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Termination of pregnancy (TOP) over 30 years

Doctoral thesis

NTNU
Norwegian University of Science and Technology
Thesis for the Degree of
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Medfødte utviklingsavvik hos terminerte fostre gjennom 30 år – Sammenhengen mellom funn ved ultralydundersøkelse i svangerskapet og obduksjonsfunn

Funn ved ultralydundersøkelse i svangerskapet og ved obduksjon danner grunnlaget for diagnosen hos fostre som termineres på grunn av medfødte utviklingsavvik. Risikoen for falske positive diagnoser er av stor bekymring i prenatal diagnostikk, spesielt hvis det resulterer i terminering av svangerskapet. Verifisering av ultralydfunn ved obduksjon er viktig; spesielt for foreldrene, samt som tilbakemelding til helsepersonell og ved fremtidig genetisk veiledning. Målet med denne avhandlingen var å sammenlikne medfødte utviklingsavvik oppdaget ved prenatal ultralyd mot funn ved obduksjon hos terminerte fostre gjennom 30 år.

Materialet består av 1029 fostre terminert mellom første og tredje trimester, med en eller flere alvorlige/letale medfødte strukturelle og/eller kromosomale utviklingsavvik. Studien strekker seg mellom 1985 og 2014. Obduksjonsfunn ble sammenliknet med ultralydfunn i hvert enkelt foster. Studien er et samarbeid mellom Avdeling for patologi og Nasjonalt senter for fostermedisin (NSFM), begge lokalisert på St. Olavs Hospital i Trondheim. De gravide kvinnene kom fra sykehusets nedslagsfelt eller var henvist fra resten av landet. Dette dannet til sammen grunnlaget for de tre artiklene i avhandlingen.

Anomalier i sentralnervesystemet og medfødte hjertefeil utgjorde de to største gruppene av medfødte utviklingsavvik. Det var full overenstemmelse mellom ultralyd- og obduksjonsfunn hos 88.1% av fostrene (907/1029), og hoveddiagnosen var korrekt hos 97.8% (1007/1029). Hos 1.3% (13/1029) ble enkelte ultralydfunn ikke verifisert ved obduksjon. Dette hadde ikke betydning for håndteringen av svangerskapene da andre alvorlige avvik ble verifisert ved obduksjon.

Avhandlingen finner at den prenatale deteksjonen av medfødte utviklingsavvik har økt. Dette kan forklares av høyere kompetanse blant helsepersonell som utfører ultralyd i svangerskapet, samt pga bedre kvalitet på ultralydutstyret. Selv om deteksjonen øker, er det viktig å fortsette valideringen ved obduksjon, spesielt grunnet utfordringer ved ultralydfunn påvist tidlig i svangerskapet. Detaljert diagnostikk prenatalt og postnatalt er nødvendig for å sikre adekvat medisinsk praksis, særlig når avgjørelsen om å avslutte svangerskapet baseres på utviklingsavvik i et enkelt organ. Fosteret bør derfor undersøkes på et tertiærsenter med fostermedisinere og andre klinikere i tett samarbeid med perinatalpatologer.

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Trondheim, June 2021
Camilla Struksnæs

List of papers

Paper I

Struksnæs C, Blaas H-G. K., Eik-Nes S.H., Vogt C. Correlation between prenatal ultrasound and postmortem findings in 1029 fetuses following termination of pregnancy. *Ultrasound Obstet Gynecol* 2016; 48: 232-238.

Paper II

Struksnæs C, Blaas H-G. K., Vogt C. Autopsy findings of central nervous system (CNS) anomalies in intact fetuses following termination of pregnancy (TOP) after prenatal ultrasound diagnosis. *Pediatr Dev Pathol*, 2019; 22: 546-57.

Paper III

Struksnæs C, Blaas H-G. K., Eik-Nes S.H., Tegnander E., Vogt C. Postmortem assessment of isolated congenital heart defects remains essential following termination of pregnancy. *Pediatr Dev Pathol*, 2021 May 17; DOI: 10.1177/10935266211016184. Online ahead of print.

Abbreviations and terminology

AMA	Advanced maternal age
ARS	Amniotic rupture sequence
AVSD	Atrioventricular septal defect
BPD	Biparietal diameter
CHD	Congenital heart defect
CNS	Central nervous system
CRL	Crown-rump length
DWM	Dandy-Walker malformation
FL	Femur length
HLHS	Hypoplastic left heart syndrome
IUGR	Intrauterine growth restriction
IUFD	Intrauterine fetal death
LBWC	Limb-body wall complex
LMP	Last menstrual period
MRI	Magnetic resonance imaging
NT	Nuchal translucency
NTD	Neural tube defect
TOP	Termination of pregnancy
TOPFA	Termination of pregnancy for fetal anomalies
US	Ultrasound
VSD	Ventricular septal defect

* There are other definitions of PNM that include early fetal death (week 20-27).

Terminology	**Definitions** (1,2)
Fetal mortality	Intrauterine death irrespective of gestational age
Perinatal mortality (PNM)	WHO definition*: Includes late fetal death (death ≥ 28 weeks) and early neonatal deaths (during first week of life)
Neonatal mortality	Death of a liveborn child during the first 4 weeks of life
Spontaneous abortion, miscarriage or early fetal death	Loss of a fetus before it is sufficiently mature to survive
Stillbirth or late fetal death	Delivery of a potential viable dead fetus - intrapartum death = fresh stillbirth - antepartum death =macerated stillbirth
Termination of pregnancy	Induced abortion

Summary in English

Introduction

A prenatal ultrasound (US) examination and a postmortem examination provide the basis for the correct diagnosis in fetuses terminated due to congenital anomalies. The risk of false-positive diagnoses with congenital anomalies is a major concern in prenatal diagnostics, in particular when termination of pregnancy (TOP) might be an option. The verification of US findings by postmortem examination is especially important for the involved parents, but also as feedback to health personnel and in future genetic counselling. The aim of this thesis was to correlate congenital anomalies detected by prenatal US with autopsy findings following TOP throughout 30 years.

Material and methods

The material consists of 1029 terminated fetuses from first to third trimester with one or more serious/lethal structural and/or chromosomal anomalies. The study extends over a 30-year period (1985-2014). Autopsy findings were compared with US findings in each fetus. The study is a collaboration between the Department of Pathology and the National Center for Fetal Medicine (NCFM), St. Olavs Hospital, University Hospital of Trondheim. NCFM (later renamed Norwegian National Unit for Advanced Intervention and Invasive Therapy in Fetal Medicine) was established in 1990 and serves as a tertiary center. The material comprised pregnant women from the catchment area of the hospital and referrals from the rest of the country.

Results

In the first paper, prenatal and postmortem findings of fetal anomalies in 1029 terminated fetuses were compared. There was full agreement in 88.1% (907/1029), and the main diagnosis was correct in 97.8% (1007/1029). In 1.3% (13/1029) of all pregnancies, US findings were not verified at autopsy, but the confirmation of other serious findings indicated that the 13 pregnancies were not mismanaged. When comparing the second 15-year period (2000-2014) with the first period (1985-1999), there were significant differences in the correlation rate for full agreement and main

diagnosis. Moreover, there has been an increase in early TOPs, while late TOPs have declined. There were non-significant differences in the correlation rate for full agreement and main diagnosis between early TOP and second trimester TOP.

In the second paper, from a pathological perspective, we focused on all fetuses with central nervous system (CNS) anomalies, with or without associated structural/ chromosomal anomalies, giving a total of 420 among 1029 fetuses (40.8%). About half were terminated due to isolated serious or lethal CNS anomalies, while the rest were CNS anomalies associated with other structural and/or chromosomal anomalies**.** Neural tube defects (NTDs) constituted the most common group of CNS anomalies.

From a total of 320 fetuses with congenital heart defects (CHDs) in the total material of 1029 fetuses, 67 fetuses with isolated CHDs or CHDs associated with heterotaxy syndrome were studied in the third paper. Hypoplastic left heart syndrome (HLHS) was the most common main diagnosis (32.8%, 22/67). There was full agreement between US and autopsy findings in 97.4% of the 228 subdiagnoses among the 67 fetuses.

Discussion and conclusion

Since the introduction of routine US examination during pregnancy, numerous studies have evaluated the correlation between prenatal US and autopsy findings in fetuses with congenital anomalies. However, the inclusion and evaluation criteria differ and correlation results vary. Throughout the years, the detection of congenital anomalies by US scan has continuously improved, also during the first trimester. These improvements may be explained by an increased expertise of the ultrasonographers and higher quality of the US equipment. Even though the correlation is improving, it is necessary to continue the validation practice, in particular due to the challenges of diagnoses made early in pregnancy. A detailed assessment of the anatomy, prenatally and at autopsy, is necessary to secure adequate medical practice, especially when the decision to terminate a pregnancy relies on isolated organ anomalies. Consequently**,** a fetus should be examined at a tertiary medical center with fetal medicine specialists and other clinicians in close collaboration with perinatal pathologists.

Summary in Norwegian

Introduksjon

Funn ved prenatal ultralydundersøkelse og obduksjon danner grunnlaget for diagnosen hos fostre som termineres på grunn av medfødte utviklingsavvik. Risikoen for falske positive diagnoser er av stor bekymring i prenatal diagnostikk, spesielt når terminering av svangerskapet (TOP) er et mulig utfall. Verifiseringen av ultralydfunn ved obduksjon er viktig, spesielt for foreldrene, men også som tilbakemelding til helsepersonell og ved fremtidig genetisk veiledning. I dette prosjektet var målet å korrelere medfødte utviklingsavvik oppdaget ved prenatal ultralydundersøkelse opp mot obduksjonsfunn hos terminerte fostre over en tidsperiode på 30 år.

Materiale og metode

Materialet består av 1029 terminerte fostre mellom første og tredje trimester med en eller flere alvorlige/letale medfødte strukturelle og/eller kromosomale utviklingsavvik. Studien strekker seg over en 30-årsperiode (1985-2014). Obduksjonsfunn ble sammenliknet med ultralydfunn i hvert enkelt foster. Studien er et samarbeid mellom Avdeling for patologi og Nasjonalt senter for fostermedisin (NSFM), St. Olavs Hospital, Trondheim. NSFM (senere kalt Nasjonal behandlingstjeneste for avansert invasiv fostermedisin) ble etablert i 1990 og fungerer som et tertiærsenter. De gravide kvinnene kommer fra sykehusets nedslagsfelt eller de er henvist fra resten av landet.

Resultater

I første artikkel ble ultralydfunn av medfødte utviklingsavvik sammenliknet med postmortale funn blant 1029 terminerte fostre. Det var full overenstemmelse mellom ultralyd- og obduksjonsfunn i 88.1% (907/1029), og hoveddiagnosen var korrekt i 97.8% (1007/1029). Hos 1.3% (13/1029) ble enkelte ultralydfunn ikke verifisert ved obduksjon. Dette hadde ikke betydning for håndteringen av svangerskapene da andre alvorlige avvik ble verifisert ved obduksjon. Det var signifikant forskjell i korrelasjon for full overenstemmelse og hoveddiagnose mellom første 15-årsperiode (1985-99) og

andre periode (2000-14). I løpet av studiet økte andelen tidlige TOP, mens andelen sene TOP avtok. Det var ikke signifikant forskjell i korrelasjon for full overenstemmelse og hoveddiagnose mellom tidlige TOP og andre trimester TOP.

Fra et patologisk perspektiv fokuserte vi i andre artikkel på alle terminerte fostre med utviklingsavvik i sentralnervesystemet (SNS), med eller uten assosierte strukturelle/kromosomale utviklingsavvik, totalt 420 av 1029 fostre (40.8%). Omtrent halvparten ble terminert pga isolerte alvorlige eller letale SNS-avvik, mens resten av fostrene med SNS-avvik hadde assosierte strukturelle og/eller kromosomale utviklingsavvik. Nevralrørsdefekter var gruppen med hyppigst avvik i SNS.

Fra i alt 320 fostre med medfødte hjertefeil av totalt 1029 fostre, tok vi i tredje artikkel for oss alle fostre med isolerte hjertefeil eller hjertefeil assosiert med heterotaksi syndrom, i alt 67 fostre. Hypoplastisk venstre hjertesyndrom var den vanligste hoveddiagnosen (32.8%, 22/67). Av totalt 228 hjertefeil blant de 67 fostrene, var det full korrelasjon mellom ultralyd- og obduksjonsfunn i 97.4%.

Diskusjon og konklusjon

Siden introduksjon av prenatal rutineultralydundersøkelse har flere studier evaluert korrelasjonen mellom ultralyd- og obduksjonsfunn hos fostre med medfødte utviklingsavvik. Inklusjons- og evalueringskriteriene mellom studiene varierer, og det er spredning i korrelasjonsresultatene. I løpet de siste 30 årene har deteksjonen av medfødte utviklingsavvik gradvis økt, også i første trimester. Denne økningen kan blant annet forklares med høyere kompetanse blant helsepersonell som utfører ultralyd, samt bedre kvalitet på ultralydutstyret. Selv om korrelasjonen øker, er det viktig å fortsette valideringen, spesielt grunnet utfordringer ved ultralydfunn påvist tidlig i svangerskapet. Detaljert diagnostikk prenatalt og postnatalt er nødvendig for å sikre adekvat medisinsk praksis, særlig når avgjørelsen om å avslutte svangerskapet er basert på isolerte organavvik. Fosteret bør derfor undersøkes på et tertiærsenter med fostermedisinere og andre klinikere i tett samarbeid med perinatalpatologer.

1. Introduction

Since the systematic examination of the fetal population was introduced in the eighties, correlation between prenatal ultrasonographic (US) findings and autopsy results has been assessed over time with respect to various organ groups. The prenatal US exam has become an essential part of antenatal diagnostics in order to locate disorders which may influence the care of the pregnancy. In certain cases, disorders detected are of such a severe nature that termination of the pregnancy (TOP) may be an option. It is then of utmost importance that the US diagnosis is correct. The risk of false-positive diagnoses in cases with congenital anomalies is a major concern, and the verification of US findings leading to TOP is therefore essential, especially for the involved parents, but also as feedback to health personnel, in future genetic counselling and for epidemiological analyses (3-20).

