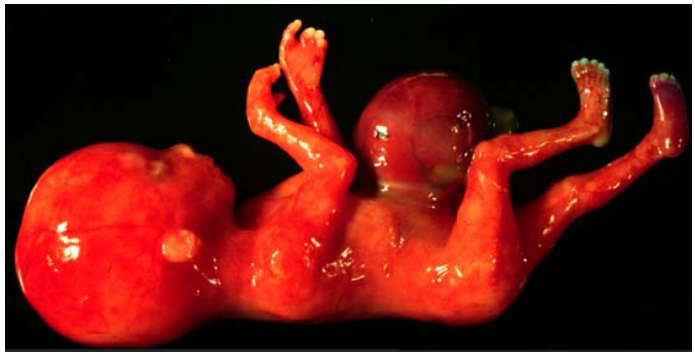
Anne Brantberg

Fetal and perinatal implications of anomalies in the gastrointestinal tract and the abdominal wall

Thesis for the degree of doctor medicinae

Trondheim, June 2007

Norwegian University of Science and Technology
Faculty of Medicine
Department of Laboratory Medicine,
Children's and Women's Health



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FØTALE OG PERINATALE KONSEKVENSER AV UTVIKLINGSAVVIK I FORDØYELSESKANALEN OG I BUKVEGGEN

Studien tar for seg tilstandene *gastroschise* og *omfalocele*, som er forskjellige former for bukveggsdefekter samt utviklingsavvik som gir forsnevringer på ulike nivå i fordøyelseskanalen: spiserør (*øsofagusobstruksjon*), tolvfingertarm (*duodenalobstruksjon*) og endetarm (*imperforert anus*). Nyfødte med disse tilstandene trenger snarlig kirurgisk behandling. Diagnostisering før fødsel, ved hjelp av ultralyd, gir mulighet for optimalisert overvåking og omsorg både under svangerskapet og i forbindelse med fødsel, noe som kan forbedre prognosen for disse barna. Behandlingen av fostre med medfødte utviklingsavvik har tradisjonelt vært bygd på kunnskap om fødte individer. Vi har hatt mangelfull kunnskap om den betydningen utviklingsavvik har for fosteret – både i løpet av svangerskapet og i tiden rundt fødselen.

Nøyaktigheten av de prenatale diagnosene var stor for alle de undersøkte tilstandene. I den *ikke-selekterte populasjonen* var oppdagelsesraten høy for tilfeller med gastroschise (100%), omfalocele (95%) og duodenalobstruksjon (82%), mens oppdagelsesraten for øsofagusobstruksjon var relativt lav (43%), og for imperforert anus veldig lav (11%). Alle disse diagnosene var betydelig vanligere i vår studiepopulasjon som inkluderte fostre, sammenliknet med tidligere beskrevet forekomst blant nyfødte. Fosterpopulasjoner er dermed forskjellige fra nyfødtpopulasjoner og har flere utviklingsavvik.

Fostre med gastroschise eller duodenalobstruksjon har økt risiko for fosterdød og bør overvåkes nøye i slutten av svangerskapet.

Gastroschise
64 fostre ble fulgt fra diagnosetidspunkt, som var 19. svangerskapsuke i gjennomsnitt. Alle hadde normale kromosomer, 6% hadde andre utviklingsavvik i tillegg. Tegn på utvidelse av den del av tarmen som lå inni fosterets buk var assosiert med obstruksjon av tarmen. I tidligere studier er det beskrevet fosterdød hos ca 10-15% av fostre med gastroschise, men i denne studien var det bare ett foster som døde. Tegn på fosterstress som gjorde akutt keisersnitt nødvendig, oppstod hos 22%. Fostre med gastroschise har økt risiko for å utvikle fosterstress, med fosterdød som ytterste konsekvens, og de bør derfor overvåkes nøye med hyppige CTG-registreringer de siste ukene for fødsel.

Omfalocele
90 fostre ble fulgt fra diagnosetidspunkt (18. svangerskapsuke). Omfalocelene ble delt inn i ulike typer basert på plasseringen: epigastriske, sentrale og hypogastriske. Kromosomfeil (oftest trisomi 18) forekom hos 69% av fostrene med sentralt omfalocele, sammenliknet med 13% hos de med epigastrisk omfalocele. Dette kan tyde på at sentrale og epigastriske omfaloceler er to helt forskjellige tilstander. 89% hadde assosierte, til dels dødelige avvik, og dermed ble resultatene dårlige. Bare 8 (9%) overlevde og var friske. I overvåkingen av fostre med omfalocele bør en fokusere på de tilfellene hvor prognosen kan tenkes å være god.

Duodenalobstruksjon
29 fostre ble fulgt fra gjennomsnittlig diagnosetidspunkt i 29. svangerskapsuke. 21% hadde trisomi 21 (Down syndrom). Totalt hadde 62% assosierte avvik. Isolert duodenalobstruksjon med et forventet godt resultat forekom hos 11 (38%) fostre. Likevel døde 5 av disse før fødselen, eller de ble født med betydelige nevrologiske

symptomer/skader som medførte varige funksjonshemninger – sannsynligvis på grunn av oksygenmangel. Vår hypotese er at utvidelse av nedre del av spiserøret kan påvirke fosterets hjerterytme og medføre hjertestans og død. Fostre med duodenalobstruksjon har økt risiko for dårlig utkomme. Siden fosterdød synes å inntreffe akutt, kan det være vanskelig å overvåke disse fostrene, men de bør følges nøye i slutten av svangerskapet og en bør vurdere forløsning før termin.

Imperforert anus
Av 69 fostre med imperforert anus var det bare 16% som fikk diagnosen før fødselen. Kromosomfeil forekom hos 13%. Assosierte avvik var hyppige (86%), og imperforert anus var ofte en del av ulike syndromer. Resultatet var dårlig, med bare 35% overlevelse. Ved isolert imperforert anus eller bare én ekstra anomali var overlevelsen 94% sammenliknet med bare 14% for de med flere anomalier. Oppdagelsesraten før fødsel kan nok forbedres framover, men enkelte tilfeller med imperforert anus vil aldri kunne diagnostiseres før fødsel.

Øsofagusobstruksjon
Hos 48 fostre med øsofagusobstruksjon var oppdagelsesraten før fødsel 44%. Unormalt stor fostervannsmengde og symptomer som følge av dette førte til diagnostisering. Dermed ble diagnosen stilt sent (32 uker). 23% hadde kromosomfeil og totalt hadde 79% assosierte avvik. Overlevelsen var høyere, men ikke signifikant høyere, for dem som hadde isolert øsofagusobstruksjon og for dem som fikk diagnosen før fødsel. Økt bevissthet om muligheten for øsofagusobstruksjon, som kan føre til en målrettet undersøkelse, bør kunne forbedre den framtidige diagnostikken.

Målene med studiene. Materiale og metoder
Målet med studiene var å beskrive resultatene fra tidspunktet for prenatal diagnose, gjennom svangerskap og fødsel og inn i nyfødtperioden. Dessuten var målet å identifisere risikofaktorer og bestemme hvorvidt overvåking kan bedre utfallet. Et annet mål var å finne ut hvor stor andel som fikk diagnosen før fødsel, og å kartlegge mulighetene for forbedret diagnostisering.

Alle studiene var basert på en *selektert populasjon* som bestod av henviste pasienter i tillegg til vår egen *ikke-selekterte populasjon*. Den *ikke-selekterte populasjonen* ble dessuten undersøkt separat. Fostrene med gastroschise, omfalocele og duodenalobstruksjon ble i den *selekterte populasjonen* fulgt fra tidspunktet for prenatal diagnose. Diagnosene øsofagusobstruksjon og imperforert anus i den *selekterte populasjonen* ble stilt enten før eller etter fødselen og populasjonen inkluderte alle som hadde gjennomgått minst én ultralydundersøkelse.

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

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CONTENT

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Anne Brantberg

LIST OF PAPERS

The present thesis is based on the following papers:

I Brantberg A, Blaas H-GK, Salvesen KÅ, Haugen SE, Møllerløkken G, Eik-Nes SH. Fetal duodenal obstructions: increased risk of prenatal sudden death. *Ultrasound Obstet Gynecol*. 2002 Nov;20(5):439-446.

II Brantberg A, Blaas H-GK, Salvesen KÅ, Haugen SE, Eik-Nes SH. Surveillance and outcome of fetuses with gastroschisis. *Ultrasound Obstet Gynecol*. 2004 Jan;23(1):4-13.

III Brantberg A, Blaas H-GK, Haugen SE, Eik-Nes SH. Characteristics and outcome of 90 cases of fetal omphalocele. *Ultrasound Obstet Gynecol*. 2005 Oct;26(5):527-537.

IV Brantberg A, Blaas H-GK, Haugen SE, Isaksen CV, Eik-Nes SH. Imperforate anus: A relatively common anomaly rarely diagnosed prenatally. *Ultrasound Obstet Gynecol*. 2006 Dec;28(7):904-910.

V Brantberg A, Blaas H-GK, Haugen SE, Eik-Nes SH. Esophageal obstruction – prenatal detection rate and outcome. *Ultrasound Obstet Gynecol.* (Accepted)

ABBREVIATIONS

ALTE	Apparent life-threatening episodes
AVSD	Atrioventricular septal defect
BE	Base excess
BPD	Biparietal diameter
CHD	Congenital heart defect
CRL	Crown rump length
CS	Cesarean section
CTG	Cardiotocography
EFSUMB	European Federation of Societies for Ultrasound in Medicine and Biology
ISUOG	The International Society of Ultrasound in Obstetrics and Gynecology
IUFD	Intrauterine fetal death
IUGR	Intrauterine growth retardation
LMP	Last menstrual period
MFRN	Medical Birth Registry of Norway
MRI	Magnetic Resonance Imaging
NCFM	National Center for Fetal Medicine
NT	Nuchal translucency
OIES	Omphalocele – Imperforate anus – Exstrophy of the bladder – Spinal defects
RCOG	Royal College of Obstetricians and Gynaecologists
SGA	Small for gestational age
SIDS	Sudden infant death syndrome
TEF	Tracheo-esophageal fistula
TOP	Termination of pregnancy
VO	Vagal overactivity
VSD	Ventricular septal defect
WFUMB	World Federation for Ultrasound in Medicine and Biology

INTRODUCTION

Background

Congenital anomalies occur in approximately 3% of all infants (Kalter and Warkany 1983), and about 90% occur in fetuses born to parents with no recognizable risk factor. Fetal anomalies are a leading cause of premature years of life lost and contribute to a high rate of all nations' chronic disease burden (Oakley 1986). In the United States, congenital malformations were the leading cause of infant mortality in the 1990's (Lee *et al.* 2001). Fetal examinations by ultrasound during pregnancy provide the possibility to detect anomalies prenatally and thereby present an opportunity to optimize the care for the various conditions including treatment, surveillance and the planning of the mode, time and place of delivery. Fetal examinations also provide important information needed in counseling parents. If the fetus has a lethal or serious condition, a prenatal diagnosis gives the parents an option to terminate the pregnancy. Prenatal diagnosis may also prevent unnecessary cesarean sections (de la Vega and Verdiales 2001) and aid in counseling for future pregnancies (Boyd *et al.* 2004).

Congenital anomalies present diagnostic challenges in fetal medicine. First and foremost an accurate and high prenatal detection rate of the main anomalies is crucial. Many anomalies are accompanied by lethal associated conditions, thus the ability to recognize or to exclude the presence of possible associated anomalies and conditions that may affect the outcome is also crucial. In the beginning of the ultrasound era, many were concerned about the accuracy of prenatal diagnosis and whether it could lead to termination of pregnancies with healthy fetuses that had falsely been thought to have an anomaly. "False positive cases", and the ethics regarding prenatal diagnosis were heavily debated. There is now, however, research that shows a good correlation between prenatal diagnoses and postmortem findings (Isaksen *et al.* 1998; Isaksen *et al.* 1999; Isaksen *et al.* 2000; Stiller *et al.* 2001; Wald *et al.* 2004).

Traditionally, the outcome of infants with congenital anomalies has been based on available data registered from newborns. However, because of the great differences

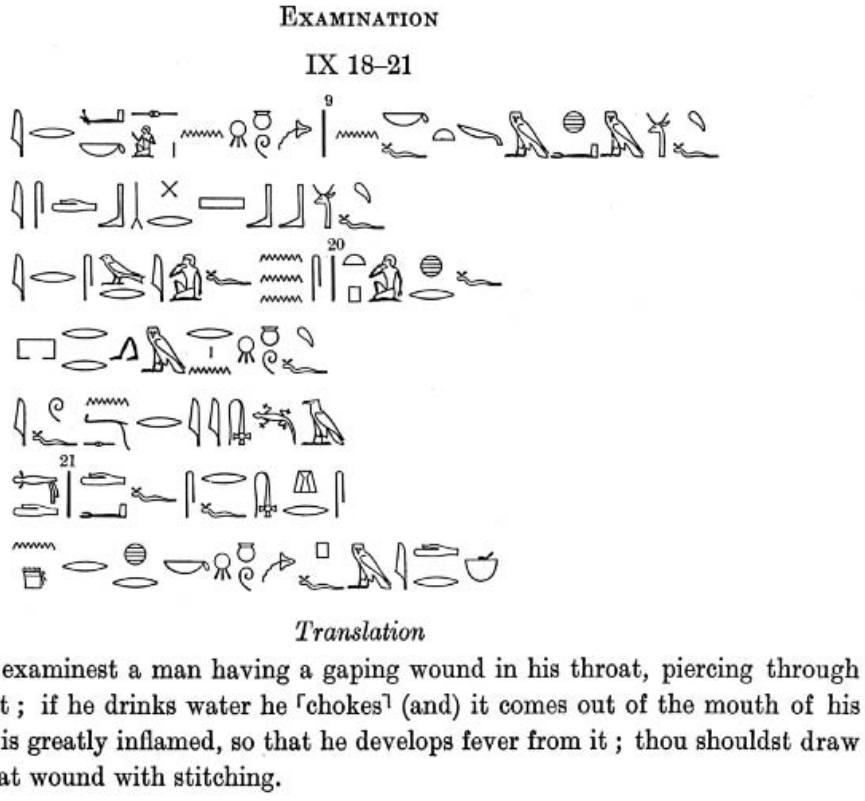
between neonatal and fetal populations, information gleaned from a neonatal population may be misleading regarding surveillance and treatment. It is also inappropriate in our counseling of parents who are interested in the prognosis for their fetuses at the time of the diagnosis, not only the prognosis from the time after birth. In our efforts to refine intrauterine surveillance, treatment and knowledge about prognoses, we must focus on natural intrauterine development of certain anomalies throughout pregnancy. This knowledge may help us. However, to obtain the knowledge of intrauterine development of certain anomalies we need large populations, centralized institutions with a high frequency of anomalies, accurate pre- and postnatal examinations as well as accurate pathological examinations. The registration and follow-up must be meticulous.

Many gastrointestinal anomalies and abdominal wall defects can be repaired with surgery. Historically, there have been several attempts to correct a number of anomalies but it was not until the 1940's, when incubators were invented and neonatal intensive care became a specialized profession, that the attempts resulted in improved survival for more than a few isolated cases. Infants with gastrointestinal tract anomalies and abdominal wall defects need early neonatal surgery and will benefit from delivery at a specialist center with appropriate neonatal facilities. A prenatal diagnosis of anomalies in the gastrointestinal tract and abdominal wall gives several advantages. For example, it provides important information that aids us in counseling and preparing the parents for the postnatal surgery and treatment (Hancock and Wiseman 1989). The possibility to survey the fetuses appropriately may reduce the risk for intrauterine fetal death (IUFD). In addition, prenatal diagnosis makes it possible to plan the mode and time of delivery and to transport the fetus in utero to the appropriate medical unit. By optimizing the conditions, the perinatal morbidity and mortality may be reduced. A reduction in morbidity has been shown in fetuses with prenatally diagnosed gastroschisis and intestinal obstruction (Romero *et al.* 1988; Saari-Kemppainen *et al.* 1994; Bittencourt *et al.* 2004). Improvement of the outcome over years for fetuses with duodenal obstruction has also been reported (Murshed *et al.* 1999). This improvement most likely represents a combination of better surgical techniques, improved neonatal intensive care and anesthesia, and increased numbers of prenatally diagnosed cases.

History of congenital anomalies

Hippokrates (460 - 370 B.C.), known as the father of western medicine, emphasized the importance of observing the natural course of diseases. He believed that the natural course had to be studied to be able to improve the knowledge of the etiology, treatment and prevention of diseases. Based on this knowledge it would be possible to diagnose (*dia:through, gnosis:knowledge*) and thereby establish a prognosis for various conditions (Lindegård and Åström 1989). This is the foundation for evidence-based medicine. Historical descriptions of conditions may, in this context, improve our knowledge and evidence.

Figure 1
Reprint from The Edwin Smith Surgical Papyrus by Breasted (Breasted 1930).



EXAMINATION

IX 18–21

Translation

If thou examinest a man having a gaping wound in his throat, piercing through to his gullet ; if he drinks water he ⌜chokes⌝ (and) it comes out of the mouth of his wound ; it is greatly inflamed, so that he develops fever from it ; thou shouldst draw together that wound with stitching.

"Smith Surgical Papyrus", transcribed in the years 3000 to 2500 B.C., contains the first written anatomic, physiologic, clinical and pathologic observation recorded by man (Breasted 1930; Brewer 1980). All cases in the Smith papyrus were classified as (1) "an ailment which I will treat" (believed curable), (2) "an ailment which I will contend"

(possibly curable), or (3) “an ailment which will not be treated” (incurable). The surgical treatise is mostly a series of discussions of injuries, not of diseases. The papyrus includes a case (Case 28) with “A gaping wound in the throat penetrating to the gullet” and this may be the first description of an esophageal injury (Breasted 1930) *(Figure 1)*.

Esophageal obstruction

The first report of an esophageal anomaly was made in 1670 when Durston (Durston 1670-1671) described a blind-ending upper esophagus in one of a pair of female thoracopagus conjoined twins. A classic esophageal atresia with distal tracheo-esophageal fistula was first described and documented by Thomas Gibson in 1697 (Spitz 2006). In 1840, Thomas Hill reported a case with esophageal atresia in connection with imperforate anus (Hill 1840). He tried to perform anorectal surgery on the case, which is referred to as the first attempt to perform “posterior sagittal anorectal procedure”. The first attempt to operate on a case with esophageal atresia was made by Charles Steele in 1888 (Steele 1888). Scientific discoveries at the end of the 19th century made solid abdominal surgery possible. Thoracic surgery followed in the 20th century, with rapid strides during World War II. These wartime advances stimulated an interest in esophageal surgery in the postwar era (Brewer 1980). Various surgeons made several attempts to operate on esophageal atresia during the 1930’s and 1940’s. The first survivors were operated on with staged reconstruction in 1939 and were independently reported by Leven (Leven 1941) and Ladd (Ladd 1944). Two years later, in 1941, Haight and Towsley performed the first successful primary repair of an esophageal atresia (Haight and Towsley 1943), a method that is still used. Prenatal suspicion/diagnosis of esophageal atresia by ultrasound was reported in 2 cases in 1982 (Jassani *et al.* 1982).

Duodenal obstruction

In 1808, Aubéry described a case of duodenal obstruction (Aubéry 1808), which probably was the first known description**.** About a century later, Cordes presented (Cordes 1901) a detailed description of all 57 cases of duodenal obstruction known at that time. In 1914, Ernst performed the first successful duodeno-jejunostomy on an infant with duodenal atresia (Ernst 1916). The surgical techniques were discussed and evaluated during the

beginning of the 20th century and Webb and Wangenstein concluded, in 1931, that all cases that had survived so far had undergone surgery with anastomotic procedure, while none of the cases recovered after enterostomy had been performed (Webb and Wangenstein 1931). The current surgical procedure of choice is commonly duodenoduodenostomy (Murshed *et al.* 1999; Escobar *et al.* 2004). The prenatal appearance by ultrasound in a case with duodenal atresia was reported already in 1975 (Loveday *et al.* 1975).

Imperforate anus

A successful operation for imperforate anus was described in the seventh century by Paulus of Ægineta in Greece in his famous "Medical Compendium in Seven Books" ("Epitomes iatrikes biblio hepta") (Ægineta, translated 1844). According to Bradham (Bradham and Charleston 1958), a case of congenital anal stenosis was successfully dilated with gentian roots in 1640 and the first perineal dissection was performed in 1787. Campbell performed a successful operation for imperforate anus in 1790 (Bradham and Charleston 1958). In 1835, Amussat (Amussat 1835) recommended proctoplasty by careful dissection of the perineum, mobilization of the rectum, and suture of the rectum and anal site. Nowadays, the posterior sagittal approach is the surgical method of choice (Pena 1995), however, careful evaluation is necessary (Pena and Hong 2000). The first prenatal description of a case with imperforate anus was presented in 1978 (Bean *et al.* 1978).

Abdominal wall defects

In 1733, Calder described a case with gastroschisis, and in the same paper, another case with duodenal duplication and solid pylorus (Calder 1733). His description of the gastroschisis case is interesting:

> *The child seemed otherwise to be as lively and brisk as any newborn infant uses to be, and for 12 or 14 hours it received milk and syrups by the mouth, without any appearance of uneasiness; but after that time it vomited every thing till its death, which happened four days after, and all the while it had no passage by the anus. The guts which were inflated, and had no peristaltic motion that I could observe, gradually inflamed, and before the child died, were become perfectly black (Calder 1733).*

This description of the condition also included a thorough description of the gastroschisis, an autopsy report and a maternal history. Calder's paper emphasizes the value of thorough case reports, which may be read with interest 270 years later. In 1878, Fear described another *true* case of gastroschisis including a successful repair (Fear 1878).

