Kristin Offerdal

Improved ultrasound imaging of the fetus and its consequences for severe and less severe anomalies

Thesis for the degree of philosophiae doctor

Trondheim, December 2008

Norwegian University of
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Forbedret ultralydavbildning og konsekvenser ved alvorlige og mindre alvorlige utviklingsavvik hos foster

I Norge ble rutineultralyd rundt uke 18 innført i 1986 som en del av svangerskapsomsorgen. Målet med undersøkelsen er terminbestemmelse, påvisning av morkakens leie og bestemmelse av antall foster. I tillegg gjøres en detaljert gjennomgang av fosterets anatomi. Hvis det oppdages utviklingsavvik hos fosteret, kan dette føre til konsekvenser for behandlingen av både foster, svangerskap og den nyfødte. I noen tilfeller kan ultralydfunnet føre til et ønske om å avbryte svangerskapet. Utviklingen av ultralydteknologien og økt kompetanse hos de som utfører ultralydundersøkelser, har medført en økt oppdagelse av foster med utviklingsavvik.

Et mål med studien var å studere mindre utviklingsavvik som klumpfot og leppe-kjeve-ganespalte, som kan være alvorlige hvis de opptrer i forbindelse med kromosomfeil, syndromer ol. I tillegg ble alle med diagnosen Down syndrom i vår populasjon studert. Hovedmålet med studien var å se på konsekvensene av rutineultralyd ved 18 uker i forhold til svangerskapsavbrudd ved ultralydfunn.

Det ble utført en prospektiv oppfølgningsstudie i en uselektert norsk populasjon fra 1987 til og med 2004 med til sammen 49 314 fødsler. Studien ble delt opp i tidsperioder for å se på forandringer over tid når det gjaldt oppdagelsesrater, samt for å se om alvorlighetsgraden for årsaken til svangerskapsavbrudd hadde forandret seg over tid.

I den første studien undersøkte vi alle 113 foster/barn med diagnosen klumpfot, som var blitt registrert i løpet av atten år. Det forelå en signifikant forbedret oppdagelsesrate av klumpfot over tid. De tre største gruppene av assosierte utviklingsavvik ble funnet å være syndromer og sekvenser, kromosomfeil og muskel-skjelettsykdommer. Vår studie viste også at det i noen tilfeller av antatt isolert klumpfot forelå kromosomfeil eller alvorlige syndromer som først ble oppdaget etter fødselen.

I studie nummer to ble 101 registrerte fostre eller nyfødte med leppe-kjeve-ganespalte undersøkt i samme 18-års periode. Isolert ganespalte ble aldri påvist prenatalt. Det var en signifikant økt oppdagelsesraterate av både leppespalte og leppe-kjeve-ganespalte over tid. Førtitre prosent av foster/barn med leppe-kjeve-ganespalte og 58% med ganespalte hadde utviklingsavvik i tillegg. Studien viste også tilfeller av antatt isolert leppe-kjeve-ganespalte der det etter fødselen viste seg å foreligge alvorlige syndromer eller kromosomfeil.

I den tredje studien undersøkte vi alle 88 med registrert Down syndrom over en 18-års periode. Den prenatale oppdagelsesraten var 43%. Fjorten prosent ble påvist ved fostervannsprøve pga. mors alder på 38 år og eldre, 29% ble påvist ved ultralyd. Det kunne ikke påvises forandring i oppdagelsesrate i 18-års perioden. Studien viste at et program basert på mors alder for å påvise Down syndrom har liten effekt, og at ultralyd rundt uke 18 er en dårlig metode for å påvise Down syndrom. Raten av svangerskapsavbrudd etter påvisning av Down syndrom var uforandret i de tre periodene, rundt 84%.

Den fjerde studien viste at det hadde vært utført svangerskapsavbrudd pga. utviklingsavvik i 163 tilfeller på 15 år i populasjonen på 49 314 gravide. Det forelå en økt oppdagelsesrate av foster med utviklingsavvik i samme tidsperiode, men det var en signifikant nedgang av svangerskapsavbrudd. Det ble ikke sett noen forandring over tid i alvorlighetsgrad av diagnosene hos foster der svangerskapet ble avbrutt. Raten av avbrudd forårsaket av dødelige så vel som svært alvorlige sykdomstilstander var i første periode 90%, i andre periode 94% og i tredje periode 84%. Studien viser at det har vært mulig å opprettholde et tilbud til alle gravide om ultralydundersøkelse ved 18 uker uten at en fryktet økning av svangerskapsavbrudd har funnet sted. Fagområdet fostermedisin og den over tid oppbygde rådgivningen til gravide ved påviste funn, tillegges stor vekt for disse resultatene.

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Veiledere: Sturla H. Eik-Nes og Harm-Gerd K. Blaas

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CONTENT

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LIST OF PAPERS

The present thesis is based on the following papers:

Paper 1

Offerdal K, Jebens N, Blaas H-GK, Eik-Nes SH.

Prenatal ultrasound detection of talipes equinovarus in a non-selected population of 49 314 deliveries in Norway.

Ultrasound Obstet Gynecol. 2007 Nov;30(6):838-44.

Paper 2

Offerdal K, Jebens N, Syvertsen T, Blaas H-GK, Johansen OJ, Eik-Nes SH.

Prenatal ultrasound detection of facial clefts: a prospective study of 49 314 deliveries in a non-selected population in Norway.

Ultrasound Obstet Gynecol. 2008 Jun;31(6):639-46.

Paper 3

Offerdal K, Blaas H-GK, Eik-Nes SH.

Prenatal detection of trisomy 21 by second-trimester ultrasound examination and maternal age in a non-selected population of 49 314 births in Norway.

Ultrasound Obstet Gynecol. 2008 Sep;32(4):493-500.

Paper 4

Offerdal K, Blaas H-GK, Kjøllesdal AM, Eik-Nes SH.

Termination of pregnancy following ultrasound examination in a non-selected population of 41 382 deliveries in Norway: trends over a 15-year period.

Submitted August 2008

ABBREVIATIONS

AC	Amniocentesis
ASD	Atrial septal defect
AVSD	Atrioventricular septal defect
CHD	Congenital heart defect
CL(P)	Cleft lip with or without palate
CP	Cleft palate
CNS	Central nervous system
CVS	Chorionic villus sampling
DORV	Double outlet right ventricle
DILV	Double inlet left ventricle
HLHS	Hypoplastic left heart syndrome
IUFD	Intrauterine fetal death
LMP	Last menstrual period
NT	Nuchal translucency
PAPP-A	Pregnancy associated plasma protein A
PDA	Patent ductus arteriosus
TEV	Talipes equinovarus
TGA	Transposition of the great arteries
TOP	Termination of pregnancy
VSD	Ventricular septal defect

INTRODUCTION

The introduction of ultrasound in obstetrics in the late 1950s was the beginning of a new era. In the decades that followed, improved ultrasound equipment, better skills and increasing knowledge have changed prenatal care. In the early 1980s it was controversial whether ultrasound should be used as an examination method for all pregnancies or whether it should be reserved for specific indications. Which application of ultrasound would have a positive impact on the outcome? Additionally, a number of ethical questions arose as a consequence of prenatal detection of anomalies on the background of cultural, political and economic differences in different countries.

Ian Donald pioneered the development of ultrasound technology for clinical use and initiated the first clinical studies in the field of obstetrics and gynecology. In 1955 he started to explore pelvic tumors in vitro before he developed obstetrical ultrasound. His Lancet publication in 1958 was a landmark paper describing ovarian cysts, fibroids, ascites, abdominal carcinomatosis and various conditions related to pregnancy (Donald et al. 1958). The first fetal anomaly displayed by ultrasound was reported shortly thereafter and described a case of fetal hydrocephaly (Donald and Brown 1961). In 1964, Bertil Sundén from Lund in Sweden was the first to address the use of ultrasound in obstetrics and gynecology in a doctoral thesis. Amongst numerous first-time observations, he described the first anencephalic fetus (Sunden 1964). In 1968, Stuart Campbell (Campbell 1968) introduced an improved method to measure the fetal biparietal diameter, today a standard measurement in fetal biometry. In 1972, Campbell published reports on detection of anencephaly (Campbell et al.

1972) and later of spina bifida (Campbell et al. 1975). The first fetal kidney anomaly was described by Garrett in Australia (Garrett et al. 1970). In the years that followed, several anomalies were detected, parallel to improvement of ultrasound technology (Levi et al. 1995; Levi 1997; Zimmer et al. 1997). More recent studies have pointed out that detection rates have increased not only because of improved technology, but also because of improved sonographer skills (Taipale et al. 2003; Tegnander and Eik-Nes 2006).

Development of ultrasound technology in obstetrics

The increasing use of ultrasound in obstetrics raised the awareness of the efficacy of performing systematic fetal ultrasound examinations in every pregnancy as opposed to using ultrasound only when a problem was identified on the basis of classical clinical findings. Randomized controlled trials were carried out to investigate benefits of systematic use of ultrasound examination in pregnancy (Bennett et al. 1982; Bakketeig et al. 1984; Eik-Nes et al. 1984; Neilson et al. 1984; Waldenström et al. 1988; Saari-Kemppainen et al. 1990; Ewigman et al. 1993; Salvesen 1993; Saari-Kemppainen et al. 1994; Saari-Kemppainen 1995; Eik-Nes et al. 2000).
A Cochrane review (Neilson 2004) on second trimester ultrasound examination before 24 weeks, compared an offer of ultrasound examination to all pregnant women, with offering ultrasound examinations for specific indications only. The review showed that the main benefit of an offer to all was a more precise estimate of the gestational age, resulting in a 70% reduction of induction for overdue pregnancies (Eik-Nes et al. 1984; Waldenström et al. 1988). Further advantages amongst the systematically examined group were earlier detection of multiple pregnancies and earlier detection of

clinically unsuspected fetal malformation at a time when termination of pregnancy (TOP) is possible. In the main results there were no differences in a particular clinical outcome, such as perinatal mortality. However, a Helsisinki trial showed a reduced perinatal mortality of nearly 50% due to early detection of major anomalies that led to termination of pregnancy (Saari-Kemppainen et al. 1990). A one stage second trimester ultrasound examination also demonstrated to be very cost effective, with significantly fewer perinatal deaths in systematically examined groups (Leivo et al. 1996; Buechler 1998). The RADIUS trial (Ewigman et al. 1993), which was included in the Cochrane review, has been one of the most controversial studies because of their negative results in favor of offering an ultrasound examination to all pregnant women. The RADIUS study authors concluded that systematic use of second trimester ultrasound examination did not improve perinatal outcome as compared with the selective use of ultrasound on the basis of the clinician's judgment. The low detection rate of anomalies of 17% before 24 weeks of gestation was far below standards and has been criticized; the poor results in the RADIUS study were most probably due to insufficient sonographer skills (Romero 1993; Eik-Nes et al. 2000; Neilson 2004).

The first program using ultrasound systematically in pregnancy was initiated in Malmö, Sweden in 1974. A single scan was performed in pregnancy week 28 in order to detect twin pregnancies. Over the years, the examination was moved towards week 17. From 1976 on, a second routine examination was included, at 32 gestational weeks (Grennert et al. 1978). The health authorities in Sweden have never officially introduced the program. However, the Malmö program was later adopted throughout Sweden and influenced a similar German program in 1980.

Germany was then the first country to officially introduce a two-stage-screening program to all pregnant women (Mutterschafts-Richtlinien 1980). In Norway, a consensus panel recommended offering one ultrasound examination at approximately 18 gestational weeks to all pregnant women (Backe and Buhaug 1986). The recommendation was based on the reported decrease in post-term pregnancies, following the introduction of routine ultrasound (Eik-Nes et al. 1984). Moreover there was a need to regulate the already extensive use of ultrasound in pregnancy and to reduce the number of scans (Eik-Nes 1986). Following the introduction of the program, it was shown that the number of scans was reduced (Backe and Buhaug 1986; Eik-Nes 1986; Backe 1997). In a number of other European countries, the health authorities introduced routine ultrasound examination. Iceland followed the Norwegian one-stage model in 1987 (Geirsson 1987) and Austria followed the German two-stage model in 1988. In 1995, Germany expanded the program by offering an early fetal scan at 10 weeks (Änderung der Mutterschafts-Richtlinien 1995). In 1996, Switzerland introduced an early scan at 10 weeks followed by a scan at 18 weeks. Although not all countries have officially introduced a systematic program, today most countries in the industrialized world offer ultrasound examinations to their pregnant population (Care 1998). The major reasons for the systematic introduction of ultrasound are the benefits of management of pregnancy and fetal outcome, as well as accurate pregnancy dating and early twin detection (Care 1998; Neilson 2004).

Detection of congenital fetal anomalies

Congenital anomalies are found in approximately 3% of all infants (Kalter and Warkany 1983; EUROCAT 1997). The reported incidence varies, depending on ethnicity, populations (selected or non-selected) and period of follow up. Additional criteria such as inclusion or exclusion of spontaneous abortions, intrauterine fetal deaths and terminations may affect the figures.