1.1. Congenital anomalies

Congenital anomalies, also known as birth defects or congenital malformations, can be defined as structural or functional anomalies that occur during intrauterine life and can be detected prenatally, at birth or later in life (21). Central nervous system (CNS) anomalies constitute the largest group, around 30%, followed by congenital heart defects (CHDs) and urinary system anomalies (22,23). The complexity of different anomalies varies and they can be classified as major (i.e. anencephaly) and minor (i.e. clubfoot) (24). Major anomalies have medical and/or social implications with impact on morbidity and mortality and may require surgical repair.

An estimated 6% of babies worldwide are born with a congenital anomaly, but the true number of cases may be much higher because statistics do not often consider terminated pregnancies and stillbirths (25). Together with preterm birth and disorders related to placental impairment, congenital anomalies account for most of perinatal mortality. The perinatal mortality rate (PMR) in developed countries is below 10/1000 births, including Norway at 4,1/1000 births (26,27). However, in less developed

countries the PMR is higher, up to 53/1000 births, which can be explained by factors such as poor maternal nutrition, by more environmental exposures and by differences in resources in health systems, screening policies for congenital anomalies, and availabilities of termination of pregnancy (26). It is estimated that 94% of all severe congenital anomalies occur in middle and low-resource countries (21).

In ancient times, birth defects were viewed as a result from the action of supernatural forces, for example sironemelia and holoprosencephaly. The latter has been known since antiquity through the figure of the cyclopean shepherd Polyphemos in Homer's *Odyssey* (800 BC) (28). In the 18th century, holoprosencephaly and other anomalies were recognized as congenital conditions, and during the 20th century they were studied systematically.

Today, causative factors can only be identified in approximately 50% of congenital anomalies (Table 1). However, advances in cytogenetic and molecular techniques in the last decades are allowing the identification of previously undetected chromosomal anomalies and gene mutations, and it is estimated that more than ¼ of all congenital anomalies may have a genetic cause (29). In cases with chromosomal anomalies, more than 90% of embryos/fetuses do not survive to term, and abnormal karyotype is more often present when multiple organs are involved in structural anomalies (12,30,31). Advanced maternal age (AMA) increases the risk of chromosomal anomalies (32).

Table 1. Etiology of congenital anomalies (29)

Etiology		**%**	**Example**
1	Single gene disorders	17	Adult versus infantile polycystic kidney disease (Autosomal dominant versus autosomal recessive mutation), Fragile X syndrome (X-linked disorder)
2	Chromosomal anomalies	10	Trisomy 13, 18 and 21, Turner syndrome (45,X)
3	Environmental and maternal factors (including teratogens)	4-10	CHDs (maternal diabetes), microcephaly (zica virus, retinoic acid), fetal hydrops (TORCH infection), skeletal anomalies (exposure to thalidomide)
4	Unknown/multifactorial	66	

1.2. Prenatal ultrasonography

As the vast majority of anomalies occur in pregnancies of low-risk women, routine US exam during pregnancy is considered an important part of prenatal care (33). The detection of anomalies contributes to optimizing obstetric care and improves the survival rates by assuring appropriate neonatal care. In cases with lethal or serious anomalies, a detailed and preferably early detection is important before eventual TOP.

Ultrasonography in obstetrics has changed our concepts of life, and US screening for fetal anomalies was introduced almost 20 years after the first US demonstration of fetal anomalies in the 1960s, with Bertil Sundén as one of the pioneers (34,35). He described anencephaly in a 31-week-old fetus in 1964. At a Norwegian consensus conference in 1986, the panel recommended a routine US examination around 17th gestational week, in order to reduce the number of antenatal exams, reach a greater part of the population and obtain information to enable delivery of optimal antenatal care with the best possible outcome for mother and fetus (36). The basic program for antenatal care in Norway includes one US scan at 18-19th gestational week, performed by Certified Nurse-Midwives with one-year university based Postgraduate Certificate in Obstetric Ultrasound (37-39). In May 2020, the Parliament voted for changes in the Biotechnology Act, in which all women will be offered early US examination and non-invasive prenatal test (NIPT). Moreover, the age limit when pregnant women are offered fetal diagnostics will be lowered from 38 to 35 years of age at term. Until the new guidelines are implemented, the law from 2003 is applicable (40,41).

In Scandinavia, almost all pregnant women attend the routine exam (42). The scan provides the following information; fetal number and biometry, documentation of fetal cardiac activity, placental localization and appearance, the amount of amniotic fluid and an assessment of fetal anatomy to detect congenital anomalies, including signs of aneuploidy (4). Gestational age and weight are estimated from fetal biometry. The use of routine US exam has led to a more accurate determination of gestational age, resulting in a reduced incidence of induction of labour in apparent post-date

pregnancies (43-47). Moreover, US scan is regarded as a modality with a very low risk-benefit ratio, especially in the hands of a trained operator (48,49).

Since the implementation of routine US exam, higher expertise and better US equipment have increased the quality of the US scan. Several studies have validated the correlation between US and postmortem findings, and the overall detection rates of congenital anomalies vary depending on the type of anomaly (11,14,15,19,23,50-53). CNS anomalies tend to be among the easiest to diagnose, while the sensitivity for detecting CHDs is increasing. *Sensitivity* is defined as the proportion of sick people who are correctly identified as having illness, while s*pecificity* measures the proportion of healthy people who are correctly identified as not having some illness (54).

As US technology has rapidly progressed, assessment of fetal anatomy in the first trimester has become a reality and there has been a shift towards detection of anomalies at earlier gestational ages (55,56). High-frequency transvaginal US and 3D US provide further insight into fetal disease (9,57). Some structural anomalies of the conceptus can be sonographically detected as early as during the embryonic period at 7 to 8 weeks of gestational age, while a scan at the end of the first trimester at 11-13 weeks can detect numerous types of anomalies (58,59). However, detection of fetal anomalies in the first trimester is limited by the small size of the fetus and the ongoing fetal development, and the detection rate varies between studies (55,60).

When anomalies are suspected or found at an US scan, an expert obstetrician is called upon to make a final US diagnosis and inform the pregnant women and her partner. This is usually followed by invasive tests for identification of karyotype and eventually other genetic conditions, and it is also common to consult other experts, such as clinical geneticists, neurologists, pediatric cardiologists and pediatric surgeons. In antenatally diagnosed cases, a detailed parental counseling is of great importance, with a discussion of options; continuation of pregnancy including the choice of postnatal interventions or termination of pregnancy.

1.3. Termination of pregnancy (TOP)

The practice of termination of pregnancy, abortion, has been known since ancient history, and at various times abortion has been banned or restricted in many countries (61). During the 20th century abortion-rights movements were successful in having abortion bans repealed in most of the western world, but abortion is still illegal in several countries (62). Consequently, unsafe abortion is a major factor in maternal morbidity and mortality and accounts for a proportion of maternal deaths worldwide each year (63).

According to Norwegian law from 1975 with later revisions, a fetus considered viable outside the mother's womb cannot be terminated (64). The limit for viability was initially assumed to be approximately 23+6 weeks until the 90s and later gradually restricted. Since 2001, the upper limit for termination of a viable fetus is 21+6 weeks. In the context of possible termination, from week 22 (21+6) a fetus is assumed to be viable. In Norway, women have the right to self-determined abortion before gestational week 12. Terminations after the 12th week of pregnancy must be approved by a local committee and can only take place if certain indications are met. Reasons for most committee-handled abortions include serious/lethal fetal anomalies, social factors and/or maternal health (65). The proportion of terminations that are carried out after 12 weeks in Norway is just over 4%. After week 18, weighty reasons must be present, and after 22 weeks only fetuses with lethal conditions may be aborted (66).

What is the definition of a serious/lethal anomaly or condition? In *Termination of Pregnancy for Fetal Abnormality in England, Scotland and Wales* (2010), The Royal College of Obstetricians and Gynaecologists discussed the legal status of termination of pregnancy (67), and stated that a substantial risk is if the child was born, it would suffer from such physical or mental abnormalities as to be seriously handicapped. However, the most commonly cited definitions are those provided by the World Health Organization (1980) in The International Classification of Impairments, Disabilities, and Handicaps (68):

- Impairment: Any loss or abnormality of psychological, physiological or anatomical structure or function.
- Disability: Any restriction or lack (resulting from an impairment) of ability to perform an activity in the manner or within the range considered normal for a human being.
- Handicap: A disadvantage for a given individual that limits or prevents the fulfillment of a role that is normal.

The more severe prognoses increase the termination rate (30,69). European Surveillance of Congenital Anomalies (EUROCAT) recorded a total prevalence of major congenital anomalies of 23.9 per 1000 births for 2003-2007 (70), 17.6% of these were terminated following prenatal diagnoses (TOPFA/Termination of pregnancy for fetal anomaly). The prevalence of chromosomal anomalies was 3.6 per 1000 births, and 48% of all TOPFA had chromosomal anomalies. In 2010, the Medical Birth Registry of Norway reported 277 TOPs for birth defects of approximately 60,000 births (71).

In Norway, abortion statistics are available since 1979, and The Department of Health Registries at the Norwegian Institute of Public Health (NIPH) is responsible for the Registry of Pregnancy Termination (65). Norway introduced medical abortion with mifepristone in 1998. Since then, there has been an almost complete shift from mainly surgical to medical abortion (Figure 1). About 90% of induced abortions are medical (72), and the most commonly used medicaments are mifepristone and misoprostol. As a result, the fetuses are usually intact at autopsy. In contrast, in USA, 76% of terminations at gestational ages ≤13 weeks were performed via vacuum aspiration, and 15% were medical abortions, but the use of medical abortions has increased (73). Dilatation and evacuation (D&E) procedures involve mechanically opening the uterine cervix followed by evacuation of intrauterine contents (74). This procedure fragments the fetus, which makes the postmortem examination challenging and the verification of eventual ultrasonographic findings of anomalies very difficult or impossible.

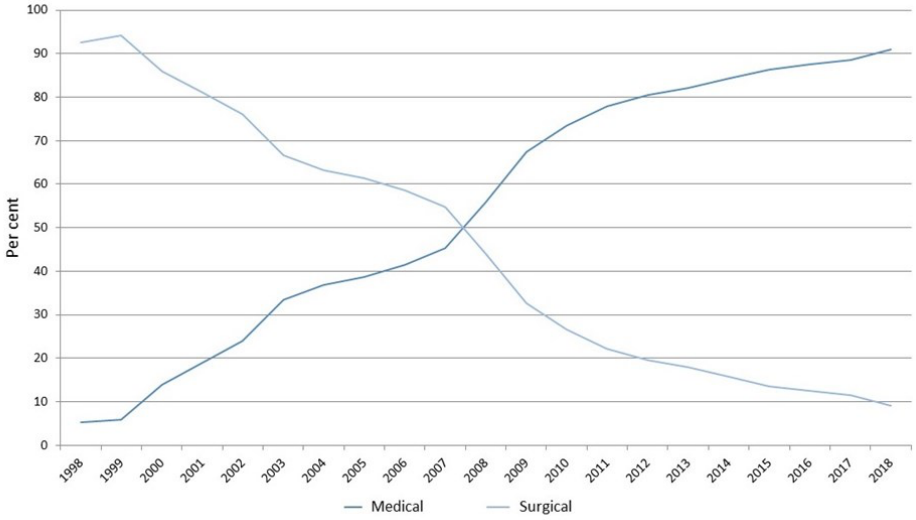

Figure 1. Medical abortion vs surgical abortion in Norway. Source: Registry of Pregnancy Termination (65)

Finally, as anomalies are detected earlier in pregnancy, the gap to the gestational week when legal abortions in Norway are permitted (gestational week 12) is decreasing and thereby giving the parents the option of self-determined TOP. As different countries have different laws on termination of pregnancy when anomalies are present, the prevalence of anomalies varies. The Helsinki trial (1999) reported that prenatal diagnosis of congenital anomalies followed by TOP might decrease PMR by 50% in developed countries (75). For instance, Egbe et al. (2014) wrote that there is a possible association between reduced prevalence of severe CHDs and increased rate of TOPs with prenatally diagnosed CHDs (76). Lytzen et al. (2018) also showed increased detection rates of major CHDs in Denmark from 1996-2013, followed by increased TOP rates and a subsequent 39% decrease in the incidence of live births with major CHDs (77).

1.4. Postmortem examination/autopsy

When a pregnancy is terminated due to congenital anomalies detected by US exam, verification of findings by autopsy is necessary. A postmortem examination or autopsy of aborted fetuses has been considered as the "gold standard" and was implemented as a quality control of the work performed by ultrasonographers.

History

The word *"autopsy"* is derived from the Greek *autopsia*, meaning *"the act of seeing for oneself "* (78). The first real dissections for the study of disease were carried out about 300 BCE by the Alexandrian physicians, but it was a Greek physician in the late second century CE who were the first to correlate the patients symptoms and signs with postmortem findings, an ancient barrier in medical history (79).

The Scottish obstetrician Ballantyne was probably the first perinatal pathologist, and in 1902 he wrote "Manual of antenatal pathology and hygiene" (80)**.** Edith Potter founded from the 1930s onwards the modern specialty of perinatal pathology, and she stated: "*Most pathologists are not interested in babies, largely because adult pathology is so much more spectacular. For too many years, the concern was the mother. A baby's death was considered an act of God about which not much could be done"* (81). Her name is linked with the facial characteristics of infants with bilateral renal agenesis, and *"*Pathology of the fetus and infant", first published in 1953, is a major contribution to the field, in which she wrote: "*In addition to the ultimate aim of the pathologist [to promote the well-being of the living], of immediate practical importance is the demonstration to the attending physician of the pathological changes found in any fetus or infant who fails to survive and the correlation of these findings with the symptoms observed during life. When symptoms can be recognized as associated with specific pathologic processes a great stride has been made toward their prevention and cure ... It is hoped that [this book] will be of practical value to the pediatrician and the obstetrician as well as the pathologist".*

Perinatal autopsy

For many years pathologists regarded perinatal autopsies as an unrewarding task contributing little to perinatal care, though after the introduction of US from the 1970s this changed. Since the implementation of routine US examination in Norway in 1986, there has been an increasing demand for continuous quality control of ultrasonography (82). Classifying perinatal death is a complex process that is best accomplished at a multidisciplinary meeting where a conclusion is reached after discussion of all available clinical and pathological findings.

