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Results and consequences of routine ultrasound screening in pregnancy

A geographic based population study

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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 midwifes 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. Midwifes 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.**
Nakling J, Backe B. Acta Obstet Gynecol Scand, 2002; 81: 846-51.

Paper II **Pregnancy risk increases from 41 weeks of gestation.**
Nakling J, Backe B. Acta Obstet Gynecol Scand 2006 (in press).

Paper III **Routine ultrasound screening and detection of congenital anomalies, outside a university setting.**
Nakling J, Backe B. Acta Obstet Gynecol Scand, 2005; 84: 1042-8.

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.**
Nakling J, Buhaug H, Backe B. Early Hum Dev. 2005;81(10):833-9.

Paper V **Term prediction with ultrasound: Evaluation of a new dating curve for BPD measurements.**
Backe B, Nakling J. Acta Obstet Gynecol Scand 2006 (in press).

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

	Number of examinations
Midwife 1	4477
Midwife 2	4348
Midwife 3	3662
Midwife 4	905
OB in hospital	4501
OB outside hospital and GP	737

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 that 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 α=0,05, β= 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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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 des/gn: 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

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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:

$$\sigma^2_{LMP} = \sigma^2_P + \sigma^2_G \qquad \text{(I)}$$

(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:

$$\sigma^2_{US} = \sigma^2_A + \sigma^2_G \qquad \text{(II)}$$

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):

$$\sigma^2_{DIFF} = \sigma^2_P + \sigma^2_A \qquad \text{(III)}$$

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

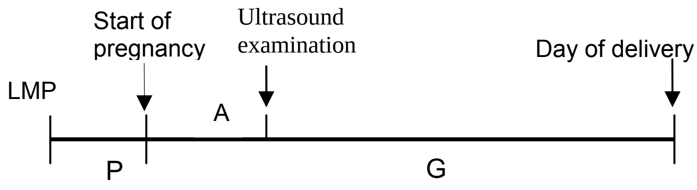

Figure 1 Different components of the total gestational period: *P* is the interval from the first day of last menstrual period (LMP) to start of pregnancy, G is the time from start of pregnancy to spontaneous delivery and *A* is the foetal age at the time of routine ultrasound measurement.

Table 1 Exclusions from the background population of 19,823 deliveries (100%), some of the exclusions were for multiple reasons

	Number	%
Duplex pregnancies	593	(3-0)
No LMP recorded	2069	(10.4)
No ultrasound exam	627	(3.2)
BPD outside range 34—51 mm	1943	(9.8)
Induced labour	1206	(6.0)
Elective Caesarean section	1019	(5.1)
Oral contraceptives used	4321	(21.8)

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

and (III). We can then combine and solve the equations to calculate estimates of σ_A, σ_P and σ_G. The underlying assumptions are that the term is predicted with two independent methods, and that the factors *A, G* and *P* are mutually independent.

2.2. The clinical material

We analysed a geographically based cohort of deliveries comprising women residing in Oppland county, Norway. The county has two equally sized obstetrical departments, with a total of approximately 2000 deliveries annually. When the patients are discharged from the hospitals after delivery, information about the pregnancy and the delivery is prospectively recorded in an obstetrical database by senior obstetricians examining the records.

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

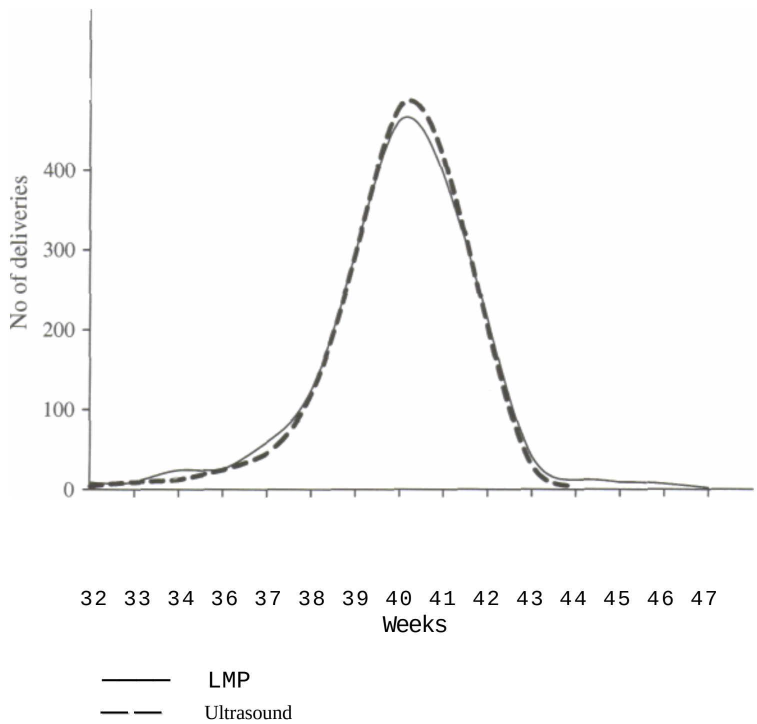

Figure 2 Distribution of deliveries around ultrasound term and term calculated from last menstrual period (*n* = 11,238 singleton, spontaneous onset of labour).