The accuracy of ultrasound detection of fetal anomalies in high-risk populations was evaluated during the early 1980s in Europe by Campbell and Pearce (Campbell and Pearce 1983), Gembruch and Hansmann (Hansmann and Gembruch 1984) and in the USA by Sabbagha et al. (Sabbagha et al. 1985).

Detection of congenital anomalies in large series was evaluated in the late 1970s by Campbell and Pearce (Campbell and Pearce 1983) and then in Sweden (Kullendorff et al. 1984) and in the USA (Hill et al. 1985; Li et al. 1988). Systematic routine ultrasound for identification of congenital anomalies was performed in strictly low-risk pregnancies in larger populations from the late 1980s through early 1990s (Levi et al. 1989; Chitty et al. 1991; Saari-Kemppainen et al. 1994) .

Studies have shown great variation in the detection rates of anomalies. A review of 36 studies published between 1978-1997 (Levi 2002), showed that the sensitivity for prenatal detection of fetal anomalies varied from 8-90%. It is therefore understandable that the reliability and utility of ultrasound examination for fetal anomalies have

become the subject of so many controversies, and that there was hesitation in initiating routine ultrasound examination, instead of performing ultrasound examination on specific indications (Ewigman et al. 1993; Romero 1993; Eik-Nes et al. 2000; Neilson 2004).

Most fetuses with major chromosome aberrations have structural anomalies (Wladimiroff 1995) which are possible to detect by ultrasound examination (Nicolaides et al. 1993). Although there are certain patterns of structural defects (Hill 1996), specific fetal structural anomalies are not pathognomonic for individual chromosomal abnormalities. Consequently, studies have shown a huge variation in ultrasound detection rates from 7% to 80% of all chromosomal abnormalities (Stoll et al. 1991; Gagnon et al. 1992; Nicolaides 1992; Twining and Zuccollo 1993; Claussen et al. 1994; Den Hollander et al. 1994; Meagher et al. 1994; Hill 1996; Grandjean et al. 1998; Bromley et al. 2002).

There is a well-known association between all trisomies and maternal age. The association between trisomy 21 and increased maternal age was noted in 1909 by Shuttleworth (Shuttleworth 1909), the risk rapidly increasing after 40 years of age. Due to this association, most western countries offered additional tests to rule out any chromosome aberrations to pregnant women over 35 years of age. Trisomy 13, 18 and 21 account for 67% of all fetuses born with a karyotypic abnormality (Snijders et al. 1994).

Detection of fetal chromosomal aberrations – especially trisomy 21

In 1966, it became possible to diagnose trisomy 21 prenatally by karyotyping cultured amniotic fluid cells (Steele and Breg 1966; Valenti et al. 1968). Currently, both chorionic villus sampling (CVS) and amniocentesis (AC) are used as highly accurate diagnostic tests for fetal chromosomal aberrations (Hahnemann and Vejerslev 1997). Amniocentesis at 16 weeks is associated with a 0.5-1% risk of fetal loss (Tabor et al. 1986; Saltvedt and Almstrom 1999). CVS performed at 11-13 weeks carries a fetal loss rate similar to mid-trimester amniocentesis (Smidt-Jensen et al. 1992; Kuliev et al. 1996). Studies of the effect of early AC performed at 10-13 weeks show an increased risk of fetal loss and increased risk for talipes equinovarus (CEMAT 1998). AC performed at 16 weeks and onwards seems to be the safest, and is therefore the predominant choice at our center (Tabor et al. 1986; Smidt-Jensen et al. 1992). A complete analysis of the fetal chromosomes by karyotyping takes around two weeks, irrespective of the method used. By using a FISH test (fluorescent in situ hybridisation) diagnosis of selected chromosomal aneuploidies, e.g. trisomy 13, 18 and 21, X, and Y may be performed within 2-3 days (Eiben et al. 1998; Isaksen et al. 2000).

Trisomy 21 is the most common chromosomal aberration in infants, with a prevalence of about 1.6 in 1000 newborns in Norway (Medisinsk fødselsregister 2003/2004). Due to its known association with all trisomies, maternal age was the first criterion for screening for trisomy 21 (Hook 1981; Ferguson-Smith and Yates 1984; Adams et al. 1987). Karyotyping of fetuses of mothers beyond 35 years of age is claimed to

prenatally identify about 30% of all fetuses with trisomy 21, assuming that 5-8% of all pregnant women are within this age group (Nyberg et al. 1990; Snijders et al. 1998). Obviously, the detection rate is a function of the maternal age distribution in the population. The maternal age is increasing in Norway as elsewhere in the western world. At present the mean maternal age at delivery in Norway is 30 years (Statistisk sentralbyrå 2007).

In the 1980s, another screening method for trisomy 21 was established including measurement of various maternal serum proteins of fetoplacental origin. These second trimester multiple-markers mostly comprise alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG), unconjugated estriol (E3) and Inhibin-A, and are offered as a routine to pregnant women in the UK, USA, Europe and Australia etc. since the 1990s (Canick et al. 1988; Palomaki et al. 1997). With a 5% false-positive rate, these tests yield sensitivities of 67-76% for trisomy 21, depending on whether menstrual or sonographic dating is used (Wald et al. 1997).

In the 1990s, a correlation between nuchal fluid accumulation and trisomy 21 was found at first trimester ultrasound (Szabo and Gellen 1990).This led to an introduction of a first trimester scan combining maternal age with measurements of the fetal nuchal translucency (NT) thickness at 11-13^{+6} weeks of gestation. Studies reported that approximately 75% of trisomy 21 fetuses had increased nuchal translucency (NT) thickness (Nicolaides et al. 1992; Pandya et al. 1995). Subsequently, maternal age was combined with fetal NT and maternal serum biochemistry (free β-hCG and PAPP-A, the double test) yielding detection rates as high as 87% - 92% for trisomy 21 with a false positive rate of 5% (Spencer et al. 2000; Cuckle 2002; Nicolaides 2004;

Nicolaides et al. 2005). Studies have reported detection rates up to 97% for trisomy 21 when adding the absence of nasal bone to NT measurements, serum biochemistry and maternal age (Cicero et al. 2003).

Invasive prenatal diagnosis for trisomy 21 with amniocentesis or chorionic villus sampling is offered to women with advanced maternal age in most western countries at 35 years of age, and in Norway at 38 years. Additionally, invasive testing is offered to women who have fetal abnormalities at the second trimester ultrasound examination.

Second trimester ultrasound examination alone has never and will probably never become a preferred procedure to detect trisomy 21, because it largely relies on detection of typical associated anomalies. Such anomalies in trisomy 21 fetuses may be found in only 33% of fetuses (Nyberg et al. 1990). At 18 weeks, trisomy 21 fetuses may have brachycephaly, mild ventriculomegaly, flattening of the face, nuchal edema, atrioventricular septal defects, duodenal atresia and echogenic bowel, mild hydronephrosis, shortening of the limbs, “sandal gap” between first and second toe and clinodactyly or mid-phalanx hypoplasia of the fifth finger (Nicolaides 1992). Detection rates vary, as in unselected populations between 6.3% in a Scandinavian multicenterstudy (Jørgensen et al. 1999), and 26% in a European multicenter study (De Vigan et al. 2001). An overall detection rate of 46% was achieved in a French register study, when only the cases with anomalies detected by ultrasound were counted (Cans et al. 1998). In this study, the detection rate increased in the last period of investigation due to the introduction of an additional first trimester scan.

The detection rate of trisomy 21 was 68% based on maternal age and mid-trimester ultrasound scan in a maternity unit in Southampton, UK, between 1993 and 1998. However, the detection rate was only 41% in younger women (<35 years), when cases detected as a result of privately arranged serum or nuchal translucency screening were excluded (Howe et al. 2000). It is difficult to find recently published studies on detection rates of trisomy 21 based purely upon the second trimester scan. This is a consequence of the fact that first trimester scans in addition to biochemical tests, are offered in most countries. This obviously has a strong influence on the published results and the interpretation thereof.

In selected populations, trisomy 21 could be identified with ultrasound in the second trimester with a sensitivity of 43%-90% (Benacerraf et al. 1987; Rotmensch et al. 1997; DeVore 2000). These results are most likely due to a selection bias, as indications for referrals often were advanced maternal age, abnormal biochemical screening, previous children with trisomy 21, pathological routine scans etc., and the figures cannot be compared to results from non-selected populations.

In conclusion: The increased detection rate of trisomy 21 in most countries, is due to a shift away from the second trimester scan including second trimester biochemical tests, toward a first trimester scan including the double test, which has improved the detection rates significantly (Cicero et al. 2003).

Facial clefts

Cleft lips with or without cleft palate rank among the most frequent birth defects (Kraus et al. 1963; Benacerraf and Mulliken 1993), occurring in approximately 1 per 1000 live births. There is a variation between racial and ethnic groups. The prevalence is higher in Orientals and lower among Africans (Ferguson 1988; Bianchi et al. 2000). Approximately 350 syndromes have been linked with facial clefting, some of which are lethal or include severe morbidity (Gorlin et al. 1971). Multiple nutritional and toxicological factors have been identified as causal agents (Wyszynski and Wu 2002; Murray and Schutte 2004; Hrubec et al. 2006).

The palate is formed during the intrauterine LMP-based weeks 8-12; the primary palate is a very small anterior part of the palate, comprising the anlage of the premaxilla. This part of the bone must fuse with the posterior part, called the secondary palate. This is the major portion of the palate formed by fusion of two maxillary outgrowths named palatine shelves. The anatomical junction between the anterior and posterior shelves is called the incisive foramen (Figure 1). The incisive foramen is considered the dividing landmark between the anterior and posterior cleft deformities. Those anterior to the incisive foramen include cleft lip and cleft upper jaw. Such defects are due to a partial or lack of fusion of the maxillary prominence with the medial nasal prominence on one or both sides. Those defects that lie posterior to the incisive foramen include cleft palate and cleft uvula, and result from a lack of fusion of the palatine shelves.

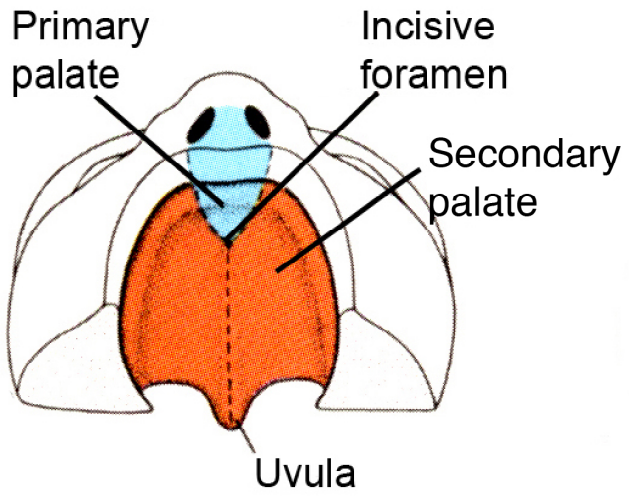


Figure 1.

Ventral view of the normal palate, gum, lip and nose. Reprint from Langman's Medical Embryology, 10th Edition 2006, T.W.Sadler, Head and Neck, Firgure 16.28, Page 276, with permission of Lippincott Williams & Wilkins.

The initial detection of cleft lip and palate may result in the finding of associated further malformations in 36%-63% of the cases (Shprintzen et al. 1985; Stoll et al. 2000). Thus, most authorities emphasize that the prenatal detection of anomalies should always generate a more extensive examination including karyotyping and a search for additional anomalies to obtain a precise diagnosis and prognosis (Levi 2002). Several studies have shown considerable variation in the detection rates of facial clefts, ranging from 0 to 91% (Levi et al. 1991; Bronshtein et al. 1994), which implies that the ultrasound diagnosis of facial clefts still remains a challenge.

The clefts can be found as either isolated clefts of the anterior or posterior part, or a combination thereof, as shown in Figure 2.