Several autopsy protocols, both national and international (83,84), have been implemented in order to record all deviations from normal. Firstly, seeking consent from the involved parents to perform autopsy is obligatory, and the medical history of the mother and fetus should be available before autopsy. A complete systematic examination of the fetus is performed, regardless of gestational age. Fetal growth, presence of maceration, edema, dehydration, cyanosis, jaundice, dysmorphic features and injuries related to delivery are some of the external features that are looked for. Total skeletal x-ray and photo documentation as well as measurements (body weight, length, crown-rump length, head circumference, abdominal circumference and foot length) should be performed before the autopsy. The macroscopic examination must also include a detailed description of all visible anomalies. The internal examination should be meticulously performed with description of all organs, including weights. Slides from organs are formalin fixed and processed for microscopic examination. Material from selected organs should be routinely frozen for eventual genetic examinations. The placenta must always be examined.

Prenatal ultrasound examination versus autopsy

Since the 80s, numerous studies have evaluated the correlation between prenatal US findings and autopsy findings (5-8,10-18,85-89). In the review article of Rossi et al. from 2016 (23), 19 articles included 3534 fetuses that underwent autopsy after TOP or stillbirth. In 68.0% of fetuses the autopsy confirmed prenatal findings, while autopsy provided additional information in 22.5%. In 9.2 % of fetuses the autopsy did not

confirm the ultrasonographic findings, in which 3.2% were false positive and 2.8% false negative cases. To sum up, the studies showed high agreement between prenatal and postmortem findings, but there were cases with additional findings at autopsy or findings not confirmed at autopsy. Moreover, the diagnostics and verification may also be challenged by the trend of US diagnoses of congenital anomalies at earlier gestational age and thereby smaller fetuses (56,58,60,90).

Autopsy rates

Parallel to the advances in US diagnostics and the increased detection of anomalies by US, the need of fetal autopsy has been up for discussion (85,91-94). Even though studies have shown that autopsy helps to establish the cause of death and can provide additional significant information in up to 40% of cases (95-97), fetal autopsy rates have dropped in the western world during the last 30 years (15,98,99). This decrease may be a result of improvements in diagnostic imaging, centralization of pathology services (100) and/or due to poor counseling of parents provided by non-experts in fetal medicine (101). Breeze et al. (2012) stated that the most important consideration underlying the parents´ decision for autopsy or not was that knowledge could give them information about the cause of pregnancy loss or fetal abnormalities, and prognosis for future pregnancies (102). Dislike of the invasiveness of procedure and religious objections are other factors that also have been identified as parental barriers to standard autopsy (15). However, Breeze et al. stated that these barriers were less influential in the parents´ decision making for performing autopsy (102).

If the consent for a full autopsy is not given, limited examination may be of value, and may include (84):

- Autopsy limited to one or more body cavities
- Open or needle biopsy of specific internal organs
- External examination of the body with x-ray, photography and genetics
- Placental examination only
- Imaging (CT, MRI) alone or with targeted biopsies (103,104)

1.5. Spectre of congenital anomalies

In this thesis, the material consists of a broad range of different structural and/or chromosomal anomalies. In the following pages the main groups of different anomalies are described. Moreover, when studying fetal pathology, it is important to be aware of the distinction between the definition of different pathological concepts, see table 2.

Table 2. Definitions of different pathological concepts (24)

Pathology	Definition	Examples
Congenital anomaly	Significant definable and/or developmental abnormality observed at birth	Omphalocele
Malformation	Defects of organs or body parts due to an intrinsically abnormal developmental process.	Polydactyly
Disruption	Secondary change in an otherwise normal developmental field	Amniotic rupture sequence
Deformation	Normal anatomy deformed by external forces	Foot deformity because of oligohydramnios
Sequence	Cascade of secondary malformations as a result of a focal primary defect	Urethral obstruction with megacystis
Syndrome	Intrinsic alterations of several developmental fields by one etiologic agent	Meckel-Gruber syndrome
Dysplasia	Abnormal cellular organisation within tissues and its morphological result	Thanataphoric dysplasia
Association	Non-random occurrence of several malformations consistently observed together, unknown etiologic agent	VACTERL – vertebral, anal, cardiac, tracheoesophageal, renal, limb disorder

Central nervous system (CNS) anomalies

Together with anomalies in the cardiovascular and urinary system, anomalies of the CNS are among the most common prenatally diagnosed anomalies, and neural tube defects (NTDs) are the most common of severe anomalies of the CNS (105) (Table 3). The etiology of CNS anomalies is very heterogenous and genetic conditions such as trisomy 13 and 18 are important causing factors (106). However, the underlying cause of most cerebral anomalies is still unknown (107).

Table 3. Most prevalent CNS anomalies (108)

Anomalies	**Subgroups/Main findings**
Neural tube defects (NTDs)	- Anencephaly (40-50%): Acrania with secondary degeneration of brain. - Myelomeningocele/spina bifida (40-50%): The neural arch, usually in lumbosacral region, is incomplete with damage to the nerves. - Encephalocele (5%): Cranial defects, usually occipital, with herniated fluid-filled or brain-filled cysts.
Ventriculomegaly	Enlargement of the lateral ventricles
Holoprosencephaly	A spectrum of cerebral abnormalities resulting from incomplete cleavage of the forebrain; 3 types (alobar, semilobar and lobar)
Microcephaly	Small head and brain
Dandy-Walker malformation	A spectrum of abnormalities of the cerebellar vermis, cystic dilatation of the fourth ventricle and enlargement of the cisterna magna
Agenesis of corpus callosum	Partial or total

Major CNS anomalies are traditionally easily diagnosable by prenatal US (23,50). The detection of serious CNS anomalies at US scan may result in TOP, and around 30% of TOPs performed after the 12th gestational week have been reported to be due to CNS anomalies (109).

During the last decades, first trimester scan has evolved (56,59,60,110-112), and about 45% of CNS anomalies are detected in the first trimester (58). NTDs were among the first to be reported diagnosed during first trimester with 80-90% detection rates (113),

with later improvement (114). The corpus callosum and the cerebellum are not sufficiently developed to allow complete assessment in the first trimester US. The diagnosis of certain anomalies can often not be confirmed in the first trimester because the structures do not become sonographically apparent until second and third trimester (59). The gestational age at termination of pregnancy is therefore often related to the type of anomaly, such as earlier terminations in cases of NTDs compared to later terminations of vermian anomalies like Dandy-Walker malformation (DWM) (Figure 2) (115-117).

A detailed postmortem neuropathological examination is important in verification of US findings. Moreover, pre- and postmortem MRI has become a valuable tool in the diagnosis of suspected brain and spine abnormalities (104,118,119), especially helpful after the 20th week of gestation (120-124).

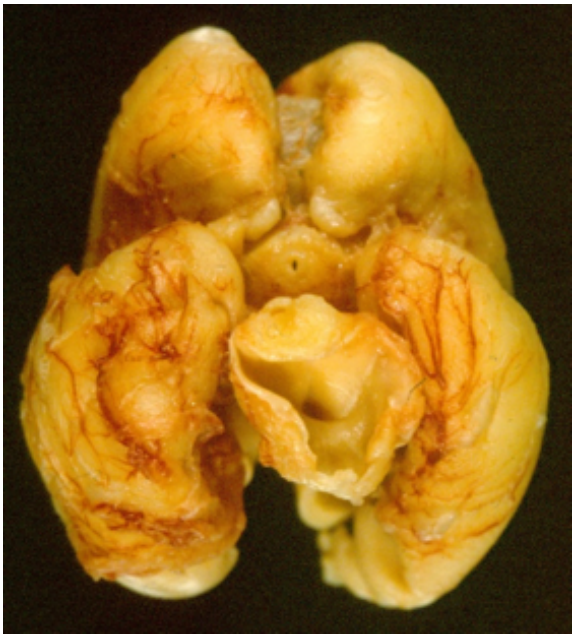

Figure 2. Postmortem photograph of 15 week old fetus with Dandy-Walker malformation, 1997. Photo by Christina Vogt.

Cardiovascular system anomalies/congenital heart defects (CHDs)

CHDs are defined as structural abnormalities of the heart or intrathoracic vessels with functional or potentially functional significance (125). They are found in approximately 1% of live births and are the leading cause of infant mortality due to birth defects (126,127). Table 4 shows the main groups of CHDs. CHDs occur in association with other anomalies or as part of a syndrome in 25-49% (33,128). The risk of aneuploidy varies depending on the anomaly: 46-73% in atrioventricular septal defects (AVSD) and 4-9% in hypoplastic left heart syndrome (HLHS) (Figure 3) (129).

Table 4. Subgroups of cardiovascular system anomalies (108)

Subgroups	**Anomalies**
Cardiac chambers and connections	- Transposition of great vessels (TGA) - Double outlet right ventricle (DORV) - Double inlet right ventricle (DIRV) - Truncus arteriosus
Cardiac septa	- Atrial septal defect (ASD) - Ventricular septal defect (VSD) - Atrioventricular septal defect (AVSD) - Tetralogy of Fallot *
Pulmonary and tricuspid valves	- Pulmonary valve stenosis - Triscupidal atresia - Hypoplastic right heart syndrome (HRHS) **
Aortic and mitral valves	- Aortic valve stenosis - Hypoplastic left heart syndrome (HLHS) ***
The great arteries	- Coarctation of the aorta - Overriding aorta - Atresia/hypoplasia of the aorta - Atresia/hypoplasia of pulmonary artery
The great veins	- Anomalous venous return

* Tetralogy of Fallot: VSD, pulmonary stenosis, overriding aorta, right ventricular hypertrophy
** Hypoplastic right heart syndrome (HRHS): Pulmonary valve atresia, hypoplastic right ventricle, tricuspid valve stenosis/atresia, hypoplastic pulmonary artery
*** Hypoplastic left heart syndrome (HLHS): Aortic valve atresia, hypoplastic left ventricle, mitral valve stenosis/atresia, hypoplastic ascending aorta

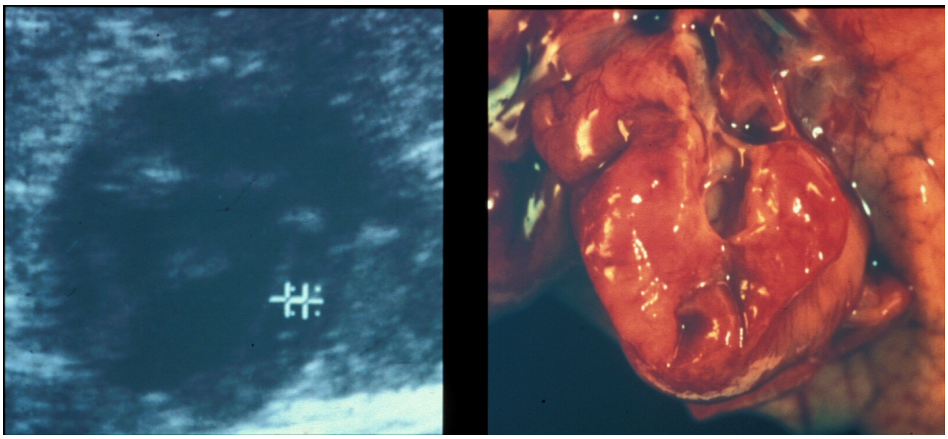

Figure 3. Ultrasound image and postmortem photograph of HLHS. Photo by Christina Vogt.

Most CHDs occur in low-risk pregnancies, thus, the routine mid-trimester fetal anatomy scan is an important tool to detect CHDs (33,130-132). CHDs have traditionally been regarded as difficult to detect at US scan (51,133,134). However, fetal cardiac evaluation has evolved and the detection rate has increased (33,135). This can partly be explained by the introduction of the five short axis views for the heart examination and the focus on teaching the examiners (134,136-138). The optimum age for assessing CHDs remains 18-22 weeks of gestation (139), but there is a move towards an early US scan at 11-13 weeks (140). Increased nuchal translucency, abnormal ductus venosus blood flow and tricuspid regurgitation in the first trimester are associated with an increased risk of CHD (141,142).

Advances in pediatric cardiac surgery have permitted treatment of some CHDs, and an early prenatal diagnosis may lead to changes in medical management (133,143,144). Following diagnosis, counselling is important for discussing options, including fetal intervention, termination of pregnancy or continuation of pregnancy. However, the broad variety of CHDs and possible extracardiac/chromosomal anomalies make prognostic counselling challenging.

Urinary system anomalies

Urinary system anomalies are common, with an incidence of 2-5 per 1000 births (145), and the majority are not lethal (Table 5). They are usually discovered because of reduced/deficient urine production with anhydramnios/oligohydramnios and/or abnormal US findings (52). The use of routine ultrasonography in pregnancy has resulted in early detection and changed the spectrum of diseases seen postnatally. For example, detection of urinary-tract dilatation has led to better planned neonatal management. Poor prognostic signs are echogenic kidneys indicating the presence of bilateral multicystic or severely hydronephrotic kidneys (146). Potential candidates for intrauterine surgery are fetuses with bilateral moderate/severe pelvicalyceal dilatation with or without megacystis, and normal cortical echogenicity (147).

Table 5. Most prevalent urinary system anomalies (108)

Anomalies	**Subgroups/main findings**
Renal agenesis	Suspected when combination of anhydramnios and failure to visualize the fetal bladder at ultrasound: Uni -or bilateral
Cystic renal disease	- Multicystic dysplastic kidneys with or without lower urinary obstruction: Uni -or bilateral - Autosomal recessive polycystic kidney disease (ARPKD): Bilateral
Hydronephrosis	Dilatation of the renal pelvis
Low urinary tract obstruction	With/without megacystis

Anomalies of the body wall and gastrointestinal tract

Abdominal-wall anomalies are one of the commoner fetal anomalies demonstrated by US. The spectrum of defects extends from minor exomphalos with bowel herniating into the base of the cord to major defects, including pentalogy of Cantrell, body stalk defects and early amnion rupture sequence (ARS) (Table 6). By 12 weeks' gestation the bowel has returned to the abdomen, so herniated abdominal contents after this time is abnormal (148). It is difficult to exclude anterior abdominal wall defects in the presence of severe oligohydramnios/anhydramnios. Since many defects are associated with bladder anomalies, the presence of a normal bladder indicates that the lower abdominal wall probably is intact, but omphalocele or gastroschisis are still possible.