Table 2 Mean difference (days) between actual day of delivery and predicted day of delivery, and the mean difference between the two predicted terms

	Mean	Median	Mode	Range	S.D.	variance
Actual-LMP predicted day of delivery	-0.1	1	2	- 143 to 84	14.3	204.1
Actual-ultrasound predicted day of delivery	-0.7	1	3	- 145 to 60	13.0	168.2
Term ultrasound— term LMP	0.7	0	- 1	- 92 to 85	7.9	63.0

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).

labour, where both an ultrasound term based on second trimester BPD measurement and an LMP-term was recorded. Elective Caesarean sections and cases where labour was induced were excluded. From a total of 19,823 deliveries recorded in the database from 1989 to 1999 we excluded 8585 deliveries, details are shown in Table 1. A total of 11,238 deliveries (56.7%) remained for analysis.

Data were managed and analysed with SPSS version 12.0.

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).

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 (σ_P) was 7.0 days, the standard deviation of the period from this point in time to delivery (σ_G) was 12.4 days and the standard deviation of the gestational age at the time of ultrasound dating (σ_A) 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

	Variance	S.D.
Time from LMP to start of pregnancy	49.5	7.0
Time from pregnancy start to delivery	154.7	12.4
Random error of ultrasound	27.1	5.2

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

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 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 LMPlications 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 (DD_{LMP}) 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+P+G -(LMP + P' + G') = *P-P' + G-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:

$$\sigma^2_{LMP} = \sigma^2_P + \sigma^2_G \qquad \textbf{(I)}$$

where σ^2_P is the variance of the time from LMP to start of pregnancy and σ^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 (DD_{US}):

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

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:

US - *A* + *G* - (US - *A'* + G') = *A'* - *A* + *G* - *G',*

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:

$$\sigma^2_{US} = \sigma^2_A + \sigma^2_G \qquad \text{(II)}$$

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 (σ^2_G, σ^2_P and σ^2_A). When we solve the three equations with respect to the three unknown variables, we get:

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

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

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

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

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9. Tore Syversen: EFFECTS OF METHYLMERCURY ON RAT BRAIN PROTEIN.
10. Torbjørn Iversen: SQUAMOUS CELL CARCINOMA OF THE VULVA.

1984
11. Tor-Erik Widerøe: ASPECTS OF CONTINUOUS AMBULATORY PERITONEAL DIALYSIS.
12. Anton Hole: ALTERATIONS OF MONOCYTE AND LYMPHOCYTE FUNCTIONS IN REALTION TO SURGERY UNDER EPIDURAL OR GENERAL ANAESTHESIA.
13. Terje Terjesen: FRACTURE HEALING AN STRESS-PROTECTION AFTER METAL PLATE FIXATION AND EXTERNAL FIXATION.
14. Carsten Saunte: CLUSTER HEADACHE SYNDROME.
15. Inggard Lereim: TRAFFIC ACCIDENTS AND THEIR CONSEQUENCES.
16. Bjørn Magne Eggen: STUDIES IN CYTOTOXICITY IN HUMAN ADHERENT MONONUCLEAR BLOOD CELLS.
17. Trond Haug: FACTORS REGULATING BEHAVIORAL EFFECTS OG DRUGS.

1985
18. Sven Erik Gisvold: RESUSCITATION AFTER COMPLETE GLOBAL BRAIN ISCHEMIA.
19. Terje Espevik: THE CYTOSKELETON OF HUMAN MONOCYTES.
20. Lars Bevanger: STUDIES OF THE Ibc (c) PROTEIN ANTIGENS OF GROUP B STREPTOCOCCI.
21. Ole-Jan Iversen: RETROVIRUS-LIKE PARTICLES IN THE PATHOGENESIS OF PSORIASIS.
22. Lasse Eriksen: EVALUATION AND TREATMENT OF ALCOHOL DEPENDENT BEHAVIOUR.
23. Per I. Lundmo: ANDROGEN METABOLISM IN THE PROSTATE.

1986
24. Dagfinn Berntzen: ANALYSIS AND MANAGEMENT OF EXPERIMENTAL AND CLINICAL PAIN.
25. Odd Arnold Kildahl-Andersen: PRODUCTION AND CHARACTERIZATION OF MONOCYTE-DERIVED CYTOTOXIN AND ITS ROLE IN MONOCYTE-MEDIATED CYTOTOXICITY.
26. Ola Dale: VOLATILE ANAESTHETICS.

1987
27. Per Martin Kleveland: STUDIES ON GASTRIN.
28. Audun N. Øksendal: THE CALCIUM PARADOX AND THE HEART.
29. Vilhjalmur R. Finsen: HIP FRACTURES

1988
30. Rigmor Austgulen: TUMOR NECROSIS FACTOR: A MONOCYTE-DERIVED REGULATOR OF CELLULAR GROWTH.
31. Tom-Harald Edna: HEAD INJURIES ADMITTED TO HOSPITAL.
32. Joseph D. Borsi: NEW ASPECTS OF THE CLINICAL PHARMACOKINETICS OF METHOTREXATE.