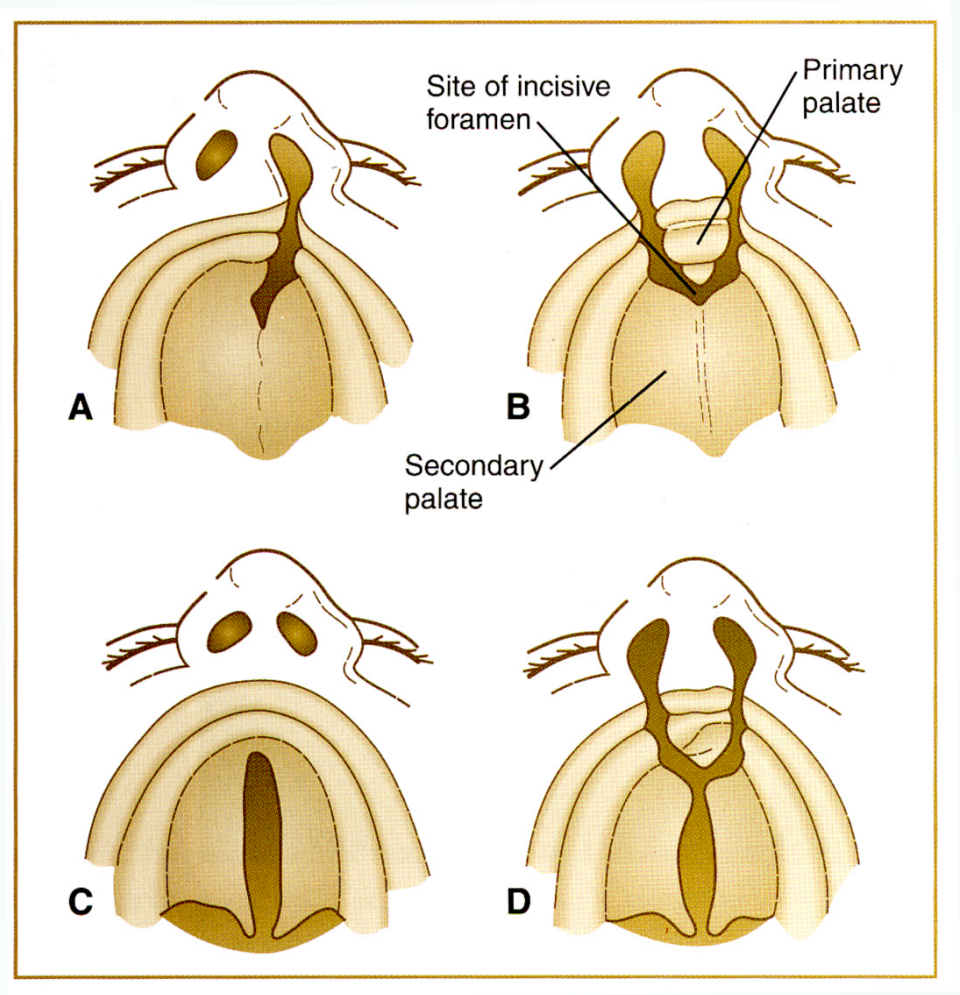


Figure 2.

Common varieties of cleft lip and palate. A, Unilateral cleft passing through the lip and between the premaxilla (primary palate) and secondary palate. B, Bilateral cleft lip and palate. C, Midline palatine cleft. D, Bilateral cleft lip and palate continuous with a midline cleft of the secondary palate. Reprint from: Human Embryology and Developmental Biology, B.M. Carlson, Third Edition, 2004, Head and Neck, Figure 14-18, Page 337, Mosby Inc (Carlson 2004) with permission from Elsevier.

The parents should be explained that children with facial clefts ought to be treated by a multidisciplinary specialist “cleft team” that may include surgeons, ear-nose-and-throat specialists, orthodontists, speech therapists, audiologists and dentists. The

timing for surgery varies, but usually an operation to close a cleft lip will be done when the child is three months old. Surgery for cleft palates is usually performed around 12 months. Further surgery may be needed later in childhood to improve the appearance of the lip and nose and the function of the palate.

Talipes equinovarus

Clubfoot, or congenital talipes equinovarus (TEV), is one of the most common congenital birth defects (Drvaric et al. 1989; Lochmiller et al. 1998). The prevalence of isolated TEV is 1 per 1000 live births (Wynne-Davies 1972; Cowell and Wein 1980). TEV is characterized by a deformity of the fetal foot fixed in adduction, supination, and varus position. There is subluxation of the talo-calcaneo-navicular joint, with underdevelopment of the soft tissues on the medial side of the foot and frequently of the calf and peroneal muscles (Drvaric et al. 1989), (Figure 2).

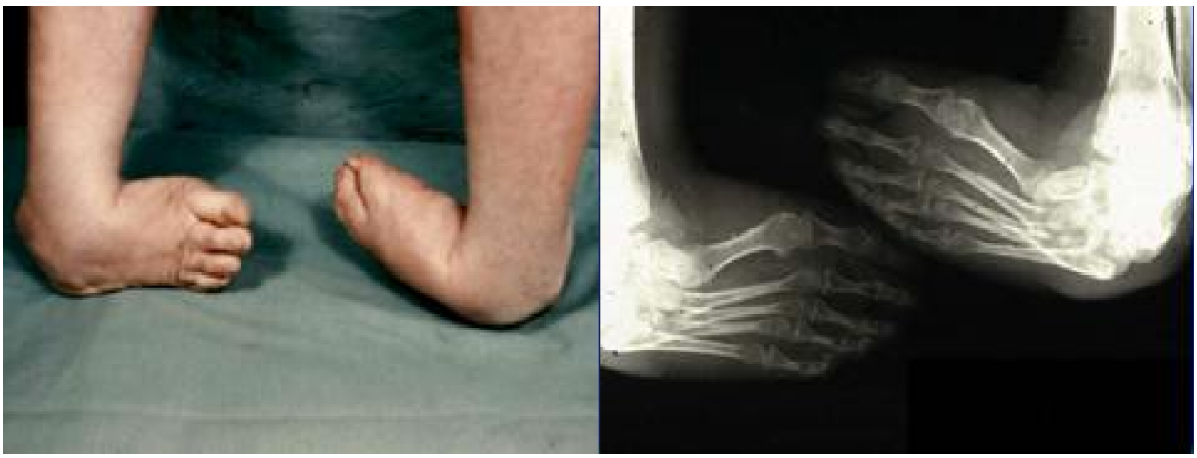


Figure 2.

TEV, with X-ray

As a result, the foot is typically turned inwards giving the foot a club-like appearance. At prenatal ultrasound the diagnosis of TEV is made when the foot is orientated in the same plane as the lower leg, and visualization of the tibia and fibula are possible in the same section as the foot (Figure 3).

Clubfoot was first depicted in ancient Egyptian tomb paintings, and treatment was described in India as early as 1000 B.C. The first written description of clubfoot was given by Hippocrates (circa 400 B.C.), who believed the causative factor to be mechanical pressure due to deforming forces in the uterus. Today a number of hypotheses still remain, and research findings do not clearly support any particular one. Proposed mechanisms are uterine restriction, abnormalities of joint and/or bone formation, connective tissue, distal limb vasculature, neurological development, muscle migration or an underlying developmental abnormality or developmental arrest (Miedzybrodzka 2003). There is strong evidence that a genetic component may be the etiology of talipes equinovarus (Idelberger 1939). In Idelberger's twin study, monozygotic twin concordance (32.5%) was much greater than dizygotic twin concordance (2.9%). Most authors seem to regard both environmental and genetic factors as playing a role. Toxins, temperature and seasonal-infective pathogens have been postulated as possible etiological factors as well (Pryor et al. 1991). There have been studies supporting seasonal changes (Pryor et al. 1991; Barker and Macnicol 2002) and studies concluding with its non-existence (Loder et al. 2006). A high incidence of TEV is associated with early amniocentesis (11-12 gestational weeks) versus amniocentesis in the second trimester (15-16 weeks) (Tredwell et al. 2001).

When diagnosed in the neonatal period, approximately one third of the cases of TEV are reported to be isolated (Wynne-Davies 1972). TEV is frequently associated with other fetal anomalies, including aneuploidy; thus, a thorough examination of the whole fetus is important whenever the diagnosis of TEV is suspected in the prenatal ultrasound examination (Yamamoto 1979; Benacerraf 1986; Mammen and Benson 2004). It is reported that after detection of a clubfoot, further scrutiny can result in detection of additional defects in 80% of cases (Rijhsinghani et al. 1998).

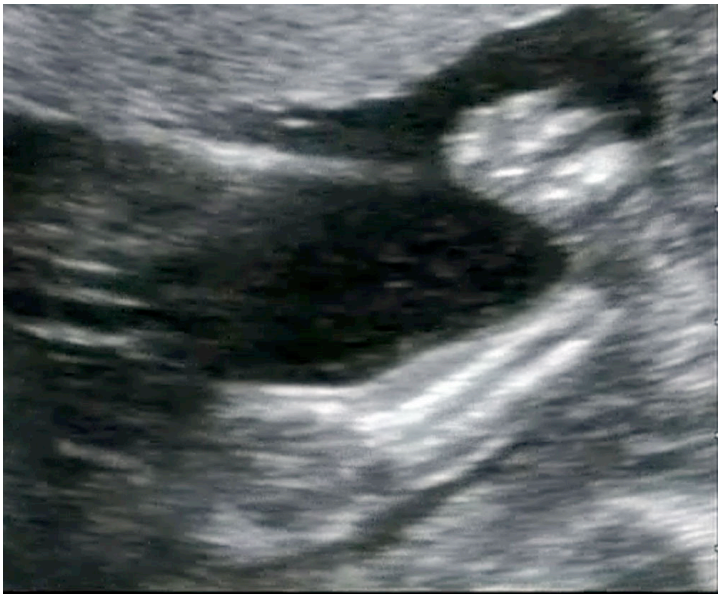


Figure 3.

Prenatal ultrasound demonstrating the visualization of the fetal foot and tibia and fibula in the same plane

There are two methods of treatment for talipes equinovarus: medical and surgical. The aim of the medical therapy is to correct the deformity early and fully and to maintain the correction through manipulation, casting, and splintage alone. The most frequently used surgical approach is the posteromedial release, which has many

variations. However, long-term follow-up studies have shown that the results of surgical treatment are disappointing. Increasing foot pain, weakness, and stiffness often lead to premature arthritis and disability of the foot (Hutchins et al. 1985; Aronson and Puskarich 1990; Kite 2003).

Ponseti, at the University of Iowa, developed an alternative non-operative method in the 1950s. This method comprises weekly repetitive manipulations of the clubfoot with plaster casting where the components of the clubfoot are treated in sequence. For approximately 40 years, Iowa City was the only place where the Ponseti Method was practiced. He reported satisfactory functional results in 89% of the individual cases he treated (Laaveg and Ponseti 1980). After 30 years of follow-up, he concluded that excellent or good functional outcomes were achieved. Ponseti published a book on his method in 1996 (Ponseti 1996) and the Internet has been instrumental in getting the word out worldwide to parents and surgeons (Morcuende et al. 2003). The Ponseti Method is now the universal method of choice (Colburn and Williams 2003; Heilig et al. 2003; Morcuende et al. 2004; Faulks and Luther 2005).

European registry studies

Detection of a congenital anomaly by ultrasound is a rare event. Thus, large numbers of fetuses need to be examined in order to find enough cases to draw scientifically sound conclusions on prevalence and typical ultrasound appearance. In Europe there

are two major registries, the EUROCAT and the Euroscan study, which contain some of the largest published ultrasound materials on congenital malformations.

In 1979 the EUROCAT registry was started with the aim of recording congenital anomalies. This European registry records congenital anomalies in 30 geographical areas from 15 countries, mostly from within the European Union. The purpose is epidemiological surveillance of birth defects. Data from approximately 300 000 births and 5 000 congenital anomalies per year have been gathered (EUROCAT 1997).

The aims of the Euroscan study were to evaluate the feasibility of routine ultrasound scanning across Europe, and to evaluate the prenatal detection rate of all congenital malformations and termination of pregnancies in unselected populations. Data were provided from 16 registries collaborating with the EUROCAT registry and four registries without EUROCAT collaboration, from a total of 12 European countries. The study period was from 1996 to 1998. Altogether, 8 126 malformed fetuses/newborns were diagnosed in a total of 709 030 consecutive births in the areas covered by the registry (Clementi and Stoll 2001). Facial clefts (Clementi et al. 2000) and chromosomal anomalies (De Vigan et al. 2001) are among the anomalies that have been studied within the large population.

In a region around the city of Strasbourg, northern France, all fetuses, terminations and newborns were included in the registry covering 11 maternity hospitals for the period 1979-1999. The registries included approximately 280 000 consecutive births. From this material, several important reports have been published, for example

addressing oral clefts (Stoll et al. 1991) and fetal chromosome abnormalities (Stoll et al. 1993).

Additionally, a multicenter study called Multicentric Eurofetus Study was designed to evaluate the sensitivity of ultrasound routine screening for fetal malformations. The screening was applied to 200 000 pregnant women examined by ultrasound in 60 obstetrical ultrasound hospital laboratories in 14 European countries (Levi and Montenegro 1998; Grandjean et al. 1999). Alltogether, 3 685 malformed fetuses were recorded prospectively between 1990-1993. The main study results have been summarized by Grandjean et al. showing a 61.4 % sensitivity of the 3 685 minor and major malformed fetuses, and a 41% elective termination rate for severe malformations (Levi et al. 1991; Levi et al. 1995; Levi and Montenegro 1998; Grandjean et al. 1999). In addition, Levi contributed with several important studies (Levi et al. 1991; Levi et al. 1995; Levi and Montenegro 1998).