Table 6. Most prevalent anomalies of the body wall and gastrointestinal tract (108)

Anomalies	**Definitions/possible findings**
Omphalocele/ exomphalos	A midline abdominal wall defect, the herniated sac with its visceral contents and the umbilical cord insertion at the apex of the sac.
Gastroschisis	Evisceration of the intestine occurs through a small abdominal wall defect located lateral to an intact umbilical cord. The intestinal loops are floating freely in the amniotic cavity.
Diaphragmatic hernia	Most often left sided. When the defect is large, most of the abdominal viscera are present in the thorax and the mediastinum is displaced.
Limb-body-wall-complex (LBWC)	Abdominoschisis and other possible findings (ectopia cordis, scoliosis and anomalies of the lower limbs).
Oesophagal atresia	Most often associated with tracheaoesophageal fistula.
Duodenal atresia	The stomach and the duodenum each forming fluidfilled structures.

Skeletal abnormalities

There are several hundred types of skeletal abnormalities, in which skeletal anomalies such as clubfeet (9,5 in 10 000 births) and polydactyly (8,9 in 10 000 births) are common. Skeletal dysplasia are less common (1,69 in 10 000 births) (Table 7) (149). According to the newest version of the Nosology and Classification of Genetic Skeletal Disorders, 2019 revision, there are 437 different diseases that are classified into 42 groups (150), for example thanatophoric dysplasia in group 25 (Osteochondroplasia). Undetected severe cases of skeletal dysplasia result in perinatal/neonatal death due to lung hypoplasia and respiratory complications (151).

Table 7. Some of the most common skeletal abnormalities (108,152,153)

Skeletal abnormalities	**Subgroups/main findings:**
Skeletal anomalies	Example: Vertebral anomalies, clubfeet, polydactyly, syndactyly
Most common skeletal dysplasias	- Achondroplasia – most common bone dysplasia: Short limbs, lumbar lordosis, short hands, macrocephaly with frontal bossing, narrow thorax (lethal type). Mutation in fibroblast growth factor receptor (FGFR3) gene. - Thanatophoric dysplasia (TD) – most common lethal dysplasia: Severe shortening of the limbs, narrow thorax, large head with prominent forehead, “curved telephone receiver femur” (type 1) and temporal lobe dysplasia. Mutation in fibroblast growth factor receptor (FGFR3) gene.

	- Achondrogenesis – second most common lethal dysplasia: Very short limbs, narrow thorax and large head. Mutation in the TRIP11 gene or DTDST gene. - Osteogenesis imperfecta (OI): Fragility of bones, blue sclera, loose joints. Severe bone shortening and bowing due to multiple fractures (type II). Most often mutation in alpha chains of the type 1 collagen gene.

Fetal hydrops

Fetal hydrops is defined as accumulation of fluid, edema, in at least two fetal compartments, that include subcutaneous tissue, pleura (pleural effusion), pericardium (pericardial effusion) and abdomen (ascites) (154,155). It is a non-specific finding, and the etiology is divided into immune type (10-25%, due to maternal haemolytic antibodies,) and non-immune type (75-90%). In the latter type, intrauterine anemia (i.e. after an intrauterine infection like parvo virus), heart failure and hypoproteinemia are common mechanisms. Fetal hydrops is usually detected at US scan and the use of echocardiography may reveal the etiology. The prognosis is poor, and the abnormality often remains unexplained, even after autopsy.

Chromosomal anomalies

Trisomy 21, 18 and 13 are the most common chromosomal anomalies. Most fetuses with major chromosomal anomalies have structural abnormalities detectable by detailed US examination (145). In the first trimester, a common feature (soft marker) of several chromosomal anomalies is increased nuchal translucency (NT) (Table 8). Each chromosomal anomaly has often specific structural patterns (Table 9). However, no single anomaly is pathognomonic for a given chromosomal defect. The overall risk for chromosomal anomalies increases with the number of structural abnormalities that are identified. Therefore, it is recommended that when an abnormality/soft marker is detected at the US scan, a thorough check is made for other features of the chromosomal anomaly known to be associated with that marker.

Table 8. Soft markers of chromosomal anomalies

Marker	**Definition**
Nuchal edema and nuchal translucency (NT)	Nuchal edema is defined as soft-tissue thickening >6 mm in the dorsal cervical region. An increased NT during the first trimester may be associated with abnormal karyotype (i.e. Trisomy 21). In the second trimester it might evolve into nuchal edema or cystic hygroma.
Cystic hygroma (CH)	Abnormal development of lymphatic vessels resulting in accumulation of lymphatic fluid in tissues of the neck. Associated with Turner syndrome.

Table 9. Chromosomal anomalies (145)

Chromosomal anomalies	**Possible associated structural findings**
Trisomy 13, *Patau syndrome* (47,XY, +13 or 47,XX,+13),	Holoprosencephaly, facial abnormalities, microcephaly, omphalocele, CHDs, renal anomalies, polydactyly
Trisomy 18, *Edward syndrome* (47,XY, +18 or 47,XX,+18),	Strawberry-shaped head, choroid plexus cysts, absent corpus collosum, facial cleft, nuchal edema, CHD (VSD), omphalocele, diaphragmatic hernia, oesophageal atresia, renal anomalies, myelomeningocele, IUGR, shortening of the limbs, radial aplasia, overlapping 2. and 5. finger
Trisomy 21, *Down syndrome* (47, XY, +21 or 47,XX,+21),	Brachycephaly, hypoplastic nasal bone, mild ventriculomegaly, flattening of the face, nuchal edema, AVSD, duodenal atresia, shortening of the limbs, sandal gap, clinodactyly
Triploidy (69,XXX or 69,XXY)	- Maternal extra chromosome: Severe IUGR, ventriculomegaly, CHDs, myelomeningocele, syndactyly, “hitch-hiker” toe - Paternal extra chromosome: Partial molar placenta, pregnancy persists rarely >20 weeks
Turner syndrome (45,X0)	- Lethal type: Large cystic hygroma, generalized edema, CHDs - Non-lethal type: Seldom ultrasonographic abnormalities

CHDs, congenital heart defects; VSD, ventricular septal defect; IUGR, intrauterine growth restriction; AVSD, atrioventricular septal defect

Syndromes

A syndrome is a group of disorders that consistently occur together, affects several areas of the body and is defined as intrinsic alterations of several developmental fields by one etiologic agent (Table 2). Table 10 shows syndromes relevant in this thesis.

Table 10. Some syndromes with common structural features (156)

Syndromes	**Common features**
Noonan	Short stature, CHDs, pectus excavatum, flat nose. Mutation in PTPN11 gene.
Silver-Russell	Short stature, IUGR, triangular shaped face. Mutation in IGF-2 gene.
Meckel-Gruber	Renal cystic dysplasia, occipital encephalocele, postaxial polydactyly. Mutations in NPHP6, NPHP8, and MKS genes.
Marfan (MFS)	Affects connective tissue (heart, aorta, etc.), excess growth of long bones. Mutation in FBN1 gene.

1.6 Summary

A thorough US examination of the first and mid trimester fetus, performed with current US technology by an expert examiner, allows the detection of congenital anomalies. Some areas of fetal anatomy have traditionally been more difficult to investigate, i.e. the cardiovascular system. A postmortem examination of aborted fetuses has been considered as the “gold standard” and implemented as a quality control.

Since the introduction of routine US examination during pregnancy, numerous studies have evaluated the correlation between US and autopsy findings. However, the inclusion and evaluation criteria differ, and the studies vary in their results in correlation between US and autopsy findings. Moreover, the diagnostics and verification are challenged by the trend of US diagnoses of congenital anomalies at earlier gestational age.

2. Aims

The overall aim of this thesis was to correlate prenatal ultrasound findings of congenital anomalies with results of postmortem examination in cases of termination of pregnancy (TOP) over a 30-year period from 1985 to 2014. This is a quality control of TOPs carried out because of sonographically diagnosed fetal anomalies and includes cases from all over Norway.

Paper I

Correlation between prenatal ultrasound and postmortem findings in 1029 fetuses following termination of pregnancy

The aim was to correlate congenital anomalies detected by ultrasound examination with autopsy findings following termination of pregnancy (TOP) throughout a 30-year period, and to evaluate the correlation rate at different gestational ages.

Paper II

Autopsy findings of central nervous system (CNS) anomalies in intact fetuses following termination of pregnancy (TOP) after prenatal ultrasound diagnosis

The aim was to investigate the distribution of different CNS anomalies with associated anomalies and karyotype in a fetal autopsy population of terminated pregnancies over a 30-year period, and to correlate the ultrasonographic diagnoses of CNS anomalies with autopsy findings.

Paper III

Postmortem assessment of isolated congenital heart defects remains essential following termination of pregnancy

The aim of this study was to investigate the correlation between prenatal US diagnoses and autopsy findings in pregnancies terminated due to isolated CHDs, including CHDs associated with heterotaxy syndrome.

3. Material and methods

3.1. Study population

The total material consists of 1029 terminated fetuses from first to third trimester with one or more serious/lethal structural and/or chromosomal anomalies. The study spans over a 30-year period from January 1985 to December 2014. Autopsy findings were reviewed and compared with US findings in each terminated fetus. The study is a collaboration between the Department of Pathology and the National Center for Fetal Medicine (NCFM), both located at St. Olavs Hospital, University Hospital of Trondheim. NCFM (later renamed Norwegian National Unit for Advanced Intervention and Invasive Therapy in Fetal Medicine) was established in 1990 and serves as a tertiary center. The material comprised pregnant women from the catchment area of the hospital and referrals from the rest of the country.

3.2. Prenatal ultrasonography

Fetal medicine experts were responsible for the final US examinations at the NCFM. Some of the US machines employed were Hitachi EUB 565, Dornier AI 3200, Vingmed Sound CFM 750, Simens Acuson and GE Voluson 730 Expert. All cases were over time prospectively registered in a database at the NCFM and continuously validated. The database includes variables such as maternal age, obstetric history, structural and chromosomal anomalies and results of fetal invasive procedures. Information on invasive antenatal testing to determine fetal karyotype was based on chorionic villous sampling or amniocentesis.

In Norway, pregnancy length and expected day of delivery are determined at the routine scan by measurement of biparietal diameter (BPD) and femur length (FL). In early pregnancies, BPD or crown-rump length (CRL) is used (56). In cases where the anomaly affected fetal size (ex. skeletal dysplasia), gestational age was based on the best estimate of clinical data, such as last menstrual period (LMP).

3.3. Termination of pregnancy (TOP)

All terminations of pregnancy followed approval by an abortion committee. All fetuses were terminated due to congenital anomalies considered as very serious or lethal. Genetic analyses were performed prior to the request for termination. The termination of pregnancy was performed as soon as feasible, preferably the day after the decision for termination was made. In cases where anomalies were detected as early as week 9 to 10, TOP was delayed 2-3 weeks to enable a proper postmortem assessment.

Abortions were induced medically to preserve completeness of the specimen in order to make verification possible. In the early 90s, TOPs were performed by using prostaglandin analogues (gemeprost) alone, applied in the vagina. Since the end of the 90s, all TOPs were performed by using a combination of anti-progesterone (mifepristone) with prostaglandin analogues (gemeprost, later misoprostol).

3.4. Postmortem examination/autopsy

The autopsy was performed as early as possible after the TOP, preferably within two days, in order to avoid autolysis of the fetus. US reports were available to the pathologist at the postmortem examination. Between the years 1985 to 1990 and 2005 to 2014, doctors in training, supervised by a senior pathologist, performed the autopsies. Between the years 1991 to 2004, two consultant pathologists with experience in perinatal pathology were responsible for all the autopsies. From 1990, a standardized autopsy protocol was followed, which included full body radiology and photographic documentation. All organs were examined, including in situ examination of the heart and removal of the brain under water so as to minimize trauma (83). From 2008, formalin zinc sulphate has been used for fixation of the brain.

3.5. Study methods

Information about all fetuses and anomalies were saved in an exel file. The final diagnoses at the last US examination and the autopsy findings were documented. In the papers three of the authors (CS, CV and HGKB) discussed the correlation between US and autopsy findings, and categorized the results into 5 categories, according to a modification of the method described by Isaksen et al. (50).

1. Full agreement between ultrasound and autopsy findings
2. Minor autopsy findings not seen or recorded at ultrasound examination
3. Major autopsy findings not detected at ultrasound examination
4. None of the autopsy findings suspected at ultrasound examination
5. Ultrasound findings not confirmed or not possible to confirm at autopsy

The thesis is based on three papers, illustrated in the following flowchart (Figure 4).

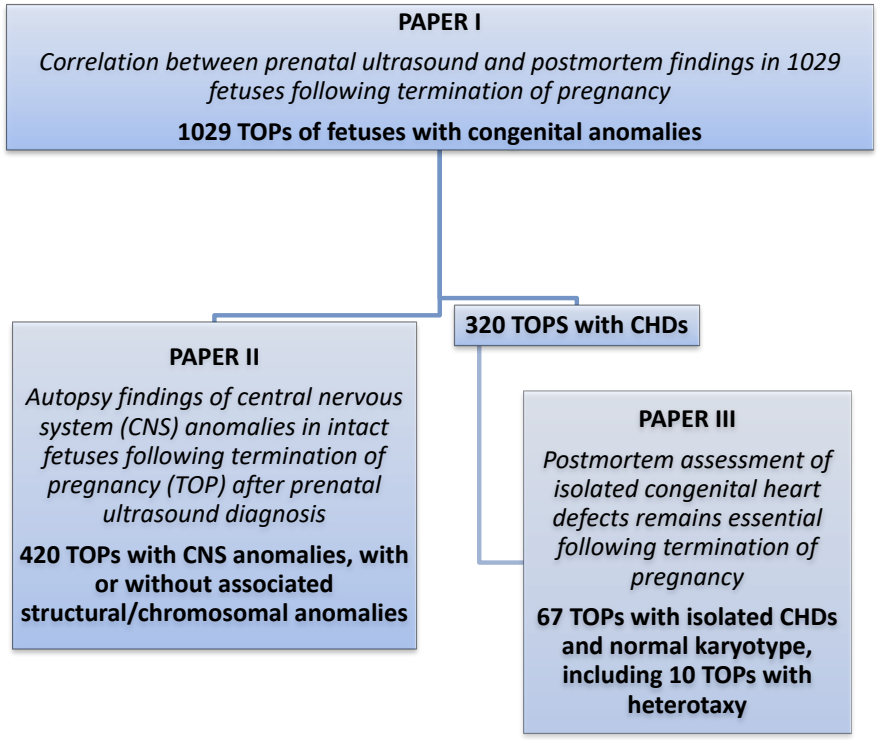

Figure 4. Flowchart illustrating the three papers

Paper I

In the first paper, prenatal and postmortem findings of fetal anomalies in 1029 terminated fetuses were compared, and the correlation at different gestational ages was evaluated. The gestational age span between 11 and 33 weeks was differentiated into 3 groups: weeks 11+0 to 15+6 (early TOP), weeks 16+0 to 21+6 (intermediate TOP) and weeks 22+0 to 33+6 (late TOP). The distinction between the second and third group at 21+6/22+0 weeks is based on the Norwegian Act relating to termination of pregnancy (64).

