases where the biological EDD differ from the EDD made by ultrasound.
- Research on the usefulness for the newborn child of finding a congenital anomaly at routine ultrasound screening.

1.2 Establishment of a perinatal database in Oppland

Quality assurance and quality improvement of obstetrical care has always been one of my main interests. Systematic recording of results is a prerequisite for quality assurance of clinical work. In 1986, at Lillehammer Central Hospital we started to develop a computer program to record information from the ultrasound screening, and information about the deliveries. A pilot version was taken in use in May 88 and from January 1. 1989 the registration program was integrated in the data system at the hospitals in Lillehammer and Gjøvik as part of the hospital record system.

In the county of Oppland, the rule is that routine ultrasound examinations are performed by midwives and doctors in the obstetrical departments of Lillehammer and Gjøvik Central Hospitals. Also, two specialists in gynaecology and obstetrics working in the city of Lillehammer and one general practitioner working in Otta 110 km from Lillehammer perform the routine examinations in their own patients.

The deliveries in the county are managed by the obstetric departments of Lillehammer and Gjøvik Central Hospitals, and two small cottage hospitals (Lom and Valdres fødestogo). The cottage hospital in Lom had only very few deliveries, and was closed in 1995.
When the patients are discharged from the obstetric departments after delivery, information about the pregnancy and the delivery is prospectively recorded in the database by obstetricians examining the records. From the cottage hospitals, information about the deliveries is sent to Lillehammer and recorded in the database.

The annual number of deliveries in the county is approximately 2000. Thus, the perinatal databases presently comprise detailed information about more than 30 000 deliveries. The completeness of the database is routinely checked against the hospital discharge registry.

The utility of collecting this information has repeatedly been demonstrated. For example, in January every year since 1989 the obstetrical department of Lillehammer central hospital has issued an annual report highlighting relevant topics in antenatal care and obstetrical care. One of the topics has been smoking in pregnancy, where there is a large and consistent difference between women in Gudbrandsdalen and women from the southern part of Oppland, where smoking is more prevalent. Also, from 1989 the ultrasound operators receive an annual personal report on their performance. For each individual ultrasound operators, the mean difference between EDD according to ultrasound and observed day of delivery is computed. Then, the individual operator can compare her own performance with that of the others, but the identity of the others is not revealed. There are examples that doctors and midwives have adjusted their measurement technique and improved their results following this feed back. Also, in the follow up of an increase in obstetric sphincter injuries we were able to identify care providers with results indicating the need for improvement. Midwives are also given an annual report. She can then compare her own results against the mean of the delivery department. This has often resulted in a change in midwifery practice.

Thus, our experience is that a computerized record system compiling relevant information in a perinatal database is an excellent tool for quality assurance, management and planning of obstetrical services. The database has led to a number of other publications (6-9). This dissertation will provide additional proof that a county wide perinatal database can be useful for research purposes.
2. Aims of the study

The aims of the study were:

To assess the risk for adverse obstetrical outcome in women where the EDD had been postponed more than 14 days with ultrasound.

To evaluate the mortality and morbidity of conservatively managed post-term pregnancies (gestation 294 days and beyond).

To assess the sensitivity for detecting fetal congenital anomalies with routine mid second trimester ultrasound performed in a routine clinical setting.

To estimate the random or biologic uncertainty of gestational age based on LMP and on routine ultrasound.

To compare the performance of the new Norwegian reference values for BPD measurement with the old reference values.
3. List of papers

The thesis is based on five papers. The papers will be referred to by their Roman numerals.

**Paper I**  
Adverse obstetric outcome in fetuses that are smaller than expected at second trimester routine ultrasound examination.

**Paper II**  
Pregnancy risk increases from 41 weeks of gestation.

**Paper III**  
Routine ultrasound screening and detection of congenital anomalies, outside a university setting.

**Paper IV**  
The biologic error in gestational length related to the use of the first day of last menstrual period as a proxy for the start of pregnancy.

**Paper V**  
Term prediction with ultrasound: Evaluation of a new dating curve for BPD measurements.
Erratum:

Paper I:
Figure 1 and Figure 2 are confused. The legends are correct but the figures should be replaced with each other.

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4. Material and methods

4.1 The study population

The thesis is based on information collected in the perinatal database from January 1, 1989 until December 31, 1999. Included in the study were women who were residents of Oppland county and who received their antenatal care inclusive the routine ultrasound examination in Oppland. Obstetrical care is provided by the two hospitals situated in the county (Lillehammer and Gjøvik) and two small cottage hospitals. Women living in the southernmost community, Jevnaker, in Oppland have routine ultrasound and delivery at Ringerike hospital in Hønefoss, in the neighbouring county of Buskerud. Women from this community were not included. Also, women temporarily living outside the county (i.e. students) were not included.

Cases with extreme prematurity (< 28 weeks gestation) are referred to the regional hospital in Oslo (Ullevaal University Hospital) and cases with fetal malformations are referred to the National Centre for Fetal Medicine at St Olavs Hospital in Trondheim. Information about patients who delivered at one of the two tertiary care hospitals after referral was collected and recorded in the database.

Thus, the total background population comprised 23,158 women (10), who had a total of 19,823 deliveries during the 11 year period 1989 to 1999.