Compared to these European data, our material highlighted some significant differences between our non-selected Norwegian population and other European countries, which are addressed in this thesis.

Improved fetal imaging – improved detection of anomalies

The technology of ultrasound has had an extensive development from its early introduction into medical use in the 1950s. Additionally, the practitioners have

developed better skills with introduction of formal education. Approved by the American Institute of Ultrasound in Medicine, the American Society of Ultrasound Technical Specialists was established in 1970, the first accreditation of educational programs occurred more than ten years later in 1982 (Baker 2005). Today, postgraduate ultrasound programs for sonographers are established in several countries, such as the USA, Canada, Australia and the United Kingdom. In 1997, the National Center for Fetal Medicine established a postgraduate educational program in obstetric ultrasound for nurse/midwives at the university level in Trondheim. So far, unfortunately, this is the only program of its kind in Scandinavia. The importance of operator education is obvious, and has been confirmed by a study showing that education and experience of the operator had a significant impact on the detection rate of congenital heart defects (Tegnander and Eik-Nes 2006).

Many authors have described improved detection rate of anomalies over time (Carrera et al. 1995; Grandjean et al. 1999; Stoll et al. 2002; Richmond and Atkins 2005; Tegnander et al. 2006). A second important development resulting from improved fetal imaging is the increased use of ultrasound in the first trimester. Early sonography at 11- 14 weeks may detect major structural defects; reported detection rates vary between 41% - 65% (Hernadi and Torocsik 1997; D'Ottavio et al. 1998; Economides and Braithwaite 1998; Whitlow et al. 1999).

Grandjean reported that in fetuses with malformations, the average number of malformations per fetus was 1.25, so a search for other anomalies should always be included (Grandjean et al. 1999). In an editorial, Clementi and Stoll stated that: " in all countries all malformations have a significantly lower detection rate if isolated,

confirming that anomalies have a higher chance of being detected if associated with at least one other major malformation" (Clementi and Stoll 2001). This statement has been confirmed at our center as well (Tegnander et al. 2006; Offerdal et al. 2007).

Consequences of prenatal diagnosis of fetal anomalies

The potential advantages of prenatal diagnosis are fetal treatment, customized surveillance and improved outcome (Touloukian and Hobbins 1980; Romero et al. 1988; Bonnet et al. 1999; Brantberg et al. 2002; Lindley et al. 2006). Intrauterine therapy, selective preterm delivery, choice of the mode of delivery, transportation of a sick fetus in utero and selective termination of pregnancy may all be consequences of prenatal diagnosis (Crombleholme et al. 1996). Intrauterine therapy, including fluid aspiration or permanent drainage, blood transfusions (Hansmann et al. 1989), shunting, laser coagulations (Hecher et al. 2000; Ong et al. 2006; Middeldorp et al. 2007; Oepkes et al. 2007) and pharmaceutical therapy (Gembruch et al. 1989) are all factors that represent the increasing spectrum of fetal treatment.

Fetal/neonatal lives can be saved by prenatal diagnosis and adequate fetal medicine. Several papers show improved conditions preoperatively for newborns with a heart defect when detected prenatally (Bonnet et al. 1999; Tworetzky et al. 2001; Franklin et al. 2002). Although surgical results are similar, the reduced morbidity decreases surgical delays and potentially may impact on neurodevelopmental outcomes and long-term outcome (Jacobs and Norwood 1994; Eapen et al. 1998; Kumar et al. 1999; Mahle et al. 2000). A study on prenatal detection of gastroschisis, indicated improved

outcome by close CTG surveillance in the third trimester, through detection of intrauterine stress and thereby reducing the risk of IUFD (Brantberg et al. 2004).

Counseling

Improved knowledge of the occurrence of different anomalies as they appear in a non-selected population, and knowledge of the frequency of isolated and associated anomalies is necessary for providing correct counseling. In our department, we have a multidisciplinary perinatal team, who participate in the counseling process when anomalies are detected. Depending on the diagnosis, pediatric surgeons, neurosurgeons, plastic surgeons, pediatricians, pediatric cardiologists, obstetricians, specialists in fetal medicine as well as midwives and social workers are included in the counseling team. In some cases other parents of a child with a particular disorder have taken part in the counseling process. Most parents are unfamiliar with the diagnosis, so it is important to explain about the nature of the anomaly, the prognosis as well as the management options. In this setting it is challenging to give a balanced presentation of the prognosis. Over the years as we have realized the difficulty and importance of counseling and our counseling process has continuously been developed. In 1997, two social workers were added to the team, one of their contributions is to provide detailed information about the postnatal support program offered by the health authorities for the various developmental disorders. We have empirical reason to believe that the discussion concerning whether or not to terminate a pregnancy with a fetus with a future disability is partly influenced by the support our

society offers. Counseling parents is a difficult task involving the fine-tuned balance between being objective and directive.

Fetal medicine is a relatively new field. For many conditions, the prognosis of the developmental disorder is dominated by the experience from cases that survived pregnancy, birth and the immediate neonatal period: the neonatal population. However, it is incorrect to inform about the prognosis based mainly on the neonatal population as long as the time of diagnosis usually takes place between 12 and 20 weeks in pregnancy. Counseling has to be based on long-term follow up of large prenatally diagnosed populations. An example is counseling about the diagnosis of omphalocele. In a study by Brantberg with 90 fetuses with omphalocele, only 21 (23%) survived and only 8 (9%) infants were alive and healthy (Brantberg et al. 2005). This is due to a strong association between omphalocele and other associated anomalies including an abnormal karyotype. It reflects a strong contrast to a neonatal population of omphalocele with survival rates in the range of 90% (Mayer et al. 1980; Rankin et al. 1999). Similar results were found in a study of prenatally detected congenital heart defects (Tegnander et al. 2006). This emphasizes how important it is to base the counseling process on large follow up data from the time of diagnosis, through pregnancy, birth, the neonatal period and possibly further on.

All counseling and all treatment decisions following detection of anomalies should also be based on international nomenclature and standards.
The term congenital anomaly usually refers to structural defects (congenital anomalies, disruptions and dysplasia), chromosome aberrations, inborn errors of metabolism and hereditary diseases. In contrast, a malformation may be defined as:

"Any anomaly detected at birth or apparent within the first postnatal years, which is likely to result in death, disfigurement or disability, and which is likely to require medical or surgical treatment" (National Perinatal Epidemiology Unit 1995).

The World Health Organization defines disability as: "Any restriction or lack (resulting from an impairment) of ability to perform an activity in the manner or within the range considered normal for a human being" (International Classification of Impairments, Disabilities and Handicaps. Geneva. WHO 1980). It is of importance to define the grade of disability when counseling, and discussing the clinical domains in which it can appear. Disability can be measured according to: malformation and congenital abnormality, neuromotor function, auditory function, communication, visual function, cognitive function or other physical disabilities. In clinical domains there are grades of severity from severe to moderate to mild disabilities. There are different classification systems to group disabilities and anomalies (National Perinatal Epidemiology Unit 1995; Marlow et al. 2005). Severe disability is defined as an ability that makes the child highly dependent on caregivers and IQ score more than 3 SD below the mean, profound sensorineural hearing loss, or blindness (National Perinatal Epidemiology Unit 1995; Marlow et al. 2005).

We extended the prognostic categories suggested by others (Report of the RCOG Working Party 1997; Bricker et al. 2000) and added examples (Table 1).

Table 1 The prognostic categories with examples

Prognostic category	Expected consequence	Examples
1	Antenatal death	Triploidy Turner syndrome or trisomy 21 with cystic hygroma and severe hydrops Severe conditions with hydrops as lethal multiple pterygium syndrome
2	Death within 7 days after birth	Bilateral renal agenesis Anencephaly Trisomy 18 with major associated anomalies and severe growth restriction Short-rib-polydactyly syndrome
3	Death within the first year of life	Trisomy 18 with less severe associated anomalies Trisomy 13
4	Death before school age	Lissencephaly (Miller-Dieker syndrome)
5	Death or survival with severe handicap	Severe hydrocephaly Marshall-Smith syndrome Major congenital heart defects Myelomeningocele with associated central nervous system anomalies such as significant cerebellar hypoplasia
6	Survival with presumed severe disability and mental retardation	Trisomy 21 with associated anomalies
7	Survival with presumed severe disability without mental retardation	Complete amelia Treacher-Collins syndrome
8	Survival with moderate disability	Dysmelia, amelia of one limb Silver-Russell syndrome
9	Survival without or with a minor disability after treatment	Gastroschisis Duodenal atresia Cleft lip and palate

Most studies report that the prenatal detection of congenital anomalies is seen as advantageous by the parents (Detraux et al. 1998). It is widely accepted that prenatal detection is of benefit for the postnatal course of parental distress, because parents will be prepared before the hospitalization period of their future child (Detraux et al. 1998). Detraux et al. concluded: "Antenatal diagnosis made with more and more sophisticated techniques and competencies, is desirable. It allows not only for better psychological preparation in making a decision regarding termination of pregnancy, but also in taking care of the future impaired child. It should be stressed however, that any detection is ethically correct only if consequences are correctly assumed. Women are able to cope with a birth defect, but need professionals who are responsive to their psychological difficulties" (Detraux et al. 1998). It is known that prenatal consultation by pediatric surgeons may have a significant impact on the perinatal management of the fetus with a surgically correctable congenital anomaly (Crombleholme et al. 1996). Changes in management including termination of pregnancy, in utero intervention, mode or timing of delivery have been described (Crombleholme et al. 1996). To our knowledge few authors contradict the positive effect of parents' experience by prenatal diagnostic and counseling (Hunfeld et al. 1999).

Counseling is not only of high importance when the anomalies are severe, but also when the anomalies are correctable after birth, leaving only slight cosmetic impairment. Prenatal counseling when facial clefts were diagnosed prenatally, showed that prenatal contact with a cleft team was experienced as valuable (Matthews et al. 1998). Sagi postulated in a study with 77 parents of children with clefts that the knowledge gained reduced uncertainty and gave the parents an increased sense of personal control (Sagi et al. 1992). In a 2004 study from Switzerland, with 29 couples

interviewed, 93% of the parents felt well prepared psychologically for the birth of their child and 96% considered prenatal diagnosis a benefit (Rey-Bellet and Hohlfeld 2004).

Clubfoot is a minor structural anomaly. But parents who had no antenatal diagnosis, almost all referred to the initial shock at birth and the lack of immediate information and reassurance that the condition was correctable (Burgan et al. 1999). The same authors concluded "that parents required adequate antenatal counseling to improve the understanding of the history and treatment of this condition". The ability to counsel patients appropriately necessitates accurate diagnosis of both the foot deformities itself and of the associated anomalies (Treadwell et al. 1999).

In contrast, Skari concluded that prenatal diagnosis of congenital malformations was associated with increased parental psychological distress after birth compared to distress in parents of babies with postnatal diagnosis (Skari et al. 2006). The suggested explanation from Skari et al. was that the duration of the latency from prenatal diagnosis to definitive surgical treatment was inversely related to parental distress. The lowest distress levels were seen in parents who were told about pathology after birth, and this group was characterized by short latency from diagnosis to surgical treatment. The authors however, did not discuss that a prenatally undiagnosed anomaly sometimes might be of a minor character and therefore the psychological distress might not be correlated to the same extent of burden or grief.

Termination of pregnancy

Termination of pregnancy (TOP) after prenatal diagnosis of major congenital anomalies is allowed in the second trimester (< 22^{nd}-24^{th} gestational week) in most countries. In France, Spain, UK and Germany, TOP is possible at any time of the gestation provided there is a severe fetal condition. There are large variations between countries regarding the rate of TOP. The lowest rates of TOP were observed in countries without an offer of a routine fetal examination and the Eastern European countries, while the highest were found in countries with three routine scans as Germany, France, Italy, Spain, Croatia and in the UK (Clementi and Stoll 2001).

According to Norwegian law (LOV 1975-06-13 nr 50 1975), the woman has a right to make the final decision about a termination of pregnancy before completed 12 weeks gestation. After 12 completed weeks, the woman must apply for a termination, and grounds for this are enumerated in subparagraphs. Still major consideration should be given to the woman's own assessment of her situation, but the conditions for authorization of termination of pregnancy becomes more stringent as the duration of the pregnancy increases. One of five criteria must be fulfilled to qualify for a termination of pregnancy after completed 12 weeks.

According to Norwegian Law (LOV 1975-06-13 nr 50 1975) these are:

1. The pregnancy, childbirth, or care of the child may cause unreasonable strain upon the physical or mental health of the woman.
2. The pregnancy, childbirth, or care of the child may place the woman in a difficult position.
3. There is a major risk that the child may suffer from a serious disease as a result of its genotype or a disease or harmful influences during pregnancy.
4. The woman became pregnant as a consequence of incestuous sexual relations or rape.
5. The woman is suffering from severe mental illness or is mentally retarded to a considerable degree.