In 1894, Taruffi subclassified "gastroschisis" into seven categories according to location and content: A. Epi-gastro-schisi (aperture in the epigastric region), B. Epi-omphalo-schisi (aperture in the epigastrium in continuation with the umbilicus), C. Thoraco-omphalo-schisi (umbilical aperture continued into the sternum), D. Ipo-gastro-schisi (aperture in hypogastrium), E. Pleurosomo-schisi (lateral aperture of the trunk), F. Ipogastro-etro-schisi (aperture of the hypogastric region, including the symphysis pubis), G. Olo-gastro-etro-schisi (aperture of the whole abdomen, extending to the symphysis pubis) (Taruffi 1894a). Taruffi's description of "gastroschisis" included all known varieties of abdominal wall defects including gastroschisis and omphalocele. In addition, his book contained a description of "omphalocele", including umbilical hernias and omphaloceles (Taruffi 1894b). In 1904, Ballantyne also used the term "gastroschisis" for all abdominal wall defects but, in contrast to Taruffi, preferred to describe extroversion of the bladder by itself (Ballantyne 1904). Ballantyne discussed the problems of nomenclature and classification and also indicated that the term exomphalos (omphalocele) focuses attention on the umbilicus and should not be used as synonomous with gastroschisis. Ballantyne cited Lycosthenes' *Chronicon* of 1557 as the earliest recorded case of "gastroschisis", a case from 1547. However, according to the nomenclature used today, this probably was a case of limb body-wall complex. Lycosthenes' description highlights the difficulty of comparing various diagnoses from old literature with modern nomenclature and classification of abdominal wall defects. For example, thoracoschisis, ectopia cordis, OIES-complex etc. have been incorporated under the term of "gastroschisis" *(from Greek: gastro – belly; schism – separation/cleft)*. In addition, the diagnoses of limb body-wall complex and amniotic rupture sequence have commonly been misdiagnosed as gastroschisis (Pribram 1927) because these diagnoses, among a number of anomalies, may include an abdominal wall bowel defect with uncovered bowel protruding through the defect.

Treatment of gastroschisis was reported in Watkins' article on an early successful surgical repair of a *true* gastroschisis in 1943 (Watkins 1943). He attributed the success of this case to early and frequent rehydration, early repair, the use of prostigmine to stimulate peristalsis, and the fact that the case had less disproportion than usual between the abdominal cavity and eventrated viscera. In 1951, Moore and Stokes encountered their first two cases with "uncovered abdominal wall evisceration of intestine in the newborn" (Moore and Stokes 1953; Moore 1977). Still, at this time there was a multiplicity of terms applied to anterior abdominal wall defects and it was difficult to evaluate the conditions due to the lack of a clear and established classification (Kiesewetter 1957). Gastroschisis was the term commonly used for what we today call omphalocele (Shaw 1975). In addition, gastroschisis was often considered an omphalocele with ruptured sac (Rickham 1963; Hutchin and Goldenberg 1965; Moore 1977). New surgical techniques for abdominal wall defects were established during the 1950's - 60's and the importance of prompt surgery was emphasized (Cavanagh and Welty 1965; Hutchin 1965). In spite of the attention paid to techniques and timing, the mortality of infants with gastroschisis was 90% as late as in 1967 (Swift *et al.* 1992). With this in mind, it is easier to understand the following citation from 1985, which demonstrates that only 20 years ago gastroschisis was still considered a serious anomaly with a high mortality.

> *Although one of the cases of gastroschisis was diagnosed at 20 weeks sonographically, the parents opted to continue the pregnancy, and their neonate had an excellent outcome after surgery. This case illustrates that not all of the gastrointestinal abnormalities, severe as they may seem, are hopeless and that with neonatal-pediatric surgical expertise, intervention can be successful after birth (Barss et al. 1985).*

Few other conditions have had the same level of improvement, as has been the case for gastroschisis. A fetus with gastroschisis is a classic example of the importance of prenatal diagnosis and subsequent transportation of the fetus in utero to the place where delivery and postnatal surgery is to be performed. Antenatal diagnosis of gastroschisis by ultrasound was reported in 1977 (Lee and Warren 1977). Omphalocele was diagnosed prenatally in 3 fetuses in 1978 by Campbell (Campbell *et al.* 1978) and the same year Schlensker described an additional case (Schlensker 1978).

Embryology of the gastrointestinal tract and abdominal wall

The majority of fetal anomalies develop during the embryonic period. Therefore, the knowledge of the normal human embryonic development is a prerequisite for the understanding of certain anomalies and their association with other conditions/anomalies. The purpose of this section is to provide a brief overview of available knowledge and research on the embryo and its development.

All statements of gestational age in this chapter are based on last menstrual period and are expressed either in completed weeks and days or in measurements of crown rump length (CRL). In the early literature of pathology and embryology, the measurements of CRL were performed on dead embryos/fetuses, which might have been somewhat different than ultrasound measurements of living embryos/fetuses. Since the research is sometimes based on age and sometimes on length, the following table *(Table 1)* is included for ease of comparison.

Table 1
Approximate correlations of CRL (ultrasound measurements) and gestational weeks (Blaas 1999).

Gestational week (weeks + days)	CRL (mm)
5 + 0 - 6	0 - 3
6 + 0 - 6	4 - 8
7 + 0 - 6	9 - 14
8 + 0 - 6	15 - 22
9 + 0 - 6	23 - 31
10 + 0 - 6	32 - 42
11 + 0 - 6	43 - 54

Normal embryology

The human embryo develops from a unicellular stage through a bilaminar and three-laminar disc into a cylindrical body. At week 4, the embryo has a bilateral symmetry with dorsal and ventral surfaces, rostral and caudal ends and left and right sides. The

neurulation starts and the oropharyngeal and cloacal membrane and the primitive heart tube appear. The folding process that transforms the embryonic disc into a cylindrical body takes place from approximately 4 weeks + 6 days to 5 weeks + 1 day (±1 day). This folding process (O'Rahilly and Müller 1987) draws the amniotic membrane, and thus the amniotic cavity over the embryo *(Figures 2, 3)*.

Figure 2
Development during approximately the 5th completed gestational week. Reprinted from "Human Embryology and developmental biology", Bruce M. Carlson, Third edition, 2004, Establishment of the basic embryonic body plan, Picture 6-18, Page 121, Mosby Inc (Carlson 2004) with permission from Elsevier.

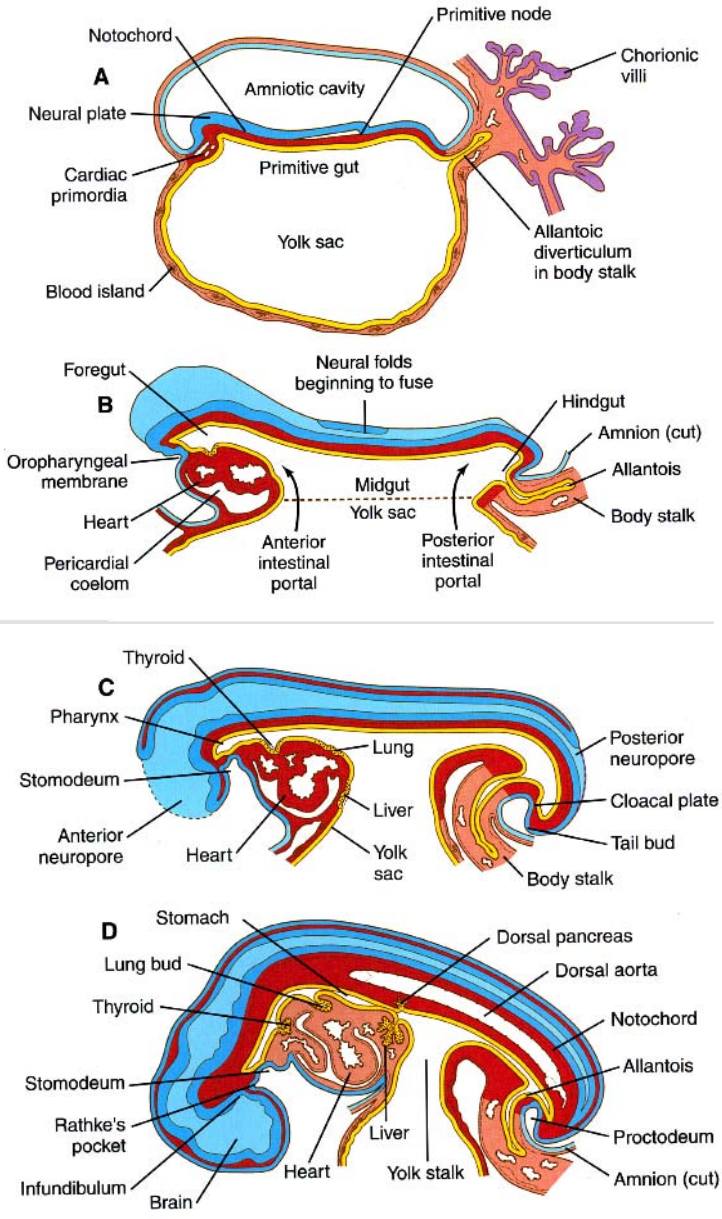
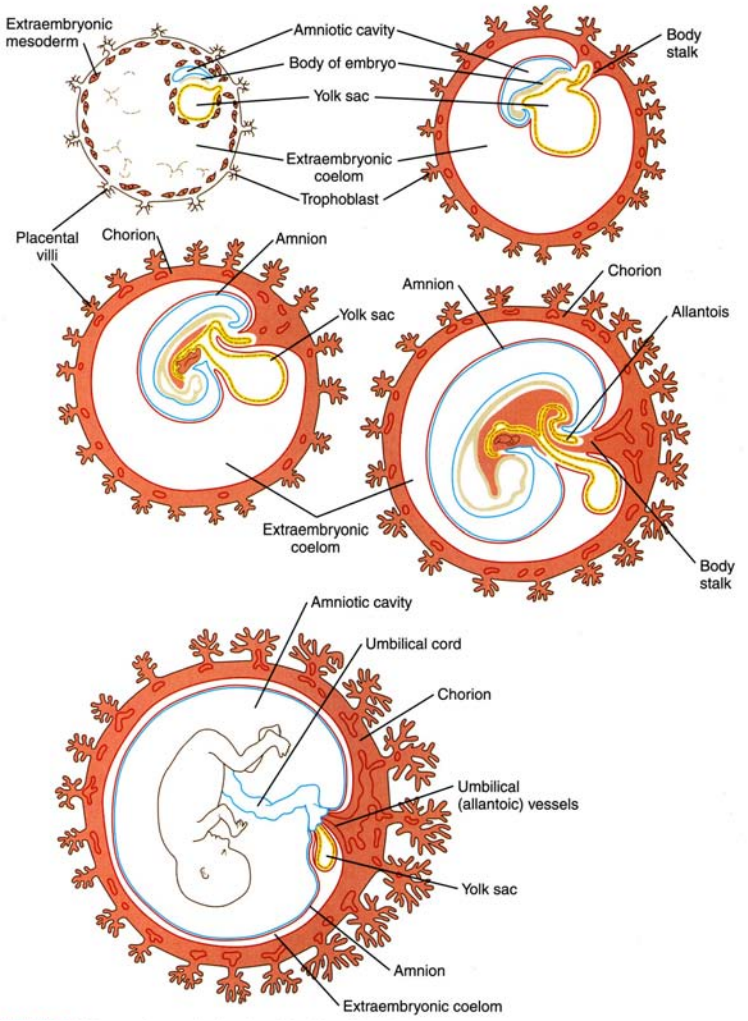


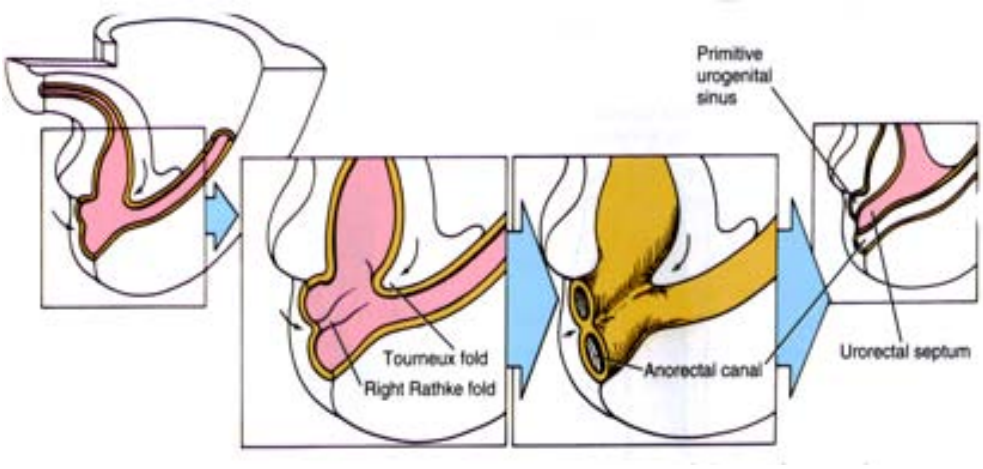
Figure 3
Human embryos showing the relationship of the chorion and extraembryonic membranes. Reprinted from "Human Embryology and developmental biology", Bruce M. Carlson, Third edition, Placenta and extraembryonic membranes, Picture 7-1, Page 130, 2004, Mosby Inc (Carlson 2004) with permission from Elsevier.



The amniotic membrane subsequently ensheathes the body stalk or umbilical cord (remnants of allantois, umbilical vessels and vitelline duct). The endoderm and the yolk sac are in continuity and become incorporated in the embryo as the primitive gut (Lauge-Hansen 1973). At a CRL of 7 - 8 mm, the gastrointestinal tract shows all its fundamental features, with distinct differentiation of its various segments, its mesenteries and its viscera (Lauge-Hansen 1973). At a CRL of 7 - 10 mm, the primary bowel loop has been described as entering the umbilical cord (Kiesselbach 1952) and at approximately 7

weeks and 6 days, the primary intestinal loop can be seen further projecting into the umbilical cord (Streeter 1948) and the counterclockwise rotation begins. Meckel reported on the development of the embryonic gastrointestinal tract in 1817 and stated that the midgut herniation in embryos was physiological (Meckel 1817). A remnant of the vitelline duct, called Meckel's diverticulum, is sometimes found at the ileum. At a CRL of 12 mm, the ultimate shape of the stomach is seen (Lauge-Hansen 1973) and at 8 weeks, the stomach shows the fornix, corpus and pars pylorica (Pernkopf 1923).The cloacal membrane ruptures from urinary pressure (Ludwig 1965) and the anal membrane breaks down around this time (Ludwig 1965; deVries and Friedland 1974; O'Rahilly 1978). The subdivision of the cloaca into an anterior primitive urogenital sinus and a posterior rectum takes place between 6 - 8 gestational weeks. The urorectal septum that divides the cloaca comprises three distinct septae: the Tourneaux fold that initially grows inferiorly to the level of the future pelvic urethra, after which the separation is completed by the left and right Rathke folds that grow in a coronal plane (Larsen 2001) *(Figure 4).*

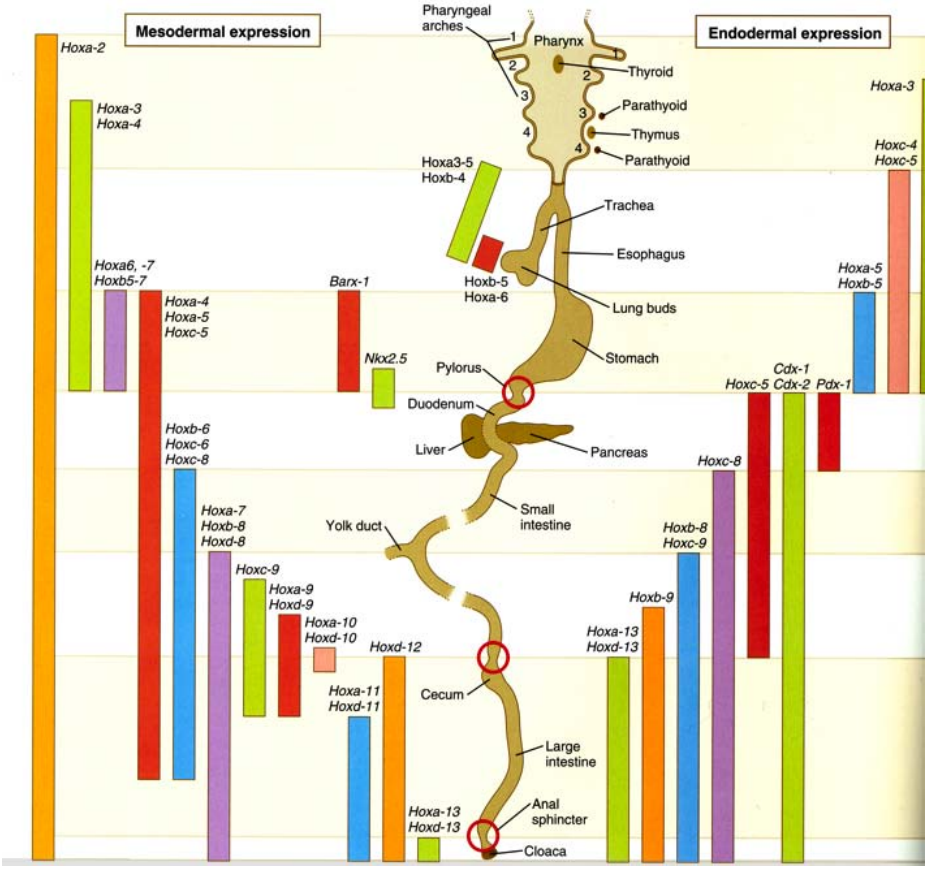
Figure 4
Subdivision of the cloaca into an anterior primitive urogenital sinus and a posterior rectum (between approximately 6 and 8 weeks of gestation). Reprinted with permission from "Human Embryology", William J. Larsen, 2001, Churchill Livingstone (Larsen 2001).



The stomach has been found to have a considerable diameter of mean 2.3 mm (in the fundus) in transverse section at 9 weeks (Hawass *et al.* 1991). With ultrasound, the stomach can be visualized from 8 weeks and normal diameter values are established from 8 to 12 gestational weeks (Blaas *et al.* 1995). The lumen of the esophagus is partially

occluded by epithelium by the 8th week and large vacuoles appear (Carlson 2004). At the same time, the plugging and vacuolization of the duodenum takes place (Tandler 1902; Boyden *et al.* 1967). This embryonic development concerning the duodenum has been discussed and some authors doubt the existence of complete plugging followed by vacuolization and recanalization (Moutsouris 1966; Cheng and Tam 1998). During weeks 10+0 to 11+6, the intestine returns to the abdominal cavity after a rotation of 270º and the physiological herniation should be completed after week 11+6 (Kiesselbach 1952; Lauge-Hansen 1973). The ultrasound appearance of the midgut herniation was first described by Cyr in 1986 (Cyr *et al.* 1986); both its appearance and its size from week 7 - 12 were later described by Blaas (Blaas *et al.* 1995).

Figure 5
Hox gene expression along the developing digestive tract. Expression along the gut endoderm (right) and in the gut-associated mesoderm (left). The circles represent areas where sphincters are located. Reprinted from "Human Embryology and developmental biology", Bruce M. Carlson, Third edition, 2004, Digestive and respiratory systems and body cavities, Picture 15-1, Page 354, Mosby Inc (Carlson 2004) with permission from Elsevier.



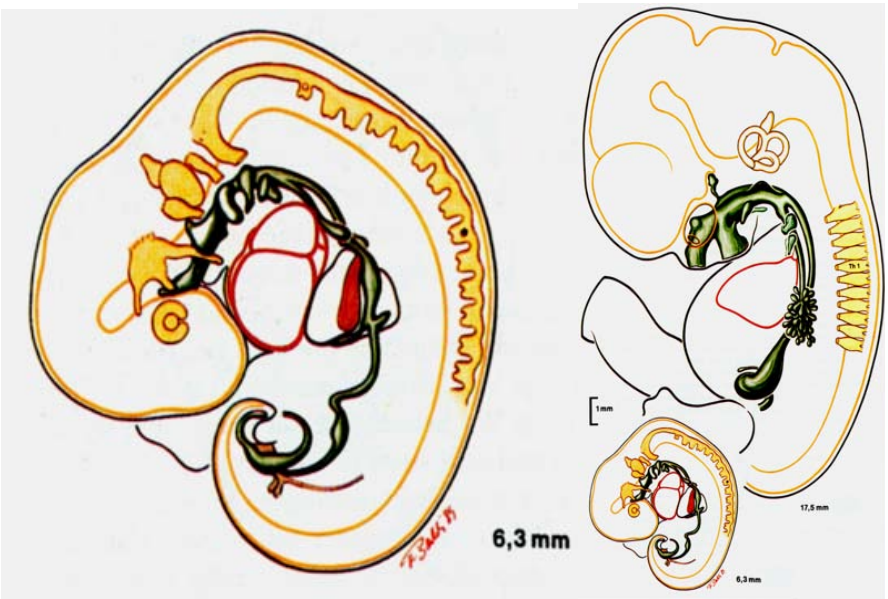
The fetal gastrointestinal tract arises from different divisions of the embryonic endoderm (Gleason *et al.* 2000). The esophagus, stomach, duodenum, liver and pancreas arise from the foregut. The jejunum, ileum, and proximal 2/3 of the colon arise from the midgut and the distal colon, rectum and anus from the hindgut. The splanchnic mesoderm is the origin of the peritoneal and muscular components of the gastrointestinal tract (Gleason *et al.* 2000). The blood supply of the foregut (lower esophagus to duodenum) is through the celiac artery. The superior mesenteric artery supplies the midgut and the inferior mesenteric artery the hindgut (Carlson 2004). The gastrointestinal tract develops from a simple tube into a complicated digestive system. This development is dependent on the amount and concentration of various signal molecules (sonic hedgehog, hox genes, etc.) for the determination of the cranio-caudal, left/right and ventro-dorsal development and orientation of organs in the embryonic body *(Figure 5)*.

Assumed pathological embryology of the gastrointestinal tract and abdominal wall

During the early development, abnormal separation of the tracheal bud from the esophagus leads to a variety of tracheoesophageal fistulas frequently found in connection with stenosis or atresia of the trachea or esophagus (Carlson 2004) *(Figure 6)*.

Figure 6

In green: the gastrointestinal and respiratory tract and their close relation in embryos at approximately 6 and 8 gestational weeks, respectively. Reprint from Hinrichsen, Human-Embryologie, (Abbildung 20-23, Intestinaltraktus). Klaus V. Hinrichsen, 1990 (Hinrichsen 1990). With kind permission of Springer Science and Business Media.



A number of genes are important in the normal mesenchymal partition of esophagus and trachea. Mutants of some transcription factors and of the sonic hedgehog may result in the absence of septation between the trachea and esophagus (Carlson 2004). Is it thought that stenosis or atresia of the esophagus is caused by abnormal recanalization of the esophagus, as a result of defective growth of endodermal cells, after epithelial occlusion of its lumen (Moore and Persaud 2003).