33. Olav F. M. Sellevold: GLUCOCORTICOIDS IN MYOCARDIAL PROTECTION.
34. Terje Skjærpe: NONINVASIVE QUANTITATION OF GLOBAL PARAMETERS ON LEFT VENTRICULAR FUNCTION: THE SYSTOLIC PULMONARY ARTERY PRESSURE AND CARDIAC OUTPUT.
35. Eyvind Rødahl: STUDIES OF IMMUNE COMPLEXES AND RETROVIRUS-LIKE ANTIGENS IN PATIENTS WITH ANKYLOSING SPONDYLITIS.
36. Ketil Thorstensen: STUDIES ON THE MECHANISMS OF CELLULAR UPTAKE OF IRON FROM TRANSFERRIN.
37. Anna Midelfart: STUDIES OF THE MECHANISMS OF ION AND FLUID TRANSPORT IN THE BOVINE CORNEA.
38. Eirik Helseth: GROWTH AND PLASMINOGEN ACTIVATOR ACTIVITY OF HUMAN GLIOMAS AND BRAIN METASTASES - WITH SPECIAL REFERENCE TO TRANSFORMING GROWTH FACTOR BETA AND THE EPIDERMAL GROWTH FACTOR RECEPTOR.
39. Petter C. Borchgrevink: MAGNESIUM AND THE ISCHEMIC HEART.
40. Kjell-Arne Rein: THE EFFECT OF EXTRACORPOREAL CIRCULATION ON SUBCUTANEOUS TRANSCAPILLARY FLUID BALANCE.
41. Arne Kristian Sandvik: RAT GASTRIC HISTAMINE.
42. Carl Bredo Dahl: ANIMAL MODELS IN PSYCHIATRY.

1989

43. Torbjørn A. Fredriksen: CERVICOGENIC HEADACHE.
44. Rolf A. Walstad: CEFTAZIDIME.
45. Rolf Salvesen: THE PUPIL IN CLUSTER HEADACHE.
46. Nils Petter Jørgensen: DRUG EXPOSURE IN EARLY PREGNANCY.
47. Johan C. Ræder: PREMEDICATION AND GENERAL ANAESTHESIA IN OUTPATIENT GYNECOLOGICAL SURGERY.
48. M. R. Shalaby: IMMUNOREGULATORY PROPERTIES OF TNF-α AND THE RELATED CYTOKINES.
49. Anders Waage: THE COMPLEX PATTERN OF CYTOKINES IN SEPTIC SHOCK.
50. Bjarne Christian Eriksen: ELECTROSTIMULATION OF THE PELVIC FLOOR IN FEMALE URINARY INCONTINENCE.
51. Tore B. Halvorsen: PROGNOSTIC FACTORS IN COLORECTAL CANCER.

1990

52. Asbjørn Nordby: CELLULAR TOXICITY OF ROENTGEN CONTRAST MEDIA.
53. Kåre E. Tvedt: X-RAY MICROANALYSIS OF BIOLOGICAL MATERIAL.
54. Tore C. Stiles: COGNITIVE VULNERABILITY FACTORS IN THE DEVELOPMENT AND MAINTENANCE OF DEPRESSION.
55. Eva Hofsli: TUMOR NECROSIS FACTOR AND MULTIDRUG RESISTANCE.
56. Helge S. Haarstad: TROPHIC EFFECTS OF CHOLECYSTOKININ AND SECRETIN ON THE RAT PANCREAS.
57. Lars Engebretsen: TREATMENT OF ACUTE ANTERIOR CRUCIATE LIGAMENT INJURIES.
58. Tarjei Rygnestad: DELIBERATE SELF-POISONING IN TRONDHEIM.
59. Arne Z. Henriksen: STUDIES ON CONSERVED ANTIGENIC DOMAINS ON MAJOR OUTER MEMBRANE PROTEINS FROM ENTEROBACTERIA.
60. Steinar Westin: UNEMPLOYMENT AND HEALTH: Medical and social consequences of a factory closure in a ten-year controlled follow-up study.
61. Ylva Sahlin: INJURY REGISTRATION, a tool for accident preventive work.
62. Helge Bjørnstad Pettersen: BIOSYNTHESIS OF COMPLEMENT BY HUMAN ALVEOLAR MACROPHAGES WITH SPECIAL REFERENCE TO SARCOIDOSIS.
63. Berit Schei: TRAPPED IN PAINFUL LOVE.
64. Lars J. Vatten: PROSPECTIVE STUDIES OF THE RISK OF BREAST CANCER IN A COHORT OF NORWEGIAN WOMAN.

1991

65. Kåre Bergh: APPLICATIONS OF ANTI-C5a SPECIFIC MONOCLONAL ANTIBODIES FOR THE ASSESSMENT OF COMPLEMENT ACTIVATION.
66. Svein Svenningsen: THE CLINICAL SIGNIFICANCE OF INCREASED FEMORAL ANTEVERSION.
67. Olbjørn Klepp: NONSEMINOMATOUS GERM CELL TESTIS CANCER: THERAPEUTIC OUTCOME AND PROGNOSTIC FACTORS.