4.2 The routine ultrasound examination

In Oppland county, routine ultrasound was introduced about 1985. Thus, the practice in Oppland was already in correspondence with the recommendations when the Health Directorate issued their guidelines in 1986. The routine ultrasound examination is performed in gestational week 18. The women are referred from the general practitioner of midwife.
The standard procedure comprises measurement of fetal biparietal diameter and assessment of gestational age by use of the standard Norwegian reference chart, and localization of the placenta. Also, the fetal anatomy is checked systematically. The checklist for fetal anatomy introduced by Eik Nes in 1985 (“blåskjema”) is used.

About 70% of the routine ultrasound examinations were performed by four midwives, trained at the National Centre for Fetal Medicine, St Olavs Hospital, Trondheim. The largest part of the remaining examinations (Table 1) was performed by consultant obstetricians at the two obstetric departments. The two obstetrician gynaecologists in private practice and the one general practitioner performed only a limited number of routine examinations.

Table 1 Number of examinations

<table>
<thead>
<tr>
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<th>Number of examinations</th>
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</thead>
<tbody>
<tr>
<td>Midwife 1</td>
<td>4477</td>
</tr>
<tr>
<td>Midwife 2</td>
<td>4348</td>
</tr>
<tr>
<td>Midwife 3</td>
<td>3662</td>
</tr>
<tr>
<td>Midwife 4</td>
<td>905</td>
</tr>
<tr>
<td>OB in hospital</td>
<td>4501</td>
</tr>
<tr>
<td>OB outside hospital and GP</td>
<td>737</td>
</tr>
</tbody>
</table>

Pregnant women in Oppland comply with the recommendation to have one routine examination. Of the 19,823 deliveries, only 609 (3.1%) had missing information about the routine ultrasound examination.

At the ultrasound session, the midwife or doctor examine the women about the previous obstetric history, use of OC and the smoking habits. The information collected is recorded in the computer, using a locally developed obstetric data program. LMP is classified as reliable provided that the date of the LMP is recalled with certainty and the menstruation has been regular with interval within 26-32 days, and oral contraceptives have not been used during the last three months prior to conception. When the LMP is reliable, the EDD is calculated by addition of 282 days to the date of the LMP. This calculation is performed automatically by the computer when the data are entered.
The ultrasound equipment used was Hitachi EUB-410, Hitachi EUB-415, with 3·5 MHz and 5 MHz curvilinear transducers. Sound velocity was calibrated to 1540 m/s. The biparietal diameter was measured from the outer to the outer contour of the parietal bone echo. The day of delivery was predicted according to the standard Norwegian reference values issued by Eik-Nes (11), assuming a pregnancy length of 282 days. An EDD was only recorded when the fetal biparietal diameter was within the range of 35 to 60 mm, corresponding to 15-22 completed weeks of pregnancy.

All clinical decisions were based on EDD ultrasound.

4.3 Definitions

Women were classified as smokers if they were daily smokers at the time of routine ultrasound examination. Perinatal death was defined as stillborn fetuses exceeding 22 completed gestational weeks (154 days) and deaths within 7 days after delivery, according to the WHO recommendations (12). Pregnancies were classified as post-term when gestational length exceeded 296 days, which is 14 days after EDD ultrasound.

The standard Swedish-Danish normal weight-for-gestational age curve for births after 153 days of gestation (13) was used as reference. SGA was defined as birth weight < 2 SD from the mean.

All newborns at Lillehammer and Gjøvik hospitals were routinely examined by a paediatrician. The first examination was during the first 48 hours after delivery. The children born in the two cottage hospitals were examined by a general practitioner. The results of the examination were recorded in the database.

4.5 Statistical methods

Statistical Package for the Social Sciences (SPSS) Version 10.0 and 12.0 was used for data management and statistical analyses.
Statistical tests included univariate tests (T-test and Chi square test) and multivariate tests with multiple logistic regression analysis. Relative risks and odds ratio with 95% confidence intervals were used. The p-values and 95% confidence intervals are reported where appropriate. p-values <0.05 are termed significant.

4.6 Paper I

Adverse obstetric outcome in fetuses that are smaller than expected at second trimester routine ultrasound examination.

Included in the study were women with singleton pregnancies, who had a reliable LMP and an EDD based on routine ultrasound scan. A total of 16,302 singleton pregnancies (82.2%) were eligible for analyses.

Outcome variables were perinatal death, preterm delivery (< 37 weeks), birth weight < 2,500g and SGA.

4.7 Paper II

Pregnancy risk increases from 41 weeks of gestation.

Included were women with singleton pregnancies who had a second trimester ultrasound examination and delivery after 37 weeks (259 days) gestation. A total of 17,493 pregnancies were included. 1,336 (7.6 %) of the pregnancies continued beyond 294 days of gestation.

Outcome variables were perinatal death, Apgar score<7 at 5 minutes and transferral to NICU.

The relative risk for adverse perinatal outcome was calculated the conventional way comparing perinatal mortality in foetuses of certain gestational age to perinatal
mortality for all pregnancies. We also calculated perinatal mortality and relative risk per ongoing pregnancy, using the number of ongoing pregnancies as the denominator.

4.8 Paper III

Routine ultrasound screening and detection of congenital anomalies, outside a university setting.

We excluded 676 women where the routine midtrimester ultrasound examination had been performed outside the county, and 317 women who were examined in the county with normal results, but who delivered outside the county. A total of 18,181 pregnancies were included. Outcome variables were congenital anomalies detected at ultrasound examination and by postpartum paediatric examination.

The fetal anomalies were grouped according to their likely clinical consequences according to the classification system proposed by the UK Royal College of Obstetricians and Gynaecologists in 1997 (14). The anomalies were also categorized according to the anatomical localization.