Stenosis and/or atresia of the duodenum is also thought to be caused by failure of vacuolization and recanalization following the so-called solid stage of duodenal development. This theory was first postulated by Tandler in 1902 (Tandler 1902). However, the theory has been questioned on several occasions over the years and is still questioned (Cheng and Tam 1998). It has also been suggested that the atretic segment of the duodenum is an abnormally situated bile duct (Gourevitch 1971).

Imperforate anus is caused by an abnormal development of the urorectal septum and/or of incomplete separation of the cloaca into urogenital and anorectal portions (Larsen 2001; Carlson 2004). Imperforate anus can hide a number of underlying conditions such as anal and rectal atresias of various lengths with or without fistulas (anoperineal, rectovaginal, rectourethral and rectovesical). Imperforate anus is also seen in cloacal anomalies.

The etiology of omphalocele is believed to be a folding defect (Duhamel 1963; Thieme 1992). The complete embryological development of the various types of omphalocele is not yet entirely understood. The process may be complex and the etiology may vary for the various types of omphalocele. The timing of the folding process may also play a role. Recent studies indicate a central role for epithelial-mesenchymal interactions in ventral body wall closure, either in the transition at the umbilicus or in cell-cell communication from the ectoderm to the mesoderm of the body wall (Brewer and Williams 2004a; Brewer and Williams 2004b).

These new theories may also apply to gastroschisis. Most likely, the etiology for ventral body wall defects is complex and includes a number of signal substances and genes. Gastroschisis has been believed to be the result of a vascular compromise in the

embryonic period. The most favored hypothesis is that there is an interruption in the development of the omphalomesenteric artery (Hoyme *et al.* 1981; Hoyme *et al.* 1983). Another theory is that an abnormal involution of the right umbilical vein may cause a weakness in the abdominal wall leading to protrusion of the bowel through that weakness (deVries 1980). These hypotheses are questioned in a recent review and a novel hypothesis that gastroschisis is a result of abnormal folding is proposed (Feldkamp *et al.* 2007).

Epidemiology of anomalies

Fetal gastrointestinal anomalies are rather common: in newborns, the general incidence of gastrointestinal anomalies is approximately 6:1000 (Heinonen *et al.* 1977). Intestinal obstruction has been one of the most common emergencies in the neonatal period accounting for approximately ¼ of admissions to neonatal surgery units (Lister 1978). Esophageal atresia has an incidence of approximately 1:3500 in liveborns (Depaepe *et al.* 1993; Torfs *et al.* 1995; Sparey *et al.* 2000). The incidence of duodenal atresia is approximately 1:10000 in newborns (Fonkalsrud *et al.* 1969). Imperforate anus has an approximate incidence of 1:1500 - 5000 in liveborns (Christensen *et al.* 1990; Stoll *et al.* 1997; Cho *et al.* 2001). The birth prevalence of omphalocele has been stable for a long time at approximately 1:5000 (Baird and MacDonald 1981; Lindham 1981; Rankin *et al.* 1999; Stoll *et al.* 2001). The incidence of gastroschisis has been increasing world-wide for unknown reasons (Penman *et al.* 1998; Rankin *et al.* 1999; Curry *et al.* 2000; Mastroiacovo *et al.* 2006). The previous incidence of approximately 1:10000 in most western countries has raised to 4.4:10000 in some countries (Brantberg *et al.* 2004; Kilby 2006). Especially the incidence of gastroschisis among mothers younger than 20 years has dramatically increased and is now 1:400 in Great Britain (Kilby 2006). Except for low maternal age, no *clear* risk factors or etiology for the increased incidence of gastroschisis have been found. Maternal use of vasoactive drugs has been discussed, and use of aspirin in early pregnancy has been shown to increase the risk (Werler *et al.* 2002). Recent studies have discussed the effect of nutrition and increased fat intake (Siega-Riz *et al.* 2006) and the combination of young mothers, smoking and malnutrition have been suggested as part of risk factors (Lam and Torfs 2006).

It is important to emphasize that the incidence of anomalies is higher in a fetal population than among newborns. From our results in the non-selected population, the fetal incidence of esophageal obstruction was 1:3500, of duodenal obstruction 1:3517, of imperforate anus 1:1800, of omphalocele 1:2000 and of gastroschisis 1:2290. Altogether, the incidence of these 5 diagnoses that are discussed in this thesis was approximately 2:1000. This means that they contribute to a high number of fetuses, all with a potential need for postnatal surgery.

The epidemiology of fetal anomalies is still far from elucidated. In most epidemiologic studies of the incidence of anomalies, only liveborns are considered; spontaneous abortions and intrauterine fetal deaths are usually not counted or data are missing. In addition, termination of pregnancies have not always been included in the numbers (Leck 1993). There is also an intermingling of diagnoses because various diagnoses were not as well mapped in previous studies as they are today. For example, abdominal wall defects were previously considered as basically the same condition while we now discriminate between several conditions with different outcomes. Our knowledge about biotechnology is improving very fast and genes that were not detected some years ago are now not only known but also eligible for prenatal DNA-testing and thereby new diagnoses are discovered (Cooper *et al.* 2005; Rooks *et al.* 2005).

The completeness and validation of the data is also an issue when we compare and discuss the epidemiology of anomalies. In Norway, we have a *well-defined* population and available data of anomalies from the Medical Birth Registry of Norway (MFRN), which was started 40 years ago. However, there is a limitation in that the MFRN did not include terminations of pregnancies and stillbirths in their registration of birth anomalies prior to 1999. In addition, sometimes only one amongst several anomalies in the same fetus/infant is registered and anomalies that are not obvious at birth are not always included in the registry. As an example, in our non-selected population, from 1987 to 2000, we had 11 cases of duodenal obstruction registered prospectively in our database. For the same population during the same time period, the MFRN had only 5 cases registered in their database, an underreporting of fifty percent. Of our 11 cases, 10 were

liveborn and should definitely have been included in the national registry. Further studies about the validity of the official registry of birth defects in Norway ought to be initiated. Underreporting of information in large official registries is known (Källén and Knudsen 1989; Salvesen *et al.* 1990; Hey *et al.* 1994) and the quality assurance of the Norwegian birth registry has been discussed previously (Egenaes and Bjerkedal 1982). As the use of local high quality-assessed registries increases, we need to address the quality of the official registries.

Fetal examination

Ultrasound has given us the possibility to get detailed information about the fetus and the intrauterine environment. Ian Donald from Scotland was the first to introduce diagnostic ultrasound to obstetrics and gynecology (Donald *et al.* 1958; Donald 1962). Bertil Sundén, University of Lund in Sweden was inspired by Ian Donald's work and indeed the first commercially made ultrasound machine, Diasonograph, was sold to the University of Lund. Sundén's thesis from 1964 represents a pioneer work of the use and value of ultrasound in obstetrics and gynecology (Sundén 1964). Stuart Campbell initiated his work in the mid 60's, and in 1968 presented his seminal work in which both A- and B-mode scans were used to measure the fetal biparietal diameter (BPD) (Campbell 1968), a classical principle still used today. In 1969, he presented a normal growth curve for BPD (Campbell 1969). Kratochwil, from Austria, reported on fetal heart pulsation already from 7 gestational weeks in 1967 (Kratochwil and Eisenhut 1967) and in 1972, Hugh Robinson confirmed that fetal heart movement could be reliably detected with pulsed ultrasound from 7 gestational weeks onwards (Robinson 1972).

Sundén demonstrated already in 1964 that acrania can be diagnosed with ultrasound (Sundén 1964). In 1972, Campbell was the first to report termination of an anencephalic fetus following prenatal detection (Campbell *et al.* 1972) and in 1975, he presented a case with spina bifida diagnosed by ultrasound (Campbell *et al.* 1975). The use of ultrasound in obstetrics rapidly expanded as the development of the technique and equipment continued (Levi 1997).

At the General Hospital in Malmö, University of Lund, Sweden, ultrasound was first introduced for systematic use during pregnancy in 1973 - 1974 (Grennert *et al.* 1978). The primary intention was to detect twins and the examinations were performed at approximately 28 weeks' gestation. Soon the examination was moved to approximately 17 weeks and later a second routine examination at 32 gestational weeks was added. The first country to introduce a routine fetal examination to their whole pregnant population was Germany in 1980 (Mutterschafts-Richtlinien 1980).

In Norway, a routine fetal examination at approximately 18 gestational weeks for all pregnant women was introduced in 1986. The introduction was preceded by a consensus conference concerning the use of ultrasound in 1986 (Backe and Buhaug 1986). The recommendations to introduce a routine fetal examination were based on the reported decrease in post-term pregnancies (Eik-Nes *et al.* 1984) and the need to organize the already extensive use of ultrasound (Eik-Nes 1986). During the years that followed, additional European countries introduced routine fetal examinations such as Iceland in 1987 (Geirsson 1987) and Austria in 1988. The Royal College of Obstetricians and Gynecologists (RCOG) published a report in 1984 on the routine use of ultrasound in pregnancy (RCOG 1984). At that time, among the concerns raised was the concern about the biological safety of ultrasound. The general conclusions were that the evidence that ultrasound may produce biological damage was not well founded and that benefits were likely from an ultrasound scan performed at approximately 16-18 gestational weeks. The report underscored the importance of adequate training. In the USA, the decision against a routine fetal examination was based on the RADIUS study (Ewigman *et al.* 1993) which did not show any improvement of perinatal outcome of those who underwent a routine fetal examination. However, the low detection rate of anomalies in the RADIUS study indicated that the potential of the examination was not fully exhausted, probably due to suboptimal basic skills of the ultrasound operators (Romero 1993; Eik-Nes *et al.* 2000). Nowadays, most countries in Europe offer routine fetal ultrasound examinations, including evaluation of the anatomy, during pregnancy (SBU-rapport nr. 139, 1998). In Norway, a second consensus conference concerning the use of ultrasound in pregnancy was held in 1995 (Konsensuskonferanse 1995). One major reason for the conference was

the concern that fetuses with non-lethal anomalies would be terminated since the improving technology was making it possible to detect minor anomalies. The conference panel emphasized the importance of informed consent of the women, but decided to continue to offer a routine fetal examination. In Norway, midwives with special education in ultrasound usually perform these routine fetal examinations at approximately 18 weeks' gestation. Additional ultrasound examinations are made only on clinical indication.

The purpose of the routine fetal examination was primarily to assess the gestational age in a better way than by the last menstrual period and to detect multiple pregnancies. Several studies have shown that the routine use of ultrasound for assessing the gestational age has decreased the number of post-term pregnancies (Eik-Nes *et al.* 1984; Waldenström *et al.* 1988; Geerts *et al.* 1996; Eik-Nes *et al.* 2000; Neilson 2000). According to the Cochrane database, the reduction was almost 40% (Neilson 2000). Another benefit of the dating by ultrasound was that the rate of SGA fetuses was reduced (Goldenberg *et al.* 1989; Waldenström *et al.* 1992) and it was possible to identify the fetuses with intrauterine growth retardation later in pregnancy with higher accuracy than previously. An additional purpose of the routine ultrasound examination was to determine the location of the placenta.

Another purpose of the routine fetal examination was to perform an anatomical evaluation of the fetus. The benefit of the routine ultrasound examination in detecting fetal anomalies has been questioned. Some authors have emphasized the benefit of altering the obstetric management regarding timing and place of delivery (Luck 1992) while others have criticized it, claiming that no improvement of the perinatal outcome of fetuses who underwent a prenatal ultrasound examination has been proven (Ewigman *et al.* 1993). Indeed, the reduction in perinatal mortality after the introduction of routine fetal examination has been suggested to be an effect of increased rate of termination of pregnancies (Saari-Kemppainen *et al.* 1990; Zimmer *et al.* 1997; Liu *et al.* 2002). It has also been shown that a routine fetal examination with a high detection of fetal anomalies

is cost-effective in relation to perinatal mortality (Leivo *et al.* 1996; Vintzileos *et al.* 2000).

The ability to detect fetal anomalies varies greatly (14% - 95%) in different studies (Campbell *et al.* 1983; Campbell and Pearce 1983; Lys *et al.* 1989; Chitty *et al.* 1991; Luck 1992; Ewigman *et al.* 1993; Saari-Kemppainen *et al.* 1994; Carrera *et al.* 1995; Chitty 1995; Stoll *et al.* 1995; Zimmer *et al.* 1997; Boyd *et al.* 1998; Grandjean *et al.* 1998; Stefos *et al.* 1999; Levi 2002; Garne *et al.* 2005; Nikkilä *et al.* 2006; Saltvedt *et al.* 2006). These differences reflect the experience of operators (Ewigman *et al.* 1993; Crane *et al.* 1994; Saari-Kemppainen *et al.* 1994; Chitty 1995), the selection of the examined population, the number of examinations and gestational age when the examinations were performed. The detection rate is also dependent on the classification of anomalies and the quality of the postnatal/postabortem examinations. In addition, the length of follow-up is important for the determination of the accuracy of the prenatal diagnosis (Levi 2002).

In a review of 36 studies from 1978 - 1997, with a computed standardized sensitivity at 2% prevalence, the sensitivity for prenatal detection of fetal anomalies varied from 8 - 89.8% (Levi 2002). In the same review, which included 925 675 fetuses, the total sensitivity for detected anomalies was 40.3%. The studies are difficult to compare due to a large number of factors, but another review of routine fetal examinations concluded with 41.3% detection of fetal abnormalities before 24 weeks' gestation (Bricker *et al.* 2000). The importance of a second opinion and not relying on one single examination has been emphasized in order to increase the prenatal detection rate and avoid false positive diagnoses (Walkinshaw *et al.* 1992).

In Scandinavia, the detection rate of fetal anomalies in non-selected populations at the routine fetal examination varied between 22 - 28% in 3 Swedish studies (Eurenius *et al.* 1999; Nikkilä *et al.* 2006; Saltvedt *et al.* 2006) and was 39% in a Norwegian study (Nakling and Backe 2005).

The use of ultrasound at 11+0 - 13+6 gestational weeks has become more common and the detection rate of fetal anomalies in non-selected populations at the 11+0 - 13+6 week scan has been presented as 17 - 18% (Taipale *et al.* 2004; McAuliffe *et al.* 2005). The detection rate of fetal anomalies may be further improved when both an early scan and a routine examination in the second trimester are performed (Achiron and Tadmor 1991; Carvalho *et al.* 2002; Chen *et al.* 2004; Taipale *et al.* 2004).

Many authors have described an increased detection rate of anomalies over time (Carrera *et al.* 1995; Levi *et al.* 1995; Stoll *et al.* 1995; Zimmer *et al.* 1997; Taipale *et al.* 2003) indicating a learning curve of the examiners. In our non-selected population, the detection rate for CHD's increased from 18 to 57% between the periods 1986 - 1988 to 1991 – 2001. The experience of the operator had a significant impact on the detection rate of CHD's (Tegnander and Eik-Nes 2006). As a comparison, in a recent study with similar settings of population and examiners, the detection rate of major CHD's was 13% (Westin *et al.* 2006). The increased detection rate in the study by Tegnander (Tegnander *et al.* 2006) was achieved after focus was placed on the fetal heart examination.

Focusing on the detection of fetal anomalies in general may most likely increase the detection rate. However, the basic level of skills of the examiners must be satisfactory. ISUOG (ISUOG Educational committee 1996) and EFSUMB (Valentin *et al.* 2003) have proposed minimum training requirements for the practice of ultrasound in Europe and internationally. At the National Center for Fetal Medicine (NCFM) in Trondheim a postgraduate educational program in obstetric ultrasound for nurses/midwives was suggested in 1990 and was formally established in 1997. This educational program is run under the Norwegian University of Science and Technology. At present, it is the only program of its kind in Scandinavia. This one-year, part-time study combines theoretical education with clinical practice. The education of physicians and sonographers/midwives who are performing the fetal ultrasound examination is a prerequisite if fetal examinations are to be of benefit. In Scandinavia, recent studies from Sweden (Nikkilä *et al.* 2006; Saltvedt *et al.* 2006) show depressing results concerning detection rates of anomalies. One might discuss whether this reflects the lack of skill of the operators and

whether a formal education should be initiated. It is worth emphasizing that a few highly skilled specialists in fetal medicine make no difference for the population unless all "first-line" examiners have the sufficient basic skills and knowledge to recognize the fetuses with abnormal findings and refer them for further evaluation. The quality of the fetal examinations will vary, but unless governments and professional societies give priority to the education of the operators, the level of quality might further decrease. As long as the basic education is insufficient, it will be impossible to meet the expectations of parents and society.

It takes time to prove the advantages of new technology, especially when most single diagnoses have a very low incidence. In addition, it has often been the serious cases with a high mortality that have been detected prenatally. Despite this, improved outcomes for infants with a prenatal diagnosis of various anomalies have been demonstrated (Miro and Bard 1988; Romero *et al.* 1988; Bonnet *et al.* 1999; Tworetzky *et al.* 2001; Vilela *et al.* 2001; Franklin *et al.* 2002; Bittencourt *et al.* 2004). Several studies emphasize the importance of rapid diagnosis and/or surgery after birth for improved outcome of certain anomalies (Cavanagh and Welty 1965; Lister 1978; Touloukian and Hobbins 1980; Lindley *et al.* 2006). The impact of prenatal diagnosis in Brazil has been discussed in studies of gastroschisis and duodenal obstruction, respectively (Vilela *et al.* 2001; Bittencourt *et al.* 2004). A study in Paris showed improved outcome for infants with anomalies that have been delivered at appropriate hospitals with specialized facilities (De Vigan *et al.* 1997). In Norway, with long distances to specialized neonatal care, a prenatal diagnosis might be significant for the outcome.

Prenatal diagnosis of conditions that need postnatal surgery has been shown to reduce parental anxiety (Kemp *et al.* 1998) and the authors concluded:

> *Fetal medicine centers have given pediatric surgeons the opportunity to change neonatal surgery from a predominantly unplanned emergency service, with all that implies in terms of anxiety and stress, to one that is almost semielective and planned, with a consequent reduction in the parental anxiety over what is still a major life event (Kemp et al. 1998).*

The ultrasound examination during pregnancy has also been recognized as an opportunity for the parents to relate to their unborn child for the first time. The routine fetal ultrasound examination is important in this psychological "bonding" function (Sioda and Rybakowski 1984; Villeneuve *et al.* 1988; Sedgmen *et al.* 2006). The bonding (maternal-fetal; paternal-fetal) has been discussed as having both psychological and moral significance (Fletcher and Evans 1983). It has been suggested that three-dimensional ultrasound has an even more positive influence on the maternal-fetal bonding (Ji *et al.* 2005), but a later study has not confirmed these findings (Sedgmen *et al.* 2006). The verbal information during the ultrasound examination is important for the positive experience (Villeneuve *et al.* 1988) and verbal feed-back has been shown to reduce pregnancy anxiety and lead to fewer obstetric complications in primiparous mothers (Field *et al.* 1985). Further studies are needed to show if the impact of bonding might lead to a positive impact on the well-being of the fetus through a change in the mothers' health behavior (Campbell 2006).

Prenatal detection of gastroschisis and omphalocele

It may be possible to detect abdominal wall defects prenatally in 100% of the cases. However, there has often been an intermingling of the various diagnoses of the abdominal wall (Walkinshaw *et al.* 1992). In two large European studies, the prenatal detection rate was 77% and 75% respectively for omphalocele, and 89% and 83% respectively for gastroschisis (Barisic *et al.* 2001; Garne *et al.* 2005). In our studies, the prenatal detection rate in the non-selected population was 100% for gastroschisis (Brantberg *et al.* 2004) and 95% for omphalocele (Brantberg *et al.* 2005). It is possible to diagnose gastroschisis already in the first trimester; the diagnosis has a high accuracy already then. Omphalocele is also possible to diagnose early (Brown *et al.* 1989; Blaas *et al.* 1995; van Zalen-Sprock *et al.* 1997; Blaas and Eik-Nes 1999). Epigastric defects are detectable before 12 weeks of gestation (Brown *et al.* 1989; Blaas and Eik-Nes 1999) and central defects may also be detectable at that early stage (Blaas *et al.* 1995; Blaas and Eik-Nes 1999). However, caution should be taken prior to the completion of the physiological herniation (Schmidt *et al.* 1987; Blaas *et al.* 1995; van Zalen-Sprock *et al.* 1997; Blaas and Eik-Nes 1999). One should also be aware that a transient umbilical

hernia might mimic an omphalocele. One study reported several cases of isolated omphalocele diagnosed at 12 - 16 weeks which disappeared totally during pregnancy (Blazer *et al.* 2004).

Prenatal detection of esophageal obstruction

A prenatal diagnosis of gastrointestinal obstructions is not always possible. The more proximal the obstruction is situated, the more clinical symptoms it will give due to polyhydramnios. On the other hand, approximately 80 - 90% of cases with esophageal atresia have a tracheo-esophageal fistula (TEF) (Louhimo and Lindahl 1983) allowing the fluid proximal to the obstruction to be drained through the fistula and thereby giving fewer symptoms. A small or not visible stomach should always alert the examiner for a possible esophageal obstruction and additional polyhydramnios should increase the suspicion. The positive predictive value of a small or empty stomach and polyhydramnios is, however, low due to several other possible conditions (Stringer *et al.* 1995).

The blindly ending proximal part of the esophagus, usually called the proximal or upper esophageal pouch, was described prenatally already in 1983 (Eyheremendy and Pfister 1983). Prenatal visualization of this proximal esophageal pouch has received increasing interest during the last decades due to a high specificity for esophageal atresia (Satoh *et al.* 1995; Vijayaraghavan 1996; Centini *et al.* 2003; Has and Gunay 2004; Has *et al.* 2004) and the pouch should always be searched for in suspected cases. The level of the pouch has been suggested to be of prognostic value (Kalache *et al.* 2000; Shulman *et al.* 2002). Prenatal MRI (Langer *et al.* 2001) and three-dimensional ultrasound (Yagel *et al.* 2005) might improve the accuracy of the prenatal diagnosis of esophageal obstruction.

Although prenatal diagnosis of esophageal atresia was described already in the early 80's (Farrant 1980; Zemlyn 1981; Pretorius *et al.* 1983), the rate of prenatal detection has been reported to be low, ranging between 9 - 42% (Pretorius *et al.* 1987; Stringer *et al.* 1995; De Vigan *et al.* 1997; Sparey *et al.* 2000; Kalish *et al.* 2003) and the diagnosis is usually not made before the third trimester. The fetal esophagus is possible to visualize already in

the first trimester (Blaas *et al.* 1995) and the esophagus can be detected in approximately 90% of normal fetuses in the second and third trimester (Avni *et al.* 1994; Malinger *et al.* 2004). The prenatal detection rate was 43% in our non-selected population and 44% in the selected population.