A pregnancy may not be terminated after 18 completed weeks of gestation, unless there are particular important grounds for doing so, as for example severe fetal malformations. If there is a reason to believe that the fetus is viable, authorization for a pregnancy termination shall not be granted. According to practice this has led to a limit of completed 22 weeks of gestation. Later in gestation termination of pregnancy is only permitted if the diagnosed anomaly is lethal.

When parents are confronted with a fetal diagnosis, a number of questions arise and many decisions have to be made. The necessity to make a decision is by itself a source of stress. Parents may have to decide whether or not to karyotype or to attempt intrauterine therapy, whether or not to change mode of delivery or deliver early, or deliver in a tertiary center. The decision to terminate or not is often dependent upon

the diagnostic information of the ultrasound results and subsequent test results (Levi 2002). The prenatal detection of serious and lethal anomalies has been shown to increase the termination rate and causes a reduction in neonatal mortality rates (Stoll et al. 2002). Termination rates can differ, depending on organ system involved, and structural anomalies are terminated at other rates than chromosomal. A study from a well-defined population in northeastern France showed increased termination rates following increased prenatal detection rates in the time period 1979-1999 (Stoll et al. 2002), with higher TOP rates for chromosomal anomalies than for non-chromosomal anomalies. The same was seen in a population based study of over 500 000 infants born over a 16-year period in Northern England, where it was concluded that diagnostic accuracy improved over time. At the same time termination of pregnancy for fetal malformation more than doubled (Richmond and Atkins 2005). A study of Mansfield (Mansfield et al. 1999) showed that TOP following prenatal diagnosis of trisomy 21 and anencephaly were estimated to be 92% and 82%, respectively, based on a systematic review, including studies from different countries in the USA, UK and Europe. The termination rates occurred in 41% of severe malformations (Grandjean et al. 1999) in the Eurofetus study from 61 European obstetric units. However, in the Eurofetus study, a large difference in the ratio of termination was detected, independently of the ultrasound scan policy as well. This attitude was considered dependent on religious, ethical, cultural and private reasons, as well as the medical counseling received (Clementi and Stoll 2001).

Several researchers have tried to find the determinants of parental decisions to terminate a pregnancy. Studies mainly agree that the severity of anomalies directly correlates with the termination rate (Drugan et al. 1990; Evans et al. 1996;

Schechtman et al. 2002; Mezei et al. 2004; Shaffer et al. 2006). In addition, Shaffer found that the type of diagnostic procedure, maternal age and ethnicity contributed to patient's decision making in the setting of fetal aneuploidy (Shaffer et al. 2006). The author discussed that women who select CVS rather than amniocentesis are likely a different group of patients, and may have a lower tolerance for fetal abnormality and are more likely to have made their decision to terminate for any abnormality. Older maternal age at diagnosis has also been associated with a higher rate of decision to terminate an affected pregnancy (Drugan et al. 1990; Schechtman et al. 2002; Forrester and Merz 2003; Shaffer et al. 2006), although some studies have found an association with the decision to continue the affected pregnancy (Holmes-Siedle et al. 1987). Hispanic women were less likely to terminate an affected pregnancy (Cunningham and Tompkinison 1999) than Filipino women (Shaffer et al. 2006), which shows that cultural and religious factors are likely contributing factors to the complex and challenging decision of whether or not to terminate an affected pregnancy.

Interestingly, in some studies the diagnosis of an anomaly in the first trimester was not more likely to lead to a termination of pregnancy than in the second trimester (Drugan et al. 1990; Evans et al. 1996) whereas the gestational age was a significant factor in another study (Kramer et al. 1998).

The influence of termination of pregnancy on perinatal mortality

During the 1960s and 1970s, the overall infant mortality rates in industrialized countries declined substantially because of improved perinatal care, including the advent of neonatal intensive care and the increased use of cesarean delivery (Williams and Chen 1982). However, the rates of infant deaths due to congenital anomalies remained unchanged, and consequently the proportion of infant deaths attributable to congenital anomalies rose during this period (Goldenberg et al. 1983). A report on congenital anomaly-related infant mortality rates in Canada, England, Wales and the US was published by Liu (Liu et al. 2002). It showed that fetal deaths caused by congenital anomalies at very early gestation (20-25 weeks) had increased dramatically in recent years, while fetal and infant deaths at later gestation had declined. Prenatal diagnosis and selective termination of pregnancies affected by congenital anomalies were concluded to be the major factors responsible for the accelerated decline in infant deaths. It was suggested that further declines in infant mortality in industrialized countries could be expected as a result of increased use of prenatal diagnosis. Such consequences of prenatal diagnosis of congenital anomalies followed by termination of pregnancy on the perinatal mortality have also been described by others (Wen et al. 2000; van der Pal-de Bruin K.M. 2002).

Prenatal screening program

The first nationwide official prenatal screening program in Norway was introduced in December 1983. At that time Torbjørn Mork, head of the Norwegian Directory of Health, issued a letter with a short list of the indications for prenatal screening: (IK-1077, 1983).

1. Parents who already have a child with chromosome aberrations.
2. Parents who already have a child with a neural tube defect.
3. Parents who already have a child with hereditary metabolic disease, where genetic diagnosis is possible.
4. Parents who already have a child with severe X-linked recessive disease, or when there is a high risk that the mother is a carrier.
5. In cases were one of the parents is a carrier of a chromosome aberration and therefore has a high risk for a child with a severe developmental disease.
6. Parents with a high risk of having a child with a chromosome aberration due to the woman's age. Prenatal diagnosis is offered women over 38 years.

Initially, women at risk were offered an amniocentesis for analysis of the karyotype and amnion alphafetoprotein, the latter to detect neural tube defects. Later, chorionic villus sampling and chordocentesis were added. Since 2004, selected women at risk have been offered a first trimester NT ultrasound examination. Screening for trisomy 21 using serum biochemistry tests were officially forbidden by the health authorities until 2006. First in late 2006 a serum marker-screening program (double test) was introduced in combination with a first trimester NT ultrasound examination, but only

to the specific group of pregnant women at risk. In addition, prenatal diagnostic has been offered when fetal anomalies were diagnosed at the ultrasound examination.

Following a consensus conference one ultrasound examination at 18 weeks of pregnancy was introduced in 1986 in Norway for all pregnant women (Backe and Buhaug 1986). Within a few years a survey concluded that approximately 98% of the women accepted the offer (Backe 1994).

In the late 80s and early 90s, the diagnosis of fetal anomalies was increasingly discussed in Norway. In 1995 a second consensus conference was held. The offer of a routine fetal examination to all pregnant women was continued, but informed consent by the pregnant women was requested (Konsensuskonferansen 1995). Additional ultrasound examinations were available based on clinical indications such as bleeding, pain, uterus larger or smaller than expected, anxiety etc.

A new Norwegian law was introduced in 2003 (LOV-2003-12-05-100. 2003) in part with the intention to limit the use of early ultrasound. Early prenatal ultrasound (11+0-13+6 week scan) was thereafter centralized to 6 teaching hospitals. Women and pregnancies who did not fulfill the previous criteria could be admitted to early ultrasound examination in case of clinical indications and now also in case of anxiety. Instead of limiting the number of early ultrasounds, the public discussions of the topic led to an increased number of early ultrasound examinations.

The rate of women who have accepted the offer of amniocentesis due to maternal age throughout Norway is registered in a national register at the Directorate for Health

and Social Affairs. It is the responsibility of the first line medical health care to inform patients about this offer. However, from experience it is well known that some patients do not get this information.

Ethics

Whether it concerns prenatal diagnosis, giving treatment or rejecting treatment prenatally or terminating a pregnancy, fetal medicine has been, and still is in the crossfire of ethical discussions. This ethical debate has been particularly intense in Norway (Solberg 2003) in comparison with other Scandinavian countries. Norway has until now always had a political culture of protecting the individual strongly, also the fetus after 12 weeks. There is a strong focus on integration of disabled people. The association for disabled people, Norges Handikapforbund, has been active in political discussions when new proposals and regulations have been discussed. Also well-known people in Norway have fronted their life with disabled children and showed that it can be a positive challenge. Many parents even claim to experience a new perspective of values in their lives as a consequence of having disabled children. Some have been rather critical towards the possibilities of termination of pregnancy. It seems important to have a strong political and public focus on the topic of termination of pregnancy, as well as on the detection of chromosome and/structural anomalies and the rights of disabled people. It leads to a broad acceptance of disabled people participating in the communities.

The topic of termination of pregnancy is a sensitive issue. It may be related to personal opinion, religion, public opinion or the national political guidelines, as well as common public perception. The decision of a termination of pregnancy is one of the most difficult ethical dilemmas parents can be confronted with (Zeanah et al. 1993). Women who terminate pregnancies for fetal anomalies, grieve as intensely as those who experience a spontaneous perintal loss (Zeanah et al. 1993). The long-term psychological stress response associated with termination of pregnancy for fetal anomalies does not differ from the stress response seen in women who experience a perinatal loss (Salvesen et al. 1997).

In the counseling process it is of vital importance for the prenatal team that the counseling is based on a correct diagnosis. False positive diagnosis leading to termination of pregnancy is not acceptable. Our perinatal pathologist, Isaksen found good correlation between prenatal diagnoses and postmortem findings, with the main diagnosis correct in over 90% (Isaksen et al. 1998; Isaksen et al. 1999; Isaksen et al. 2000). This corresponds well with other studies, where similar results were found (Chescheir and Reitnauer 1994; Julian-Reynier et al. 1994; Stiller et al. 2001; Wald et al. 2004; Kaasen et al. 2006). In all the diagnostic results in this thesis, there was no major false positive diagnosis and in no cases a false positive diagnosis led to termination of pregnancy.

AIMS OF THE STUDIES

The second trimester routine ultrasound examination determines the gestational age, locates the placenta and detects multiple pregnancies. Another main purpose of the examination is to detect fetal structural anomalies. The detection of fetal disease including anomalies is the basis for fetal medicine. As part of a continuous quality assessment of prenatal ultrasound it is important to evaluate various consequences of a routine ultrasound examination program. The overall aim of this study is to contribute to this quality assessment in detection of both severe and less severe anomalies, as in studying the prenatal detection of trisomy 21 and studying the overall rate of termination of pregnancy, as well as the detection of talipes equinovarus (TEV) and facial clefts. It was of interest to also study specific anomalies that may be harmless and have good prognosis when occurring in isolation. Because the same anomalies could also be associated with very severe anomalies, some of which are difficult to diagnose anatomically; they then may have a completely different and very severe prognosis.

The primary aims of the studies were:

1. To evaluate prenatal ultrasound examination regarding the detection of talipes equinovarus (TEV) in a large non-selected population. Moreover, to study trends in detection rates over time, as well as the prevalence and outcome of isolated TEV and TEV with associated anomalies.

2. To evaluate prenatal detection of facial clefts by ultrasound in a large non-selected population, and to study trends in detection rates over 18 years. We also studied the prevalence and outcome of the isolated cases as well as cases with associated anomalies.

3. To evaluate the contribution of second trimester routine ultrasound examination as well as karyotyping due to maternal age, in the prenatal detection of trisomy 21 in a large non-selected population, in a time period when maternal biochemical screening and first trimester nuchal translucency screening were not used.

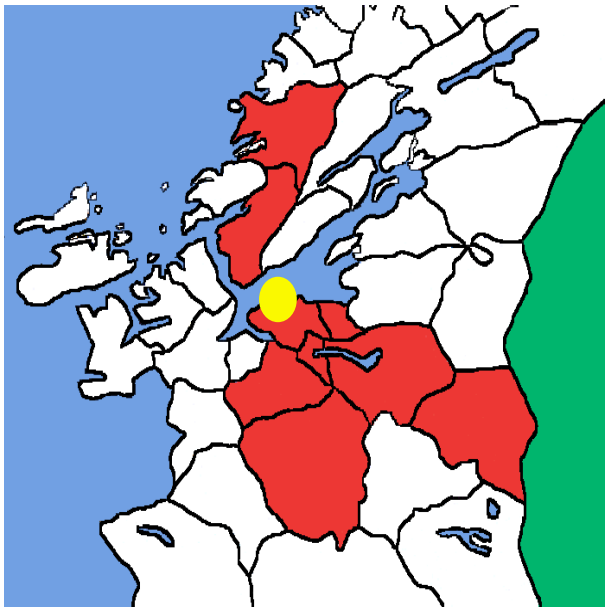
4. To evaluate the influence of fetal ultrasound examination on termination of pregnancies in a large non-selected population and to look for changes in the rate of terminated pregnancies and the severity of the terminated anomalies over time.