Paper II

In the second paper, from the total material of 1029 TOPs, 420 fetuses with CNS anomalies, with or without associated structural/chromosomal anomalies were included. We examined the distribution of all CNS anomalies from a pathological perspective, and categorized the CNS anomalies according to ICD-10, described in table 11.

ICD 10 Code	Congenital malformations of the CNS
Q00	Anencephaly and similar malformations
Q01	Encephalocele
Q02	Microcephaly
Q03	Congenital hydrocephalus
Q04	Other congenital malformations of brain
Q05	Spina bifida
Q06	Other malformations of spinal cord
Q07	Other malformations of nervous system

Table 11. WHO classification of congenital malformations of the CNS, ICD-10 codes (108)

Paper III

In the total material of 1029 TOPs, there were 320 fetuses with CHDs. In the third paper, we included only fetuses with isolated CHDs for detailed evaluation, altogether 67 cases. All fetuses with CHDs having extracardiac and/or chromosomal anomalies were excluded. Fetuses with heterotaxy syndrome were included as none of these had extracardiac anomalies except for the abnormal arrangement of internal organs, which did not influence the decision for TOP. We categorized the CHDs according to ICD-10, described in table 12 (108).

Table 12. WHO classification of congenital malformations of the circulatory system, ICD-10 codes (108)

ICD10 Code	Congenital malformations of the circulatory system
Q20	Congenital malformations of cardiac chambers and connections
Q21	Congenital malformations of cardiac septa
Q22	Congenital malformations of pulmonary and tricuspid valves
Q23	Congenital malformations of aortic and mitral valves
Q24	Other congenital malformations of heart
Q25	Congenital malformations of great arteries
Q26	Congenital malformations of great veins
Q89	Other congenital malformations, not elsewhere specified

3.6. Statistics

All information from the examinations and the correlation between US and autopsy findings were systematized in Microsoft Excel, and selected data was exported to SPSS Statistics version 21.0-25.0 software (SPSS Inc., Chicago, Ill., USA) for further statistical analyses. Correlation analyses were performed using Independent samples t-test. $P<0.05$ was considered statically significant.

3.7. Ethics

The studies in this thesis were approved by the Regional Committee for Medical and Health Research Ethics (REC) as parts of a larger project (document reference 2009/790). Since this is an autopsy material REC gave dispensation from informed consent, though in cases from 2004 the parents had to give written consent to use the autopsy material for research and/or education.

4. Results

4.1. Paper I

Struksnæs C, Blaas H-G. K., Eik-Nes S.H., Vogt C. Correlation between prenatal ultrasound and postmortem findings in 1029 fetuses following termination of pregnancy. *Ultrasound Obstet Gynecol* 2016; 48: 232-238.

There were altogether 1845 different anomalies in the 1029 fetuses, and the dominating were CNS anomalies (22.8%, 420/1845), CHDs (17.3%, 320/1845) and urinary system anomalies (14.6%, 270/1845) (Table 13). In fetuses with multiple organ anomalies, the lethal anomaly or the anomaly considered the most serious was chosen as the "primary diagnosis", while the others were classified as "secondary diagnoses".

Table 13. Distribution of congenital anomalies in 1029 TOPs

Diagnoses	**Primary diagnoses**		**Secondary diagnoses**		**Total diagnoses**	
	n	%	n	%	n	%
Chromosomal anomalies with normal morphology	34	3.3	-	-	34	1.9
Central nervous system anomalies	354	34.4	66	8.1	420	**22.8**
Cardiovascular system anomalies	187	18.2	133	16.3	320	**17.3**
Respiratory system anomalies	6	0.6	35	4.3	41	2.2
Diaphragmatic/abdominal wall defects	55	5.3	52	6.4	107	5.8
Gastrointestinal system anomalies	7	0.7	102	12.5	109	5.9
ARS/LBWC	33	3.2	1	-	34	1.9
Urinary system anomalies	135	13.1	135	16.5	270	**14.6**
Genital system anomalies	-	-	29	3.6	29	1.6
Skeletal anomalies *	11	1.1	146	17.9	157	8.5
Skeletal dysplasia **	67	6.5	-	-	67	3.6
Arthrogryposis, including LMPS	32	3.1	-	-	32	1.7
Facial defects	5	0.5	66	8.1	71	3.9
Fetal hydrops, cystic hygroma	97	9.4	51	6.3	148	8.0
Conjoined twins	6	0.6	-	-	6	0.3
Total	**1029**	**100**	**816**	**100**	**1845**	**100**

ARS, Amnion-rupture-sequence; LBWC, Limb-body-wall-complex; LMPS, multiple lethal pterygium syndrom

* Skeletal anomalies include vertebral anomalies, clubfeet, polydactyly, syndactyly, etc.

** Skeletal dysplasia include osteochondrodysplasias such as thanatophoric dysplasia, etc.

In the total population of 1029 fetuses, the karyotype was normal in 59.5% and unknown in 10.1%. Thirty percent (313/1029) of all cases had an abnormal karyotype, in which trisomy 18 (8.7%, 90/1029) and trisomy 21 (8.3%, 85/1029) were most common. 34/1029 cases with normal morphology were terminated due to chromosomal anomalies.

The mean maternal age was 29.2 years (range: 16-45). The median gestational age was week 19+0 (range: 11+0 to 33+6). A gradual reduction in the relatively late (weeks 22+0 to 33+6) diagnosis of anomalies was paralleled with a similar increase in early (weeks 11+0 to 15+6) detection of anomalies (Figure 5). 13.7 % (141/1029) of the fetuses were terminated between weeks 11+0 to 15+6 (early TOP), 79.0% (813/1029) between weeks 16+0 to 21+6 (intermediate TOP) and 7.3% (75/1029) between weeks 22+0 to 33+6 (late TOP).

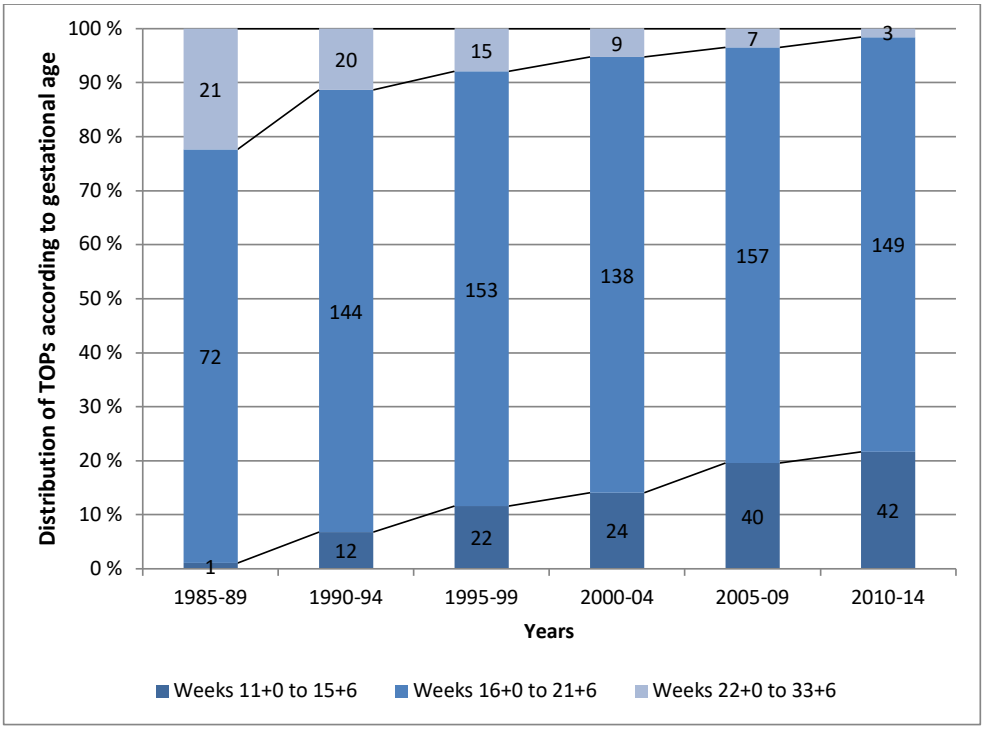

Figure 5. The rate of terminations in weeks 11+0 to 15+6 (early TOP), weeks 16+0 to 21+6 (intermediate TOP) and weeks 22+0 to 33+6 (late TOP) over five-year intervals between 1985 and 2014 for 1029 fetuses. The numbers in each column represents the number of TOPs.

Correlation between prenatal US and postmortem findings

Sensitivity (Category 1-4):

Seen over the 30-year period, there was full agreement (Category 1) between US and autopsy findings in 88.1% (907/1029), and the main diagnosis (Category 1+2) was correct in 97.8% (1007/1029) (Table 14). Minor and major autopsy findings not detected at US scan (category 2 and 3), constituted 9.7% (100/1029) and 0.9% (9/1029) respectively. There were no cases in category 4. The discrepant findings in the 9 cases in category 3, involved particularly CNS anomalies (occipital myelocele), CHDs (VSD) and urinary system anomalies (renal agenesis).

Moreover, table 14 also shows the correlation in the three different groups by gestational age. There were non-significant differences in the correlation rates for full agreement (p=0.43) and main diagnosis (p=0.66) between first (weeks 11+0 to 15+6) and second gestational age group (weeks 16+0 to 21+6).

Table 14. Correlation at different gestational ages

	Detection rate at different gestational ages							
	Week 11+0 to 15+6		**Week 16+0 to 21+6**		**Week 22+0 to 33+6**		**Week 11+0 to 33+6**	
Correlation	n	%	n	%	n	%	**n**	**%**
Category 1	122	86.5	722	88.8	63	84.0	**907**	**88.1**
Category 2	17	12.1	75	9.2	8	10.7	**100**	**9.7**
Category 1 + 2	139	98.6	797	98.0	71	94.7	**1007**	**97.8**
Category 3	1	0.7	5	0.6	3	4.0	**9**	**0.9**
Category 4	0	0	0	0	0	0	**0**	**0**
Category 5	1	0.7	11	1.4	1	1.3	**13**	**1.3**
Total	**141**	**100**	**813**	**100**	**75**	**100**	**1029**	**100**

Specificity (Category 5):

In 1.3% (13/1029) of the pregnancies, US findings other than those leading to termination, were not confirmed at autopsy (Category 5) (Table 14). In 3 of 13 cases, US findings were not possible to confirm at autopsy due to maceration/traumatization of the fetus. However, in all 13 cases, the unconfirmed findings did not affect the

decision to terminate the pregnancy since there were other serious findings present. The discrepant findings included DWM and hydrocephaly in the CNS, CHDs such as AVSD, double outlet right ventricle (DORV) and overriding aorta, and cystic dysplastic kidneys in the urinary system. See Table 7 (S2) in paper I for details.

Figure 6 illustrates the distribution in each correlation category over time. When comparing the second 15-year period (2000-14) with the previous period (1985-99), there were significant differences in the correlation rate for full agreement (p=0.003) and main diagnosis (p=0.008).

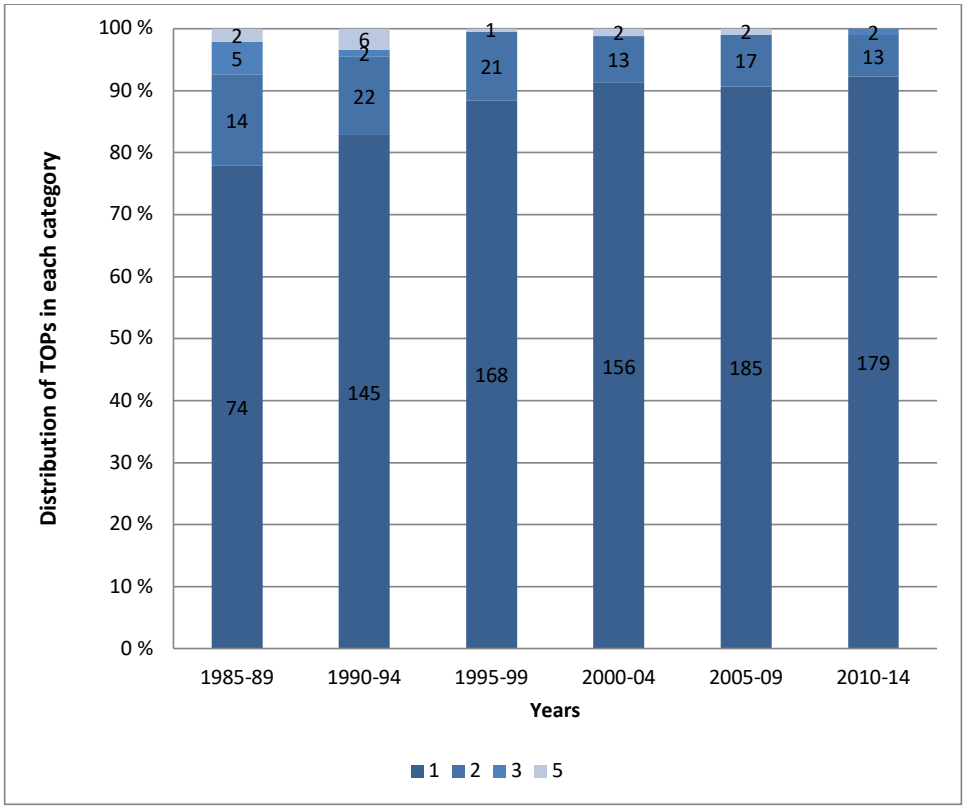

Figure 6. The distribution of TOPs in each correlation category (1,2,3,5) among 1029 terminated fetuses over five-year intervals between 1985 and 2014. The numbers in each column represent the number of TOPs in each category.