Prenatal detection of duodenal obstruction

The accuracy of the diagnosis of duodenal obstruction is high. The diagnosis is based on the typical "double-bubble" sign that arises from the dilated stomach and distended upper part of the duodenum and has a high specificity for duodenal obstruction. It is, however, important to confirm a clear connection between the stomach and duodenum for maintaining a high accuracy of the diagnosis. Polyhydramnios is usually present and its clinical signs are the most common reason for referral, leading to a targeted ultrasound examination. The diagnosis of duodenal obstruction is rarely made early in pregnancy. This may be due to immaturity of the gastric emptying, which reflects immaturity of the autonomic function (Lawrence *et al.* 2000). Fetal gastric motility is sporadic and infrequent before 20 weeks of gestation. Both gastric motility and gastric emptying significantly increase at around 24 weeks (Sase *et al.* 1999; Sase *et al.* 2000). However, it is important to note that any dilatation of the duodenum in the second trimester might be abnormal (Levine *et al.* 1998) and serial scans may be valuable (Nelson *et al.* 1982). The prenatal detection rate of duodenal obstruction in our non-selected population was 82% (Brantberg *et al.* 2002).

Prenatal detection of imperforate anus

Imperforate anus is usually not diagnosed until after birth and the diagnosis can rarely be verified prenatally. Antenatal diagnosis of imperforate anus has been reported (Bean *et al.* 1978; Grant *et al.* 1990; Guzman *et al.* 1995) sometimes as early as 12 weeks' gestation (Lam *et al.* 2002; Taipale *et al.* 2005). Dilatation of the distal colon and/or rectum is the most common finding in prenatal detection of imperforate anus (Bean *et al.* 1978; Harris *et al.* 1987; Hearn-Stebbins *et al.* 1991; Bronshtein and Zimmer 1996; Taipale *et al.* 2005). Abdominopelvic masses (Miller *et al.* 1990) or intraluminal calcifications may also raise suspicion of imperforate anus (Shalev *et al.* 1983; Grant *et*

al. 1990; Mandell *et al.* 1992). The appearance of fetal bowel changes with maturation (Zilianti and Fernandez 1983; Nyberg *et al.* 1987; Parulekar 1991) and dilatation of the bowel may also be a transient finding in normal fetuses (Bronshtein and Zimmer 1996) emphasizing the risk of over diagnosing, which may cause unnecessary parental anxiety. The prenatal detection rate in our study was 15.9% in the selected population and 11.1% in the non-selected population (Brantberg *et al.* 2006).

Safety of ultrasound

The possible side effects of ultrasound in obstetrics have been widely discussed due to the extensive use of the technique, also in normal pregnancies. Few other medical techniques have been investigated as thoroughly as ultrasound. So far, based on evidence currently available, performing routine ultrasound examination in pregnancy is not contraindicated (Salvesen 2002; Abramowicz *et al.* 2003). The international ultrasound societies have updated comments and statements concerning safety available on the internet: (ISUOG) www.isuog.org, (WFUMB) www.wfumb.org and (EFSUMB) www.efsumb.org. It is important to emphasize that every ultrasound operator is responsible for the safety; this implies the necessity of proper education. It is also worth emphasizing that all fetal examinations should have a clinical indication. The routine use of ultrasound at 18 weeks is considered a clinical indication.

Ethics

Diagnosis of diseases and anomalies in fetuses gives the possibility for treatment, focused surveillance and optimized postnatal care. However, some conditions represent a severe anomaly or disease and the parents may opt for a termination of the pregnancy. This option has been the reason for the ethical debates parallel with the development of ultrasound. In Norway, the concerns have primarily been related to the assumed risk of false positive diagnosis of anomalies leading to termination of pregnancies with normal fetuses. Later the question of whether or not the selective abortion of fetuses with certain characteristics is “ethical” was, and still is, heavily debated. There is no true, easy or overruling answer to these questions (Ethics Committee of the Swedish Medical Society

1993; Solberg 2003). It has been argued that human rights and dignity may be threatened if humans are not all accorded the same value. The Council of Europe has published a treaty with clear statements concerning preservation of human dignity, rights and freedom through a series of principles and prohibitions against the misuse of biological and medical advances (European Council 1997).

The pregnant woman should give her informed consent prior to the examination. She is in a vulnerable condition and every ultrasound operator has to be educated and concerned about the way information is given. When a suspicion of an adverse development in an expected child is revealed to the parents, strong psychological reactions may be generated. When an anomaly or an adverse development is detected, a "perinatal team" comprised of various health professionals should be formed. The information to parents depends on the condition and gestational age of the fetus and the possibility for treatment. Our general experience is that thorough, repeated information with the possibility to ask questions, along with readily accessible health personnel, are of utmost importance in the acute phase. The ethical aspect must consider the autonomy of the pregnant woman, especially when it comes to decisions concerning possible termination of a pregnancy (Chervenak and McCullough 1991). 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).

Centralization

Most diagnoses of the fetus are such rare conditions that, under normal circumstances, a physician will only see a few in a lifetime. The field of fetal medicine is still under development and every single diagnosis is rare. Many fetal conditions are so rare that populations of several hundred thousands are needed to be able to draw any conclusions about the consequences that management has for the outcome. It is important that we use all possible knowledge that can be gleaned from rare cases. It is our responsibility to maintain and improve the knowledge of rare conditions. To improve our knowledge and thereby our management, it is important to collect the data from many cases which individually are rare. To be able to derive all possible data from every single rare case, it

is necessary to manage these cases at centralized units. For some diagnoses, the surveillance of the fetuses makes the difference between life and death for the infant. This surveillance is also the responsibility of a specialized, centralized unit.

Several studies have shown an increased detection rate of fetal anomalies at tertiary centers compared to the detection rate by examiners at other institutions (Crane *et al.* 1994; Saari-Kemppainen *et al.* 1994; Ogunyemi and Buskye 2000; Wong *et al.* 2003). Most likely this is due to a generally higher level of experience and an academic environment with more thorough knowledge.

However, to receive the benefit of centralization, good co-operation with peripheral units is needed. A center and the peripheral units alike must recognize and experience that the benefits are dependent on a reciprocal relationship. The ability to find abnormal findings peripherally and the peripheral units' willingness to refer these cases is crucial for a center in its efforts to obtain more experience and knowledge. A center can provide second opinion for the peripheral units as well as help and planning of the management of the cases that are in need for special management, including invasive procedures. Knowledge and outcome improvement is a result of continuous education and feedback.

In countries with small populations, like Norway, it is especially important to centralize the care of rare conditions to be able to improve the outcome for fetuses and infants with certain conditions.

Fetal population versus neonatal population

Traditionally, the outcome of infants with congenital anomalies has been based on available data from liveborns, mostly including individuals that have survived through pregnancy and the immediate postnatal period. These selected individuals have been incorporated in the medical and surgical follow-up evaluations. Thus, the evidence of improved outcome over time has usually been based on selected individuals.

The routine fetal examination has provided us with new information that shows major differences between the fetal population and the neonatal population regarding the incidence and the development of anomalies. During the last 20 years, with a nationwide offer of routine fetal examination to all pregnant women, an increasing number of anomalies are detected already in utero. Most anomalies detected prenatally are diagnosed at the routine fetal examination at approximately 18 weeks. An increasing number of women have an ultrasound examination earlier in pregnancy and, depending on when an ultrasound examination is performed, various anomalies are detected at various gestational ages. Approximately 10 - 15% of clinically recognized pregnancies miscarry but the total reproductive losses, from conception to live birth, are approximately 50 - 70% (Chard 1991; Rai and Regan 2006). Based on a mathematical hypothesis, estimates of early pregnancy loss may be as high as 78% (Roberts and Lowe 1975). Women are well aware of the risk for spontaneous abortions early in pregnancy and most know that the longer the pregnancy continues, the lower the risk for spontaneous loss. Approximately 50% of early (before 12 weeks) spontaneous abortions are due to abnormal karyotype (Boué *et al.* 1975; Plachot 1989; Chard 1991; Stephenson *et al.* 2002).

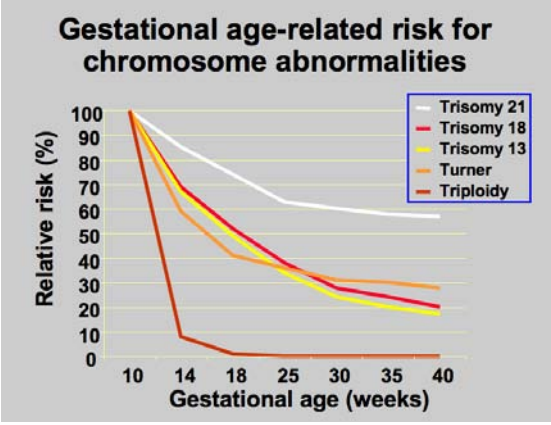


Figure 7
Gestational age-related risk for the most common chromosome abnormalities. The lines represent the relative risk according to the risk at 10 weeks' gestation.
Redrawn from data in "The 11-13+6 weeks scan" by Kypros H. Nicolaides, Fetal Medicine Foundation (FMF), London 2004.

The risk for a fetus to have an abnormal karyotype is higher early in gestation. A fetus with an abnormal karyotype has a high risk for intrauterine death and/or spontaneous abortion and the risk is higher the earlier in pregnancy. Of fetuses diagnosed at 10 weeks with triploidy almost all are dead at 25 weeks' gestation. Of fetuses with trisomy 13 and 18, approximately 80% die during pregnancy, and of fetuses with trisomy 21,

approximately 40% die during pregnancy *(Figure 7)*. When a diagnosis of abnormal karyotype is made at 18 weeks' gestation, the risk for death is lower than at 10 weeks' gestation due to the large number of fetal losses that have already occurred. These numbers are of value in the evaluation of fetuses with abnormal karyotype. Many fetal anomalies are associated with abnormal karyotype and it is important to be aware of these numbers in this context. When a prenatal diagnosis is made, the population includes a high number of fetuses with abnormal karyotype and also a high number of fetuses with the whole spectrum of fetal anomalies, syndromes, sequences etc. The numbers vary depending on the time of diagnosis, but in general, an early prenatal diagnosis reflects a more severe anomaly that is also more often associated with abnormal karyotype and other associated anomalies and syndromes. The spectrum of the severity of a specific diagnosis is more extensive, the earlier in pregnancy the diagnosis is made.

Intrauterine fetal death occurs for many of the fetuses with abnormal karyotype and associated anomalies. Some women choose to terminate their pregnancies when the fetus has a serious or lethal condition. Thus, for some conditions like omphalocele, with a strong association with lethal abnormal karyotypes the fetal incidence is approximately 1:1000 at 11 - 14 weeks' gestation (Snijders *et al.* 1995; Snijders *et al.* 1995) while the live birth incidence is 1:5000. Of the 90 fetuses with omphalocele in our study (Brantberg *et al.* 2005) only 21 (23%) survived and only 8 (9%) infants were alive and healthy. This reflects a profound contrast to data based on neonatal populations with survival rate of approximately 90% (Mayer *et al.* 1980; Grosfeld *et al.* 1981; Mabogunje and Mahour 1984; Rankin *et al.* 1999). Similar results were found in a study of prenatally detected congenital heart defects (Tegnander *et al.* 2006). Obviously, it is important to be aware of the differences of fetal and neonatal populations. This difference may apply to most fetal anomalies.

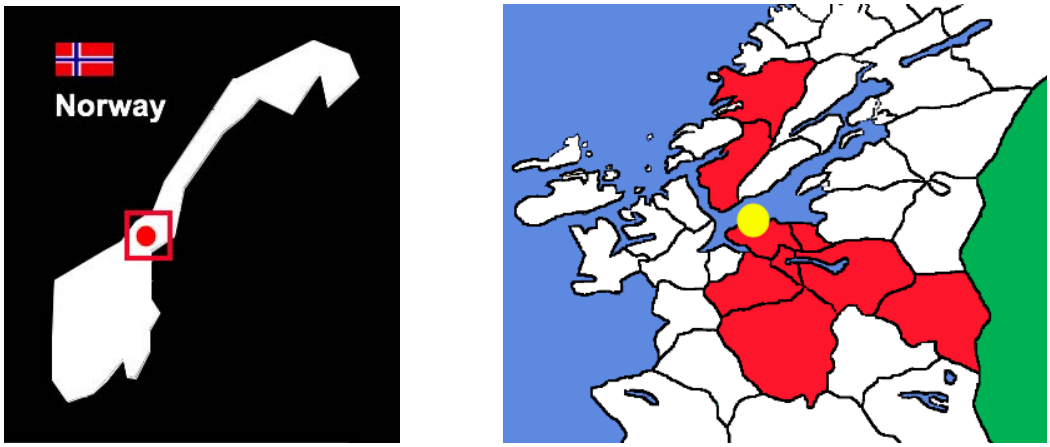
A woman wants to know about the prognosis for her fetus at the time of diagnosis. To counsel and inform about the outcome based on neonatal populations is incorrect and may also mislead the woman who is trying to make a decision concerning her pregnancy. For a couple in a vulnerable situation, it must be of highest priority to provide as accurate

information as possible. It is also essential in maintaining the couple's confidence in health personnel. Our main aim is to provide the best possible chances for fetuses with anomalies and diseases. On the other hand, we are obliged to keep in mind that some conditions are incurable and parents should be informed about that.

Selected versus non-selected populations

At a routine fetal examination offered to all pregnant women in a non-selected population, the whole spectrum of anomalies is present. However, the various anomalies appear rarely and the examiners need to be focused at every examination. The sensitivity for detection of anomalies is dependent on the prevalence in the examined population. Non-selected populations comprise both a low-risk and a high-risk population. A non-selected population is not the equivalent of a low-risk population and it is incorrect to use the definitions interchangeably. However, a confusion of these definitions is commonly seen. A bias of the selection is also commonly seen due to inclusion of referred cases.

Figure 8
The non-selected population of Trondheim including 9 municipalities.



The non-selected population in our studies came from a geographically well-defined area including the city of Trondheim and eight surrounding municipalities *(Figure 8)*. Within this non-selected population, approximately 97% of the pregnant women who lived there had a routine fetal examination at the NCFM and were later delivered at the Trondheim University Hospital. The area is served only by Trondheim University Hospital for all

health care services including the Neonatal Intensive Care Unit, Pediatrics and Pediatric Surgery. Consequently, this is a true non-selected population.

In non-selected populations, the prevalence of anomalies is relatively low. The detection rate of fetal anomalies is dependent on the operator's ability to identify the fetuses that may need further evaluation. The challenge for them is to be focused at every examination. Operators examining non-selected populations are "specialists" in the normal appearance of the fetal anatomy and must trigger if something appears abnormal. The education of sonographers/midwives/physicians performing the routine fetal examination is extremely important in this regard. Appropriate education and sufficient experience of operators examining non-selected populations might increase the overall detection rate.

In high-risk populations, fetuses are usually examined thoroughly, sometimes several times. The operators are skilled and use high quality equipment and the detection rate is high. For example, in non-selected or low risk populations examined by the routine staff at 18 - 22 weeks gestation 0 - 66% of congenital heart defects were detected (Crane *et al.* 1994; Saari-Kemppainen *et al.* 1994; Rustico *et al.* 1995; Tegnander *et al.* 1995; Buskens *et al.* 1996; Todros *et al.* 1997; Tegnander *et al.* 2006; Westin *et al.* 2006) while 86% of major cardiac anomalies were detected already at examinations at 11 - 14 weeks in a high-risk population (Weiner *et al.* 2002).

The increasing use of "tests in sequence" with early scans offered to a high number of women may affect the populations and an apparently non-selected population at 18 weeks may then become a low-risk population. This may be an important issue when results are compared. For example, if all pregnant women are offered 11+0 - 13+6 week scans for measuring the nuchal translucency, many of the fetuses with abnormal karyotype and some of the fetuses with congenital heart defects and other anomalies might already have been diagnosed prior to the routine examination. Consequently, fewer anomalies are expected within the population submitted to a routine fetal examination in the second trimester.

AIMS OF THE STUDIES

The primary aim of the studies was to describe in a *selected population:*

1. the outcome of fetuses with duodenal obstruction, gastroschisis and omphalocele from the time of prenatal diagnosis through the pregnancy and delivery and into the postnatal period (Papers I-III).
2. the risk factors for poor outcome for fetuses with duodenal obstruction, gastroschisis and omphalocele, and to determine whether surveillance may be of benefit (Papers I-III).
3. the different types of omphalocele and identify possible differences between these different types regarding associated anomalies and outcome (Paper III).
4. the rate of prenatal diagnosis of esophageal obstruction and imperforate anus and elucidate possible strategies for improved diagnosis and their impact on the outcome (Papers IV-V).

The additional (secondary) aim was to describe, in a *non-selected population*, the incidence, prenatal detection rate and accuracy of the diagnoses of gastroschisis, omphalocele, imperforate anus, duodenal and esophageal obstruction (Papers I-V).

MATERIALS AND METHODS

Papers I, II and III were based on cases with a prenatal diagnosis of duodenal obstruction, gastroschisis and omphalocele, respectively. The cases were followed prospectively from the time of the diagnosis, through birth and into the postnatal period. Long-term outcome of fetuses was determined from postnatal charts after discharge from the hospital with a follow-up time of 0 - 16 years for Paper I (duodenal obstruction), 6 months - 15 years for Paper II (gastroschisis) and 1 - 17 years for Paper III (omphalocele). In Papers IV and V the study populations consist of all cases that had been through at least one prenatal ultrasound examination at the National Center for Fetal Medicine at any time during pregnancy and had been given the diagnosis of imperforate anus or esophageal obstruction either pre- or postnatally.

In Norway, women have been offered one routine fetal examination at around 18 weeks' gestation since 1986. Additional ultrasound examinations prior to or following the routine fetal examination have only been made on clinical indications. Around the country, midwives and physicians with varied training in obstetric ultrasound have performed the routine fetal examinations. In recent years, most midwives have passed the official education program introduced in 1997. At the National Center for Fetal Medicine, all midwives had at least basic training in obstetric ultrasound since 1986. When an anomaly was suspected physicians with special training in fetal medicine performed the examinations.

Gestational age was expressed in completed weeks and days based on ultrasound measurements of the biparietal diameter at the routine fetal examination. Small for gestational age (SGA) was defined as a birth weight of less than mean -2 SD^s (Maršál *et al.* 1996).

All 5 papers are based on a *selected* population consisting of referred cases, in addition to our own non-selected population. The *non-selected* population has also been investigated separately in order to establish the incidence and the prenatal detection rate as well as the

accuracy of the different diagnoses in such a population. The non-selected population comes from a geographically well-defined area consisting of the city of Trondheim and eight surrounding municipalities. Within the non-selected population, approximately 97% of the pregnant women who lived there had a routine fetal examination at the National Center for Fetal Medicine (NCFM) *and* were later delivered at the University Hospital of Trondheim. The NCFM has an extensive database in which data have been prospectively registered from the first ultrasound examination through pregnancy and birth. Since 1986**,** all newborns have been examined by a pediatrician (mostly one single person) and the immediate postnatal data are included in the database. Long-term postnatal follow-up data as well as results of the autopsies have gradually been incorporated in the database. In Paper I, the investigated time period of the *non-selected population* was 1987 - 2000 and 38 683 infants were born during this period. The investigated time period in Paper II was 1988 - 2001 and included 38 924 births; Paper III, 1987 - 2002 included 43 957 births and Papers IV and V 1987 - 2004 included 49 232 births.

Statistical analysis of the difference in abnormal karyotypes between the different types of omphaloceles was performed by Fisher's exact test (SPSS, version 11.0) (Paper III). Statistical analyses of the outcome for various esophageal obstructions were performed by Pearsons's chi-square analysis (Paper V).

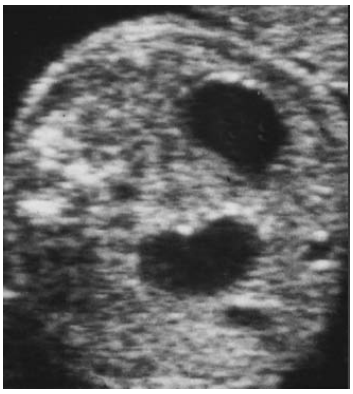
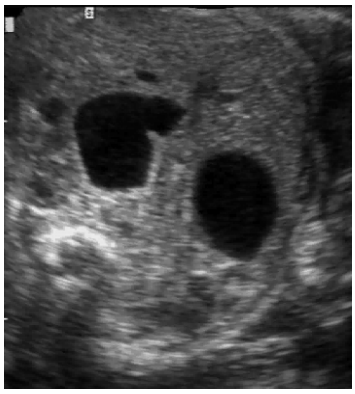
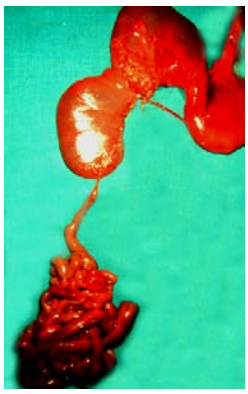
RESULTS AND COMMENTS

Paper I

Fetal duodenal obstructions: increased risk of prenatal sudden death

Our data indicated that duodenal obstruction diagnosed prenatally represented a serious condition with a risk of prenatal bradycardia, asphyxia and death even when the karyotype was normal and no associated anomalies were present.

Figure 9
Ultrasound images of the "double-bubble" appearance typically seen in fetuses with duodenal obstruction (a,b). Duodenal atresia shown in a specimen from a fetus (c).

a  **b**  **c** 

Results

Twenty-nine cases with duodenal obstruction were followed from the time of prenatal diagnosis at mean 29+2 (range, 19+1 - 37+3) weeks. A routine fetal examination at approximately 18 gestational weeks had been performed in 26/29 cases but only three cases were detected at that examination. In all diagnosed cases, the "double-bubble" sign, caused by the dilated stomach and distended upper part of the duodenum, was observed at the ultrasound examination *(Figure 9)*. The main reason for referral was polyhydramnios and its associated clinical conditions. Polyhydramnios was noted in 24/29 (83%) cases. Amniodrainage due to extensive polyhydramnios and a subjective feeling of pressure was performed in 12 cases; in 8 of these 12, the diagnosis was made after 32 weeks of gestation.