68. Trond Sand: THE EFFECTS OF CLICK POLARITY ON BRAINSTEM AUDITORY EVOKED POTENTIALS AMPLITUDE, DISPERSION, AND LATENCY VARIABLES.
69. Kjetil B. Åsbakk: STUDIES OF A PROTEIN FROM PSORIATIC SCALE, PSO P27, WITH RESPECT TO ITS POTENTIAL ROLE IN IMMUNE REACTIONS IN PSORIASIS.
70. Arnulf Hestnes: STUDIES ON DOWN´S SYNDROME.
71. Randi Nygaard: LONG-TERM SURVIVAL IN CHILDHOOD LEUKEMIA.
72. Bjørn Hagen: THIO-TEPA.
73. Svein Anda: EVALUATION OF THE HIP JOINT BY COMPUTED TOMOGRAMPHY AND ULTRASONOGRAPHY.

1992

74. Martin Svartberg: AN INVESTIGATION OF PROCESS AND OUTCOME OF SHORT-TERM PSYCHODYNAMIC PSYCHOTHERAPY.
75. Stig Arild Slørdahl: AORTIC REGURGITATION.
76. Harold C Sexton: STUDIES RELATING TO THE TREATMENT OF SYMPTOMATIC NON-PSYCHOTIC PATIENTS.
77. Maurice B. Vincent: VASOACTIVE PEPTIDES IN THE OCULAR/FOREHEAD AREA.
78. Terje Johannessen: CONTROLLED TRIALS IN SINGLE SUBJECTS.
79. Turid Nilsen: PYROPHOSPHATE IN HEPATOCYTE IRON METABOLISM.
80. Olav Haraldseth: NMR SPECTROSCOPY OF CEREBRAL ISCHEMIA AND REPERFUSION IN RAT.
81. Eiliv Brenna: REGULATION OF FUNCTION AND GROWTH OF THE OXYNTIC MUCOSA.

1993

82. Gunnar Bovim: CERVICOGENIC HEADACHE.
83. Jarl Arne Kahn: ASSISTED PROCREATION.
84. Bjørn Naume: IMMUNOREGULATORY EFFECTS OF CYTOKINES ON NK CELLS.
85. Rune Wiseth: AORTIC VALVE REPLACEMENT.
86. Jie Ming Shen: BLOOD FLOW VELOCITY AND RESPIRATORY STUDIES.
87. Piotr Kruszewski: SUNCT SYNDROME WITH SPECIAL REFERENCE TO THE AUTONOMIC NERVOUS SYSTEM.
88. Mette Haase Moen: ENDOMETRIOSIS.
89. Anne Vik: VASCULAR GAS EMBOLISM DURING AIR INFUSION AND AFTER DECOMPRESSION IN PIGS.
90. Lars Jacob Stovner: THE CHIARI TYPE I MALFORMATION.
91. Kjell Å. Salvesen: ROUTINE ULTRASONOGRAPHY IN UTERO AND DEVELOPMENT IN CHILDHOOD.

1994

92. Nina-Beate Liabakk: DEVELOPMENT OF IMMUNOASSAYS FOR TNF AND ITS SOLUBLE RECEPTORS.
93. Sverre Helge Torp: *erb*B ONCOGENES IN HUMAN GLIOMAS AND MENINGIOMAS.
94. Olav M. Linaker: MENTAL RETARDATION AND PSYCHIATRY. Past and present.
95. Per Oscar Feet: INCREASED ANTIDEPRESSANT AND ANTIPANIC EFFECT IN COMBINED TREATMENT WITH DIXYRAZINE AND TRICYCLIC ANTIDEPRESSANTS.
96. Stein Olav Samstad: CROSS SECTIONAL FLOW VELOCITY PROFILES FROM TWO-DIMENSIONAL DOPPLER ULTRASOUND: Studies on early mitral blood flow.
97. Bjørn Backe: STUDIES IN ANTENATAL CARE.
98. Gerd Inger Ringdal: QUALITY OF LIFE IN CANCER PATIENTS.
99. Torvid Kiserud: THE DUCTUS VENOSUS IN THE HUMAN FETUS.
100. Hans E. Fjøsne: HORMONAL REGULATION OF PROSTATIC METABOLISM.
101. Eylert Brodtkorb: CLINICAL ASPECTS OF EPILEPSY IN THE MENTALLY RETARDED.
102. Roar Juul: PEPTIDERGIC MECHANISMS IN HUMAN SUBARACHNOID HEMORRHAGE.
103. Unni Syversen: CHROMOGRANIN A. Phsysiological and Clinical Role.