4.2 Paper II

Struksnæs C, Blaas H-G. K., Vogt C. Autopsy findings of central nervous system (CNS) anomalies in intact fetuses following termination of pregnancy (TOP) after prenatal ultrasound diagnosis. *Pediatr Dev Pathol* 2019; 22: 546-57.

CNS anomalies were found in 420 of 1029 terminated fetuses, and of these about half were terminated due to isolated serious CNS anomalies, while the rest were CNS anomalies associated with other structural and/or chromosomal anomalies (Figure 7). In fetuses with abnormal karyotype, 91% (80/88) had other organ system anomalies. Trisomy 18 was the most common abnormal karyotype (9%, 38/420). Among the 420 fetuses, 12 % (50/420) were terminated before week 16+0, 80% (338/420) between week 16+0 to 21+6 and 8% (32/420) between week 22+0 to 33+6.

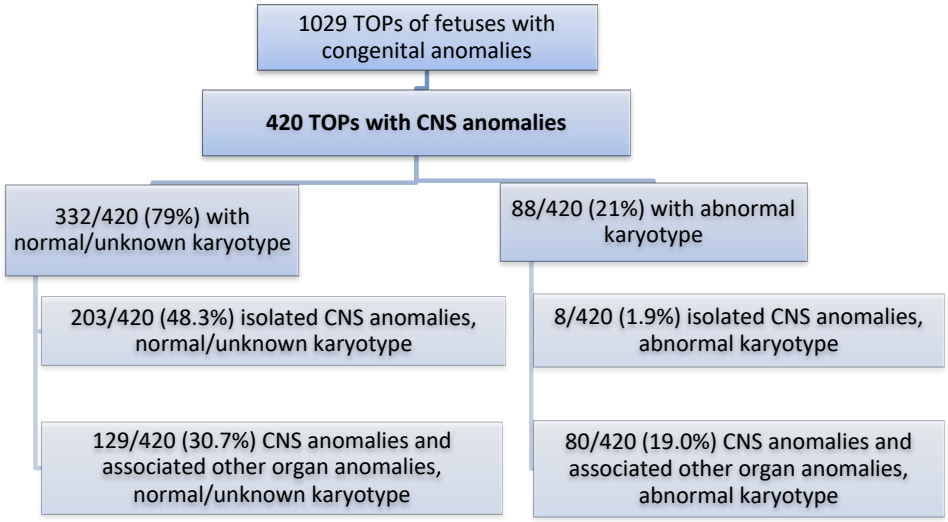

Figure 7. Distribution of karyotype and associated organ anomalies in autopsies of 420 fetuses aborted because of CNS anomalies

Among the 420 fetuses, there were 477 single CNS diagnoses, in which 92.2 % (440/477) diagnoses were detected in fetuses terminated before week 22+0, and 11.9% (57/477) were detected during the first trimester. NTDs such as anencephaly (22.4%, 107/477) and spina bifida (22.2%, 106/477) constituted the most common CNS

anomalies (Table 15). Most cases with anencephaly, encephalocele, microcephaly, congenital hydrocephalus or spina bifida had a normal karyotype. CHDs, skeletal anomalies and urinary anomalies were the most common associated organ anomalies.

Table 15. CNS anomalies categorized according to ICD-10

	Subgroup	Week 11+0 to 33+6		
		n	N	%
Q00 Anencephaly and similar malformations	Anencephaly (incl. acrania)	107	**107**	**22.4**
	With cervical rachischisis	21		
	With craniorachischisis	18		
Q01 Encephalocele	(Meningo-)encephalocele		**34**	**7.1**
Q02 Microcephaly	Microcephaly		**17**	**3.6**
Q03 Congenital hydrocephalus	Malformations of Sylvian aqueduct	25	**85**	**17.8**
	Other (incl. unspecified)	48		
	Dandy-Walker malformation	12		
Q04 Other congenital malformations of brain	Agenesis of corpus callosum		**16**	**3.4**
	Holoprosencephaly	46	**46**	**9.6**
	Alobar	26		
	Semilobar	5		
	Lobar	15		
	Other reduction anomalies	40	**40**	**8.4**
	incl. cerebellar hypoplasia	21		
	Cerebral cysts	20	**20**	**4.2**
	incl. choroid plexus cysts	16		
Q05 Spina bifida	Cervical and/or thoracic	9	**106**	**22.2**
	With A-C malformation type II	5		
	Lumbar and/or sacral	97		
	With A-C malformation type II	82		
Other	Miscellaneous *		**6**	**1.3**
Total			**477**	**100**

A-C, Arnold Chiari

* Miscellaneous: Microphthalmos (1 case), Krabbe disease (1 case), Fraser syndrome (1 case), Apert syndrome (2 cases), ependymoblastoma (1 case)

Throughout the study period, there was full agreement (category 1) between US and postmortem findings of CNS anomalies in 96.9% (407/420) of TOPs. There were nine cases in category 2, one case in category 3 and no cases in category 4. Concerning the three fetuses in category 5, two cases of DWM and one with hydrocephalus were not confirmed as the brains were macerated/autolytic. However, other serious findings justified TOP. See Table 6 in paper II for details.

4.3 Paper III

Struksnæs C, Blaas H-G. K., Eik-Nes S.H., Tegnander E., Vogt C. Postmortem assessment of isolated congenital heart defects remains essential following termination of *pregnancy. Pediatr Dev Pathol,* 2021 May 17; DOI: 10.1177/10935266211016184. Online ahead of print.

In the total material of 1029 terminated pregnancies, CHDs were found in 320 fetuses, and of these, 67 fetuses with isolated CHDs, including CHDs associated with heterotaxy syndrome, were evaluated in detail in paper III (Figure 8). Among the 67 fetuses, the mean gestational age at termination was 19+0 weeks (range: 12+0 to 22+6), and 11 (16%) of the pregnancies were terminated between weeks 12+0 and 16+6. The dominating main diagnosis was HLHS, found in 22/67 (32.8%) of the fetuses.

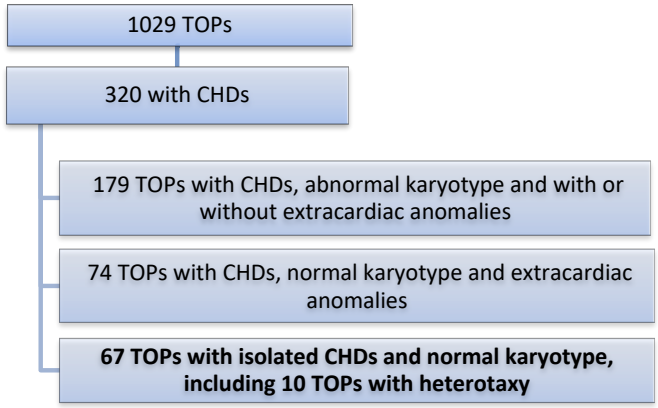

Figure 8. Flowchart of total material of TOPs with CHDs, distributed into groups according to isolated CHDs, associated anomalies and/or karyotype

To facilitate a detailed comparison of prenatally detected anomalies of the heart with autopsy findings, each single anomaly (e.g. VSD) and all subdiagnoses involved in a main diagnosis or syndrome (e.g. HLHS), were subcategorized and registered separately, all categorized according to ICD-10. There were in total 228 single CHDs among the 67 fetuses, in which anomalies of the cardiac chambers and connections (Q20) comprised the largest category (39.9%, 91/228), including TGA and DORV. The

second largest category was anomalies of the aortic and mitral valves (Q23) (20.6%, 47/228), followed by anomalies of the cardiac septa (Q21) (14.9%, 34/228). For details, see table 3 in paper III.

All 10 fetuses with heterotaxy syndrome had serious or lethal CHDs. In the fetuses with left atrial isomerism (LAI), AVSD and TGA were common, while both fetuses with right atrial isomerism (RAI) had hypoplastic left ventricle and DORV. Overall, five fetuses (50%) with heterotaxy syndrome had hypoplastic left or right ventricle.

Throughout the study period, there was full agreement between US and autopsy findings (category 1) in 222 of 228 single CHDs (97.4%). The discrepant findings were in three terminated fetuses (Table 16).

Table 16. Cases with disagreement between US and postmortem findings of single CHDs

Case	GA	Ultrasound diagnosis	Final diagnosis after autopsy	Disagreement
1	18	Tricuspid atresia, hypoplastic RV, suspected truncus arteriosus	HRHS with tricuspid atresia, hypoplastic RV, complete TGA, VSD and LVOTO	VSD not seen at US (category 2). Suspected truncus arteriosus at US was diagnosed as complete TGA (category 3), VSD and LVOTO at autopsy (category 3)
2	17	HLHS with mitral atresia, VSD, DORV, hypoplastic aorta with preductal coarctation	HLHS with mitral atresia, VSD, hypoplastic aorta with preductal coarctation	DORV not verified at autopsy (category 5, false positive)
3	21	TOF with VSD, overriding aorta and pulmonary artery smaller than aorta. Suspected DORV variant	DORV, aortic stenosis, VSD, interrupted aortic arch, left subclavian artery rising from pulmonary artery	Aortic stenosis, interrupted aortic arch, left subclavian artery rising from pulmonary artery were not seen at US (category 3). Overriding aorta and pulmonary artery smaller than aorta were not confirmed (category 5, false positive)

GA, gestational age; RV, right ventricle; HRHS, hypoplastic right heart syndrome; TGA, transposition of the great arteries; VSD, ventricular septal defect; LVOTO, left ventricle outflow tract obstruction; US, ultrasound; HLHS, hypoplastic left heart syndrome; DORV, double outlet right ventricle; TOF, Tetralogy of Fallot

5. Discussion

Since the introduction of US examination during pregnancy, routine US has become an important tool to assess fetal anatomy, including congenital anomalies. There are some differences in the local guidelines for prenatal US between countries, but most industrialized countries have at least one mid- trimester US examination as part of the standard prenatal care (4). A postmortem examination of aborted fetuses was implemented as quality control of the work performed by ultrasonographers, and many studies have evaluated the correlation between US and autopsy findings, but the inclusion and evaluation criteria differ. To our knowledge, there are few studies focusing on congenital anomalies solely in a population of TOP (23).

5.1. Main findings and clinical considerations

Correlation between US and postmortem findings

Sensitivity (Category 1-4):

In the first paper, in a population of 1029 fetuses terminated due to serious/lethal structural and/or chromosomal anomalies, there was full agreement between US and autopsy findings in 88.1%, and the main diagnosis was correct in 97.8%.

A review of 10 studies on TOP between 2006 and 2015 compares a complete sonographic anatomic survey with autopsy findings (Table 17). In category 1, there is a range between 44.0-88.1% (mean 58.2, 95% CI: 46.6, 69.8). The studies previous to our study are relatively small (range: 52-378 TOPs). Based on the evaluation of full agreement cases (category 1) and additional findings by autopsy (categories 2 and 3), it seems that the higher proportion of full agreement in the present study and Rodriguez' study might be due to a better detection of minor anomalies, e.g. small VSD, horseshoe kidney, clubfoot and polydactyly (34).

Specificity (Category 5):

The risk of false-positive diagnoses with congenital anomalies is a major concern in prenatal diagnostics, in particular when TOP might be an option. In 1.3% of the total material, US findings were not confirmed at autopsy. We found a range between 0-17.0% (mean 8.9, 95% CI: 5.4,12.4) in category 5 among studies on TOP during the last decade (Table 17). We have distinguished between whether the unconfirmed findings at autopsy implied wrong management of the pregnancy. In 10/13 cases in our study, other major findings were confirmed at autopsy, whereas in 3/13 cases, confirmation of the prenatal diagnosis was difficult due to fetal maceration. However, in all 13 cases, confirmation of other serious findings indicated that the pregnancy was not mismanaged.

Table 17. Studies on TOP comparing US examination and autopsy findings

Study	Year	TOP (n)	Full agreement Category 1 (%)	Additional findings by autopsy Category 2-3 (%)	Disagreement Category 5 (%)	Gestational age (weeks)
Struksnæs et al.	2016	1029	88.1	10.6	1.3 (1.0*, 0.3†)	11-33
Rodriguez et al.	2014	151	86.0	4.6	9.1 (1.9*, 7.2†)	11-24
Vimercati et al.	2012	144	49.0	34.0	17 (13.0*, 4.0†)	12-24
Hauerberg et al.	2012	52	46.0	44.0	9.6 (7.7*, 1.9†)	12-25
Lomax et al.	2012	71	44.0	46.0	10 (8.6*, 1.4†)	16-22
Antonsson et al.	2008	112	44.6	40.2	15.2 (11.6*, 3.6†)	Second trimester
Akgun et al.	2007	107	51.0	42.0	0	13-28
Kaasen et al.	2006	274	58.4	31.4	9.9*	12-24
Amini et al.	2006	328	53.4	37.8	8.8 (7.0*, 1.8†)	11-24
Ramalho et al.	2006	76	61.1	33.6	5.3†	7-35

* Proportion of TOPs with US findings that were not confirmed by autopsy. These findings came in addition to other findings that were confirmed by autopsy, and they did not affect the clinical indication for terminating the pregnancy.

† Proportion of TOPs where the clinical indication for terminating the pregnancy, based on specific US findings, could not be supported by the autopsy findings. The disagreements between prenatal US and autopsy findings were often due to the presence of prenatally oligo/anhydramnion and/or postmortem fetal maceration/autolysis.

CNS anomalies

In the second paper, we focused on the most common group of congenital anomalies, CNS anomalies, and we studied this group from a pathological perspective. There are few studies describing CNS anomalies in perinatal autopsy populations (23,50,105,116,117,157,158). About half the population of 420 fetuses with CNS anomalies were associated with other structural and/or chromosomal anomalies. We found full agreement between US and postmortem findings in 96.9% of 420 terminated fetuses.