Associated anomalies were found in 18 fetuses (62%) *(Table 2)*. Six (21%) had trisomy 21. One pregnancy was terminated; the fetus had trisomy 21 and atrioventricular septal defect (AVSD) in addition to the duodenal obstruction. In 11 fetuses, the duodenal obstruction was an isolated finding.

Table 2
Type of associated anomalies in the 18 fetuses with duodenal obstruction and associated anomalies.

		Associated anomalies			
Case no	*Karyotype*	*Cardiac*	*Gastrointestinal*	*Skeletal*	*Miscellaneous*
12	Tri 21				
13	Tri 21				
14	Tri 21				
15	Tri 21	AVSD			
16	Tri 21	PDA			
17	Tri 21	ASD secundum			
18	N		Hypoplastic gallbladder		
19	N		Annular pancreas		
20	N		Annular pancreas		
21	N		Annular pancreas		
22	N	ASD secundum	Annular pancreas		
23	N	ASD, VSD			
24	N			Adduction of thumbs, bilateral	
25	N	ASD, CoA		Vertebral anomalies	Goldenhar syndrome, non lobulation of lungs
				Bifid metacarp dig I hand (r)	Ear and mouth anomalies, double spleen
26	N	VSD, FO open	Meckel diverticulum	Adduction of right thumb	Renal agenesis unilateral, ear-channel atresia
27	N	PDA, VSD, TGA, AV-canal Pulm art atresia, IVC anomaly Functional single ventricle	Anal atresia	Vertebral anomalies Tracheal stenosis	Asplenia, hypoplastic right lung
28	N			Missing thumbs, bilateral Radius aplasia (r), hypoplasia (l) Pes equinovarus	Renal agenesis unilateral, Ear anomalies
29	?	DORV, Rudimentary left ventricle VSD, Mitral atresia, AV-block PDA, IVC aplasia, ASD prim	Anal atresia	Adduction of thumbs, bilateral	Situs inversus, dysmorphic face

AVSD, atrioventricular septal defect; ASD, atrial septal defect; VSD, ventricular septal defect; DORV, double outlet right ventricle; AV, atrioventricular; CoA, coarctatio aortae; IVC, inferior vena cava; PDA, patent ductus arteriosus; FO, foramen ovale; TGA, transposition of great arteries; (r), right; (l), left; ?, not known; N, normal.

Four fetuses (14%) died in utero at 31-35 gestational weeks. Two fetuses had no associated anomalies; one of these two had an episode of unexplained bradycardia 2 days before death. One had a hypoplastic gallbladder, diagnosed at the autopsy. One case had Goldenhar syndrome with facial anomalies and anomalies of columna, heart, lungs and hand. This fetus had long lasting episodes of bradycardia 1 week before the IUFD. All four died unexpectedly. In three cases, the mothers were staying in the hospital ward and

had normal CTG recordings within a day before death occurred. The fourth case presented because of reduced fetal movements. On the ultrasound examination, bradycardia and poor cardiac contractility were noted. The fetus showed vomiting-like movements. Asystolia occurred during the examination. The fetus with Goldenhar syndrome was small for gestational age (SGA), the other three had birth weights within normal range for gestational age (Maršál *et al.* 1996). The fetuses in all four cases of IUFD had duodenal atresia.

Two infants with isolated duodenal obstruction developed severe neurological impairment; one had bradycardia during labor at 33 weeks and Cesarean section (CS) was performed. The infant had cerebral palsy, epilepsy, infantile spasms, neurological impairment and reduced motility of the left arm. The other fetus presented with reduced fetal movements at 35 weeks, the CTG recording was pathological and the fetus was immediately delivered by CS. Postnatal follow-up showed periventricular leukomalacia and the infant, who was also SGA, had epilepsy and cerebral palsy of diplegic type.

Two additional infants suffered from impaired psychomotoric development; one with isolated duodenal obstruction was delivered normally at 38+5 weeks, the other had a normal delivery at 36+4 weeks. This infant had adducted thumbs bilaterally, but despite thorough tests and examinations with follow-up until the age of 7 years, no other associated anomalies or specific genetic syndrome has been diagnosed.

In another fetus, a sustained period of bradycardia was observed during amniodrainage at 32 weeks. Emergency CS was performed. Apgar scores were 9 and 10 after 1 and 5 minutes. Arterial umbilical cord pH was 7.16 and base excess was -6.4 mmol/L. No obvious reason for the bradycardia was found during the amniodrainage or at the CS. The karyotype was normal and there were no associated anomalies. The postnatal development has been normal.

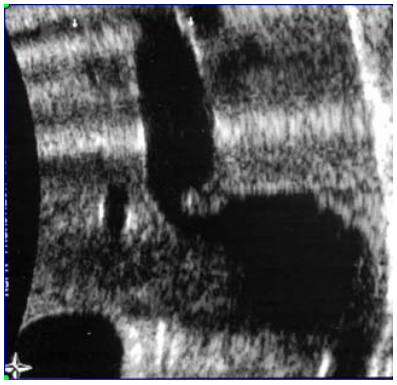
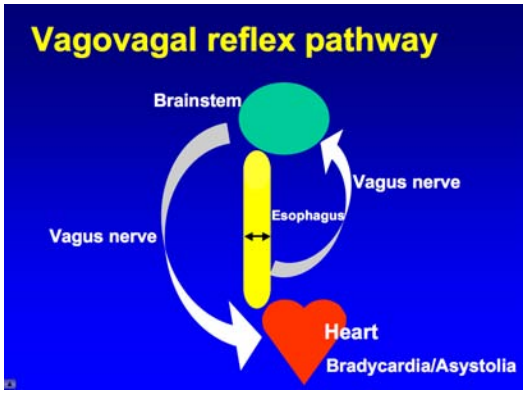
Twenty-one of the 29 fetuses (72%) survived, but only six (21%) had normal karyotype, no associated anomalies and normal development during the postnatal period.

Comments

It seems that fetal duodenal obstruction, also in isolated cases represented a more severe condition than previously believed. Of 11 fetuses with isolated duodenal obstruction, 5 (45%) died or had substantially impaired neurological development. This means that the mortality and morbidity was high among the cases with duodenal obstruction where we would expect a good outcome following postnatal surgery. Furthermore, among cases with associated anomalies who experienced IUFD or neurological impairment, the anomaly was not of such nature that one would expect a serious outcome. All had normal karyotype, one had Goldenhar syndrome, one had a hypoplastic gallbladder and one had adducted thumbs.

The esophagus is usually not dilated during pregnancy, but in fetuses with duodenal obstruction the esophagus can be seen substantially dilated *(Figure 10a).* This may induce a vagal reaction of the brainstem and a further vagal reaction of the heart, possibly leading to bradycardia and/or asystolia *(Figure 10b).*

Figure 10
Ultrasound image showing a distended esophagus and upper part of the stomach in a fetus with duodenal atresia (a). Schematic picture of the hypothesis of vagal overactivity (b).

a  b 

This hypothesis is supported by findings in studies of nearly lost infants and siblings of sudden infant death syndrome (SIDS) victims, where gastro-esophageal reflux seems to have a central role in the occurrence of apparent life-threatening events (ALTE) (de Bethmann *et al.* 1993). Reflux may trigger vagal stimuli. The association of gastro-esophageal reflux and vagal overactivity in a study on infants who had suffered an ALTE was observed in 42% of

the ALTE group vs 18% of a control group (de Bethmann *et al.* 1993). Dilatation of the esophagus in dogs has been shown to cause frequent and reproducible cardiac response and it has been suggested that this condition in children under similar circumstances could cause ventricular defibrillation and death (Schey *et al.* 1981). Some of the children who die of SIDS may have had a vagovagal reaction initiated by esophageal dysmotility (Schey *et al.* 1981). Esophageal spasm in association with bradycardia has been shown to be mediated by a vagovagal reflex mechanism (Fontan *et al.* 1984). The possibility of reversible cardiac asystolia due to paroxysmal vagal overactivity (VO) has been studied. In a review summarizing the role of VO in infants suffering from ALTE and SIDS siblings, it was confirmed that the most common rhythm disturbances in infants at risk for SIDS, were abrupt and brief episodes of bradycardia (Lucet *et al.* 2000). Gastro-esophageal reflux was assumed to be the main cause. In some of the fetuses with duodenal obstruction we have seen vomiting-like movements and also a very distended stomach and esophagus. We have also observed episodes of sudden bradycardia. It is possible that the same kind of paroxysmal vagal overactivity due to esophageal dysmotility and gastro-esophageal reflux as seen in children with SIDS and ALTE can occur in utero. This might be the cause of the unexpected fetal deaths in our study group. Bradycardia due to VO might also explain the cases of neurological sequelae in our study.

Another possible mechanism that may affect the fetal heart rate is raised levels of fetal serum bile acids. Obstructions of the duodenum are usually situated close to the orifice of the bile duct and may affect the levels of fetal serum bile acids. The primary bile acid, taurocholate, can alter the rate and rhythm of cardiomyocyte contraction and cause abnormal Ca^{2+} dynamics in an in vitro system of neonatal rat cardiomyocytes (Williamson *et al.* 2001), a theory that also might explain the increased risk of intrauterine fetal death in obstetric cholestasis (Gorelik *et al.* 2002; Gorelik *et al.* 2004).

The hypothesis that intrauterine fetal death in cases with duodenal and jejunal atresias, is due to bleeding from an umbilical cord ulcer has also been discussed. It has been speculated that in utero regurgitation of bile acid is responsible for the development of umbilical cord ulcer (Bendon *et al.* 1991; Ohyama *et al.* 2000; Anami *et al.* 2006). The concentration of bile acids

in amniotic fluid has been shown to be severely increased in cases with intestinal obstruction distal to the papilla of Vater (Deleze *et al.* 1977). In this context, it is important to remember that the presence of blood in the vomitus of newborns has long been considered an important diagnostic sign in cases with duodenal atresia (Cowell 1912). Fetal hemorrhage in cases with intestinal atresia, also without evident umbilical cord ulcer, has been reported and abnormal heart rate patterns with prolonged bradycardia and late decelerations have been noted (Shimizu *et al.* 2003).

Our hypothesis of vagal overactivity may best explain the sudden fatalities, but more evidence is needed to establish a true etiology.

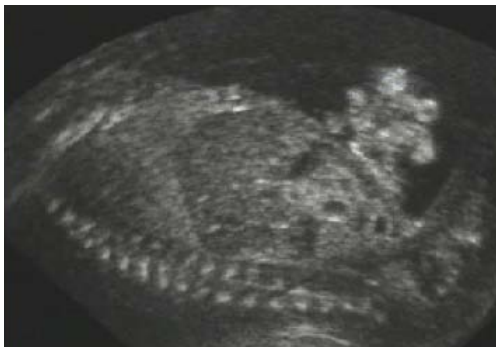
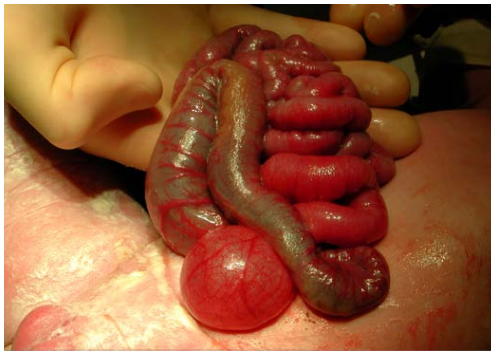
Since the potential death in fetuses with duodenal obstruction seems to occur more or less instantly, surveillance is difficult. Continuous CTG monitoring after 30 weeks' gestation in cases with intestinal atresia and polyhydramnios has been suggested (Shimizu *et al.* 2003), however, this may be impossible to accomplish. One may speculate whether it is beneficial to deliver fetuses with duodenal obstructions at approximately 32 weeks' gestation to lower the risk of IUFD and the possible risk of asphyxia. Extensive amniodrainage may prevent the possibility of distension of the upper gastrointestinal tract in cases with polyhydramnios. Treatment with atropine or atropine-like drugs has been discussed and tried in infants (Schey *et al.* 1981; de Bethmann *et al.* 1993) and intrauterine treatment with such drugs might be a possibility in the future. Further studies are needed to find out more about the etiology. Until more knowledge is obtained, evaluation of the distension of the esophagus and delivery at 32 - 34 weeks may rescue most of these fetuses.

Paper II

Surveillance and outcome of fetuses with gastroschisis

Pregnancies with fetal gastroschisis should be considered high-risk pregnancies as 22% had pathological CTG, indicating fetal distress, leading to emergency CS before the onset of labor. Surveillance with CTG in the third trimester may improve the outcome through reducing the risk for IUFD.

Figure 11
Ultrasound image of a fetus with gastroschisis (a). A newborn girl with gastroschisis (b).

a  b 

Results and comments

Gastroschisis is an abdominal wall defect, typically located on the right side of a normally inserted umbilical cord and with bowel protruding through the defect *(Figure 11)*. Sixty-four fetuses with a prenatal diagnosis of gastroschisis were followed from the time of a prenatal diagnosis. The diagnosis was usually made at the routine fetal examination. All fetuses had normal karyotype. Four (6.3%) had associated anomalies; two were cardiac anomalies (one VSD and one tetralogy of Fallot) and two had arthrogryposis of the amyoplasia type with extensive muscular atrophy.

The low rate of 6.3% (4/64) of associated anomalies (except intestinal anomalies), was in agreement with other studies (Kirk and Wah 1983; Crawford *et al.* 1992; Burge and Ade-Ajayi 1997; Rankin *et al.* 1999). The association of gastroschisis and arthrogryposis of the amyoplasia type has been previously described with a frequency of 3 - 5% (Hall *et al.* 1983; Reid *et al.* 1986). A recent study has shown an increased incidence of cardiac anomalies in fetuses with gastroschisis and suggest cardiac evaluation of these cases (Kunz *et al.* 2005).

Thirteen infants (22%) were SGA (Maršál *et al.* 1996) and the mean weight deviation at birth was -9%. The estimated and true weight deviation was in agreement in 59% of the cases. The ultrasound estimate of the day of delivery was postponed compared to the LMP estimate in 75% of the cases at the routine fetal examination.

Infants with gastroschisis are known to be smaller than normal infants (Crawford *et al.* 1992; Fries *et al.* 1993; Adair *et al.* 1996; Anteby *et al.* 1999; Barisic *et al.* 2001). The mechanism of becoming SGA in fetuses with gastroschisis has been suggested to be due to transmural loss of substances, particularly proteins. This may cause a nutritional drain from the fetus (Fries *et al.* 1993). The findings of lower serum protein concentrations and higher amniotic fluid total protein and alfa-feto protein levels in the fetuses with gastroschisis (Carroll *et al.* 2001) support this theory. It has also been proposed that the loss of proteins may cause hypovolemia and cardiovascular compromise (Dixon *et al.* 2000), which may contribute to the risk of fetal distress and IUFD. Traditional methods for estimation of fetal weight may be used in fetuses with gastroschisis since the correlation of the estimated weight and true weight was relatively good. The same results have been shown previously (Fries *et al.* 1993) and it has been suggested that it is the liver (which is normally intra-abdominal in cases with gastroschisis) that contributes most to the size in the abdominal measurements (Fries *et al.* 1993). The fact that 75% of the women had their estimated day of delivery postponed at the routine fetal examination suggests that some of the fetuses with gastroschisis are smaller already in the second trimester, since postponement of the term is usually seen in only 60% of fetuses in a non-selected population (Tunon *et al.* 1996). This may have consequences for the extensive discussions regarding when to deliver fetuses with gastroschisis. In previous studies on the timing of delivery for fetuses with gastroschisis the method for determining gestational age has rarely been described (Huang *et al.* 2002; Moir *et al.* 2004; Ergün *et al.* 2005; Logghe *et al.* 2005). Before drawing conclusions about the best time of delivery, it is necessary to know the methods for collecting the data that are to be used as evidence. Mean gestational age at delivery in our study was 36+1 weeks *(Table 3),* based on ultrasound measurements of the BPD during the routine fetal examination at approximately 18 weeks. Our policy during the period of the study was to deliver fetuses with gastroschisis by CS at 37 - 39 weeks.

Table 3
Indication, gestational age and mode of delivery in cases with gastroschisis (n = 60).

Mode of delivery	n	%	*Gestational age in weeks (mean, (range))*
Vaginal			
Spontaneous onset	2	3	32 + 4 (28 + 4 to 36 + 4)
Cesarean section			
Elective	16	27	37 + 4 (36 + 6 to 38 + 6)
Fetal distress	13	22	36 + 4 (34 + 1 to 39 + 0)
Spontaneous onset	22	37	35 + 3 (28 + 0 to 38 + 5)
Oligohydramnios	2	3	35 + 6 (34 + 5 to 37 + 0)
Pre-eclampsia	1	2	36 + 4
Abnormal umbilical artery Doppler	2	3	36 + 1 (35 + 2 to 37 + 1)
Suspect bowel complication	2	3	34 + 1 (32 + 6 to 35 + 3)
Total	60	100	36 + 1 (28 + 0 to 39 + 0)

Usually, gastroschisis is an abdominal wall defect with bowel protruding through a small hole on the right side of the umbilical cord insertion. However, also left-sided gastroschisis has been reported (Ashburn *et al.* 2002; Yoshioka *et al.* 2004). Other atypical cases with gastroschisis also exist (Pinzon and Barr 1995). It is important to be aware of these rare cases because they usually have a poor outcome. In our study group, we had one such case with a large defect reaching from the right side of the umbilicus to the left costal margin and with the whole liver exteriorized. We have called this an "epigastric gastroschisis" due to the location of the defect.

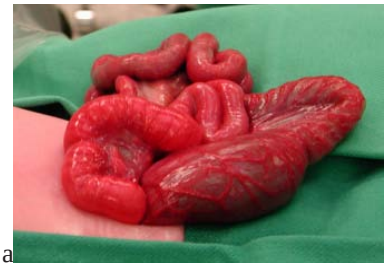
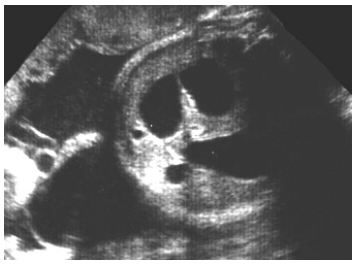
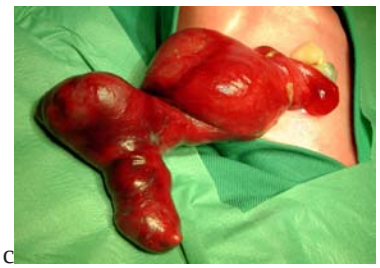
Also in typically right-sided gastroschisis, organs other than bowel may be present extra-abdominally (Hutchin 1965; Moretti *et al.* 1990; Novotny *et al.* 1993). In our study, this was particularly common among girls whose gonads and urinary bladder were more often seen extra-abdominally than among the boys *(Table 4)*. The involvement of gonads may affect future fertility (Koivusalo 2002) and caution during surgery is necessary. The stomach or part of the stomach was commonly noted extra-abdominally and this may affect the immediate postnatal management due to the increased risk of aspiration (Tannouri *et al.* 1998). It has also been suggested in a case report (Nazir *et al.* 2005) that a persistent fetal gastric distension may be associated with decreased fetal movements and non-reactive CTG.

Table 4
Viscera and organs (or part of) exteriorized before surgery in cases with gastroschisis.

	Female (n = 26)		*Male* (n = 30)		*Total* (n = 56)	
Organ	n	%	n	%	n	%
Liver			3	10	3	5
Spleen			1	3	1	2
Stomach	17	65	13	43	30	54
Duodenum	18	69	18	60	36	64
Small intestine	26	100	30	100	56	100
Large intestine	26	100	26	87	52	93
Urinary bladder	6	23	2	7	8	14
Gonads (ovaries, testes)	13	50	2	7	15	27

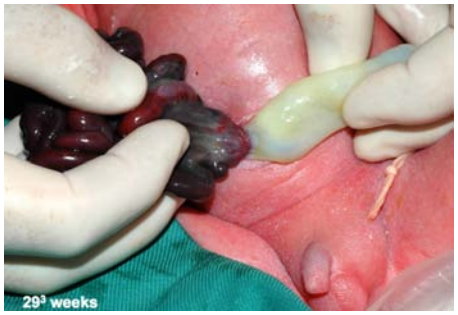
Intra-abdominal dilatation of the fetal bowel was noted in five cases in our study, and all had obstruction of the bowel *(Figure 12)*. In the years that followed, 30 additional cases were studied; the association of intra-abdominal dilatation and obstruction of the bowel was further confirmed (Brantberg *et al.* 2006). Similar results were recently published in another study (Nick *et al.* 2006). In our study, obstruction of the bowel was not associated with poor outcome. This confirms the findings reported in previous studies (Driver *et al.* 2000; Fleet and de la Hunt 2000; Snyder *et al.* 2001). However, it is worth emphasizing that cases with atresia and the presence of massive peel at birth may benefit from delayed primary anastomosis (Fleet and de la Hunt 2000).

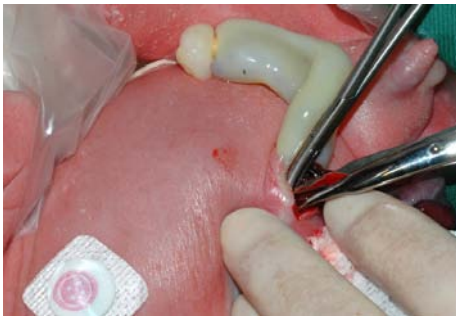
Figure 12
Normal appearance of bowel in a newborn with gastroschisis (a). Ultrasound image showing intra-abdominal dilatation of the bowel in a fetus with gastroschisis and intestinal atresia (b). Appearance of the bowel in a newborn with gastroschisis complicated by atresias and presence of "peel" (c).

a  b  c 

In this context, it is important to note that intra-abdominal dilatation of the bowel might be associated with “closed gastroschisis” (Barsoom *et al.* 2000; Davenport *et al.* 2001) which means that the abdominal wall defect narrows and eventually closes *(Figure 13a)*. In “closed gastroschisis”, the intra-abdominal dilatation is usually newly developed in the third trimester and increases over time. This complication is rare, but might be fatal since the whole bowel may be necrotic (Winter *et al.* 2005). Delivery with immediate dilation of the opening is needed on these rare occasions *(Figure 13b)*.