1995

104. Odd Gunnar Brakstad: THERMOSTABLE NUCLEASE AND THE *nuc* GENE IN THE DIAGNOSIS OF *Staphylococcus aureus* INFECTIONS.
105. Terje Engan: NUCLEAR MAGNETIC RESONANCE (NMR) SPECTROSCOPY OF PLASMA IN MALIGNANT DISEASE.
106. Kirsten Rasmussen: VIOLENCE IN THE MENTALLY DISORDERED.
107. Finn Egil Skjeldestad: INDUCED ABORTION: Timetrends and Determinants.
108. Roar Stenseth: THORACIC EPIDURAL ANALGESIA IN AORTOCORONARY BYPASS SURGERY.

109. Arild Faxvaag: STUDIES OF IMMUNE CELL FUNCTION *in mice infected with* MURINE RETROVIRUS.

1996

110. Svend Aakhus: NONINVASIVE COMPUTERIZED ASSESSMENT OF LEFT VENTRICULAR FUNCTION AND SYSTEMIC ARTERIAL PROPERTIES. Methodology and some clinical applications.
111. Klaus-Dieter Bolz: INTRAVASCULAR ULTRASONOGRAPHY.
112. Petter Aadahl: CARDIOVASCULAR EFFECTS OF THORACIC AORTIC CROSS-CLAMPING.
113. Sigurd Steinshamn: CYTOKINE MEDIATORS DURING GRANULOCYTOPENIC INFECTIONS.
114. Hans Stifoss-Hanssen: SEEKING MEANING OR HAPPINESS?
115. Anne Kvikstad: LIFE CHANGE EVENTS AND MARITAL STATUS IN RELATION TO RISK AND PROGNOSIS OF CANSER.
116. Torbjørn Grøntvedt: TREATMENT OF ACUTE AND CHRONIC ANTERIOR CRUCIATE LIGAMENT INJURIES. A clinical and biomechanical study.
117. Sigrid Hørven Wigers: CLINICAL STUDIES OF FIBROMYALGIA WITH FOCUS ON ETIOLOGY, TREATMENT AND OUTCOME.
118. Jan Schjøtt: MYOCARDIAL PROTECTION: Functional and Metabolic Characteristics of Two Endogenous Protective Principles.
119. Marit Martinussen: STUDIES OF INTESTINAL BLOOD FLOW AND ITS RELATION TO TRANSITIONAL CIRCULATORY ADAPATION IN NEWBORN INFANTS.
120. Tomm B. Müller: MAGNETIC RESONANCE IMAGING IN FOCAL CEREBRAL ISCHEMIA.
121. Rune Haaverstad: OEDEMA FORMATION OF THE LOWER EXTREMITIES.
122. Magne Børset: THE ROLE OF CYTOKINES IN MULTIPLE MYELOMA, WITH SPECIAL REFERENCE TO HEPATOCYTE GROWTH FACTOR.
123. Geir Smedslund: A THEORETICAL AND EMPIRICAL INVESTIGATION OF SMOKING, STRESS AND DISEASE: RESULTS FROM A POPULATION SURVEY.

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124. Torstein Vik: GROWTH, MORBIDITY, AND PSYCHOMOTOR DEVELOPMENT IN INFANTS WHO WERE GROWTH RETARDED *IN UTERO*.
125. Siri Forsmo: ASPECTS AND CONSEQUENCES OF OPPORTUNISTIC SCREENING FOR CERVICAL CANCER. Results based on data from three Norwegian counties.
126. Jon S. Skranes: CEREBRAL MRI AND NEURODEVELOPMENTAL OUTCOME IN VERY LOW BIRTH WEIGHT (VLBW) CHILDREN. A follow-up study of a geographically based year cohort of VLBW children at ages one and six years.
127. Knut Bjørnstad: COMPUTERIZED ECHOCARDIOGRAPHY FOR EVALUTION OF CORONARY ARTERY DISEASE.
128. Grethe Elisabeth Borchgrevink: DIAGNOSIS AND TREATMENT OF WHIPLASH/NECK SPRAIN INJURIES CAUSED BY CAR ACCIDENTS.
129. Tor Elsås: NEUROPEPTIDES AND NITRIC OXIDE SYNTHASE IN OCULAR AUTONOMIC AND SENSORY NERVES.
130. Rolf W. Gråwe: EPIDEMIOLOGICAL AND NEUROPSYCHOLOGICAL PERSPECTIVES ON SCHIZOPHRENIA.
131. Tonje Strømholm: CEREBRAL HAEMODYNAMICS DURING THORACIC AORTIC CROSSCLAMPING. An experimental study in pigs.

1998

132. Martinus Bråten: STUDIES ON SOME PROBLEMS REALTED TO INTRAMEDULLARY NAILING OF FEMORAL FRACTURES.
133. Ståle Nordgård: PROLIFERATIVE ACTIVITY AND DNA CONTENT AS PROGNOSTIC INDICATORS IN ADENOID CYSTIC CARCINOMA OF THE HEAD AND NECK.
134. Egil Lien: SOLUBLE RECEPTORS FOR **TNF** AND **LPS**: RELEASE PATTERN AND POSSIBLE SIGNIFICANCE IN DISEASE.
135. Marit Bjørgaas: HYPOGLYCAEMIA IN CHILDREN WITH DIABETES MELLITUS
136. Frank Skorpen: GENETIC AND FUNCTIONAL ANALYSES OF DNA REPAIR IN HUMAN CELLS.
137. Juan A. Pareja: SUNCT SYNDROME. ON THE CLINICAL PICTURE. ITS DISTINCTION FROM OTHER, SIMILAR HEADACHES.
138. Anders Angelsen: NEUROENDOCRINE CELLS IN HUMAN PROSTATIC CARCINOMAS AND THE PROSTATIC COMPLEX OF RAT, GUINEA PIG, CAT AND DOG.