NTDs were the most common CNS anomalies in our study, in accordance with the literature (50,159-161). Almost 20% (21/107) of cases with anencephaly had associated cervical rachischisis, and in two of these cases the rachischisis was not described in the US report. Anencephaly occurring together with rachischisis totalis (craniorachischisis) is a rare condition (162). In our study, there were 18 cases with craniorachischisis, in which 4 cases had trisomy 18 and omphalocele (Figure 9).

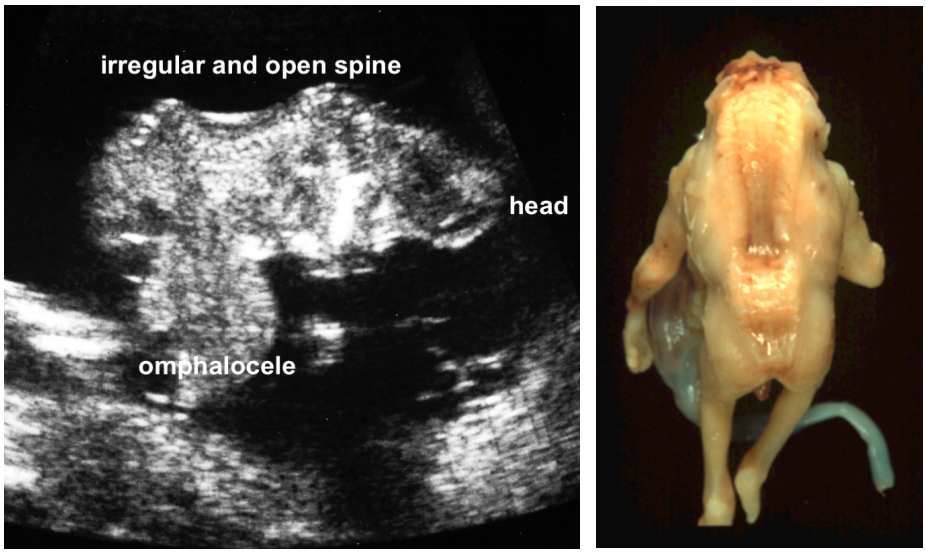

Figure 9. US image and postmortem photography of 14 week old fetus with craniorachischisis, 1996. The US image shows a sagittal section through the body with irregular and open spine, abnormal head pole and a large body wall defect – omphalocele.
US image by Harm-Gerd Karl Blaas and photo by Christina Vogt.

It is important to have insight in normal neurodevelopment in order to be able to properly detect CNS anomalies prenatally and at autopsy (115, 163).

NTDs were among the first to be reported diagnosed during first trimester with 80-90% detection rates (113) with later improvement to 100% and 84% for anencephaly and spina bifida, respectively (114). In our study, more than 20% (24/107) of all cases with anencephaly were detected during the first trimester and the overall correlation rate was good with full agreement between US and autopsy findings in 95.8% (23/24). In one terminated pregnancy at GA 11, with acrania and limb- body-wall complex at autopsy, acrania was not detected at US.

The corpus callosum and the cerebellum are not sufficiently developed to allow complete assessment in the first trimester US (115). In our study, there were more late terminations of fetuses with hydrocephalus (15.3%, 13/85) and corpus callosum agenesis (18.8%, 3/16) compared to NTDs (5.6%, 6/107). Moreover, prenatal diagnosis of DWM can also be challenging, especially in mild cases in contrast to the syndromic form of DWM with associated anomalies of the heart, face, limbs or gastrointestinal system (164). At autopsy, maceration and autolysis of the brain can make postmortem verification of DWM difficult.

Holoprosencephaly can be diagnosed early in pregnancy and the alobar type can be detected as early as the end of week 7 (28). Almost half of the cases with holoprosencephaly in the study were associated with trisomy 13, which is in accordance with the literature (165,166) and is a strong indicator for performing karyotyping/genetic examinations. In our study, in one case with microcephaly and holoprosencephaly, the microcephaly was not described at US and the lobar holoprosencephaly at autopsy was misclassified as semilobar at US.

Congenital heart defects (CHDs)

In the third paper, we focused on all fetuses terminated due to findings of serious/lethal isolated CHDs, including CHDs associated with heterotaxy syndrome. We are not aware of other studies looking into this perspective. Previous studies addressing the correlation between US and autopsy findings of CHDs have also addressed other organ groups (5,8,12,13,18,23), or included all cases with cardiac pathology, irrespective of the reason for TOP or main cause of death (167-169).

In cases with isolated CHDs, high agreement is especially important as there are no other associated organ anomalies that would justify TOP. If the cardiac diagnosis is a false positive finding when other serious or lethal extracardiac anomalies are present, the false positive diagnosis will not determine the management of the pregnancy in the same way as if the termination is performed based on a false positive isolated major CHD only. Despite the false positive diagnosis of single CHDs in two cases (category 5) in our study, both had other serious single CHDs confirmed at autopsy, thus management was not affected by the false positive single CHDs. The false positives illustrate the complexity of isolated CHDs.

To validate the quality of the US examinations, we chose to divide each major CHD into subdiagnoses as these constitute the main diagnosis and may also be important for the prognosis. Anomalies of the aortic and mitral valves (Q23) together with anomalies of cardiac chambers and connections (Q20) comprised 60% of all single CHDs. Cardiac septal defects (Q21) are traditionally the most common CHDs, but they constituted only 14.9% in our study. In the total population of 320 TOPS with CHDs, most septal defects were found in cases with abnormal karyotype and with or without extracardiac anomalies, illustrated in the flow chart (Figure 8). This finding correlates with the literature as most cardiac septal defects are related to abnormal karyotype (53).

HLHS was the most common main diagnosis among all pregnancies (32.8%, 22/67 fetuses). Previous studies have reported termination of pregnancy in 60-80% of cases

in which HLHS was detected prenatally (170,171). Developments in maternal-fetal surgery and pediatric cardiac surgery during the last three decades have permitted treatment of HLHS and other CHDs (133). However, mortality remains high, with a five-year survival rate of 65-70% even after surgical repair (172-175). In antenatally diagnosed cases, a detailed parental counselling is of great importance, with a discussion of options of termination or continuation of pregnancy, including the choice of cardiac surgery (76,144,176).

Heterotaxy syndrome was a another common finding, and all cardiac defects in these 10 cases were major anomalies. Fetuses with isolated serious/lethal CHDs combined with heterotaxy syndrome were included, as none of these had extracardiac anomalies except for the abnormal arrangement of internal organs; this anomaly did not influence the decision for TOP. The choice leading to termination of pregnancy was based on findings of serious/lethal CHDs while the abnormal arrangement of organs was of subordinate importance. However, when heterotaxy is suspected during prenatal examination, further search for other anomalies, including CHDs, is necessary. The prognosis of patients with heterotaxy varies, as they represent a heterogeneous group and surgical intervention is therefore often complex, but is recommended as the survival rate has improved versus those who were left untreated (177-179).

The broad range of CHDs and the complexity of cardiac anatomy are challenging for the prenatal detection of CHDs (180). Meticulous assessment of cardiac anatomy is particularly necessary when the decision to terminate relies solely on the correct diagnosis of the CHD. The trend of earlier termination also challenges the verification of diagnoses at autopsy. Consequently, the fetus should be examined at a tertiary medical center with fetal medicine specialists in close collaboration with a pediatric cardiologist and a perinatal pathologist. In this study, the discrepant findings were found in three of 67 fetuses. A pediatric cardiologist was involved in the evaluation of two of these three cases, illustrating the difficulties encountered in prenatal detection of CHDs.

5.2. Methodological considerations

There are several factors that might explain the discrepancy between studies in evaluating the correlation between US and autopsy findings, i.e. the prevalence of anomalies, characteristics of the population, the study design and the setting of the US and the postmortem examination (75). Previous studies have varied in their inclusion criteria as to whether or not including spontaneous abortion and intrauterine fetal death (IUFD) in addition to TOP specimens, and first and third trimester in addition to second trimester. These factors may partly explain the range of results in correlation. In this study, we chose to only include terminations of pregnancies from all gestational ages. Moreover, a strength of this study is the relatively long timespan (1985-2014, 30 years), which allowed us to collect a large material (n=1029) compared to other studies.

Bias and confounding factors is always of concern in research, and this will be discussed in the following pages:

- *Selection bias* occurs when individuals have different probabilities of being included in the study sample according to relevant study characteristics (181). In our study, we included all fetuses terminated throughout 30 years due to serious/lethal structural and/or chromosomal anomalies, both from the local area and referred pregnant women from the rest of the country. However, as not all pregnant Norwegian women are evaluated at NCFM it is difficult to draw epidemiological conclusions from our study.
- *Information bias* occurs when any information used in a study is either measured or recorded inaccurately (Example: Incomplete autopsy records) (182).
- *Confounding* occurs when a non-causal association between a given exposure and an outcome is observed as a result of the influence of the third variable, a confounder (Example: When the finding of a CNS anomaly at autopsy is influenced by tissue maceration) (183).

Ultrasound examination

The ultrasonographer and the US protocol

When several ultrasonographers are involved, both intra- and interobserver variation may affect the final result. To reduce information bias, high skills and experience of the ultrasonographer is of great importance. Several studies state that US examinations performed at tertiary centers turn out to be more accurate than exams performed in non-specialized departments (6,7,11,13,88,133). In our study, a small group of fetal medicine experts was responsible for most of the US exams at the center throughout the 30 years. Moreover, in most cases with pathological ultrasonograhic findings they consulted other collagues, for example pediatric cardiologists in cases with CHDs.

The grade of detail in the US screening protocol and the distinction between category 2 and category 3 (minor and major anomalies), may further explain the differences in correlation results between studies. At NCFM, the policy has been to search for all anomalies present, also in cases where a dominant serious finding leads to the decision to terminate a pregnancy. Even though minor anomalies do not change the management of the pregnancy, detecting these minor findings is important as they may provide the basis for a correct diagnosis. This is particularly important when TOP is based solely on isolated congenital anomalies as these minor findings may indicate the presence of a more serious anomaly.

US equipment:

The equipment type and modalities during US scan are factors that especially influence the detection rate. The sensitivity for detecting CHDs has especially been increasing due to assessment of outflow tracts in addition to a basic four chamber cardiac view during US exam (11,33,51,90,130,138,184). Moreover, the development of colour Doppler flow has also contributed significantly to the understanding of fetal circulation. During the 30-year study period, the technology of the US equipment has evolved considerably, making it possible to study the anatomy of the fetus in more detail, and to detect anomalies at an earlier gestational age.

Fetal and maternal factors:

Possible factors influencing the quality of the sonographic image are fetal position, maternal body mass index (BMI) and amount of amniotic fluid (185,186). Renal anomalies often cause difficulties because of oligohydramnios, and the frequency of poly- or an/oligohydramnios is higher in pregnancies with discrepancies between US and autopsy findings (12,146). Further, renal agenesis may be confused with the adrenals lying along the posterior abdominal wall and mimicking kidneys (52).

Postmortem examination

The pathologist and the autopsy protocol:

The autopsy is also dependent on the skills and knowledge of the pathologist, and both intra- and interobserver variation may affect the final autopsy results. Therefore, following a standard protocol is essential when investigating organ anomalies. During the 30-year study period, several pathologists performed the autopsies, but a consultant pathologist with experience in perinatal pathology was involved in most cases. From 1990, a standardized autopsy protocol was followed. The fact that US reports were available to the pathologist at the postmortem examination could introduce a bias in the evaluation of autopsy findings, though available US reports at autopsy probably reduce the possibility of missing subtle diagnoses at autopsy and therefore making the final diagnosis more complete.

Maceration/traumatization:

Maceration and traumatization are confounders because they may hinder the accuracy of the autopsy and the confirmation of US findings. Among the 1029 fetuses, some were macerated and traumatized. For instance, fetal hydrops and cystic hygroma at US are not always possible to confirm at autopsy due to desiccation. However, a factor that may contribute to the high correlation rate in our study, is that most fetuses were intact at autopsy after medical abortion and were not macerated or traumatized prior to verification at autopsy.

Concerning CNS anomalies, in addition to choroid plexus cysts, ventriculomegaly and small posterior fossa abnormalities can collapse during autopsy and therefore be difficult to verify (59,164). Moreover, all 16 fetuses with choroid plexus cysts had other organ system anomalies leading to TOP, and 75% (12/16) were associated with an abnormal karyotype. In our department the brain was removed under water in order to minimize trauma and then fixed in a zinc-formalin solution to make it firmer. Alternatively, it can be submerged in absolute alcohol for 24 hours before slicing. Maceration is usually not a problem in induced abortions, though some cases arrive at the pathology department several days after delivery which may influence verification at postmortem examination.

Gestational age

Gestational age is another confounding factor that influences the detection rate at US scan and the quality of the postmortem examination. The detection rates of most anomalies have traditionally been lower in the first trimester compared to the second trimester, especially for CHDs. However, the detection of anomalies at an earlier gestational age has evolved rapidly, especially because of the routine application of genetic screening, advances in technology and more fetomaternal specialists (60).

In the first paper, there were not significant differences in correlation rate for full agreement between early and intermediate TOPs, and the results from first trimester scan might therefore be considered reliable. However, as organs are not fully developed, early detection of anomalies should often be verified by another scan 2-3 weeks later. This is especially important in fetuses terminated due to isolated congenital anomalies (i.e. CHDs) without associated structural and/or chromosomal anomalies.

5.3. Clinical implications

Falling autopsy rates

Fetal autopsy has been regarded as quality control in diagnosing and verifying congenital anomalies detected at US (5,19,23,85,90). It is not mandatory in Norway, but the involved parents are informed about the value of autopsy and the importance of quality control and verifying congenital anomalies detected at US prior to termination of pregnancy. Even though studies have shown that autopsy helps to establish the cause of death and can provide additional clinically significant information, autopsy rates are falling in the western world (98,116,117,187). According to Boyd et al. (2004) the percentage of fetuses that underwent autopsy fell from 84% to 67% throughout the 90s (15). We found in our study an average autopsy rate of 88.8% during the 30-year period, in which 1029 of 1157 fetuses with congenital anomalies were examined postmortem after termination of pregnancy.