4.9 Paper IV

The biologic error in gestational length related to the use of the first day of last menstrual period as a proxy for the start of pregnancy

Included were women with singleton pregnancies and spontaneous onset of labor, where an EDD based on routine ultrasound was recoded as well as EDD based on a reliable LMP. The study comprised 11,238 pregnancies. The difference between observed and predicted day of delivery according to either method and the difference between the two EDDs were calculated. The variances of the differences were combined to estimate the variance of the time from LMP to the start of pregnancy, and the variance of the difference between real and ultrasound assessed gestational age.
4.10 Paper V

Term prediction with ultrasound: Evaluation of a new dating curve for BPD measurements.

The study population of Paper V is the same as in Paper IV. Included were women with singleton pregnancies and spontaneous onset of labor, where an EDD based on ultrasound was recorded as well as an EDD according to a reliable menstrual history. Elective caesarean sections and cases where labor was induced were excluded. The study population comprises a total of 11,238 deliveries.
5. Main results

Paper I

Adverse obstetric outcome in fetuses that are smaller than expected at second trimester routine ultrasound examination.

In 1,133 pregnancies (7%) the EDD was postponed with more than 14 days. The central finding is that these pregnancies carry a statistically significant increased risk for perinatal death, preterm birth, SGA and low birthweight. This effect is independent of smoking, age, parity and major anomalies (included chromosomal aberrations). Also, the effect is not associated with irregular ovulation due to recent OC use.

Paper II

Pregnancy risk increases from 41 weeks of gestation.

A total of 1,336 (7.6 %) of the deliveries were post-term. If RR is calculated per ongoing pregnancies, the risk for perinatal mortality as well as morbidity increased significantly after week 41, despite intensive surveillance of patients that were allowed to continue their pregnancies after week 42+2.

Our results indicate that management of post-term pregnancies can be improved, and that intensified observation should be started earlier than gestational week 42+2.
Paper III

Routine ultrasound screening and detection of congenital anomalies, outside a university setting.

Altogether, there were 267 foetuses and newborns with anomalies (1.5 %). 104 cases were detected with routine ultrasound (38.7 %). There were 11 false positives (renal pelvic dilatation that were not confirmed after birth) and 163 cases that remained undiagnosed (false negatives), which gives a specificity of 99.9 % and a positive predictive value of 90.4 %.

The sensitivity for detecting anomalies in the central nervous system was 69.4%, and for the cardiac system it was 14.5%. The detection rate for lethal anomalies was 80.0%, and in 31 of 32 cases a TOP was performed. All pregnancies that ended in termination (57 cases) had a second opinion examination at the National centre for fetal medicine. In all cases post-mortem examination confirmed the major ultrasound findings. There were thirty-eight chromosomal aberrations and ten of them were found at midtrimester ultrasound examination and confirmed by karyotyping (26.3%).

Paper IV

The biological error in gestational length related to the use of the first day of last menstrual period as a proxy for the start of pregnancy

The period from LMP to start of pregnancy had a biologic variation of 7.0 days (SD). The random error of ultrasound dating was estimated to 5.2 days (SD).
Paper V

Term prediction with ultrasound: Evaluation of a new dating curve for BPD measurements.

When EDD was based on the new reference values for BPD, the difference between observed and predicted day of delivery was significantly closer to zero than when the old reference values were used. Also, when EDD was based on small BPDs the prediction error of the old method increased up to 7 days.
6. Discussion

Gestational age assessment with ultrasound biometry is based on the assumption that in early pregnancy, foetuses of same age are of same size. This assumption is clearly an approximation, the individual variation increases with increasing gestational age. The assumption that all foetuses are of average size in gestational week 18 leads to a misclassification of foetuses that are larger or smaller than the average. The question is whether the resulting error is large enough to have practical consequences or whether this is purely of academic interest. So far, the published studies have been inconclusive, and the first study in the thesis (Paper I) addressed this question.

In foetuses that are smaller than expected at routine ultrasound, the EDD ultrasound will be postponed relative to EDD based on menstrual history. If the pregnancy is managed according to EDD ultrasound, it may then have adverse consequences for example in post term pregnancies falsely believed to be term pregnancies.

As reported in paper I, adverse perinatal outcome (perinatal death, preterm delivery, low birthweight and SGA) is significantly increased in pregnancies where the expected term of delivery is postponed with more than 14 days. This adverse effect was not due to confounding caused by maternal age, smoking, use of OCs and major anomalies. For three of the four outcomes there was a clear and statistically significant trend towards increasing risk with increasing discrepancy between the two EDDs. The perinatal deaths occurred at all gestational ages, and were not caused by mismanagement of post term pregnancies. Seven percent of the population had their EDD postponed with more than 14 days, and the population attributable risk proportion for each of the four outcomes varied from eight to four percent.

Thus, we can conclude that gestational age discrepancy is an important risk factor affecting about 7% of the pregnancies, and this risk factor carries a considerable proportion of perinatal morbidity and mortality. Still, we do not know how to manage pregnant women where the EDDs differ with more than two weeks. If effective
interventions were identified this would be an important contribution. This may be an
effect of early growth restriction. Routinely, in cases with two weeks discrepancy we do
now offer a follow up examination with ultrasound fetometry in week 25.

Also, I will emphasize the point that the women’s information about LMP is not
disregarded or ignored. This information should be respected and may contain valuable
information.