Figure 13
A newborn at 29+3 weeks with closed gastroschisis (a) and surgical dilation of the defect (b)

a 

b 

In 13 of the 60 cases (22%), pathological CTG’s developed, leading to emergency CS prior to labor. The typical pathological findings of the CTG were reduced short-term variability and sometimes, additionally tachycardia. Several authors have addressed the increased risk of fetal distress (Adair *et al.* 1996; Burge and Ade-Ajayi 1997; Anteby *et al.* 1999) and the increased risk of IUFD (Crawford *et al.* 1992; Adair *et al.* 1996; Burge and Ade-Ajayi 1997). The rate of IUFD in fetuses with gastroschisis has been reported to be 10 - 15% (Calzolari *et al.* 1995; Adair *et al.* 1996; Burge and Ade-Ajayi 1997; Barisic *et al.* 2001). In our study, the rate of IUFD was 1.6%, one case; the pregnant woman in this particular case did not want to follow our normal surveillance program. The CTG surveillance of the other cases may have been the reason for the low rate of intrauterine deaths. The typical CTG pathology with reduced short-term variability in our study has also been reported in previous studies (Ingamells *et al.* 1995; Axt *et al.* 1999). A tendency to develop tachycardia has also been described previously (Salomon *et al.* 2004). Antenatal surveillance has been suggested to decrease perinatal mortality in cases

with gastroschisis (Adair *et al.* 1996) and the introduction of regular CTG monitoring from 32 weeks' gestation increased the detection of fetal distress (Burge and Ade-Ajayi 1997). The increased ability to detect fetal distress, with subsequent obstetric intervention, led to a reduction of adverse neurological outcome from 21% to 6% (Burge and Ade-Ajayi 1997). Another study started CTG monitoring at median 30 weeks and, in this small study, 35.5% developed pathological CTG leading to emergency CS (Salomon *et al.* 2004). The prenatal surveillance may have been the reason for the low perinatal mortality of 3.2% (1/31) in this study.

We have intensified our surveillance with CTG monitoring daily from 33 gestational weeks as a consequence of our study. This recently introduced type of surveillance program has also been adopted by other institutions around the world. Even though the underlying reasons for the increased risk of fetal distress have not been clarified, the importance of fetal monitoring has been discussed (Drewett *et al.* 2006). The mechanism for development of pathological CTG is not known. We suggest that hypovolemia due to protein loss may be a cause. This has previously been suggested (Carroll *et al.* 2001) to cause cardiovascular compromise and may play a bigger role than previously believed. It has long been known that infants with gastroschisis are in need of substantial volumes of fluid (Philippart *et al.* 1972) and it has been thought that the reason was fluid loss due to the exposed bowel and heat loss postnatally. It has not been possible to calculate the prenatal volume losses and there are no good methods to determine hypovolemia in fetuses. One study found raised levels of amniotic fluid ß-endorfin, a neuropeptide which may be associated with fetal distress associated with hypoxia and acidosis, in fetuses with gastroschisis with worse postnatal outcome (Mahieu-Caputo *et al.* 2002). The reasons for IUFD and fetal distress in fetuses with gastroschisis are most likely multifactorial. An autonomic vagal reaction due to bowel and/or stomach affection/pressure may also play a role. Until all underlying reasons are clarified, close CTG surveillance of fetuses with gastroschisis may improve the outcome through detection of fetal distress and thereby reduce the risk of IUFD. It has been argued that the CTG pathology is not associated with fetal distress because the infants with gastroschisis that have been delivered due to pathological CTG have had normal Apgar (Dixon *et al.* 2000). On the other hand, one

may argue that the lower rate of IUFD in the studies with CTG monitoring is obvious and our aim must be to deliver in due time before irreversible damage to the fetus has occurred.

The impact of time and mode of delivery in fetuses with gastroschisis has been widely discussed (Lenke and Hatch 1986; Moretti *et al.* 1990; Sakala *et al.* 1993; Quirk *et al.* 1996; Dunn *et al.* 1999; Moore *et al.* 1999; Ergün *et al.* 2005). Randomized controlled trials have not been possible to perform concerning mode of delivery and there is no clear evidence that advocates one specific mode of delivery. One small randomized controlled trial has been performed concerning the time of delivery (Logghe *et al.* 2005) in which elective preterm delivery at 36 weeks was compared to awaiting spontaneous delivery. No benefit from either policy was demonstrated, but it is worth mentioning that four fetuses in each group (in total 8/40 (20%)) were delivered before 36 weeks. Our policy of delivering fetuses with gastroschisis by CS at 36 weeks of gestation is based on several issues. First, the mean gestational age at delivery in our study was 36 + 1 weeks, even when we had the policy to deliver as late as possible; the cases who developed pathological CTG indicating risk for fetal distress were delivered at mean 36+4 weeks. In addition, also in studies advocating vaginal delivery, the rate of CS was 37% - 51% (Blakelock *et al.* 1997; Anteby *et al.* 1999). Minor additional issues are that, even if there is no statistical evidence, both sepsis and bowel damage in the infants may be lower after CS and that the surgery for the infants can be planned appropriately.

Numbers including 63 cases from the Medical Birth Registry of Norway (MFRN) show a rate of 14.3% stillbirths and a 16.0% termination rate of pregnancies (TOP) of gastroschisis during a period of 4 years *(Table 5)*. These numbers emphasize that also in Norway, the rate of intrauterine fetal death of gastroschisis is high. However, it was most surprising to find that the rate of termination of pregnancies with gastroschisis was so high. The incidence of gastroschisis is increasing and the longterm outcome for infants that have survived the perinatal period is usually excellent.

Table 5
Outcome of cases with gastroschisis in the selected population of Trondheim presented in the study compared to outcome of cases with gastroschisis during four years from the Medical Birth Registry of Norway (MFRN).

Population	N	Live-born	Stillbirth		TOP	
		n	n	%	n	%
Selected Trondheim	64	60	1	1.6	3	4.7
MFRN						
1999	19	13	2	10.5	4	21.0
2000	12	7	4	33.0	1	8.3
2001	14	12	1	7.0	1	7.0
2002	18	12	2	11.0	4	22.0
Total 1999-2002 (MFRN)	63	44	9	14.3	10	16.0

We need to call attention to the fact that approximately 30% of the gastroschisis cases listed in the national registry either were terminated (16%) or suffered an IUFD (14.3%). Most likely, the knowledge about the prognosis among physicians managing these cases has not been updated, thus the high rate of terminations. The national figures also indicate that the antenatal surveillance ought to be improved and maybe centralized to avoid these IUFD's that most likely are unnecessary. In Norway, pediatric surgery is centralized to two institutions, Rikshospitalet University Hospital in Oslo, and St Olavs Hospital, Trondheim University Hospital in Trondheim. Despite this, we know that some infants with gastroschisis receive surgery at their local hospital and will not benefit from surgery at appropriate places with highly specialized and experienced pediatric surgeons, a fact that most probably also affects the postnatal survival.

Paper III

Characteristics and outcome of 90 cases of fetal omphalocele

This study of fetuses with omphalocele showed a poor outcome. Of those diagnosed prenatally, only 8/90 (9%) infants were alive and healthy, indicating that this is a serious diagnosis. Furthermore, our results indicated that central and epigastric omphaloceles might be different entities.

Figure 14
Epigastric omphalocele.
Ultrasound image (a). Newborn before surgery (b). Newborn after surgery (c).

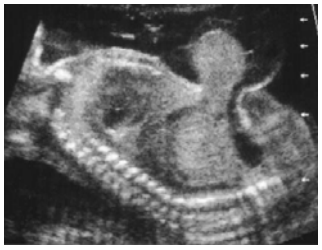
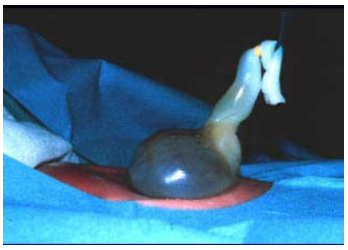
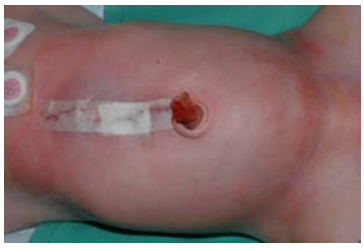
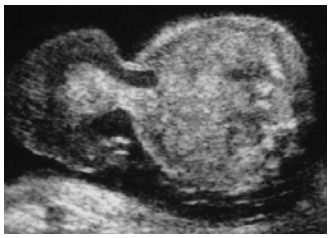
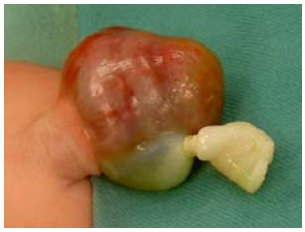
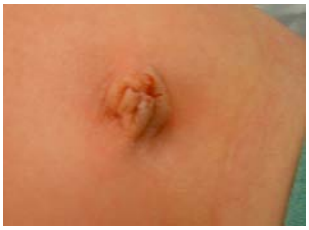
a  b  c 

Figure 15
Central omphalocele.
Ultrasound image (a). Newborn before surgery (b). Newborn after surgery (c).

a  b  c 

Results and comments

In omphaloceles, the bowel and/or liver protrude(s) into the umbilical cord. A membrane consisting of peritoneum and amnion encloses the eviscerated organs *(Figures 14, 15)*. The study comprised 90 fetuses with a prenatal diagnosis of omphalocele. The cases were followed from the time of prenatal diagnosis at mean 18+4 (range, 10+2 - 39+1) weeks. Omphaloceles were subdivided into epigastric, central and hypogastric based on the location of the defect and the insertion of the umbilical cord. Central omphaloceles were found in 58 (64%) fetuses, 32 (36%) had epigastric omphaloceles and none had a hypogastric omphalocele. Periumbilical defects were classified as central, irrespective of size or content. Omphaloceles involving the epigastric abdominal wall but not reaching below the umbilicus were classified as epigastric.

Different types of omphalocele have different risks for abnormal karyotype. The most commonly used characterization has been to differentiate between liver- and bowel-containing omphalocele. Fetuses with only bowel in the sac have a higher rate of

abnormal karyotype than fetuses with liver protruding into the sac (Hughes *et al.* 1989; Nyberg *et al.* 1989; Benacerraf *et al.* 1990; Getachew *et al.* 1992; Nicolaides *et al.* 1992; De Veciana *et al.* 1994). In our study, abnormal karyotypes were found in 40/58 (69%) of the fetuses with central omphaloceles and in 4/32 (12.5%) of the fetuses with an epigastric defect. The difference in abnormal karyotype was even stronger according to this classification system when compared with two previous large fetal series (Nicolaides *et al.* 1992; Snijders *et al.* 1995). The central and epigastric omphaloceles may be different entities. The most frequent abnormal karyotype in our study was trisomy 18 *(Table 6).*

Table 6
Abnormal karyotype in fetuses with central and epigastric omphalocele (n = 44).

	Central (n = *40)*	*Epigastric* (n = *4)*
Karyotype	n *(%)*	n *(%)*
Trisomy 18	29 (72.5)	4* (100)
Trisomy 13	5 (12.5)	
Triploidy	2 (5.0)	
Trisomy 21	1 (2.5)	
Turner syndrome	1 (2.5)	
Other†	2 (5.0)	
Total	40 (100)	4 (100)

*One case not verified cytogenetically; †*Mos 47,XY+18(27)/92 XXXY(14) and 47,XY, +der(13)(t3;13)(q29;q21,2)mat*

Normal karyotype in fetuses with a central omphalocele was present in 18/58 (31%) and 16 of these 18 (89%) had associated anomalies. Of the fetuses with an epigastric omphalocele, 28/32 (87.5%) had normal karyotype and 20 of these 28 (71%) had associated anomalies. This underscores that when an omphalocele is diagnosed prenatally not only karyotyping, but also an extensive search for additional anomalies is indicated. Cardiac anomalies are the most frequently reported anomaly in association with omphaloceles with normal karyotype (Fogel *et al.* 1991; St-Vil *et al.* 1996; Heider *et al.* 2004) emphasizing the need for fetal echocardiography when abnormal karyotype is ruled out *(Table 7).*

Table 7
The most frequent structural anomalies in 36 cases of omphaloceles with normal karyotype.

Anomalies	*Epigastric omphalocele (n = 20)* n *(%)*	*Central omphalocele (n = 16)* n *(%)*
Craniofacial	7 (35.0)	8 (50.0)
Central nervous system	3 (15.0)	5 (31.2)
Cardiac	10 (50.0)	5 (31.2)
Esophageal atresia	2 (10.0)	1 (6.2)
Diaphragmatic defect	5 (25.0)	3 (18.8)
Thoracic and/or pulmonary	9 (45.0)	7 (43.7)
Vertebral and/or scoliosis	6 (30.0)	1 (6.2)
Upper limb including hands and fingers	5 (25.0)	5 (31.2)
Lower limb including feet and toes	5 (25.0)	6 (37.5)
Renal	2 (10.0)	3 (18.8)
Genital	4 (20.0)	3 (18.8)
Anal atresia	3 (15.0)	2 (12.5)
Single umbilical artery	4 (20.0)	4 (25)

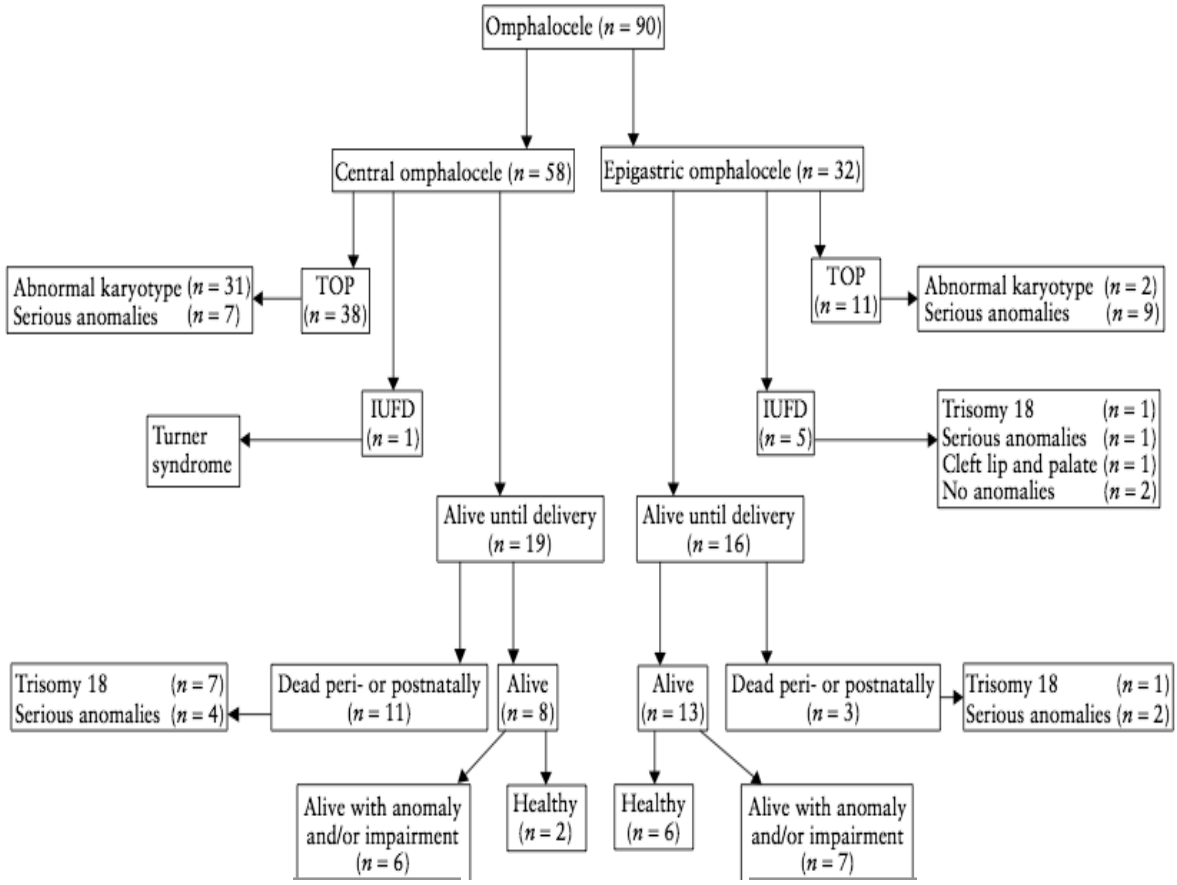
Omphaloceles may also be associated with syndromes such as Donnai-Barrow syndrome (Donnai and Barrow 1993) and acrocallosal or hydrolethalus syndrome (Christensen *et al.* 2000), both present in our study. These syndromes are both recessive inherited disorders implying the need for genetic counseling in future pregnancies. A genetic test of these syndromes might be available in the future.

Beckwith-Wiedemann syndrome (Wiedemann 1964) is the most well-known syndrome in association with omphalocele. Genetic testing is available for some of these cases and testing for uniparental disomy in chromosome 11 may be possible (Feinberg 2000; Maher and Reik 2000; Weinstein and Goldstein 2002). Owing to the wide variation in expression of this syndrome, a test may not always be helpful at the moment. With recent identification of molecular subtypes in different phenotypic expression of Beckwith-Wiedemann (Cooper *et al.* 2005), genetic testing may be most valuable in the future, both for accurate prognosis and for the postnatal surveillance. With ultrasound, the diagnosis of Beckwith-Wiedemann syndrome may be impossible early in pregnancy and fetuses

with Beckwith-Wiedemann syndrome have mistakenly been assumed, at ultrasound, to have an isolated omphalocele (Hughes *et al.* 1989; Boyd *et al.* 1998).

Isolated omphalocele was present in only 11% of all fetuses with omphalocele. The overall survival was 23%, but only 9% survived without sequelae, underscoring the fact that a fetal omphalocele is a serious condition with a high level of associated anomalies and impairments *(Figure 16)*. Abnormal karyotype or serious and/or multiple associated anomalies were consistently associated with poor outcome, with 97% mortality and 3% impairment. A thorough diagnosis makes it possible to locate this subgroup of fetuses with fatal/poor prognosis. The aim of pregnancy management must be to identify these and concentrate the surveillance on those whose prognosis is believed to be favorable.

Figure 16
Outcome of 90 fetuses with prenatally detected omphalocele.
IUFD, intrauterine fetal death; TOP, termination of pregnancy.

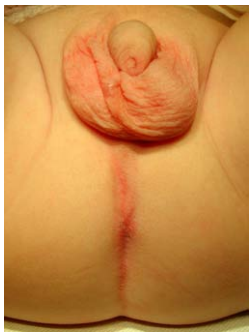
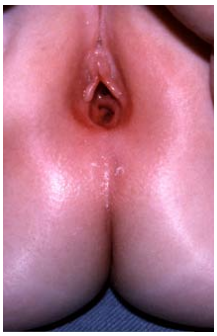
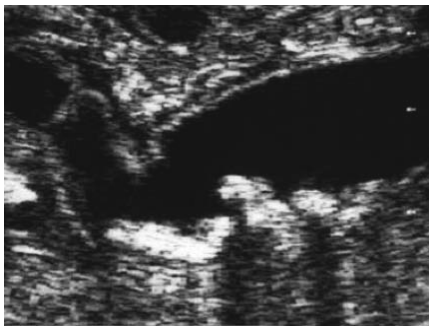


Paper IV

Imperforate anus: a relatively common anomaly rarely diagnosed prenatally

Imperforate anus was often found in conjunction with other serious anomalies, leading to a significant morbidity and mortality. In this study, including both fetuses and newborns, additional anomalies were present in 85.5%. Most additional anomalies were diagnosed prenatally but imperforate anus was diagnosed or strongly suspected prenatally in only 15.9% of the cases.

Figure 17
Imperforate anus in a newborn boy (a) and girl (b). Ultrasound image showing dilatation of the lower bowel and intraluminal calcifications in a fetus with imperforate anus at 18 weeks' gestation (c).

a  b  c 

Results and comments

The study comprised 69 cases with imperforate anus. A prenatal diagnosis of associated anomalies and/or imperforate anus was made in 53 cases while in 16 there were no pathological prenatal findings. Imperforate anus was diagnosed prenatally in 11 (15.9%) fetuses at a median gestational of 18+4 (range, 15+6 - 35+6) weeks. All 11 had a dilatation of the rectum or lower part of the bowel and two also had intraluminal calcifications *(Figure 17c).*

Isolated imperforate anus was found in 10/69 cases (14.5%) while additional anomalies including abnormal karyotype were present in 59/69 (85.5%) *(Table 8).* Most cases, 51/59 (86.4%), had multiple anomalies. The most frequent additional anomalies were found in the urogenital tract and several of them were lethal.

Table 8
The most common anomalies involved in 59 cases with imperforate anus and additional anomalies. Most (51/59) (86.4%) cases had several anomalies. TEF, tracheoesophageal fistula.