139. Fabio Antonaci: CHRONIC PAROXYSMAL HEMICRANIA AND HEMICRANIA CONTINUA: TWO DIFFERENT ENTITIES?
140. Sven M. Carlsen: ENDOCRINE AND METABOLIC EFFECTS OF METFORMIN WITH SPECIAL EMPHASIS ON CARDIOVASCULAR RISK FACTORES.

1999

141. Terje A. Murberg: DEPRESSIVE SYMPTOMS AND COPING AMONG PATIENTS WITH CONGESTIVE HEART FAILURE.
142. Harm-Gerd Karl Blaas: THE EMBRYONIC EXAMINATION. Ultrasound studies on the development of the human embryo.
143. Noèmi Becser Andersen:THE CEPHALIC SENSORY NERVES IN UNILATERAL HEADACHES. Anatomical background and neurophysiological evaluation.
144. Eli-Janne Fiskerstrand: LASER TREATMENT OF PORT WINE STAINS. A study of the efficacy and limitations of the pulsed dye laser. Clinical and morfological analyses aimed at improving the therapeutic outcome.
145. Bård Kulseng: A STUDY OF ALGINATE CAPSULE PROPERTIES AND CYTOKINES IN RELATION TO INSULIN DEPENDENT DIABETES MELLITUS.
146. Terje Haug: STRUCTURE AND REGULATION OF THE HUMAN UNG GENE ENCODING URACIL-DNA GLYCOSYLASE.
147. Heidi Brurok: MANGANESE AND THE HEART. A Magic Metal with Diagnostic and Therapeutic Possibilites.
148. Agnes Kathrine Lie: DIAGNOSIS AND PREVALENCE OF HUMAN PAPILLOMAVIRUS INFECTION IN CERVICAL INTRAEPITELIAL NEOPLASIA. Relationship to Cell Cycle Regulatory Proteins and HLA DQBI Genes.
149. Ronald Mårvik: PHARMACOLOGICAL, PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL STUDIES ON ISOLATED STOMACS.
150. Ketil Jarl Holen: THE ROLE OF ULTRASONOGRAPHY IN THE DIAGNOSIS AND TREATMENT OF HIP DYSPLASIA IN NEWBORNS.
151. Irene Hetlevik: THE ROLE OF CLINICAL GUIDELINES IN CARDIOVASCULAR RISK INTERVENTION IN GENERAL PRACTICE.
152. Katarina Tunòn: ULTRASOUND AND PREDICTION OF GESTATIONAL AGE.
153. Johannes Soma: INTERACTION BETWEEN THE LEFT VENTRICLE AND THE SYSTEMIC ARTERIES.
154. Arild Aamodt: DEVELOPMENT AND PRE-CLINICAL EVALUATION OF A CUSTOM-MADE FEMORAL STEM.
155. Agnar Tegnander: DIAGNOSIS AND FOLLOW-UP OF CHILDREN WITH SUSPECTED OR KNOWN HIP DYSPLASIA.
156. Bent Indredavik: STROKE UNIT TREATMENT: SHORT AND LONG-TERM EFFECTS
157. Jolanta Vanagaite Vingen: PHOTOPHOBIA AND PHONOPHOBIA IN PRIMARY HEADACHES

2000

158. Ola Dalsegg Sæther: PATHOPHYSIOLOGY DURING PROXIMAL AORTIC CROSS-CLAMPING CLINICAL AND EXPERIMENTAL STUDIES
159. xxxxxxxxx (blind number)
160. Christina Vogt Isaksen: PRENATAL ULTRASOUND AND POSTMORTEM FINDINGS – A TEN YEAR CORRELATIVE STUDY OF FETUSES AND INFANTS WITH DEVELOPMENTAL ANOMALIES.
161. Holger Seidel: HIGH-DOSE METHOTREXATE THERAPY IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA: DOSE, CONCENTRATION, AND EFFECT CONSIDERATIONS.
162. Stein Hallan: IMPLEMENTATION OF MODERN MEDICAL DECISION ANALYSIS INTO CLINICAL DIAGNOSIS AND TREATMENT.
163. Malcolm Sue-Chu: INVASIVE AND NON-INVASIVE STUDIES IN CROSS-COUNTRY SKIERS WITH ASTHMA-LIKE SYMPTOMS.
164. Ole-Lars Brekke: EFFECTS OF ANTIOXIDANTS AND FATTY ACIDS ON TUMOR NECROSIS FACTOR-INDUCED CYTOTOXICITY.
165. Jan Lundbom: AORTOCORONARY BYPASS SURGERY: CLINICAL ASPECTS, COST CONSIDERATIONS AND WORKING ABILITY.
166. John-Anker Zwart: LUMBAR NERVE ROOT COMPRESSION, BIOCHEMICAL AND NEUROPHYSIOLOGICAL ASPECTS.
167. Geir Falck: HYPEROSMOLALITY AND THE HEART.