The second paper (Paper II) deals with post term pregnancies. One of the important
changes in contemporary obstetrics is that the proportion of post term pregnancies is
substantially reduced. According to the annual reports from the Medical Birth Registry
of Norway (http://www.fhi.no), in the 1970-ies gestational length of 42 weeks was
recorded in about 10 percent of pregnancies and about 5 percent reached 43 weeks. In
2002, only 5.7 % of pregnancies lasted 42 weeks and 0.2 % reached 43 weeks
(http://www.fhi.no). This reduction of post term pregnancies is an effect of ultrasound
dating, providing a more reliable EDD that what can be calculated from LMP. Albeit
less frequent the individual risk associated with post term pregnancy may have
increased. In earlier times when gestational length was calculated from LMP, the group
of post term pregnancies also contained women who were wrongly classified as post
term and the risk was diluted.

The approach suggested by Hilder et al (15) computing gestation –specific risks also
triggered my interest. In my opinion this seems to be the appropriate way to assess the
woman’s individual risk when passing 42 weeks gestation. If risk is calculated the
conventional way with the total population in the denominator, the actual risk that the
individual is exposed to at 42 weeks gestation is underestimated. The gestation specific
risk reflects the clinical situation where the obstetrician must make decisions about
delivery or continued monitoring.

In Paper II, we report the obstetric risk associated with post-term pregnancy. When risk
is calculated the conventional way, perinatal morbidity is significantly increased but the
risk for mortality does not reach statistical significance. When relative risk is calculated
as risk in ongoing pregnancy, both morbidity indicators and risk for perinatal death is increased. Low Apgar score and transfer to NICU were used as indicators of morbidity, and this two parameters as well as the risk for perinatal death increased significantly after gestational week 41. Commonly, very large materials are required to analyze the impact of risk factors on perinatal mortality. With this approach, we can show that in our hands, the management of post term pregnancy is still associated with increased perinatal morbidity and mortality.

The tradition in Norway is to follow pregnancies with no complications or disorders up to 43 weeks with close monitoring from week 42+2 according to ultrasound. This approach is also described in the guidelines of the Norwegian Society for Obstetrics and Gynecology (16). However, our work (Paper II) indicates that expectant management of post term pregnancies does not eliminate the excess risk.

The problems caused by post term pregnancies previously dominated obstetrical care. The reduction of the number of pregnancies assumed to be 42 weeks is one of the important achievements of routine ultrasound, on the other hand it might well be that post term pregnancy to day implies a larger risk than in earlier times. Thus, it might be that increased surveillance should start earlier. The mean systematic error of the standard ultrasound method applied (Paper V) of two days should also be kept in mind, at gestational week 42+2 the true gestational length is probably 42+4 which might be of some importance. In our clinical work, we now use the new ultrasound standard values (Paper V) and we start monitoring post term pregnancies in week 42+0. The combined effect is that monitoring is started four days earlier than hitherto.

The issue of fetal malformations’ screening with ultrasound has been much debated in the public as well as among professionals. Paper III addresses the question of whether routine ultrasound performed in local district hospitals can achieve detection rates comparable with “centres of excellence”. Comparisons of different studies are not easy because results are reported in different ways. A standardization of the reporting is required, like for example the proposal of the Royal College of Obstetricians and Gynaecologists (14) grouping the malformations according to their likely clinical
consequences. In group 1 (lethal anomalies) 80 % of the cases were detected and the
detection rate in group 2 (anomalies associated with possible survival and long term
morbidity) was 33 %. In the small but important group of anomalies amenable to
intrauterine therapy (group 3) 2 of 3 cases were detected. One fetus with urinary
obstruction, dilated renal pelvis due to uretric obstruction, was not identified antenatally
but diagnosed after delivery. The 11 false positive findings were renal pelvic dilatation
not confirmed after delivery, and thus without clinical significance. The greatest
diagnostic problems were associated with detection of heart malformations and
detection of chromosomal aberrations that are not associated with structural anomalies.

Compared with results reported in the literature, our malformation screening provides
good results with detection rates comparable with results reported from university
centres. However, it is possible to use more resources on malformation screening. We
have deliberately limited the efforts. For example, we do not systematically screen
foetuses for markers of chromosomal disorders, and we have not yet taken up first
trimester ultrasound screening with assessment of nucheal translucency. Until presently,
in our population the emphasis on general malformation screening has been rather
limited. It is our impression that the demand for this offer is limited. Also, we provide
secondary obstetrical care in a widespread, rural population. The resources available are
limited and it is a pertinent question what the priorities should be.

The tradition which probably is older than Nägele (17) is to calculate pregnancy length
from LMP. Studies about the interval from LMP to ovulation, conception or
implantation, are remarkably few. The variation of this interval is largely unknown.
This unknown biologic variation is responsible for a considerable uncertainty in
gestational length assessment when counted from LMP. In Paper IV, we combined the
results of two methods for prediction of the EDD to obtain estimates of the magnitude
of this unavoidable random error. We estimated the SD of this interval to 7.0 days. This
value is of the same magnitude as measured values reported in smaller studies, and also
comparable with a reported estimate using a different approach. The implication is that
even in women with reliable LMP, the uncertainty about when pregnancy actually
started is considerable. Following statistical theory, this biologic variation will be within
+/- 7 days in 65 % of the pregnancies whereas in the remaining 35 % the variation is > +/− 7 days. The estimate of the random variation of ultrasound term prediction is approximately 5 days (SD). This provides an indication that ultrasound assessment of gestational length is more precise than counting from LMP. Another important message is that reliable information about the LMP is not equal to reliable information about onset of pregnancy.