MATERIAL AND METHODS

Populations and study design

The study population represented a non-selected population residing in a geographically well-defined area consisting of the city of Trondheim and eight surrounding municipalities as shown in Figure 4. Communities included in the study:

1. Klæbu
2. Malvik
3. Melhus
4. Midtre Gauldal
5. Rissa
6. Selbu
7. Trondheim
8. Tydal
9. Åfjord



Within this geographical area, 97% of the pregnant women residents had a routine fetal examination at the National Center for Fetal Medicine (NCFM) at St. Olavs University Hospital in Trondheim, and later delivered at that hospital. The University Hospital also includes the only neonatal intensive care unit and pediatric surgery/orthopaedic department for the follow up of the same population. In Norway

facial cleft surgery is centralized to two other university hospitals, University Hospital of Bergen and The National Hospital, University of Oslo.

Specially trained sonographer midwives performed the routine fetal ultrasound examination between 16+1 and 22+5 gestational weeks. At the ultrasound examination, the biparietal diameter, the mean abdominal diameter and the femur length were measured. The number of fetuses, the fetal anatomy including the extremities, and the location of the placenta were assessed. All pathology found at the second trimester ultrasound examination was presented to specialists in fetal medicine at the center; these specialists also performed all ultrasound examinations for clinical indications, before and after the second trimester routine ultrasound examination including all necessary invasive procedures.

The NCFM has a patient administrative system (PAS) in the form of an extensive database in which data have been prospectively registered for each pregnancy from the first ultrasound examination through the pregnancy, birth and the neonatal period, and thereafter. For each fetus with congenital anomalies, SVHS videos, DVD's, biochemical results and karyotype were also registered. In addition, autopsy reports including photographs and x-rays were available for evaluation of the prenatal ultrasound findings in cases of TOP or IUFD. The registry used the nomenclature and coding system from the 9th and 10th revision of the International Classification of Disease (ICD-9, ICD-10). The term congenital anomaly refers to structural defects (congenital malformations, disruptions and dysplasia), chromosome aberrations, inborn errors of metabolism and hereditary diseases.

A pediatrician examined clinically all newborns at the hospital within the first 24 hours after birth. The immediate postnatal data are included in the database. For the whole study period, the main responsibility for the pediatric examination has been in hands of *one* senior pediatrician. Routines have been established to capture all congenital anomalies or syndromes diagnosed even years later to complete our database. All live-born infants were followed up; in this study the longest follow-up was over 18 years, the shortest about 2 years. The health care program in Norway ensures all children regular physical examinations at child health care centers until school age; there have been some minor changes through the studied periods, but this examination now is done at 6 weeks, 6 and 12 months, and at 2, 4 and 6 years of age. All relevant pathology led to referral to the pediatric department at our hospital, which communicated information about malformations, and syndromes to our unit.

Cases of congenital anomalies referred to the NCFM as a tertiary referral center from outside our non-selected population were not included in the series presented in this thesis.

All four articles are prospective follow-up studies. The first study covered the 15-year period from January 1987 through December 2001, during which 41 382 fetuses/infants were registered as delivered from 16 weeks onwards. The second, third and fourth study covered the 18-year period from January 1987 through December 2004, with a total population of 49 314 fetuses delivered after 16 weeks, all scheduled to be born at St. Olavs University Hospital. Of those, 49 314 (98%) had an ultrasound examination performed at the National Center for Fetal Medicine, and thus formed the *study population*.

Depending on the diagnosis, a perinatal team consisting of an obstetrician, a sonographer/midwife, a pediatrician, a pediatric surgeon and a social worker informed the parents at the time of diagnosis, and gave support until the delivery of the fetus/newborn. If a pregnancy was terminated, the doctor in charge, the "contact sonographer/midwife" and the social worker supported the parents during the process and during the time thereafter.

Methodological considerations

It is of importance to be aware of methods used to evaluate ultrasound studies. This is described by Levi (Levi 2002) in 9 comments:

> *Assuming equivalent examiner skills, several factors act significantly on sensitivity.*
>
> *1. The choice of the population sample. Studies generally focus on a distinct geographical area, a specific hospital obstetrical clinic or on collaborative data. One type of study depicts the medical practice of a given area, in essence, a specific population screening. Another depicts an organizational approach to screening dependent upon a selected population and the motivation of the team to find malformations. A third encompasses the above features into a more standard practice.*
>
> *2. The selection of pregnant women. Studying pregnant women at 'regular risk' is equivalent to investigating results from a typical cross-sectional population. This represents a non-tertiary clinical setting. The terms 'low risk' and 'regular risk' used in many studies are probably meant to be equivalent. They are not.*

Low-risk patients have a low fetal and maternal risk, but are often poorly quantified, while high-risk patients have seriously higher and better quantifiable risks. Screening pregnant women at high risk is likely to be much more effective since the odds of finding an anomaly are higher, examiner concentration is sharpened and personnel generally better trained.

3. The gestational age at the ultrasound examination. Specific anomalies can be recognized at different gestational ages.

4. The total number of ultrasound sessions. Theoretically, the more scans that are performed on a patient, the greater would be the rate of anomaly identification. For example, the RADIUS study results indicated that a third trimester scan added to the second trimester scan's anomaly yield, but no one has yet addressed the efficacy of monthly scans.

5. The distribution of malformations among systems. Malformations of the CNS are easier to detect than congenital heart defects (CHD). An abnormal distribution of these defects might change the results appreciably.

6. The exclusion of fetal malformations. Studies that exclude certain anomalies because they are 'minor' or theoretically undetectable may have dramatically different results than when all anomalies are included in the analysis.

7. The routine practice of autopsy for abortion, fetal and postnatal deaths. Autopsy and pathology examinations are considered as the gold standard for malformation assessment. However, autopsies are not routinely performed everywhere. Also, the quality of the autopsy can impact on false-positive and false-negative rates. Lastly, even pathological examination is not always infallible, especially for fragmented specimens.

8. The accuracy of neonatal examination. This may also affect appreciably the

accuracy when only examinations of live-born infants are conducted.

9. The period length of ascertainment. Usually, the period of observation is limited to a few days during the neonatal period. Series with longer observation periods are infrequent, yet some anomalies can wait several months or years to express themselves. "Nevertheless, a balance must be struck between pragmatism and obsession regarding study design".

These 9 comments summarize some of the main issues for a good study. There are major differences between fetal populations and neonatal populations regarding the incidence and development of anomalies. Especially regarding the severity and outcome of anomalies, there are major differences between the fetal and neonatal populations, as discussed in the section on counseling. Obviously, differences between fetal populations versus a postnatal population may apply to most anomalies.

Prognostic categories

In paper 4, a set of prognostic categories of anomalies detected with ultrasound was developed, ranging from 1 to 9, where number 1 represented the most severe and 9 the best prognosis with a high survival rate (Table 1). Each of the terminated fetuses, the intrauterine and fetal deaths intrapartum or within 3 months postpartum was retrospectively categorized according to Table 1.

Table 1. The prognostic categories with examples

Prognostic category	Expected consequence	Examples
1	Antenatal death	Triploidy Turner syndrome or trisomy 21 with cystic hygroma and severe hydrops Severe conditions with hydrops as lethal multiple pterygium syndrome
2	Death within 7 days after birth	Bilateral renal agenesis Anencephaly Trisomy 18 with major associated anomalies and severe growth restriction Short-rib-polydactyly syndrome
3	Death within the first year of life	Trisomy 18 with less severe associated anomalies Trisomy 13
4	Death before school age	Lissencephaly (Miller-Dieker syndrome)
5	Death or survival with severe disability	Severe hydrocephaly Marshall-Smith syndrome Major congenital heart defects Myelomeningocele with associated central nervous system anomalies such as significant cerebellar hypoplasia
6	Survival with presumed severe disability and mental retardation	Trisomy 21 with associated anomalies
7	Survival with presumed severe disability without mental retardation	Complete amelia Treacher-Collins syndrome
8	Survival with moderate disability	Dysmelia, amelia of one limb Silver-Russell syndrome
9	Survival without or with a minor disability after treatment	Gastroschisis Duodenal atresia Cleft lip and palate

Statistical analysis

The observed frequencies were tested for significance using the chi square statistical test (SPSS 11 for Mac OS X software package) in Paper 1-4, in Paper 1 groups were compared by the Fisher's exact test. The level of significance was set at 5%.

RESULTS AND COMMENTS

Paper 1

Prenatal ultrasound detection of talipes equinovarus in a non-selected population of 49 314 deliveries in Norway

Results

A total of 113 cases of TEV were registered during the 18-year period, 49% had isolated TEV and 51% had associated anomalies. During the 3 six-year periods, there was a significant improvement (P = 0.006) in the overall detection of TEV from 43% to 67% and 77%, respectively. The detection rate for isolated TEV increased significantly (P = 0.001) during the three time periods, from 23% to 55% and 81%, respectively. In the group of TEV in association with other anomalies, there was no significant change, the detection rate of TEV over the three time periods varied from 72% for the first period and 75% and 73%, respectively. Isolated bilateral TEV cases were detected more than twice as often as isolated unilateral TEV.
The three largest groups of associated anomalies were syndromes/sequences (26%), chromosome aberrations (26%) and musculoskeletal disorders (24%). All anomalies are listed in Table 2 below. The undetected associated anomalies among fetuses with TEV are shown in Table 3.

Table 2. Developmental disorders/syndromes among 58 fetuses with bilateral or unilateral TEV and associated anomalies

Developmental disorder	n	%
Syndromes or Sequences	15	26
Chromosome aberrations	15	26
Musculoskeletal	14	24
CNS including meningomyelocele	7	12
Genitourinary	3	5
Cardiovascular	2	3
Other	2	3
Total	58	100

Table 3. Prenatally undiagnosed associated anomalies among fetuses with TEV

Main diagnosis made postnatally	TEV detected prenatally	n
Trisomy 21	Yes	1
Charcot-Marie-Tooth Disease	Yes	1
Anisomely, Smith-Lemli-Opitz Syndrome	Yes	1
Torticollis	Yes	1
Congenital hip dislocation	Yes	1
Kyphomelic dysplasia	No	1
Pulmonary stenosis	No	2
Congenital hip dislocation	No	1
Rectum atresia, unilateral missing foot below ankle joint	No	1
Total		10

Fifteen of 113 (13%) cases with TEV had chromosome aberrations and 13 of these 15 had structural anomalies in addition to the TEV that led to karyotyping. The two other fetuses with chromosome aberrations presented with no other abnormality than TEV, detected by ultrasound. One fetus was karyoptyped and had 47 XYY. The pregnancy was continued. The other fetus was not karyotyped and a child with trisomy 21 was delivered. Fetuses with chromosome aberrations, with no structural anomalies other than TEV correspond to 1.8 % of the total TEV population or 3.6% of the assumed isolated TEV population.

Pregnancies were terminated in 23% of the cases, all with severe additional anomalies. Treatment of TEV included surgery in 86% of the cases.

Comments

The overall detection rate for TEV improved significantly over time, most likely a consequence of improved equipment and sonographer experience during the 18-year period. The prenatal detection increased when TEV was bilateral, which might indicate that once a normal foot was seen, a scan of the contra lateral foot received less attention. This is supported by the fact that when other associated anomalies were present there was no difference in the detection of unilateral or bilateral TEV; this indicated that, the fetuses then were more carefully scanned for further anomalies.

Our study showed that in a small number among fetuses with TEV (Table 3), associated chromosome aberrations or severe syndromes were not diagnosed until after delivery. We therefore suggest that karyotyping should always be offered when isolated TEV is found. In a counseling situation, parents should be provided with information about possible underlying syndromes and neurodevelopmental conditions that may not be ruled out. Additionally, parents should also be informed that in suspected isolated TEV associated anomalies might remain undetected prenatally. The counseling may also include the information that the postnatal treatment is easily performed with good results based on the Ponseti method that is used worldwide.

Paper 2

Prenatal ultrasound detection of facial clefts:

a prospective study of 49 314 deliveries in a non-selected population in Norway

Results

A total of 101 fetuses or newborns with facial clefts were registered. The distribution of clefts was: 25 (25%) cleft lip, 52 (51%) cleft lip and palate and 24 (24%) cleft palate. No cleft palate was detected prenatally in the whole 18-year period. Cleft lip with or without cleft palate (CL(P)) was detected prenatally in 35/77 (45%) of the cases, with a significant increase in the detection rate (P = 0.03) from 14/41 (34%) to 21/36 (58%) between the two nine-year periods, respectively. The median gestational time of detection of CL(P) was 19+2 weeks for the total period, with no change over time. Altogether, 24/35 (69%) were detected at a second trimester routine ultrasound examination. Thirty-three of 77 (43%) CL(P) and 14/24 (58%) of CP had associated anomalies. When the condition subdivided for CL(P) associated with other anomalies, the detection rate increased from 44% to 63% and the rate for isolated CL(P) increased from 26% to 53% in the two time periods. There was a higher detection rate for bilateral CL(P), 16/26 (62%) than for unilateral CL(P), 19/49 (39%).