168. Eirik Skogvoll: CARDIAC ARREST Incidence, Intervention and Outcome.
169. Dalius Bansevicius: SHOULDER-NECK REGION IN CERTAIN HEADACHES AND CHRONIC PAIN SYNDROMES.
170. Bettina Kinge: REFRACTIVE ERRORS AND BIOMETRIC CHANGES AMONG UNIVERSITY STUDENTS IN NORWAY.
171. Gunnar Qvigstad: CONSEQUENCES OF HYPERGASTRINEMIA IN MAN
172. Hanne Ellekjær: EPIDEMIOLOGICAL STUDIES OF STROKE IN A NORWEGIAN POPULATION. INCIDENCE, RISK FACTORS AND PROGNOSIS
173. Hilde Grimstad: VIOLENCE AGAINST WOMEN AND PREGNANCY OUTCOME.
174. Astrid Hjelde: SURFACE TENSION AND COMPLEMENT ACTIVATION: Factors influencing bubble formation and bubble effects after decompression.
175. Kjell A. Kvistad: MR IN BREAST CANCER – A CLINICAL STUDY.
176. Ivar Rossvoll: ELECTIVE ORTHOPAEDIC SURGERY IN A DEFINED POPULATION. Studies on demand, waiting time for treatment and incapacity for work.
177. Carina Seidel: PROGNOSTIC VALUE AND BIOLOGICAL EFFECTS OF HEPATOCYTE GROWTH FACTOR AND SYNDECAN-1 IN MULTIPLE MYELOMA.

2001

178. Alexander Wahba: THE INFLUENCE OF CARDIOPULMONARY BYPASS ON PLATELET FUNCTION AND BLOOD COAGULATION – DETERMINANTS AND CLINICAL CONSEQUENSES
179. Marcus Schmitt-Egenolf: THE RELEVANCE OF THE MAJOR hISTOCOMPATIBILITY COMPLEX FOR THE GENETICS OF PSORIASIS
180. Odrun Arna Gederaas: BIOLOGICAL MECHANISMS INVOLVED IN 5-AMINOLEVULINIC ACID BASED PHOTODYNAMIC THERAPY
181. Pål Richard Romundstad: CANCER INCIDENCE AMONG NORWEGIAN ALUMINIUM WORKERS
182. Henrik Hjorth-Hansen: NOVEL CYTOKINES IN GROWTH CONTROL AND BONE DISEASE OF MULTIPLE MYELOMA
183. Gunnar Morken: SEASONAL VARIATION OF HUMAN MOOD AND BEHAVIOUR
184. Bjørn Olav Haugen: MEASUREMENT OF CARDIAC OUTPUT AND STUDIES OF VELOCITY PROFILES IN AORTIC AND MITRAL FLOW USING TWO- AND THREE-DIMENSIONAL COLOUR FLOW IMAGING
185. Geir Bråthen: THE CLASSIFICATION AND CLINICAL DIAGNOSIS OF ALCOHOL-RELATED SEIZURES
186. Knut Ivar Aasarød: RENAL INVOLVEMENT IN INFLAMMATORY RHEUMATIC DISEASE. A Study of Renal Disease in Wegener’s Granulomatosis and in Primary Sjögren’s Syndrome
187. Trude Helen Flo: RESEPTORS INVOLVED IN CELL ACTIVATION BY DEFINED URONIC ACID POLYMERS AND BACTERIAL COMPONENTS
188. Bodil Kavli: HUMAN URACIL-DNA GLYCOSYLASES FROM THE UNG GENE: STRUCTRUAL BASIS FOR SUBSTRATE SPECIFICITY AND REPAIR
189. Liv Thommesen: MOLECULAR MECHANISMS INVOLVED IN TNF- AND GASTRIN-MEDIATED GENE REGULATION
190. Turid Lingaas Holmen: SMOKING AND HEALTH IN ADOLESCENCE; THE NORD-TRØNDELAG HEALTH STUDY, 1995-97
191. Øyvind Hjertner: MULTIPLE MYELOMA: INTERACTIONS BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MICROENVIRONMENT
192. Asbjørn Støylen: STRAIN RATE IMAGING OF THE LEFT VENTRICLE BY ULTRASOUND. FEASIBILITY, CLINICAL VALIDATION AND PHYSIOLOGICAL ASPECTS
193. Kristian Midthjell: DIABETES IN ADULTS IN NORD-TRØNDELAG. PUBLIC HEALTH ASPECTS OF DIABETES MELLITUS IN A LARGE, NON-SELECTED NORWEGIAN POPULATION.
194. Guanglin Cui: FUNCTIONAL ASPECTS OF THE ECL CELL IN RODENTS
195. Ulrik Wisløff: CARDIAC EFFECTS OF AEROBIC ENDURANCE TRAINING: HYPERTROPHY, CONTRACTILITY AND CALCUIM HANDLING IN NORMAL AND FAILING HEART
196. Øyvind Halaas: MECHANISMS OF IMMUNOMODULATION AND CELL-MEDIATED CYTOTOXICITY INDUCED BY BACTERIAL PRODUCTS
197. Tore Amundsen: PERFUSION MR IMAGING IN THE DIAGNOSIS OF PULMONARY EMBOLISM