Ultrasound assessment of gestational duration is based upon biometry in early pregnancy. The obtained measure (in our setting BPD) is compared with a set of normal values. For more than 20 years we have used the normal values introduced by Eik-Nes (18), but new standard normal values were recently introduced (19). This urged us to evaluate the new standards, if there were large differences it would certainly cast doubt on our previous work (i.e. Paper I and Paper II) and then it would also have been pertinent to reassess some of our clinical results.

In Paper V we showed that for BPD measurements, use of the new normal values yields smaller mean and median prediction errors than the old values. For comparisons of this type, the median should be preferred for statistical reasons (Paper V). With the new standard the median difference between observed and expected EDD was +1 day and for the old method the difference was -2 days. That is, spontaneous delivery (median) occurred one day after or two days earlier then the predicted day. This is a small and usually insignificant difference. However, in post term pregnancies two days difference between true and estimated gestational age might be of clinical importance, especially if the limit for intervention is set out further two days. As described in Paper II, the tradition in Norway has been to define post term pregnancy from 296 days. Our clinical results of the management of post term pregnancies can be improved (Paper II), and we have adjusted our routines by using the new standard values and by starting increased surveillance from week 42+0. It has been suggested (20;21) that induction should be discussed with the woman after week 41+0. However, further randomized trials are needed.
More important than the small average systematic error of – 2 days is the error caused by
the old reference values when gestational age is assessed in early second trimester
(Paper V). This problem has been identified earlier (22). In Paper V, we report that the
prediction error increased up to 7 days when the ultrasound examination was done in
gestational week 15 to 16. The impact of this is error is limited as only 3 % of our
population was examined at that time in pregnancy; more than 2/3 were examined in
weeks 18 and 19 where the difference between the methods is two days.

I must however discuss the possible impact of incorrect dating of pregnancies in relation
to Paper I. The routine ultrasound examination is assumed to take place in week 18-19,
and women where gestational length for example was two weeks shorter than expected
were incorrectly estimated to be 16-17 weeks. If the new standards had been used,
gestational length would have been corrected with less than two weeks. In
epidemiological terms, the error caused by the old standard values leads to a non
differential misclassification causing a bias towards 0. The observed trend to adverse
perinatal outcome would have been larger if the new standard values had been used.

After 9 controlled randomized trials comprising more than 34,000 pregnant women, it
has been shown that routine ultrasound provides a more precise estimate of the expected
day of delivery, earlier detection of twin pregnancies and improved detection rates for
fetal malformations (23). These findings clearly reflect that routine ultrasound improves
the clinical management of the parturient women. The fetal outcome is, however, not
improved. Important outcome indicators like the distribution of Apgar score, admission
to NICU or perinatal mortality are not significantly influenced by routine ultrasound
(24). It might however be futile to claim that new elements should be taken up in the
antenatal care only on the condition that this leads to a further reduction of perinatal
mortality. Perinatal mortality is presently about 6 per 1000, and from perinatal audits we
know that only 20-30 % of the deaths are avoidable. Thus it is very hard to achieve
further reductions in perinatal mortality and very large trials would be needed.

To demonstrate a reduction of perinatal mortality from 6 to 4 per 1000 in a randomized
trial, with $\alpha=0.05$, $\beta=80 \%$, $p_1=6 \%$, $p_2=4 \%$ a randomized trial would require at least
20,000 participants.
In my opinion, improved clinical management of pregnant women is an important goal in itself, documentation of improved perinatal mortality rates should not be a mandatory requirement.
7. Conclusions

From the study population of 19,823 deliveries it was possible to answer some of the questions raised at the two consensus conferences of ultrasound in pregnancy.

1. Foetuses that are smaller than expected at the second-trimester ultrasound corresponding to a discrepancy of more than 14 days, have an increased risk for adverse obstetric outcome.

2. Expectant management of post term pregnancies allowing pregnancies to continue up to week 43 still carries a risk for perinatal mortality and morbidity, despite intensified observation from week 42+2. The risk increases already from gestational week 41.

3. Mid second trimester ultrasound examination in district hospitals can achieve a detection rate of congenital anomalies comparable with tertiary centres, without few false positives that were clinically of minor importance.

4. Even when the last menstrual period is reliable, the biological variation of the time from last menstrual period to the real start of pregnancy is substantial. Reliable information about last menstrual period is not equivalent to reliable information about the time of onset of pregnancy.

5. Using the new BPD reference values gives a better prediction of spontaneous labor and provides a more reliable assessment of gestational age than the old method.
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Papers I – V
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The biologic error in gestational length related to the use of the first day of last menstrual period as a proxy for the start of pregnancy

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KEYWORDS
Gestational age, Ultrasound; Gestational age assessment, Term prediction

Abstract

Objective: In a large unselected population of normal spontaneous pregnancies, to estimate the biologic variation of the interval from the first day of the last menstrual period to start of pregnancy, and the biologic variation of gestational length to delivery; and to estimate the random error of routine ultrasound assessment of gestational age in mid-second trimester.

Study design: Cohort study of 11,238 singleton pregnancies, with spontaneous onset of labour and reliable last menstrual period. The day of delivery was predicted with two independent methods: According to the rule of Nägele and based on ultrasound examination in gestational weeks 17-19. For both methods, the mean difference between observed and predicted day of delivery was calculated. The variances of the differences were combined to estimate the variances of the two partitions of pregnancy.