Among all 101 fetuses with facial clefts, 47/101 (47%) had associated anomalies, including chromosome aberrations, with a distribution of 33/77 (43%) of the CL(P) and 14/24 (58%) of the CP, as shown in Table 4.

Table 4 Distribution of facial clefts

	CL(P)				CP			
	n	%	*TOP/IUFD	*Death pp	n	%	TOP	*Death pp
Isolated	44	57			10	42		
Associated	33	43			14	58		
Chromosome aberrations	8	10	6/1	1	4	17	1	1
Syndromes/ sequences	9	12	2/0		9	38	3	
Structural anomalies without chromosome aberrations/ syndromes/sequences	16	21	1/1	1	1	4		
Total	77	100	9/2	2	24	100	4	1

*TOP/IUFD = Termination of pregnancy/ Intrauterine fetal death

*Death pp = Death within 6 months post partum

Twelve/101 (12%) of all fetuses with clefts had chromosomal aberrations. Nine of these 12 had prenatal ultrasound findings that led to karyotyping. In the remaining three cases, the chromosome diagnosis was made postnatally. The first was a trisomy 13 with undetected bilateral CL(P), atrial septal defect, dilated urether, microphthalmus, low set ears and a hypoplastic pelvis; the second case was an undetected Klinefelter 49 XXXXY with postnatal diagnosis of cleft palate, clinodactyly in fingers and toes, general stiffness of the joints, dysmorphic face features, micro penis and bifid scrotum; the third fetus without prenatal remarks had a deletion of chromosome p4 and presented with growth retardation, cleft palate, hypertelorism, short sternum, clinodactyly, retentio testis and micropenis. In 18/101 (18%) cases, the facial clefts were part of a syndrome (13/101) or sequence (5/101) without chromosome aberrations.

Among the 42 fetuses with CL(P) not detected prenatally, 25/42 (62%) CL(P) were isolated cases and 17/42 (46%) had associated anomalies. Of the prenatally undetected CLP with associated

anomalies,è there was one fetus with acrania, the pregnancy was terminated. The remaining associated cases were not diagnosed before birth and were as following: one trisomy 13, two Median cleft syndromes, one Silver Russell Syndrome, two heart failures (one Uhls syndrome, one ASD secundum), the remaining had finger and foot deformities.

Termination of pregnancy was performed in 13/101 (13%) of the cases of CL(P) and CP. Termination was not performed in cases with an isolated diagnosis of CL(P); it was performed when severe additional anomalies were present.

Comments

The breakdown according to type of cleft (cleft lip, cleft lip and palate, cleft palate) is in accordance with the thorough study by Gorlin that described CLP as comprising about 50% of the cases, with cleft lip and isolated cleft palate each comprising about 25% (Gorlin et al. 1971). Our other findings were also similar according to the literature when relating to gender, with a male to female ratio of 1.9 to 1 in the group cleft lip *and* palate and to the predominant affection of the left side when the cleft was unilateral.

Our average detection rate of 45% for CL/P was relatively high and increased over time. Surveys conducted at several centers have reported detection rates of CL(P) between 18% and 22% (Grandjean et al. 1998; Stoll et al. 2000; Shaikh et al. 2001). Stoll showed that the prenatal detection of isolated CL(P) was 27% in the period of 1989-1998, and that the detection rate of CL(P) with associated anomalies was 50% for the same time period (Stoll et al. 2000). Studies from other centers showed detection rates from 22% to 65%, (Chitty et al. 1991; Hafner et al.

1997; Boyd et al. 1998; Cash et al. 2001), but these studies all had small numbers of patients. The highest detection rate was published by Bronshtein who reported a detection rate of 92% (11/12) (Bronshtein et al. 1994).

Facial clefts are mostly a cosmetic challenge, and a correctable anomaly when other anomalies are absent. Nevertheless the study demonstrated that about one half of the fetuses/newborns with facial clefts had associated anomalies; 12% of all cases had chromosome aberrations and 18% of cases were part of a syndrome or sequence. Therefore, accurate examination of the fetal face is important and karyotyping should be offered in all cases where facial clefts are suspected, since chromosome aberrations cannot be excluded completely. Parents should be provided with information about possible underlying conditions.

Paper 3

Prenatal detection of trisomy 21 by second trimester ultrasound examination and maternal age in a non-selected population of 49 314 births in Norway

Results

Eighty-eight cases of trisomy 21 were registered during a time period of 18 years, between 1987-2004. The total prevalence of trisomy 21 in the non-selected population, including all prenatally and postnatally diagnosed cases, was 1.78 per 1000 births (95% confidence interval 1.4 - 2.2). The prevalence of live born trisomy 21 infants (excluding termination of pregnancies and IUFD) was 1.14 per 1000 births (95% confidence interval 0.86 - 1.47).

The total prenatal detection rate was 43% (38/88). There was no significant change (P = 0.3) in detection rate observed within the three time periods that were studied. Fourteen percent (12/88) were detected by amniocentesis due to advanced maternal age, and 29% (26/88) by prenatal ultrasound (2/26 in first trimester, 22/26 in second trimester and 2/26 in third trimester). Seventy-two percent (63/88) of all women with a trisomy 21 fetus were under 38 years of age. The percentage of women $\geq$ 38 years opting for karyotyping during the 3 time periods decreased significantly from 51% to 50% and 36%, respectively. The average termination rate of trisomy 21 fetuses was 84%, with no significant change over time. An outline of all the detected and non-detected cases are shown in Figure 5.

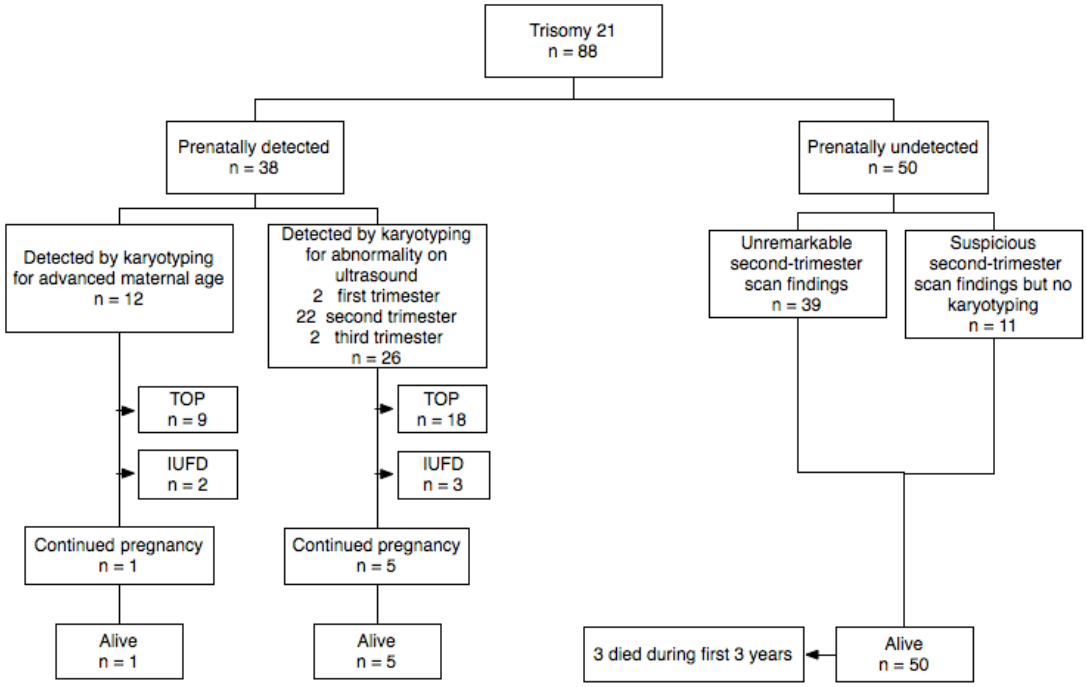


Figure 5. Outline of all detected and undetected trisomy 21 cases in the non-selected population of 49 314 births
(TOP, termination of pregnancy; IUFD, intrauterine fetal death)

Among the 56 newborns with trisomy 21, 6 cases were diagnosed prenatally. Consequently 50 cases were diagnosed postnatally, with structural anomalies found in 43/56 (77 %) of the newborns. The anomalies are listed in Table 5.

Table 5. Structural anomalies found postnatally among all 50 cases with undetected trisomy 21

Anomalies	**n**	**%**
Atrial septal defects (ASD)	9	18
Ventricular septal defects (VSD) *	11	22
Atrioventricular septal defect (AVSD)	6	12
Double outlet right ventricle (DORV)	1	2
Tetralogy of Fallot (TOF)	1	2
Pulmonary artery stenosis	1	2
Imperforate anus	2	4
Syndactyly between 3rd and 4th finger	1	2
Total	32	64

* 3 of 11 VSD's required surgery postnatally

Twenty-six of the 56 (46%) newborns needed one or more surgical treatments. During the last six-year period from 1999 to 2004 we have complete electronic data registration of hospital visits. In this period the median number of contacts with the outpatient clinic per child with trisomy 21 was 16 times during the first year of life and 10 times during the second year of life. The median number of hospitalization days per child was 18 for the first year (range 4-53 days) and median 2 days for the second year excluding hospitalizations for cardiac surgery, which is centralized to the National Hospital in Oslo.

Comments

During the 18-year study period there was no change in the maternal care program which provided one second trimester routine ultrasound examination to each pregnant woman. Only women with a maternal age of 38 years or more at term and a few other indications had the right to have an amniocentesis. In the second part of 2004, a first-trimester ultrasound examination was offered to these women, but without biochemistry.

Since a maternal biochemistry program for the detection of trisomy 21 was not available during the study period, it was possible to study the efficacy of routine ultrasound and karyotyping in women over the age of 38, in the detection of trisomy 21. The overall detection rate for trisomy 21 was as low as 43%, without increase during the whole 18-year study period. In our non-selected population, most cases were detected by ultrasound (29%). Karyotyping due to maternal age contributed only 14% of the detected cases. Karyotyping due to maternal age was offered to women aged 38 years and over, but this comprised only 3.7% of the whole non-selected population, for the whole 18-year period. In addition, the rate of women accepting the offer diminished significantly during the 18-year study period from 51% and 50% to 36%, respectively. This may show that women in general are skeptical to amniocentesis and decline the offer of karyotyping if the risk based on maternal age and ultrasound is relatively low.

As a consequence of the "Law of Biotechnology" which was introduced in 2004 (LOV-2003-12-05-100. 2003), women who qualify for fetal genetic testing are now offered an ultrasound scan and in addition a hormone screening test (PAPP A and free β-hCG) instead of karyotyping by amniocentesis. If the total risk for trisomy 21 is relatively low, they may elect to decline the offered amniocentesis. Our results showed that 72% of all trisomy 21 fetuses were born to women below 38 years, underscoring the inefficiency of screening for trisomy 21 on the basis of age. The debate in Norway now focuses on the fact that women below 38 years also may have the combined non-invasive tests to assess their individual risk.

Our study shows that if the aim is to detect trisomy 21, a program based on the maternal age is obsolete since the majority of trisomy 21 cases are born to mothers younger than 38 years. Our study also shows that the routine fetal examination offered at 18 weeks is a poor test to detect trisomy 21, since only fetuses with associated anomalies may be detected. Comparison with other

published studies is difficult since most women in the other studies either have had a second-trimester biochemistry test included in the maternal care program or have been offered first-trimester ultrasound screening, or have had a possibility for first-trimester scan in private practice.

In our study, the termination rate of trisomy 21 fetuses was 84%, with no significant change over time. A systematic review, including studies from different countries such as the USA, UK and Europe, showed that the corresponding termination rate for trisomy 21 was approximately 92% (Mansfield et al. 1999). This indicates that the attitude of Norwegian women towards termination of pregnancy once the diagnosis of trisomy 21 is made, is more conservative than in other industrialized countries. In spite of this, there are reasons to believe that also Norwegian women now are interested in the option of an early testing.

Paper 4

Termination of pregnancy following ultrasound examination in a non-selected population of 41 382 deliveries in Norway: trends over a 15-year period

Results

Termination of pregnancy was performed in 163 fetuses. There was an increase in the detection rate of anomalies across the three periods, and a significant trend towards earlier detection of fetal anomalies during the fifteen years with a median of 18+0 weeks. The rate of termination of all prenatally detected anomalies was 29.7% (163/548) for the total study period. Analysis of the three five-year periods separately showed a slight, but significant decrease in the termination rate (P = 0.039). An overview of the detected anomalies and the terminations thereof is given in Table 6. Furthermore, Table 7 shows an overview over the subgroups of anomalies that led to termination. The two largest groups with nearly 1/3 of all cases in each were the groups of chromosome aberrations and central nervous system anomalies. In the group of chromosome aberrations there were 38% trisomy 21, 34% trisomy 18, and the rest were trisomy 13 and others.