Anomaly	n *(%)*
Urogenital	37 (62.7)
Cardiac	24 (40.7)
Craniofacial	23 (39.0)
Musculoskeletal	22 (37.3)
Gastrointestinal obstruction	15 (25.4)
Esophageal atresia (11 with TEF)	12 (20.3)
Abdominal wall	11 (18.6)
Central nervous system	11 (18.6)
Hydrocephaly	7 (11.9)
Vertebral	11 (18.6)
Chromosomal	9 (15.2)
Trisomy 21	3 (5.1)
Trisomy 18	1 (1.7)
47,XX i(18p)i(18q)	1 (1.7)
mos 47,XY,+18(27)/92,XXXY(14)	1 (1.7)
47,XY, der(13)(t3;13)(q29;q21,2)mat	1 (1.7)
46,XY,del(13)(q21)	1 (1.7)
Trisomy 22	1 (1.7)
Pulmonary	8 (13.6)

The high rate of associated urogenital anomalies affecting renal function and leading to oligo-/anhydramnios may have affected the prenatal detection rate. On the other hand, the detection rate of 15.9% in our study was higher than in previous reports (Stoll *et al.* 1995; Stoll *et al.* 1996). The known association of imperforate anus and trisomy 21 (Black and Sherman 1989; Zlotogora *et al.* 1989; Torres *et al.* 1998) was confirmed and the rate of approximately 5% in our study was in line with former reports (Zlotogora *et al.* 1989; Endo *et al.* 1999). This significant knowledge, although it is well documented, is still not so well known. Imperforate anus is often part of the association of vertebral anomalies (V), anal atresia (A), tracheo-esophageal fistula with esophageal atresia (TE) and renal dysplasia (R) (VATER) or VATER plus cardiac (C) and (L) limb anomalies (VACTERL) association (Quan and Smith 1973), but other associations, syndromes and sequences have also been frequently reported to include anorectal anomalies (Hassink *et al.* 1996). Awareness of the kinds of various anomalies that may be associated with imperforate anus might improve the prenatal detection rate by a more intensified, targeted search for imperforate anus in cases with these anomalies. This suggestion was confirmed in a case

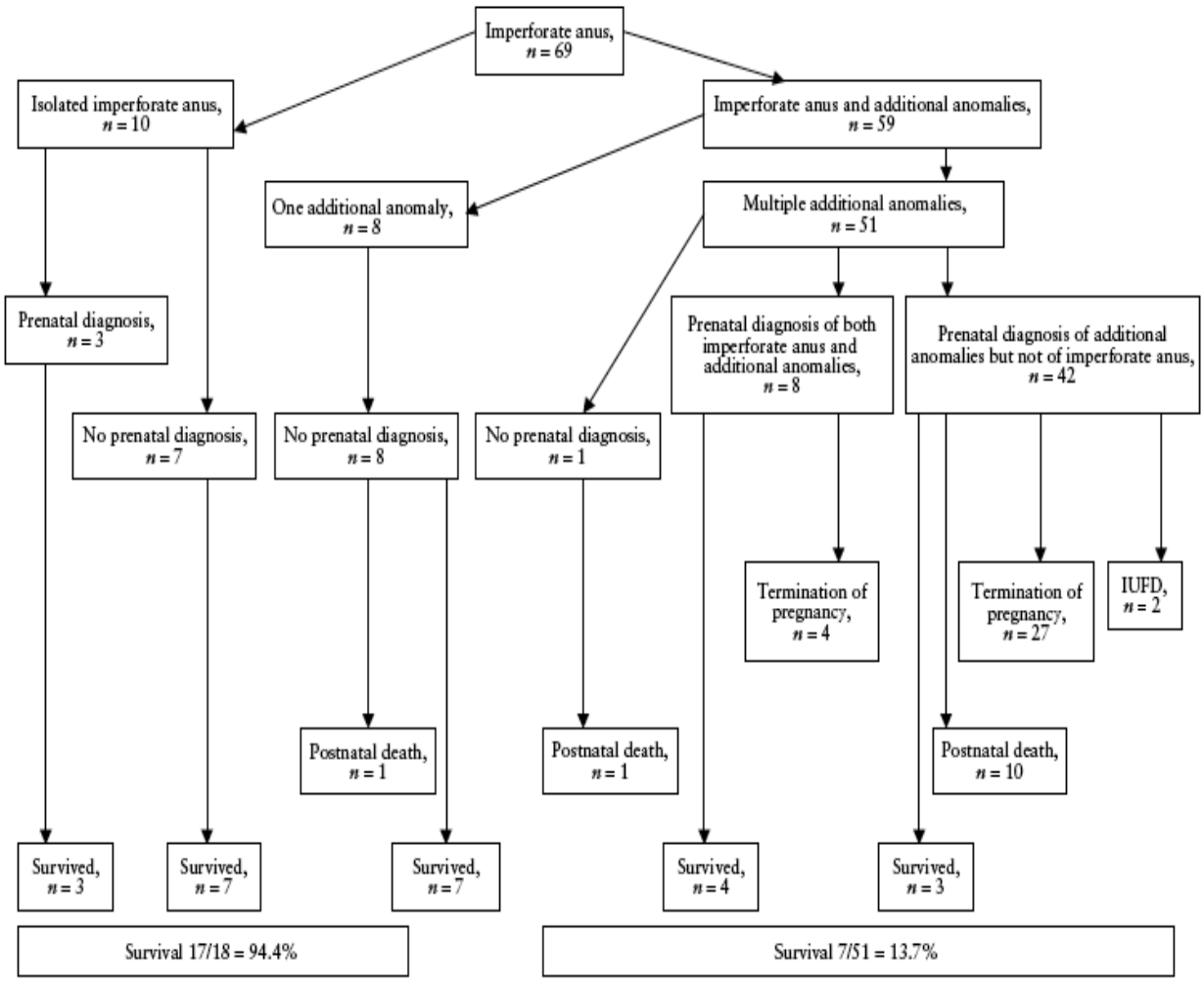
report of monoamniotic twins (Guzman *et al.* 1995) when the features of VACTERL alerted the examiner to search more specifically. It has also been suggested that additional MRI examination might add more conclusive information (Veyrac *et al.* 2004) in cases with a high suspicion of anorectal anomalies at ultrasound.

Videotapes that show the anorectal area from examinations of fetuses without a prenatal suspicion of imperforate anus were available for 22 cases, and these tapes were re-evaluated retrospectively. A strong suspicion of imperforate anus with dilatation of the rectum was apparent in one case on the tapes of examinations at both 10+0 and 13+0 weeks' gestation. In ten additional cases, signs of imperforate anus were detectable at examinations at mean 21+1 (range, 16+1 - 34+1) weeks. In 11 cases, examined at a mean of 22+2 (range, 14+6 - 34+3) weeks, no signs at all of imperforate anus were detected, even when the anorectal area was sufficiently demonstrated on the video evaluated retrospectively.

The survival rate of infants with isolated imperforate anus and of infants with only one additional anomaly was high (94.4%), irrespective of whether or not a prenatal diagnosis was made, while the survival rate among fetuses/infants with multiple additional anomalies was only 13.7% *(Figure 18).*

For the individuals that survive, issues such as fecal and urinary continence, sexuality and fertility are of importance. Females in particular have a high rate of genital anomalies that may affect future fertility (Fleming *et al.* 1986). Various types of imperforate anus are managed differently and have different surgical approaches and outcomes (Pena 1995). Even if reconstructive anorectal surgery is not urgently needed, immediate evaluation of infants with imperforate anus is necessary and decompressive surgery may be urgently required. This means that delivery at a center with neonatal intensive care and pediatric surgery facilities may be important.

Figure 18
Outcome of 69 cases with imperforate anus.
IUFD, intrauterine fetal death.



Delays in the diagnosis of anorectal malformations postnatally are common and significantly increase serious early complications (Lindley *et al.* 2006). Not only thorough examination postnatally, but also increased prenatal diagnosis might improve the outcome for these infants. Prenatal diagnosis is not always possible. Nevertheless, awareness of the condition and the ability to recognize the most typical ultrasound findings in imperforate anus may improve the detection rate. A heightened awareness of the high rate of associated anomalies and the type of anomalies commonly seen together with imperforate anus may also be important for improving the prenatal detection rate.

Paper V

Esophageal obstruction - prenatal detection rate and outcome

The clinical signs of polyhydramnios were the most important factors for prenatal detection of esophageal obstruction. Consequently, the time of diagnosis was late and the detection rate was low (44%). The detection rate might be improved by an increased awareness of the possibility of esophageal obstruction, which would lead to targeted examinations. Ninety percent of the cases with isolated esophageal obstruction survived irrespective of whether or not the diagnosis was made prenatally.

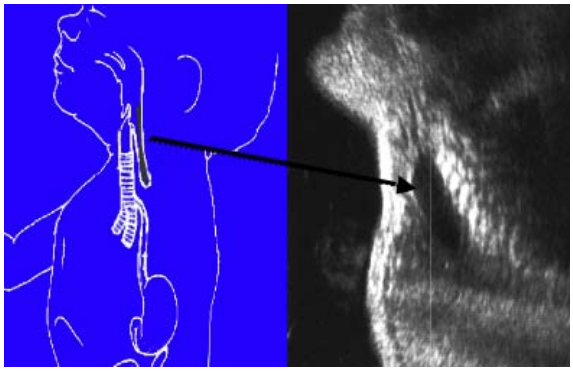


Figure 19
Schematic picture and ultrasound image of esophageal atresia with TEF and visualization of the proximal esophageal pouch.

Results

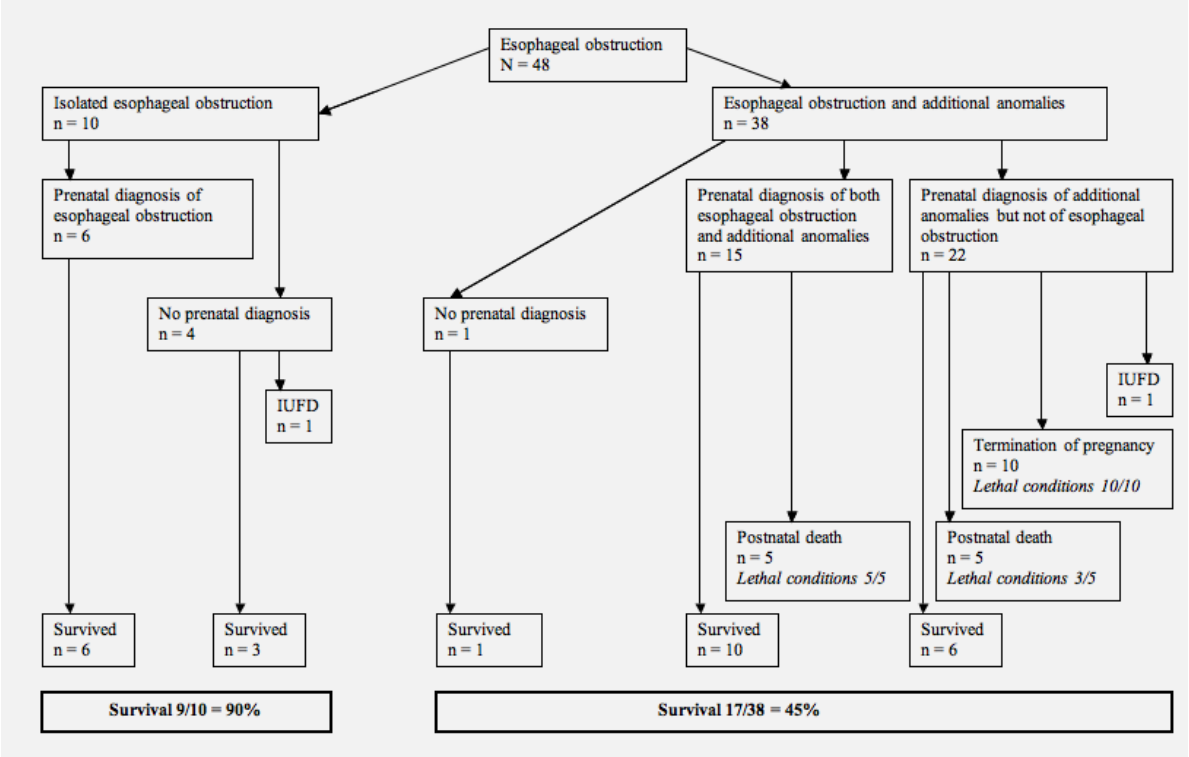
The study comprised 48 cases with esophageal obstruction, 46 with esophageal atresia, one with esophageal stenosis and one with a functional obstruction as a consequence of a laryngo-tracheo-esophageal cleft type IV.

A prenatal diagnosis of esophageal obstruction was made in 21/48 (44%) fetuses at median 32+0 (range, 17+6 - 36+6) weeks. Polyhydramnios was present in 20/21 (95%) of the prenatally detected cases and in all the fetal stomach was either small or not visible. Esophageal pouch was visualized prenatally in 9/21 (43%) of these cases *(Figure 19)*. Only one false positive case was present in our study, while previous studies have presented a high rate of false positive cases (Sparey *et al.* 2000). This means that the diagnosis had a high accuracy despite that more than half of the prenatally detected cases had only indirect signs. Seventeen (81%) of the 21 cases with prenatally detected

esophageal obstruction were diagnosed after 28 weeks, and all but one had clinical symptoms of polyhydramnios.

Associated anomalies including abnormal karyotype were present in 38/48 (79%) of all cases with esophageal obstruction. Eleven of the 48 cases (23%) had abnormal karyotype. In addition, the only case with esophageal stenosis had Di George syndrome. The most frequent associated anomalies were cardiac followed by urogenital anomalies. Among the cases with normal karyotype, the most common anomalies were urogenital followed by imperforate anus.

Figure 20
Outcome of 48 cases with esophageal obstruction.



Ten women of all 48 (21%) chose to terminate their pregnancies due to lethal associated fetal anomalies. Two fetuses (4.2%) died in utero; one with multiple associated anomalies died at 28+1 weeks, one fetus which was growth retarded had an isolated esophageal atresia with TEF and died at 22+1 weeks. Thirty-six fetuses, including all 21 with a prenatal diagnosis of esophageal obstruction, were alive until delivery. Mean birth weight was 2300g and mean

gestational age at delivery was 36+1 weeks. Thirteen infants (36%) were small for gestational age (Maršál *et al.* 1996). Of the 21 cases with a prenatal diagnosis of esophageal obstruction, 16/21 (76%) survived, compared to 10/29 (37%) of the cases without a prenatal diagnosis of esophageal obstruction (P = 0.14). When obvious lethal associated conditions were excluded, 16/16 (100%) of the cases with a prenatal diagnosis of esophageal obstruction survived and 10/14 (71%) of the cases without prenatal diagnosis of esophageal obstruction survived (P = 0.54). Of the 10 cases with isolated esophageal obstruction, 9/10 (90%) survived compared to 17/38 (45%) of the cases with esophageal obstruction and associated anomalies (P = 0.20) *(Figure 20)*.

Comments:

The clinical signs of polyhydramnios were the most important factors for prenatal detection of esophageal obstruction. Consequently, the time of diagnosis was late (median 32+0 weeks) and the detection rate was low (44%). Surprisingly, the detection rate in the non-selected population was the same (43%). Despite the possibilities of performing 3D-ultrasound or MRI in suspected cases to improve the accuracy and detection rate, this was not done in any of the cases. The accuracy was, on the other hand, high and in contrast to previous studies (Sparey *et al.* 2000) we had only one false positive case. One may argue that with a higher suspicion the detection rate might have been higher. Recently, a new method was suggested for diagnosing esophageal atresia without fistula by measuring the distance between aorta and left atrium (Develay-Morice *et al.* 2006).

In this study, associated anomalies were present in 79% of the fetuses, which is higher than in previous reports (Louhimo and Lindahl 1983; Rokitansky *et al.* 1994; Saing *et al.* 1998; Sparey *et al.* 2000; Yagyu *et al.* 2000; Kalish *et al.* 2003; Lopez *et al.* 2006). Also, the 23% rate of abnormal karyotype in the present study was higher than that reported in other studies (Louhimo and Lindahl 1983; Rokitansky *et al.* 1994; Sparey *et al.* 2000; Yagyu *et al.* 2000; Kalish *et al.* 2003). This may be explained by the relatively more prenatally diagnosed cases included in our series than have been included in previously published series. Most previous studies are based on neonatal populations (Louhimo and Lindahl 1983; Rokitansky *et al.* 1994; Saing *et al.* 1998; Yagyu *et al.* 2000; Lopez *et al.* 2006). However, the higher rate of

associated anomalies in our series may also be a consequence of inclusion of referred cases with severe anomalies.

Esophageal atresia without fistula, usually with a long gap, is known to be associated with trisomy 21 (Ein *et al.* 1993; Beasley *et al.* 1997) and the only case with trisomy 21 in our study had a long gap atresia. Twenty-five percent (12/48) of the cases with esophageal obstruction in the present study also had imperforate anus, but only 1 of these 12 had abnormal karyotype *(47 XX i(18p)i(18q))*. These findings are supported by a large epidemiological study (Depaepe *et al.* 1993) where none of the cases with the combination of esophageal atresia and imperforate anus had an abnormal karyotype. This is noteworthy since there is a well-known association with imperforate anus, usually without fistula, and trisomy 21 (Black and Sherman 1989; Zlotogora *et al.* 1989; Torres *et al.* 1998).

Increased nuchal translucency at 11 - 13+6 gestational weeks has been shown in a case with isolated esophageal atresia (Brown and Nicolaides 2000). In our study, one case was suspected to have a high gastrointestinal anomaly already at 10 weeks' gestation due to a stomach too large for the gestational age. Overdistended stomach at 12 weeks was presented in a case with esophageal atresia without fistula but with additional duodenal stenosis (Tsukerman *et al.* 1993). In our case, the physiological herniation may have given a similar situation with a transient obstruction distal to the stomach**.** Normal values of the size of the fetal stomach have been described from 8 gestational weeks (Blaas *et al.* 1995) and in our experience, the fetal esophagus is easily visualized at the 11 - 13+6 week scan (Blaas *et al.* 1995) *(Figure 21).* An early scan offered to all pregnant women may improve the prenatal detection rate due to the fact that nuchal translucency may be increased and thus trigger a more thorough evaluation. The size of the fetal stomach may be abnormal and the normal appearance of the fetal esophagus may not be visible. However, these aspects need to be studied and evaluated further.

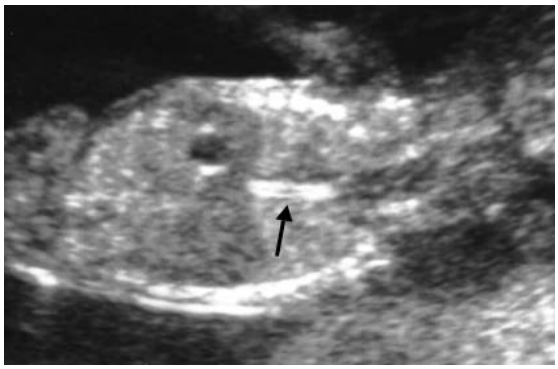


Figure 21
Ultrasound image of the esophagus (hyper echoic double-line indicated by the arrow) in a fetus at 12 weeks' gestation (CRL 59 mm).

There may also be a potential for improving the prenatal detection rate of esophageal atresia if a third trimester scan were offered to all pregnant women. Most cases detected prenatally in this study had clinical signs of polyhydramnios leading to a targeted examination. However, polyhydramnios was present in only 29% of ongoing pregnancies without prenatal diagnosis of esophageal obstruction. Targeted examination in the third trimester with evaluation of fetal swallowing and visualization of the fetal esophagus and possible esophageal pouch might improve the detection rate of esophageal obstruction, also in cases without polyhydramnios, although there may be some limitations due to acoustic shadowing.

SUMMARY

Background

Anomalies in the gastrointestinal tract and abdominal wall are relatively common. The present studies include the diagnoses of gastroschisis, omphalocele, imperforate anus, esophageal and duodenal obstruction. In all these conditions, the newborns are in need of postnatal surgery. A prenatal diagnosis may improve the outcome by optimizing the pre- and postnatal care for the newborn. Historically, the clinical course has been based on postnatally diagnosed cases and, until recently, knowledge has been lacking about the intrauterine development and thereby the possibility for optimal surveillance for certain diagnoses. There is a wide variety in the accuracy and sensitivity of detecting different anomalies prenatally.

The aims of the studies were

Selected population

To describe the outcome from the time of prenatal diagnosis into the postnatal period and to identify risk factors for poor outcome and determine whether surveillance may be beneficial. An additional aim was to describe the rate of prenatal diagnosis and elucidate possible strategies for improved diagnosis.

Non-selected population

To describe the incidence, prenatal detection rate and accuracy of the diagnoses in our non-selected population.

Materials and methods

The study populations of duodenal obstruction, gastroschisis and omphalocele were followed from the time of a prenatal diagnosis, through birth and into the postnatal period. The studies of imperforate anus and esophageal obstruction were based on all cases that had been through at least one prenatal ultrasound examination at the National Center for Fetal Medicine at any time during pregnancy and been given the diagnosis either pre- or postnatally.

All studies were based on a selected population consisting of referred cases in addition to our own non-selected population. The non-selected population was also investigated separately.

Results and comments

Duodenal obstruction

The study comprised 29 prenatally diagnosed fetuses. Trisomy 21 was present in 21%. Altogether, associated anomalies were present in 18/29 (62%). Isolated duodenal obstruction, with an expected good outcome, was present in 11/29 (38%). Of these, 5/11 (45%) died in utero or had a substantially impaired neurological development most probably due to intrauterine asphyxia. Our hypothesis is that a vagal overactivity due to distension in the lower esohageal tract leads to bradycardia, asphyxia and in some cases even asystolia and death. Fetal duodenal obstruction is a serious condition with a high risk of adverse outcome, also in cases with normal karyotype and no other anomalies. Surveillance of fetuses with duodenal obstruction is difficult because the fatalities seem to occur instantly. The prenatal detection rate in the *non-selected population* was high (82%). The incidence was approximately 1:3500. There was one false positive case.

Gastroschisis

Sixty-four fetuses with a prenatal diagnosis of gastroschisis were included. All cases had normal karyotype. Associated anomalies were present in 6%. Thirteen infants (22%) were small for gestational age. Prenatal intra-abdominal dilatation of the bowel was associated with obstruction of the bowel. Pathological CTG indicating fetal distress and leading to emergency CS developed in 22% of the fetuses already prior to labor. Intensive CTG monitoring of fetuses with gastroschisis in the third trimester may reduce the risk for fetal distress and IUFD. Of the 64 cases, 56 (87.5%) survived and all had a life without any significant gastrointestinal problems at follow-up over a period of 6-180 months. The prenatal detection rate in the *non-selected population* was 100% and there were no false positive cases. The incidence was 1:2290.

Omphalocele

The outcome of 90 fetal cases with omphalocele was poor with only 8 (9%) infants alive and healthy. The rate of associated anomalies was high (89%). Omphaloceles were subdivided into epigastric, central and hypogastric based on the location of the defect. The fact that abnormal karyotype was present in 69% of fetuses with central omphaloceles compared to 13% of fetuses with epigastric omphaloceles ($P < 0.0001$) leads us to consider the possibility that central and epigastric omphaloceles are different entities. When a thorough diagnosis was made, it was possible to identify a subgroup with fatal/poor prognosis. Surveillance should be focused on those whose prognosis is believed to be good. In the *non-selected population* the prenatal detection rate was 95% and there were no false positive cases. The incidence was 1:2000.

Imperforate anus

The study comprised 69 cases with imperforate anus. The prenatal detection rate was low (16%). Abnormal karyotype was present in 13%. Altogether, associated anomalies were frequent (86%) and imperforate anus was commonly a part of various syndromes. The outcome was poor with only 35% survival; survival for cases with isolated imperforate anus or only one additional anomaly was 94%, compared to only 14% for cases with more than one additional anomaly. The future detection rate may be improved by heightened awareness of the condition and of the type of anomalies commonly seen with imperforate anus in addition to the ability to recognize the most typical ultrasound findings in imperforate anus. In the *non-selected population,* the incidence was approximately 1:1800; a prenatal diagnosis was made in 11% and there were no false positive cases.