Results: The biologic variation of the time from last menstrual period to pregnancy start was estimated to 7.0 days (standard deviation), and the standard deviation of the time to spontaneous delivery was estimated to 12.4 days. The estimate of the standard deviation of the random error of ultrasound assessed foetal age was 5.2 days.

Conclusion: Even when the last menstrual period is reliable, the biologic variation of the time from last menstrual period to the real start of pregnancy is substantial, and
must be taken into account. Reliable information about the first day of the last menstrual period is not equivalent with reliable information about the start of pregnancy.

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1. Introduction

In human pregnancies, the day of the onset of pregnancy is usually unknown. The first day of the last menstrual period (LMP) is used as a surrogate variable. When we count pregnancy duration from LMP, we introduce a random error which is the biologic variation of the interval from LMP to the proper start of pregnancy. The length of human gestation from start of pregnancy to delivery is also subject to biologic variation. Remarkably, little is known about the biologic variations of these two partitions of gestation in normal spontaneous pregnancies [1].

According to the tradition usually attributed to Nägele [2], the delivery can be expected about 280 days from the LMP. In modern obstetrics, term prediction based on ultrasound assessment of gestational age has become the preferred method. However, the ultrasound method is also subject to random variation.

Purpose of the present paper is to assess and discuss the random variation or biologic variation of the two partitions of human gestation, and the random variation of gestational age assessment based on ultrasound.

2. Method

2.1. The variation of the different parameters of the pregnancy

In Fig. 1, the interval from the LMP to the start of pregnancy is labelled P, and the interval from start of pregnancy to delivery is labelled G. The mean difference between observed and expected day of delivery is the systematic error of term prediction. The random error is the distribution around the mean, measured by the standard deviation (σ) or the squared value which is the variance.

The random error of the Nägele prediction method is a combination of the biologic variation of the time from LMP to start of pregnancy (P) and the biologic variation of the duration of human gestation from start of pregnancy to delivery (G). The variance of the term prediction according to Nägele is the sum of the variance of these two partitions of pregnancy:

\[ \sigma^2_{\text{term}} = \sigma^2_P + \sigma^2_G \]  

(see Appendix A for details).

Ultrasound assessment of gestational length is based upon biometric measurement in early pregnancy and comparison of obtained values with a set of normal values. The foetal age at the time of ultrasound is termed A in Fig. 1, and the expected day of delivery is calculated from A assuming a fixed gestational length of usually 280 days as in the Nägele method.

The random error of the ultrasound method for term prediction is a combination of the random error of ultrasound assessed foetal age (A) and the biologic variation of human gestation from start of pregnancy to delivery (G). The variance of ultrasound term prediction can be written as:

\[ \sigma^2_{\text{us}} = \sigma^2_A + \sigma^2_G \]  

(II)

The variance of the difference between the two predicted days of delivery is the sum of the variance of time from LMP to start of pregnancy and the variance of gestational age at the time of ultrasound measurement (see Appendix A for details):

\[ \sigma^2_{\text{diff}} = \sigma^2_P + \sigma^2_A \]  

(III)

We can insert measured values for the parameters in the left side of all three equations (I), (II) and (III).

Figure 1 Different components of the total gestational period: P is the interval from the first day of last menstrual period (LMP) to start of pregnancy, G is the time from start of pregnancy to spontaneous delivery and A is the foetal age at the time of routine ultrasound measurement.
Table 1 Exclusions from the background population of 19,823 deliveries (100%), some of the exclusions were for multiple reasons

<table>
<thead>
<tr>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duplex pregnancies</td>
<td>593  (3.0)</td>
</tr>
<tr>
<td>No LMP recorded</td>
<td>2069  (10.4)</td>
</tr>
<tr>
<td>No ultrasound exam</td>
<td>627   (3.2)</td>
</tr>
<tr>
<td>BPD outside range 34—51 mm</td>
<td>1943 (9.8)</td>
</tr>
<tr>
<td>Induced labour</td>
<td>1206  (6.0)</td>
</tr>
<tr>
<td>Elective Caesarean section</td>
<td>1019 (5.1)</td>
</tr>
<tr>
<td>Oral contraceptives used</td>
<td>4321 (21.8)</td>
</tr>
</tbody>
</table>

The remaining study population consists of 11,238 pregnancies (56.7%).

All pregnant women in the county are routinely offered an ultrasound examination in gestational weeks 17 to 19, approximately 97% of the women accepted and are examined by trained midwives and gynaecologists. During the ultrasound session, the women are interviewed about their menstrual history. LMP term is calculated and recorded only if the date of the LMP is recalled with certainty and the menstruation was regular with interval within 26-32 days, and oral contraceptives were not used during the last 3 months before pregnancy. When these conditions are not met, LMP term is classified as unreliable and is not recorded. LMP term was calculated by adding 282 days to the LMP.

Ultrasound term was based on measurement of the foetal biparietal diameter between gestational weeks 15 and 20. During the time when the data were collected, the standard Norwegian normal curves (Eik-Nes SH, Grøttum P. Graviditetskalenderen Snurra, Scan-Med a/s, Drammen, Norway) were used. Clinical management was based on the ultrasound term. Ultrasound term and LMP-term were determined independently.

For the purpose of the present study, we recomputed the ultrasound term using the recently published ultrasound charts [3]. We calculated ultrasound predicted term of delivery based on 282 days expected duration of pregnancy.