Twenty-one percent (34/163) of the anomalies were detected before the routine scan, 79% (128/163) were detected at the routine scan, and 1/163 after the routine scan, a trisomy 18 was diagnosed at 26+2 weeks of gestation. There was not a significant change in prognostic categories during the three time periods, so the severity of the detected anomalies remained constant. The average median prognostic score was 2.2 for the first time period and 2.3 for the second and third time periods, respectively, with no shift in tendency to terminate less severe conditions over time.

Table 6. Overview of all deliveries, detected anomalies and terminations in the study periods

	Deliveries	Anomalies among total deliveries		TOP of total anomalies	
Periods	N	n	%	n	%
Period 1 (1987- 1991)	13 817	153	1.1	48	31.4
Period 2 (1992- 1996)	14 087	181	1.3	64	35.4
Period 3 (1997- 2001)	13 478	214	1.6	51	23.8
Total	41 382	548	1.3	163	29.7

TOP, termination of pregnancy

Table 7. Anomalies listed in subgroups that led to termination of pregnancy (TOP) for the total period and the three time periods

	Total period (1987-2001)		Period 1 (1987-1991)		Period 2 (1992-1996)		Period 3 (1997-2001)	
Anomalies	**N**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Chromosome aberrations	53	33	16	33	23	36	14	27
Central nervous system anomalies	49	30	13	27	21	33	15	29
Skeletal anomalies	16	10	7	15	7	11	2	4
Urinary system anomalies	12	7	4	8.5	2	3	6	12
Syndromes, associations	11	7	3	6	3	5	5	10
Congenital heart defects	7	4	1	2	4	6	2	4
Other severe defects	15	9	4	8	4	6	7	14
Total	163	100	48	100	64	100	51	100

There was no significant change in prognostic categories during the three time periods. The rate of termination of fetuses in the prognostic categories 1-5, which all were lethal or would lead to severe disability, was 90% in the first period, 94% and 82%, in the second and third periods

respectively. The median prognostic category for the three five-year periods was 2.2, 2.3 and 2.3, respectively, with no significant change within the time periods. The diagnoses of fetuses with a category higher than 5 are listed in Table 5 in Paper 4.

During the total study period, 8% (42/548) of the fetuses with prenatally detected very severe and/or lethal congenital anomalies were not terminated and died in-utero, during delivery or within 3 months after delivery. Seven of 42 fetuses in the group that continued the pregnancy with severe anomalies were twins, all with a healthy co-twin. The median time of detection in the three five-year periods were: 30+3, 19+1 and 18+1 gestational weeks, respectively. Intrauterine death affected 48% (20/42) of these fetuses at median of 18+5 gestational weeks (range 13-34 weeks), 52% (22/42) infants died intra partum or within 3 months after delivery with median 1.5 days of survival (range 0-91 days). The longest survivor was born with hypoplastic left heart syndrome. The infant died after 91 days following cardiac surgical interventions. There was no significant change in the number of continued pregnancies with prenatally diagnosed severe fetal anomalies, for either the total or for the separate time periods.

The median prognostic category for the anomalies found by ultrasound, which later resulted in either IUFD or death intra partum and up to 3 months after delivery, was 1.1 for the first period, and 2.2 for the second and third periods, respectively.

Comments

There was no increase in the rate of termination of pregnancies during the study period, although the detection rate of malformations increased. In fact, the termination rate decreased significantly

during the three five- year periods. This is similar to other studies where no change was found in patients' decisions over time (Evans et al. 1996), but still in contrast to several studies which over time have seen an increase in termination rates (Boyd et al. 1998; Stoll et al. 2002; Guillem et al. 2003; Rankin et al. 2005; Richmond and Atkins 2005). Nevertheless, a mean termination rate of 29.7% in our population is far lower than large published register studies that report termination rates of 57-83% of non- chromosomal anomalies (Liu et al. 2002; Neilson 2004; Garne et al. 2005).

In our study, the prognostic categories for terminated pregnancies were stable for the total period of 15 years (see prognostic categories Table 1, page 51). There was no trend towards termination of pregnancy for less severe indications over time. This is also in contrast to studies were there was an increase in termination of pregnancy thought to be due to an increase in the sensitivity of detection of anomalies, and to a widening of indications (Guillem et al. 2003).

An important finding of the study was a significant earlier detection of anomalies in the last two time periods. This applies to the group that terminated the pregnancy as well as to the group who continued their pregnancy. Although the gestational age at detection decreased, there was no increase in the termination rate. This is of particular interest regarding the group of women who continued their pregnancy. During the time periods 2 and 3 they did have the option of terminating their pregnancies, as opposed to the first 5-year period when the median gestational week of detection was 30+3. Still they chose to continue. These women were well informed about the severity of the anomaly of their fetus. Only a minority of the pregnancies were twin pregnancies, the majority were single fetuses with severe diagnosis.

In conclusion, this study clearly indicates that it has been possible to introduce a routine offer of an ultrasound examination and fetal medicine in Norway in such a way that the feared

development including an increase in the abortion rate caused by the identification of anomalies has not taken place. A liberalization of the indications for abortions over time has not happened either. On the contrary, our unit, the largest tertiary fetal medical unit in Norway, has managed the termination policy in a way which we believe will be accepted by Norwegian society in general, and which respects the autonomy of women. That policy most likely is a result of the experts dealing with the diagnosis of anomalies and being supported by our center's multidisciplinary perinatal team, which helps to give realistic information on treatment and prognosis of the respective anomalies. Such a team certainly aids parents in gaining understanding and security to make a decision they are comfortable with.

SUMMARY

Background

In Norway a second trimester routine fetal ultrasound examination around 18 gestational weeks was introduced in 1986. One of the additional aims, in addition to an improved estimation of the gestational age, detection of placenta and detection of multiple pregnancies, was to systemically examine the fetal anatomy. If fetal anomalies are found it usually implies major consequences for the management of the pregnancy and the neonatal period. In some cases the findings can lead to the wish to terminate the pregnancy. Advances in ultrasound technology and improvements in the skills of the sonographers have also resulted in an increased detection rate of malformations.

Aims of the studies

The aim was to study some rather minor anomalies that might also be associated with severe anomalies including chromosome aberrations. The diagnosis of trisomy 21 on a population basis was also studied. Further, a major aim was to evaluate the consequences of routine ultrasound at 18 weeks regarding termination of pregnancy over the time span of fifteen years.

Material and Methods

Prospective follow-up studies were carried out in a non-selected Norwegian population from 1987 to 2004 including a total of 49 314 births (papers 1-3). In paper 4 the study period was from

1987 to 2001 including a total of 41 382 births. Data of all specimens that underwent termination of pregnancy were registered. All specimens with trisomy 21, either detected by prenatal ultrasound or amniocentesis due to maternal age, or after delivery, were registered. The same prospective study was performed for fetuses with talipes equinovarus and with cleft-lip-palate. The study periods were all divided into time periods, to look for changes in detection rates.

Results

Talipes equinovarus

One hundred and thirteen cases of TEV were registered during the 18-year period, 49% had isolated TEV, 51% had associated anomalies. During the 3 six-year periods, there was a significant improvement (P = 0.006) in the overall detection of TEV. The three largest groups of associated anomalies were syndromes/sequences (26%), chromosome aberrations (26%), and musculoskeletal disorders (24%).

Our study showed that in a small number of suspected isolated TEV, associated chromosome aberrations or severe syndromes were not diagnosed until after delivery. Pregnancies were terminated in 23% of the cases, all with severe additional anomalies. Treatment of TEV included surgery in 86% of the cases.

Facial clefts

A total of 101 fetuses or newborns with facial clefts were registered. The distribution of clefts was: 25 (25%) cleft lip, 52 (51%) cleft lip and palate and 24 (24%) cleft palate. No cleft palate was detected prenatally. Cleft lip with or without cleft palate (CL(P)) was detected prenatally in 35/77 (45%) of the cases, with a significant increase in the detection rate (P = 0.03) 34% to 58%

between the two nine-year periods, respectively. Thirty-three of 77 (43%) CL(P) and 14/24 (58%) of CP had associated anomalies. Twelve/101 cases (12%) had chromosomal aberrations. In 18/101 (18%), the clefts were part of a syndrome or sequence.

Trisomy 21

Eighty-eight cases of trisomy 21 were registered. The prenatal detection rate was 43% (38/88). No significant change in the detection rate was observed over the 18 years. Fourteen percent (12/88) were detected by amniocentesis due to advanced maternal age and 29% (26/88) by prenatal ultrasound. Seventy-two percent (63/88) of all women with a trisomy 21 fetus were under 38 years of age. The termination rate of trisomy 21 fetuses was 84%, with no significant change over time.

Termination of pregnancy

Termination of pregnancy was performed in 163 fetuses. There was an increased detection rate of anomalies within the three periods, and a significant trend towards earlier detection of fetal anomalies during the fifteen years with a median of 18+0 weeks. Nevertheless there was a significant decrease in termination rate over time ($P < 0.039$). There was no shift in tendency to terminate less severe conditions over time. The termination rate of fetuses which had a lethal condition or which would lead to the most severe disabilities, was 90% in the first period, 94% and 82% in the second and third periods respectively.

Conclusions and future aspects

In the study on talipes equinovarus as well as on facial clefts, it was of interest to study specific anomalies which may be harmless and have good prognosis when occurring isolated, but which also could be associated with very severe anomalies that may be difficult to diagnose anatomically. These cases obviously have a completely different and very severe prognosis. Parents should be informed that in suspected isolated CL(P) or talipes equinovarus associated anomalies might remain undetected prenatally, and we therefore suggest that karyotyping should always be offered all patients when a facial cleft or TEV is diagnosed.

In the study on trisomy 21 fetuses it was shown that the Norwegian maternal care program with only one second-trimester ultrasound examination for all pregnant women below 38 years, resulted in a detection rate of less than 30% for trisomy 21. Many of the live-born trisomy 21 children had congenital anomalies, but not all were easily detectable. Soft markers of trisomy 21 are most easily found during a first trimester ultrasound examination, which was not included in the health care program during the study period. The study showed that a program based on maternal age to detect trisomy 21 has little effect. Ultrasound at 18 weeks also is a poor test to detect trisomy 21.

We found that termination rates were stable throughout the 15-year study period. The prognostic score for terminated fetuses remained stable. This clearly indicates that it has been possible to introduce a routine offer of an ultrasound examination and fetal medicine in Norway in such a way that the increase in the abortion rate amongst the located anomalies has not taken place.

A liberalization of the indications for abortions over time has not taken place either. That policy most likely is a result of the experts dealing with the diagnosis of anomalies and being supported by our center's multidisciplinary perinatal team, which helps to give realistic information on treatment and prognosis of the respective anomalies. It is most important that a multidisciplinary counseling team is able to give as correct and neutral counseling as possible, being both objective and supportive. Such a team ensures that parents gain the necessary understanding and security to make a decision they are comfortable with.

Approaching the anomaly of the fetus in a realistic way is the only fair way – so parents can get a perspective on how life will be if they choose to continue the pregnancy. The long-term prognosis is an important part of this information.At the same time, it is important to get reassuring counseling when minor anomalies are found.

It is interesting to note that not only medical experts take part in the discussion of prenatal detection of anomalies. It is a topic that interests most people. "Everybody" has an opinion about ethics in prenatal medicine and especially regarding termination of pregnancy.

For parents it is important to have scans, have a look at the baby, and establish a relationship with their unborn fetus. If this includes getting a diagnosis, parents want to know as much as possible about their fetus. It is therefore reassuring that the ultrasound detection rates of structural anomalies is increasing over time. Nevertheless, the detection of chromosomal aberrations might in the future be diagnosed mainly with the help of blood samples in early pregnancy. Research is ongoing with specific serum biochemistry (Laigaard et al. 2006; Christiansen et al. 2007) as well as with fetal DNA testing (Dhallan et al. 2007).

The aim for the future must be to further increase detection rates. A correct, detailed prenatal diagnosis with exclusion of associated anomalies will be a major task also in the future. If anomalies are found, it will be of great importance in giving correct and reassuring counseling to the parents, to help them to be secure in their understanding of the diagnosis and the consequences of either continuing the pregnancy or terminating it.

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12. Anton Hole: ALTERATIONS OF MONOCYTE AND LYMPHOCYTE FUNCTIONS IN REALTION TO SURGERY UNDER EPIDURAL OR GENERAL ANAESTHESIA.
13. Terje Terjesen: FRACTURE HEALING AND 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 CANCER.
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.

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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

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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.

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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

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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.
220. Siv Mørkved: URINARY INCONTINENCE DURING PREGNANCY AND AFTER DELIVERY: EFFECT OF PELVIC FLOOR MUSCLE TRAINING IN PREVENTION AND TREATMENT
221. Marit S. Jordhøy: THE IMPACT OF COMPREHENSIVE PALLIATIVE CARE
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