Esophageal obstruction

Forty-eight cases with esophageal obstruction were investigated and the prenatal detection rate was 21/48 (44%). The clinical signs of polyhydramnios were the most important factors for prenatal detection of esophageal obstruction. Consequently, the time of diagnosis was late (median 32+0 weeks). In all prenatally diagnosed cases, the stomach was small or not visible. In addition, an esophageal proximal pouch was visualized in 9/21 (43%) of the cases. Of all 48 cases, abnormal karyotype was present in 23%. Altogether 38/48 (79%) had

associated anomalies. Survival was higher, but not significantly, for cases with isolated esophageal obstruction. An increased awareness of the possibility of esophageal obstruction leading to targeted examinations whenever the suspicion is raised during pregnancy might improve the prenatal detection rate and thereby the outcome. In the *non-selected population*, the incidence was approximately 1:3500, the prenatal detection rate was 43% and there were no false positive cases.

Conclusion

For all the investigated diagnoses, the accuracy of the prenatal diagnoses was high. The prenatal detection rate in the *non-selected population* was high for cases with duodenal obstruction (82%), gastroschisis (100%) and omphalocele (95%) while the detection rate for esophageal obstruction was relatively low (43%) and for imperforate anus very low (11%). Fetal populations are different from neonatal populations. It is important to rule out cases with lethal associated anomalies. Adequate surveillance of the remaining cases gives a possibility to improve the outcome. The surveillance at our center has substantially changed for cases with duodenal obstruction and gastroschisis as a direct consequence of these studies. Knowledge of the development during intrauterine life must be further improved to be able to optimize the surveillance and care for fetuses with various anomalies.

FUTURE ASPECTS

Our aim is to provide a better start for the newborn individual through identifying fetal disease and treating the problem. The most attractive scenario concerning fetal anomalies would be the prevention of occurrence. The increased knowledge in biotechnology and molecular genetics might make that possible for some of the anomalies. A number of anomalies are now mapped genetically and for an increasing number of anomalies we have possibilities for early DNA diagnosis. For families with hereditary conditions, this may reduce their anxiety regarding their pregnancies. However, we will continue to be faced with the unexpected diagnosis of fetal anomalies. A correct, detailed prenatal primary diagnosis and the ability to rule out associated diagnoses will therefore still be the basis for treatment and surveillance. Fetal diagnoses may be made earlier and earlier as ultrasound becomes more widespread and offered to more women earlier in pregnancy**.** In addition, the technology is constantly improving and the 3D ultrasound technique and MRI may be valuable in some cases, complementary to 2D ultrasound. However, if women are to be able to benefit from increased use of prenatal diagnosis we must have the knowledge and skills to offer high quality examinations.

Information and counseling will be of even more importance with earlier diagnoses and easier access for termination of pregnancy. In this context, the socioeconomic situation in the country and the availability of health care for different conditions will play a role.

In cases of diagnosis of a fatal condition, the knowledge and information to parents will be of increasing importance. To dare to become pregnant again, knowing about risks and possibilities is important for the woman’s/parents’ psychological wellbeing.

Fetal medicine is still in an early phase of development and extensive future research is needed to determine how to best diagnose and treat the fetus.

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CORRECTIONS

Paper II

Page 5, Methods, line 9

"from January 1988 to August 2000"

Should be: "from January 1988 to August **2002**".

In references

Reference 54.

"Tunon K, Eik-Nes SH, Grottum PA. comparison between ultrasound and a reliable last menstrual period as predictors of the day of delivery in 15,000 examinations. Ultrasound Obstet Gynecol. 1996 Sep;8(3): 178-85."

Should be: "Tunon K, Eik-Nes SH, Grottum **P. A comparison** between ultrasound and a reliable last menstrual period as predictors of the day of delivery in 15,000 examinations. *Ultrasound Obstet Gynecol.* 1996 Sep;8(3): 178-85."

Paper III

Page 530, Figure 2, line 2

"Mean birth weight 2475 (range, 830-3964) g, mean gestational age 35+3 (range, 27+2 to 39+2) weeks."

Should be at the bottom line referring to the 24 infants with normal karyotype, not Beckwith-Wiedemann.

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

1995

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

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

1996

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

1997

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

1998

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

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

1999

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

2000

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

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

2001

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

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

2002

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

2003

216. Jan Pål Loennechen: HEART FAILURE AFTER MYOCARDIAL INFARCTION. Regional Differences, Myocyte Function, Gene Expression, and Response to Cariporide, Losartan, and Exercise Training.
217. Elisabeth Qvigstad: EFFECTS OF FATTY ACIDS AND OVER-STIMULATION ON INSULIN SECRETION IN MAN
218. Arne Åsberg: EPIDEMIOLOGICAL STUDIES IN HEREDITARY HEMOCHROMATOSIS: PREVALENCE, MORBIDITY AND BENEFIT OF SCREENING.
219. Johan Fredrik Skomsvoll: REPRODUCTIVE OUTCOME IN WOMEN WITH RHEUMATIC DISEASE. A population registry based study of the effects of inflammatory rheumatic disease and connective tissue disease on reproductive outcome in Norwegian women in 1967-1995.
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
222. Tom Christian Martinsen: HYPERGASTRINEMIA AND HYPOACIDITY IN RODENTS – CAUSES AND CONSEQUENCES
223. Solveig Tingulstad: CENTRALIZATION OF PRIMARY SURGERY FOR OVARAIN CANCER. FEASIBILITY AND IMPACT ON SURVIVAL

224. Haytham Eloqayli: METABOLIC CHANGES IN THE BRAIN CAUSED BY EPILEPTIC SEIZURES
225. Torunn Bruland: STUDIES OF EARLY RETROVIRUS-HOST INTERACTIONS – VIRAL DETERMINANTS FOR PATHOGENESIS AND THE INFLUENCE OF SEX ON THE SUSCEPTIBILITY TO FRIEND MURINE LEUKAEMIA VIRUS INFECTION
226. Torstein Hole: DOPPLER ECHOCARDIOGRAPHIC EVALUATION OF LEFT VENTRICULAR FUNCTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION
227. Vibeke Nossum: THE EFFECT OF VASCULAR BUBBLES ON ENDOTHELIAL FUNCTION
228. Sigurd Fasting: ROUTINE BASED RECORDING OF ADVERSE EVENTS DURING ANAESTHESIA – APPLICATION IN QUALITY IMPROVEMENT AND SAFETY
229. Solfrid Romundstad: EPIDEMIOLOGICAL STUDIES OF MICROALBUMINURIA. THE NORD-TRØNDELAG HEALTH STUDY 1995-97 (HUNT 2)
230. Geir Torheim: PROCESSING OF DYNAMIC DATA SETS IN MAGNETIC RESONANCE IMAGING
231. Catrine Ahlén: SKIN INFECTIONS IN OCCUPATIONAL SATURATION DIVERS IN THE NORTH SEA AND THE IMPACT OF THE ENVIRONMENT
232. Arnulf Langhammer: RESPIRATORY SYMPTOMS, LUNG FUNCTION AND BONE MINERAL DENSITY IN A COMPREHENSIVE POPULATION SURVEY. THE NORD-TRØNDELAG HEALTH STUDY 1995-97. THE BRONCHIAL OBSTRUCTION IN NORD-TRØNDELAG STUDY
233. Einar Kjelsås: EATING DISORDERS AND PHYSICAL ACTIVITY IN NON-CLINICAL SAMPLES
234. Arne Wibe: RECTAL CANCER TREATMENT IN NORWAY – STANDARDISATION OF SURGERY AND QUALITY ASSURANCE

2004

235. Eivind Witsø: BONE GRAFT AS AN ANTIBIOTIC CARRIER
236. Anne Mari Sund: DEVELOPMENT OF DEPRESSIVE SYMPTOMS IN EARLY ADOLESCENCE
237. Hallvard Lærum: EVALUATION OF ELECTRONIC MEDICAL RECORDS – A CLINICAL TASK PERSPECTIVE
238. Gustav Mikkelsen: ACCESSIBILITY OF INFORMATION IN ELECTRONIC PATIENT RECORDS; AN EVALUATION OF THE ROLE OF DATA QUALITY
239. Steinar Krokstad: SOCIOECONOMIC INEQUALITIES IN HEALTH AND DISABILITY. SOCIAL EPIDEMIOLOGY IN THE NORD-TRØNDELAG HEALTH STUDY (HUNT), NORWAY
240. Arne Kristian Myhre: NORMAL VARIATION IN ANOGENITAL ANATOMY AND MICROBIOLOGY IN NON-ABUSED PRESCHOOL CHILDREN
241. Ingunn Dybedal: NEGATIVE REGULATORS OF HEMATOPOIETEC STEM AND PROGENITOR CELLS
242. Beate Sitter: TISSUE CHARACTERIZATION BY HIGH RESOLUTION MAGIC ANGLE SPINNING MR SPECTROSCOPY
243. Per Arne Aas: MACROMOLECULAR MAINTENANCE IN HUMAN CELLS – REPAIR OF URACIL IN DNA AND METHYLATIONS IN DNA AND RNA
244. Anna Bofin: FINE NEEDLE ASPIRATION CYTOLOGY IN THE PRIMARY INVESTIGATION OF BREAST TUMOURS AND IN THE DETERMINATION OF TREATMENT STRATEGIES
245. Jim Aage Nøttestad: DEINSTITUTIONALIZATION AND MENTAL HEALTH CHANGES AMONG PEOPLE WITH MENTAL RETARDATION
246. Reidar Fossmark: GASTRIC CANCER IN JAPANESE COTTON RATS
247. Wibeke Nordhøy: MANGANESE AND THE HEART, INTRACELLULAR MR RELAXATION AND WATER EXCHANGE ACROSS THE CARDIAC CELL MEMBRANE

2005

248. Sturla Molden: QUANTITATIVE ANALYSES OF SINGLE UNITS RECORDED FROM THE HIPPOCAMPUS AND ENTORHINAL CORTEX OF BEHAVING RATS
249. Wenche Brenne Drøyvold: EPIDEMIOLOGICAL STUDIES ON WEIGHT CHANGE AND HEALTH IN A LARGE POPULATION. THE NORD-TRØNDELAG HEALTH STUDY (HUNT)
250. Ragnhild Støen: ENDOTHELIUM-DEPENDENT VASODILATION IN THE FEMORAL ARTERY OF DEVELOPING PIGLETS

251. Aslak Steinsbekk: HOMEOPATHY IN THE PREVENTION OF UPPER RESPIRATORY TRACT INFECTIONS IN CHILDREN
252. Hill-Aina Steffenach: MEMORY IN HIPPOCAMPAL AND CORTICO-HIPPOCAMPAL CIRCUITS
253. Eystein Stordal: ASPECTS OF THE EPIDEMIOLOGY OF DEPRESSIONS BASED ON SELF-RATING IN A LARGE GENERAL HEALTH STUDY (THE HUNT-2 STUDY)
254. Viggo Pettersen: FROM MUSCLES TO SINGING: THE ACTIVITY OF ACCESSORY BREATHING MUSCLES AND THORAX MOVEMENT IN CLASSICAL SINGING
255. Marianne Fyhn: SPATIAL MAPS IN THE HIPPOCAMPUS AND ENTORHINAL CORTEX
256. Robert Valderhaug: OBSESSIVE-COMPULSIVE DISORDER AMONG CHILDREN AND ADOLESCENTS: CHARACTERISTICS AND PSYCHOLOGICAL MANAGEMENT OF PATIENTS IN OUTPATIENT PSYCHIATRIC CLINICS
257. Erik Skaaheim Haug: INFRARENAL ABDOMINAL AORTIC ANEURYSMS – COMORBIDITY AND RESULTS FOLLOWING OPEN SURGERY
258. Daniel Kondziella: GLIAL-NEURONAL INTERACTIONS IN EXPERIMENTAL BRAIN DISORDERS
259. Vegard Heimly Brun: ROUTES TO SPATIAL MEMORY IN HIPPOCAMPAL PLACE CELLS
260. Kenneth McMillan: PHYSIOLOGICAL ASSESSMENT AND TRAINING OF ENDURANCE AND STRENGTH IN PROFESSIONAL YOUTH SOCCER PLAYERS
261. Marit Sæbø Indredavik: MENTAL HEALTH AND CEREBRAL MAGNETIC RESONANCE IMAGING IN ADOLESCENTS WITH LOW BIRTH WEIGHT
262. Ole Johan Kemi: ON THE CELLULAR BASIS OF AEROBIC FITNESS, INTENSITY-DEPENDENCE AND TIME-COURSE OF CARDIOMYOCYTE AND ENDOTHELIAL ADAPTATIONS TO EXERCISE TRAINING
263. Eszter Vanky: POLYCYSTIC OVARY SYNDROME – METFORMIN TREATMENT IN PREGNANCY
264. Hild Fjærtoft: EXTENDED STROKE UNIT SERVICE AND EARLY SUPPORTED DISCHARGE. SHORT AND LONG-TERM EFFECTS
265. Grete Dyb: POSTTRAUMATIC STRESS REACTIONS IN CHILDREN AND ADOLESCENTS
266. Vidar Fykse: SOMATOSTATIN AND THE STOMACH
267. Kirsti Berg: OXIDATIVE STRESS AND THE ISCHEMIC HEART: A STUDY IN PATIENTS UNDERGOING CORONARY REVASCULARIZATION
268. Björn Inge Gustafsson: THE SEROTONIN PRODUCING ENTEROCHROMAFFIN CELL, AND EFFECTS OF HYPERSEROTONINEMIA ON HEART AND BONE

2006

269. Torstein Baade Rø: EFFECTS OF BONE MORPHOGENETIC PROTEINS, HEPATOCYTE GROWTH FACTOR AND INTERLEUKIN-21 IN MULTIPLE MYELOMA
270. May-Britt Tessem: METABOLIC EFFECTS OF ULTRAVIOLET RADIATION ON THE ANTERIOR PART OF THE EYE
271. Anne-Sofie Helvik: COPING AND EVERYDAY LIFE IN A POPULATION OF ADULTS WITH HEARING IMPAIRMENT
272. Therese Standal: MULTIPLE MYELOMA: THE INTERPLAY BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MARROW MICROENVIRONMENT
273. Ingvild Saltvedt: TREATMENT OF ACUTELY SICK, FRAIL ELDERLY PATIENTS IN A GERIATRIC EVALUATION AND MANAGEMENT UNIT – RESULTS FROM A PROSPECTIVE RANDOMISED TRIAL
274. Birger Henning Endreseth: STRATEGIES IN RECTAL CANCER TREATMENT – FOCUS ON EARLY RECTAL CANCER AND THE INFLUENCE OF AGE ON PROGNOSIS
275. Anne Mari Aukan Rokstad: ALGINATE CAPSULES AS BIOREACTORS FOR CELL THERAPY
276. Mansour Akbari: HUMAN BASE EXCISION REPAIR FOR PRESERVATION OF GENOMIC STABILITY
277. Stein Sundstrøm: IMPROVING TREATMENT IN PATIENTS WITH LUNG CANCER – RESULTS FROM TWO MULITCENTRE RANDOMISED STUDIES
278. Hilde Pleym: BLEEDING AFTER CORONARY ARTERY BYPASS SURGERY - STUDIES ON HEMOSTATIC MECHANISMS, PROPHYLACTIC DRUG TREATMENT AND EFFECTS OF AUTOTRANSFUSION
279. Line Merethe Oldervoll: PHYSICAL ACTIVITY AND EXERCISE INTERVENTIONS IN CANCER PATIENTS

280. Boye Welde: THE SIGNIFICANCE OF ENDURANCE TRAINING, RESISTANCE TRAINING AND MOTIVATIONAL STYLES IN ATHLETIC PERFORMANCE AMONG ELITE JUNIOR CROSS-COUNTRY SKIERS
281. Per Olav Vandvik: IRRITABLE BOWEL SYNDROME IN NORWAY, STUDIES OF PREVALENCE, DIAGNOSIS AND CHARACTERISTICS IN GENERAL PRACTICE AND IN THE POPULATION
282. Idar Kirkeby-Garstad: CLINICAL PHYSIOLOGY OF EARLY MOBILIZATION AFTER CARDIAC SURGERY
283. Linn Getz: SUSTAINABLE AND RESPONSIBLE PREVENTIVE MEDICINE. CONCEPTUALISING ETHICAL DILEMMAS ARISING FROM CLINICAL IMPLEMENTATION OF ADVANCING MEDICAL TECHNOLOGY
284. Eva Tegnander: DETECTION OF CONGENITAL HEART DEFECTS IN A NON-SELECTED POPULATION OF 42,381 FETUSES
285. Kristin Gabestad Nørsett: GENE EXPRESSION STUDIES IN GASTROINTESTINAL PATHOPHYSIOLOGY AND NEOPLASIA
286. Per Magnus Haram: GENETIC VS. AQUIRED FITNESS: METABOLIC, VASCULAR AND CARDIOMYOCYTE ADAPTATIONS
287. Agneta Johansson: GENERAL RISK FACTORS FOR GAMBLING PROBLEMS AND THE PREVALENCE OG PATHOLOGICAL GAMBLING IN NORWAY
288. Svein Artur Jensen: THE PREVALENCE OF SYMPTOMATIC ARTERIAL DISEASE OF THE LOWER LIMB
289. Charlotte Björk Ingul: QUANITIFICATION OF REGIONAL MYOCARDIAL FUNCTION BY STRAIN RATE AND STRAIN FOR EVALUATION OF CORONARY ARTERY DISEASE. AUTOMATED VERSUS MANUAL ANALYSIS DURING ACUTE MYOCARDIAL INFARCTION AND DOBUTAMINE STRESS ECHOCARDIOGRAPHY
290. Jakob Nakling: RESULTS AND CONSEQUENCES OF ROUTINE ULTRASOUND SCREENING IN PREGNANCY – A GEOGRAPHIC BASED POPULATION STUDY
291. Anne Engum: DEPRESSION AND ANXIETY – THEIR RELATIONS TO THYROID DYSFUNCTION AND DIABETES IN A LARGE EPIDEMIOLOGICAL STUDY
292. Ottar Bjerkeset: ANXIETY AND DEPRESSION IN THE GENERAL POPULATION: RISK FACTORS, INTERVENTION AND OUTCOME – THE NORD-TRØNDELAG HEALTH STUDY (HUNT)
293. Jon Olav Drogset: RESULTS AFTER SURGICAL TREATMENT OF ANTERIOR CRUCIATE LIGAMENT INJURIES – A CLINICAL STUDY
294. Lars Fosse: MECHANICAL BEHAVIOUR OF COMPACTED MORSELLISED BONE – AN EXPERIMENTAL IN VITRO STUDY
295. Gunilla Klensmeden Fosse: MENTAL HEALTH OF PSYCHIATRIC OUTPATIENTS BULLIED IN CHILDHOOD
296. Paul Jarle Mork: MUSCLE ACTIVITY IN WORK AND LEISURE AND ITS ASSOCIATION TO MUSCULOSKELETAL PAIN
297. Björn Stenström: LESSONS FROM RODENTS: I: MECHANISMS OF OBESITY SURGERY – ROLE OF STOMACH. II: CARCINOGENIC EFFECTS OF *HELICOBACTER PYLORI* AND SNUS IN THE STOMACH

2007

298. Haakon R. Skogseth: INVASIVE PROPERTIES OF CANCER – A TREATMENT TARGET ? IN VITRO STUDIES IN HUMAN PROSTATE CANCER CELL LINES
299. Janniche Hammer: GLUTAMATE METABOLISM AND CYCLING IN MESIAL TEMPORAL LOBE EPILEPSY
300. May Britt Drugli: YOUNG CHILDREN TREATED BECAUSE OF ODD/CD: CONDUCT PROBLEMS AND SOCIAL COMPETENCIES IN DAY-CARE AND SCHOOL SETTINGS
301. Arne Skjold: MAGNETIC RESONANCE KINETICS OF MANGANESE DIPYRIDOXYL DIPHOSPHATE (MnDPDP) IN HUMAN MYOCARDIUM. STUDIES IN HEALTHY VOLUNTEERS AND IN PATIENTS WITH RECENT MYOCARDIAL INFARCTION
302. Siri Malm: LEFT VENTRICULAR SYSTOLIC FUNCTION AND MYOCARDIAL PERFUSION ASSESSED BY CONTRAST ECHOCARDIOGRAPHY
303. Valentina Maria do Rosario Cabral Iversen: MENTAL HEALTH AND PSYCHOLOGICAL ADAPTATION OF CLINICAL AND NON-CLINICAL MIGRANT GROUPS
304. Lasse Løvstakken: SIGNAL PROCESSING IN DIAGNOSTIC ULTRASOUND: ALGORITHMS FOR REAL-TIME ESTIMATION AND VISUALIZATION OF BLOOD FLOW VELOCITY

305. Elisabeth Olstad: GLUTAMATE AND GABA: MAJOR PLAYERS IN NEURONAL METABOLISM
306. Lilian Leistad: THE ROLE OF CYTOKINES AND PHOSPHOLIPASE A_2s IN ARTICULAR CARTILAGE CHONDROCYTES IN RHEUMATOID ARTHRITIS AND OSTEOARTHRITIS
307. Arne Vaaler: EFFECTS OF PSYCHIATRIC INTENSIVE CARE UNIT IN AN ACUTE PSYCIATHRIC WARD
308. Mathias Toft: GENETIC STUDIES OF LRRK2 AND PINK1 IN PARKINSON'S DISEASE
309. Ingrid Løvold Mostad: IMPACT OF DIETARY FAT QUANTITY AND QUALITY IN TYPE 2 DIABETES WITH EMPHASIS ON MARINE N-3 FATTY ACIDS
310. Torill Eidhammer Sjøbakk: MR DETERMINED BRAIN METABOLIC PATTERN IN PATIENTS WITH BRAIN METASTASES AND ADOLESCENTS WITH LOW BIRTH WEIGHT
311. Vidar Beisvåg: PHYSIOLOGICAL GENOMICS OF HEART FAILURE: FROM TECHNOLOGY TO PHYSIOLOGY
312. Olav Magnus Søndenå Fredheim: HEALTH RELATED QUALITY OF LIFE ASSESSMENT AND ASPECTS OF THE CLINICAL PHARMACOLOGY OF METHADONE IN PATIENTS WITH CHRONIC NON-MALIGNANT PAIN
313. Anne Brantberg: FETAL AND PERINATAL IMPLICATIONS OF ANOMALIES IN THE GASTROINTESTINAL TRACT AND THE ABDOMINAL WALL