Eligible for the study were women with singleton pregnancies and spontaneous onset of labour.
Table 2  Mean difference (days) between actual day of delivery and predicted day of delivery, and the mean difference between the two predicted terms

<table>
<thead>
<tr>
<th>Term ultrasound—term LMP</th>
<th>Mean</th>
<th>Median</th>
<th>Mode</th>
<th>Range</th>
<th>S.D.</th>
<th>variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actual-LMP predicted day of delivery</td>
<td>-0.1</td>
<td>1</td>
<td>2</td>
<td>-143 to 84</td>
<td>14.3</td>
<td>204.1</td>
</tr>
<tr>
<td>Actual-ultrasound predicted day of delivery</td>
<td>-0.7</td>
<td>1</td>
<td>3</td>
<td>-145 to 60</td>
<td>13.0</td>
<td>168.2</td>
</tr>
</tbody>
</table>

Median, mode, range, standard deviation (S.D.) and variance of the differences are shown (n = 11,238 deliveries, reliable last menstrual period, singleton pregnancies, spontaneous onset of labour).

The computed variances (Table 2) were inserted in Eqs. (I), (II) and (III). The results are summarised in Table 3. The standard deviation of the period from LMP to start of pregnancy ($\sigma_p$) was 7.0 days, the standard deviation of the period from this point in time to delivery ($\sigma_g$) was 12.4 days and the standard deviation of the gestational age at the time of ultrasound dating ($\sigma_d$) was 5.2 days (Table 2).

The computed variances (Table 2) were inserted in Eqs. (I), (II) and (III). The results are summarised in Table 3. The standard deviation of the period from LMP to start of pregnancy ($\sigma_p$) was 7.0 days, the standard deviation of the period from this point in time to delivery ($\sigma_g$) was 12.4 days and the standard deviation of the gestational age at the time of ultrasound dating ($\sigma_d$) was 5.2 days (Table 3).

Table 3  Estimates of the variance (days) of the time from last menstrual period (LMP) to start of pregnancy and of the variance of the time from start of pregnancy to delivery and of the random error of ultrasound at the time of ultrasound measurement

<table>
<thead>
<tr>
<th>Variance</th>
<th>S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from LMP to start of pregnancy</td>
<td>49.5</td>
</tr>
<tr>
<td>Time from pregnancy start to delivery</td>
<td>154.7</td>
</tr>
<tr>
<td>Random error of ultrasound</td>
<td>27.1</td>
</tr>
</tbody>
</table>

The standard deviations (S.D.) are also listed.

3. Results

The distribution of the deliveries around the expected day is shown in Fig. 2, according to ultrasound and LMP. The mean difference between observed and LMP-predicted day of delivery was -0.1 days and the variance of the difference was 204.1 days. The mean difference between actual day of delivery and ultrasound predicted day of delivery was -0.7 days and the variance was 168.2 days (Table 2).

4. Discussion

Clinical materials are always censured, as a large proportion of pregnant women do not continue their pregnancies until spontaneous labour but are delivered by Caesarean section or after induction of labour, for medical reason. These interventions will affect the distribution of deliveries around the expected term. When ultrasound and LMP are compared, the results of term prediction will probably be biased in favour of the ultrasound method because clinical decisions are based on ultrasound rather that LMP term. To reduce this bias, we used the new Norwegian standard charts to construct an expected day of delivery rather than using the ultrasound term actually determined at the routine ultrasound examination.

As shown in Table 1, the elective Caesarean section rate (5.1%) and the induction rate (6.0%) in the study population were low. The policy concerning post term pregnancies was conservative following the standard Norwegian guidelines [4], where uncomplicated pregnancies are allowed to continue until 43 weeks with close follow up during week 42. The low intervention rates imply that bias due to censoring is minimized, as far as possible.

Our method is based on the assumption that the two prediction methods are independent. Ultrasound charts are developed from measurements in pregnant women with certain dates based on LMP, so the two methods can be said to be related. At the time of ultrasound measurement, the foetus may be larger or smaller than expected, but gestational age is determined solely from the size of the foetus with no adjustments for example according to LMP or known date of cohabitation. Thus, because the two methods were used independently we believe that our assumption is correct.

Some of our estimates can be compared to measured values obtained in clinical studies. In studies of pregnancies following in-vitro fertilization [5—11], the random error of ultrasound assessed gestational length range from 4.2 days to...
1.8 days (standard deviation). Thus, our estimate of 5.2 days (Table 3) is somewhat larger than reported values. The cited studies [5-11] are from centres of excellence and contain up to 200-300 pregnancies after in-vitro fertilization whereas our material is from a routine clinical setting with over 11,000 normal pregnancies. Thus, differences in the clinical settings and the different sample sizes may explain the difference between our estimates and observed random measurement errors.

We estimated the random variation of the time from LMP to the proper start of pregnancy to 7.0 days (Table 3). There are two more publications where this time period was estimated in large clinical materials, albeit using other approaches. Mongelli and Opatola [12] estimated the standard deviation to 7.4 days, and Todros et al. reported 7.16 days [13], both estimates are fairly similar to our estimate of 7.0 days.

It is of great practical importance to know when pregnancy starts in the menstrual cycle and to know the biologic variation of this parameter. The time of conception or the time of implantation may both be defined as the start of pregnancy, and the interval between these two events also has a biologic variation. For simplicity and also because it is not possible for us to distinguish further, in the present study we use the neutral term start of pregnancy.