198. Nanna Kurtze: THE SIGNIFICANCE OF ANXIETY AND DEPRESSION IN FATIQUE AND PATTERNS OF PAIN AMONG INDIVIDUALS DIAGNOSED WITH FIBROMYALGIA: RELATIONS WITH QUALITY OF LIFE, FUNCTIONAL DISABILITY, LIFESTYLE, EMPLOYMENT STATUS, CO-MORBIDITY AND GENDER
199. Tom Ivar Lund Nilsen: PROSPECTIVE STUDIES OF CANCER RISK IN NORD-TRØNDELAG: THE HUNT STUDY. Associations with anthropometric, socioeconomic, and lifestyle risk factors
200. Asta Kristine Håberg: A NEW APPROACH TO THE STUDY OF MIDDLE CEREBRAL ARTERY OCCLUSION IN THE RAT USING MAGNETIC RESONANCE TECHNIQUES

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201. Knut Jørgen Arntzen: PREGNANCY AND CYTOKINES
202. Henrik Døllner: INFLAMMATORY MEDIATORS IN PERINATAL INFECTIONS
203. Asta Bye: LOW FAT, LOW LACTOSE DIET USED AS PROPHYLACTIC TREATMENT OF ACUTE INTESTINAL REACTIONS DURING PELVIC RADIOTHERAPY. A PROSPECTIVE RANDOMISED STUDY.
204. Sylvester Moyo: STUDIES ON STREPTOCOCCUS AGALACTIAE (GROUP B STREPTOCOCCUS) SURFACE-ANCHORED MARKERS WITH EMPHASIS ON STRAINS AND HUMAN SERA FROM ZIMBABWE.
205. Knut Hagen: HEAD-HUNT: THE EPIDEMIOLOGY OF HEADACHE IN NORD-TRØNDELAG
206. Li Lixin: ON THE REGULATION AND ROLE OF UNCOUPLING PROTEIN-2 IN INSULIN PRODUCING ß-CELLS
207. Anne Hildur Henriksen: SYMPTOMS OF ALLERGY AND ASTHMA VERSUS MARKERS OF LOWER AIRWAY INFLAMMATION AMONG ADOLESCENTS
208. Egil Andreas Fors: NON-MALIGNANT PAIN IN RELATION TO PSYCHOLOGICAL AND ENVIRONTENTAL FACTORS. EXPERIENTAL AND CLINICAL STUDES OF PAIN WITH FOCUS ON FIBROMYALGIA
209. Pål Klepstad: MORPHINE FOR CANCER PAIN
210. Ingunn Bakke: MECHANISMS AND CONSEQUENCES OF PEROXISOME PROLIFERATOR-INDUCED HYPERFUNCTION OF THE RAT GASTRIN PRODUCING CELL
211. Ingrid Susann Gribbestad: MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY OF BREAST CANCER
212. Rønnaug Astri Ødegård: PREECLAMPSIA – MATERNAL RISK FACTORS AND FETAL GROWTH
213. Johan Haux: STUDIES ON CYTOTOXICITY INDUCED BY HUMAN NATURAL KILLER CELLS AND DIGITOXIN
214. Turid Suzanne Berg-Nielsen: PARENTING PRACTICES AND MENTALLY DISORDERED ADOLESCENTS
215. Astrid Rydning: BLOOD FLOW AS A PROTECTIVE FACTOR FOR THE STOMACH MUCOSA. AN EXPERIMENTAL STUDY ON THE ROLE OF MAST CELLS AND SENSORY AFFERENT NEURONS

2003

216. Jan Pål Loennechen: HEART FAILURE AFTER MYOCARDIAL INFARCTION. Regional Differences, Myocyte Function, Gene Expression, and Response to Cariporide, Losartan, and Exercise Training.
217. Elisabeth Qvigstad: EFFECTS OF FATTY ACIDS AND OVER-STIMULATION ON INSULIN SECRETION IN MAN
218. Arne Åsberg: EPIDEMIOLOGICAL STUDIES IN HEREDITARY HEMOCHROMATOSIS: PREVALENCE, MORBIDITY AND BENEFIT OF SCREENING.
219. Johan Fredrik Skomsvoll: REPRODUCTIVE OUTCOME IN WOMEN WITH RHEUMATIC DISEASE. A population registry based study of the effects of inflammatory rheumatic disease and connective tissue disease on reproductive outcome in Norwegian women in 1967-1995.
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