The scarcity of research about when pregnancy actually starts is remarkable. Three older studies used the day of the basal body temperature increase as marker, and standard deviations of 7.3 days [14], 7.6 days [15] and 9.9 days [16] are reported.

In a recent, well-conducted study using sophisticated serial urine hormone analysis, Baird et al. [17] showed that day 14 was the most frequent day of ovulation with a standard deviation of 6.7 days. In another study based on the same material, the mean interval from ovulation to implantation was 9.1 days ranging from 6 to 12 days, the standard deviation was not reported [18]. To sum up, our estimate of a standard deviation of 7.0 days of the interval from LMP to start of pregnancy seems quite reasonable when compared with other estimates and reported observations. The practical implication of this result is that doctors, midwives and pregnant women as well, should realise that the biologic variations are considerable and that pregnancy may start virtually at any time during the menstrual cycle [1].

The gestational period from start of pregnancy to delivery after spontaneous labour had a standard deviation of 12.4 days (Table 3). Thus, even if we did know the exact time when pregnancy starts in humans, gestational length to spontaneous labour is far from constant. A substantial variation must be taken into account, and the practical consequence is that we should always present the expected term of delivery as an interval rather than a fixed day.

The utility of ultrasound is particularly high when the information about LMP is uncertain or missing. But even when the information about LMP is reliable as in our material, gestational age is more precisely assessed with ultrasound, as indicated by the distribution of deliveries around the expected term which is narrower for ultrasound than LMP (Table 2, Fig. 2). It is tempting to compare the random variation of menstrual dating of pregnancy (7.0 days) with the random error of ultrasound (5.2 days, Table 3), but because the distributions of these two parameters are different the standard deviations cannot be compared directly. The random error of ultrasound is normally distributed but the distribution of the time of the start of pregnancy is skewed and probably similar to the distribution of the ovulation, where there is a tendency towards long intervals between LMP and start of pregnancy [17,18].

More than 50 years ago, Schildbach [14] observed that gestational length at delivery had a much narrower distribution when he counted pregnancy duration from the time of ovulation rather than from LMP. His correct interpretation was that the time of implantation was not constant but varied in the menstrual cycle. His major concern was the forensic experts' practise in paternity cases, where the information about LMP was trusted and the inherent biologic uncertainty was neglected.

5. Conclusion

The biologic variation associated with start of pregnancy is large, and this knowledge has implications for how we should interpret a pregnant woman's information about the LMP. There is no reason to distrust or write off a pregnant woman's report about LMP as unlikely. The large biologic variation explains why reliable information about LMP is not equivalent with reliable information about start of pregnancy [19]. Also, the biologic variation of gestational length is large and the day of spontaneous labour cannot be predicted with high precision. The expected term of delivery should rather be expressed as an interval than a specific day.
Appendix A

A.1. Prediction of the day of delivery based on last menstrual period

As shown in Fig. 1, the day of delivery (DDLMP) can be expressed as the sum of the time from the LMP to the start of pregnancy, and the time from start of pregnancy to delivery:

$$DD_{LMP} = LMP + P + G$$

The difference between observed and expected day of delivery is: $LMP - US - A + G - (LMP + P + G')$ where $P'$ and $G'$ are the expected values. According to statistical theory, the variance of the sum of two independent stochastic variables is equal to the sum of the variances. Assumed that $P$ and $G$ are independent, the variance of the difference is:

$$\sigma^2_{A'} = \sigma^2_P + \sigma^2_G \tag{I}$$

where $\sigma^2_P$ is the variance of the time from LMP to start of pregnancy and $\sigma^2_G$ is the variance of the gestational length from start of pregnancy to delivery.

A.2. Prediction of term with ultrasound

Gestational age ($A$) is assessed with ultrasound at the routine ultrasound examination. From Fig. 1, we can write the expected day of delivery according to ultrasound (DDUS):

$$DD_{US} = US - A + G$$

where US is the day of the ultrasound examination, $A$ is the foetal age at the time of measurement and $G$ again is the gestational period from start of pregnancy to delivery (Fig. 1). The difference between observed and expected day of delivery is:


where $A'$ is the foetal age according to ultrasound and $A$ is the true value, $G'$ the expected gestational duration to delivery and $G$ is the true value. Assumed that $A$ and $G$ are independent, the variance of the difference between true and expected values is:

$$\sigma^2_{US} = \sigma^2_A + \sigma^2_G \tag{II}$$

A.3. Difference between the two predictions

Using the equations above, the difference between the two predicted days of delivery is:

$$DD_{LMP} - DD_{US} = LMP + P + G - (US - A + G)$$

As both US and LMP have fixed values, the variance of this difference is:

$$\sigma^2_{DIFF} = \sigma^2_P + \sigma^2_A$$

In Eqs. (I), (II) and (III), three variables are unknown ($\sigma^2_A$, $\sigma^2_P$ and $\sigma^2_G$). When we solve the three equations with respect to the three unknown variables, we get:

$$\sigma^2 = (\sigma^2_{US} + \sigma^2_{DIFF})/2$$

Values for $\sigma^2_{DIFF}$, $\sigma^2_{US}$ and $\sigma^2_{DIFF}$ can be taken from clinical materials (Table 2), and estimates for $\sigma^2_A$, $\sigma^2_G$ and $\sigma^2_P$ can then be calculated.

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Reliable LMP and start of pregnancy


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1997

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1998

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1999

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2000

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159. xxxxxxxx (blind number)
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2002
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2003
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