However, there are several alternatives to traditional invasive postmortem examination of congenital anomalies, from less-invasive methods to a variety of imaging modalities, that may alleviate this falling trend (188,189). Postmortem MRI has especially shown promising results, especially in CNS anomalies (103,189-192). Micro-focus CT imaging with virtual dissection of the fetal heart may become a good alternative to conventional autopsy (193) and postmortem US may in general also be an alternative to invasive autopsy (194).

Earlier diagnosis of congenital anomalies

The move towards the use of US in the first trimester in Norway during the last decade has led to detection of congenital anomalies at earlier gestational age. Early diagnosis of anomalies has several advantages. When the management of pregnancy leads to TOP, an earlier TOP has fewer medical and surgical complications, and also fewer costs and emotional barriers (195-198).

On the other hand, earlier diagnoses of congenital anomalies followed by TOPs at earlier gestational ages represent challenges for the perinatal pathologist, especially when there are few but serious pathological findings (ex. isolated CHDs). Moreover, very early TOPs may lead to traumatic destruction of the conceptus making verification impossible. Therefore, in our material the final sonographic diagnosis and TOP was delayed to approximately 12 to 13 weeks GA. In smaller fetuses, postmortem imaging methods may be of particular help in the verification process. A dissecting microscope or magnifying lenses are often necessary to discern features not visible to the naked eye, for example in cases with a small VSD. Photography is especially useful when examining small fetuses and in documenting organ anomalies, and when possible, genetic testing may verify certain syndromes (199).

When the pregnancy is not terminated, an accurate early prenatal diagnosis of congenital anomalies is also important for defining the prognosis and may help plan peripartum management. In fetuses with congenital anomalies that can be treated, thorough information to the parents regarding treatment options and possible outcomes after treatment is important. During the last two decades, advances in prenatal US, fetal surgery and pediatric surgery have improved the outcomes in fetuses with anomalies, and potential indications for fetal surgery include congenital diaphragmatic hernia, myelomeningocele and urinary obstruction (147). However, there is considerable morbidity and mortality related to fetal surgery and complex pediatric surgery, and this should be included in the counselling on parental decisions regarding continuation or termination of pregnancy.

5.4. Ethical considerations

The most basic wish of parents is the birth of a healthy child. For many parents the life of their child begins when they see the fetus on the screen during prenatal US examination. The finding of a lethal anomaly or serious handicap makes a profound impact, and the choice to terminate a pregnancy is one of the most difficult decisions for parents to make.

The verification of anomalies by doing a postmortem examination is evident, stressing the importance of having a scientific approach to quality control. As the autopsy rate has decreased and parents become more reluctant to have their fetuses autopsied, being able to demonstrate the value and utility of performing autopsies, or eventual other methods of postmortem examination, might help them to realize the importance this has for their own understanding of the fatality they experienced. Finding the correct diagnosis through a combination of prenatal examination and a conscientious autopsy may also provide them with additional knowledge of recurrence in a future pregnancy. Moreover, such verification is essential for clinicians in order to provide proper counselling.

Even though our study demonstrates a high degree of correct prenatal assessment, we cannot ignore the serious consequences of a misdiagnosis, especially when the decision to terminate a pregnancy is based on abnormalities in one organ only. It is important to inform the parents of the option of autopsy given the benefit reassurance might represent for the couple. However, an autopsy is not always an option or wish. Then it is reassuring to be aware of the high expertise of the fetal medical examiner.

6. Conclusions and future aspects

Examination for congenital anomalies during prenatal US examination is considered an important part of prenatal care. Postmortem examination of aborted fetuses was implemented as a quality control of the work performed by ultrasonographers. Since the introduction of routine US in the 80s, studies have shown differences in the correlation between US detected fetal anomalies and autopsy findings, which may be due to different inclusion and evaluation criteria. To our knowledge, there are few studies focusing on congenital anomalies solely in a population of TOP. In this study, we have validated congenital anomalies in 1029 TOPs and evaluated the correlation rate between prenatal US diagnosis and autopsy at different gestational ages throughout a 30-year period between 1985-2014.

In the population of 1029 fetuses terminated due to serious/lethal structural and/or chromosomal anomalies, there was full agreement between US and autopsy findings in 88.1%, and the main diagnosis was correct in 97.8%. Overall, there has been a significant increase in prenatal sonographic detection of congenital anomalies, and none of the terminated pregnancies were based on an US finding which retrospectively turned out to be a false positive diagnosis. By performing medical abortions, the fetuses were usually intact at autopsy, which made the verification process possible.

The dominating congenital anomalies in our study were CNS anomalies, CHDs and urinary system anomalies. 30% of all 1029 fetuses had an abnormal karyotype. CNS anomalies were found in 420 fetuses, and of these about half were terminated due to isolated serious or lethal CNS anomalies, while the rest were CNS anomalies associated with other structural and/or chromosomal anomalies. CHDs were found in 320 fetuses, and of these, 67 fetuses were terminated due to isolated CHDs, including CHDs associated with heterotaxy syndrome. High agreement between US and postmortem findings was especially important in fetuses terminated due to isolated CHDs as there were no other associated organ anomalies that would justify TOP.

The increasing accuracy of ultrasonography has led to earlier diagnosis of anomalies, and there has been a shift towards earlier US scans, resulting in an increase in the number of early TOPs and a decrease in late TOPs during the 30 years. There were non-significant differences in correlation rate for full agreement between early and intermediate TOP, and the results from first trimester scan can therefore be considered reliable. However, as organs are not fully developed, early detection of anomalies should be verified by a later scan.

Throughout the 30 years of US diagnostics, the detection of congenital anomalies by US scan has continuously improved, also during the first trimester. These improvements may be explained by an increased expertise of ultrasonographers, a detailed US screening protocol and higher quality of US equipment. Even though the correlation is improving, we believe it is necessary to continue the validation practice, in particular due to the challenges of validating diagnoses made early in pregnancy. A detailed assessment of the anatomy, prenatally and at autopsy, is necessary to secure adequate medical practice, especially when the diagnosis and the decision to terminate a pregnancy relies on isolated organ anomalies. Consequently, the fetus should be examined at a tertiary medical center with fetal medicine specialists and other clinicians in collaboration with perinatal pathologists. For further increase in the detection- and verification rate of certain anomalies and in smaller fetuses, different imaging methods and genetic tests may be helpful.

Finally, a close collaboration between clinicians and perinatal pathologists should be regarded as beneficial for both disciplines and will stimulate the development of prenatal diagnostics and perinatal pathology. As the etiology of about 50% of congenital anomalies is unknown, further research on causal factors should be considered an important part of future research in prenatal diagnostics and perinatal pathology.

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8. Appendix

Paper I

Struksnæs C, Blaas H-G. K., Eik-Nes S.H., Vogt C. Correlation between prenatal ultrasound and postmortem findings in 1029 fetuses following termination of pregnancy. *Ultrasound Obstet Gynecol* 2016; 48: 232-238.

- Main document, including tables and figures
- Supplementary tables

Paper II

Struksnæs C, Blaas H-G. K., Vogt C. Autopsy findings of central nervous system (CNS) anomalies in intact fetuses following termination of pregnancy (TOP) after prenatal ultrasound diagnosis. *Pediatr Dev Pathol*, 2019; 22: 546-57.

- Main document, including tables and figures

Paper III

Struksnæs C, Blaas H-G. K., Eik-Nes S.H., Tegnander E., Vogt C. Postmortem assessment of isolated congenital heart defects remains essential following termination of pregnancy. *Pediatr Dev Pathol*, 2021 May 17; DOI: 10.1177/10935266211016184. Online ahead of print.

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Paper I

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Correlation between prenatal ultrasound and postmortem findings in 1029 fetuses following termination of pregnancy

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KEYWORDS: autopsy; congenital anomalies; termination of pregnancy; ultrasonography

ABSTRACT

Objective *A prenatal ultrasound examination and a postmortem examination provide the basis for correct diagnosis in fetuses terminated due to congenital anomalies. The aim of this study was to correlate fetal anomalies detected by ultrasound examination with those identified at autopsy following termination of pregnancy (TOP) over a 30-year period, and to evaluate the correlation between findings at different gestational ages and assess these trends over time.*

Methods *The study group consisted of 1029 TOPs performed over a 30-year period, from 1985 to 2014. The gestational age ranged between 11 and 33 weeks. Prenatal ultrasound examinations were performed at the National Center for Fetal Medicine, St Olavs Hospital, Trondheim, Norway. Autopsies were performed at the Department of Pathology and Medical Genetics at the same hospital or a collaborating hospital.*

Results *There was full agreement between ultrasound and autopsy findings in 88.1% (907/1029) of TOPs, and the main diagnosis was correct in 97.9% (1007/1029). When comparing the 15-year period of 2000–2014 with that of 1985–1999, the difference in the rates of full agreement and agreement in the main diagnosis was statistically significant. In 1.3% (13/1029) of cases, ultrasound findings were not confirmed at autopsy. There were no false-positive diagnoses leading to TOP. Throughout the 30-year period, there was an increase in early TOPs, whereas late TOPs declined.*

Conclusions *Our study demonstrates that there is a clear correlation between ultrasound and autopsy findings, which is continuously improving. Despite this high correlation, there is reason to continue the practice of validation to ensure the safety of the diagnostic process leading to TOP. The trend towards an earlier termination emphasizes the necessity of such a practice. Copyright © 2015 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

A prenatal ultrasound examination and a subsequent detailed postmortem examination provide the basis for a correct diagnosis in fetuses terminated due to congenital anomalies[1,2]. The risk of false-positive diagnoses of congenital anomalies is a major concern in prenatal diagnostics, in particular when termination of pregnancy (TOP) might be an option. The verification of ultrasound findings is important for the parents involved, the obstetrician, genetic counseling and epidemiological analysis[3–15].

The Norwegian routine second-trimester ultrasound examination at 17–18 weeks' gestation includes a survey of the fetal anatomy[16–18]. Detection rates of different congenital anomalies vary from 44% to 86%, depending on the type of anomaly[7,8,12,19–23]. Some structural anomalies of the conceptus can be detected sonographically from as early as during the embryonic period at 7–8 weeks' gestation, based on the last menstrual period. An ultrasound examination at the end of the first trimester, at 11–13 weeks, can detect numerous types of anomaly[24].

Throughout the years of ultrasound diagnostics, detection of anomalies by ultrasound has improved, primarily due to the increasing expertise of sonographers and the higher quality of the ultrasound equipment[25]. However, ultrasound diagnosis of congenital anomalies at earlier gestational ages and the presence of more subtle conditions challenge the verification of congenital anomalies and require other premortem and postmortem examination methods[26].

This study was a quality control on TOPs carried out as a consequence of sonographically diagnosed fetal

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anomalies. The aim was to correlate fetal anomalies detected by ultrasound with those identified at autopsy following TOP, throughout a 30-year period, and to evaluate the correlation at different gestational ages and assess the trends over time.

SUBJECTS AND METHODS

This study on prenatal ultrasound and postmortem findings in fetuses with congenital anomalies that were terminated after approval by an abortion committee was a collaboration between the National Center for Fetal Medicine (NCFM), which functions as a referral center for pregnant women from all over Norway, and the Department of Pathology and Medical Genetics at St Olavs Hospital, University Hospital of Trondheim. The study included routine cases seen at our center and cases referred from the rest of the country. Criteria for inclusion in the study were a prenatal ultrasound examination performed at the NCFM, diagnosis of an anomaly that led to TOP between 11 and 33 weeks' gestation and an autopsy performed at the Department of Pathology at St Olavs Hospital or a collaborating hospital. The study was approved by the Regional Ethics Committee.

A total of 1029 terminated fetuses fulfilled the inclusion criteria during the 30-year period from 1985 to 2014. Of these, 652 were part of the general autopsy population of 863 cases reported by Vogt *et al.*[2], which also included miscarriages, intrauterine fetal deaths and liveborn infants between 1985 and 2004.

According to Norwegian law from 1975, with later revisions, a fetus considered viable outside the mother's uterus cannot be terminated[27]. The limit for viability was assumed initially to be approximately 23 + 6 weeks until the 1990s, and was later gradually restricted. Since 2001, the upper limit for termination of a viable fetus has been 21 + 6 weeks. However, a fetus with a lethal condition may be terminated later in pregnancy.

All cases were registered prospectively over time in a database at the NCFM and were validated continuously. The database includes several variables such as maternal age, obstetric history and results of fetal invasive procedures. After autopsy, organ anomalies were registered and categorized. When multiple anomalies were present, the lethal anomaly or the anomaly considered as the most serious was chosen as the 'primary diagnosis', and the others were classified as 'secondary diagnoses'[2]. The final diagnosis at the last ultrasound examination and the autopsy findings were documented. In Norway, pregnancy length and expected day of delivery are determined at the 17–18-week routine scan by measurement of biparietal diameter and femur length. In early pregnancy, biparietal diameter or crown–rump length is used[28]. In cases in which the anomaly affected fetal size, gestational age was based on the best estimate of clinical data. TOP was performed as soon as possible, preferably on the day after the decision for termination was made. In cases in which anomalies were detected as early as 9–10 weeks' gestation, TOP was delayed by 2–3 weeks to enable a proper postmortem assessment.

Fetal medicine experts were responsible for most of the ultrasound examinations at NCFM. Between the years 1985–1990 and 2005–2014, doctors in training, supervised by a senior pathologist, performed the autopsies. Between the years 1991 and 2004, two consultant pathologists with experience in perinatal pathology were responsible for all the autopsies. From 1990, a standardized autopsy protocol was followed, which included full-body radiology and photographic documentation. All organs were examined, including *in-situ* examination of the heart and removal of the brain under water in order to minimize trauma. Ultrasound reports were available to the pathologist at the postmortem examination.

Correlations between ultrasound findings and autopsy were categorized, in accordance with a modification of the method described by Isaksen *et al.*[20]: (1) full agreement between ultrasound and autopsy findings; (2) minor autopsy findings not seen or recorded at ultrasound examination; (3) major autopsy findings not detected at ultrasound examination; (4) none of the autopsy findings suspected at ultrasound examination; and (5) ultrasound findings not confirmed or not possible to confirm at autopsy.

Statistical analysis

We used SPSS 21.0 (SPSS Inc., Chicago, IL, USA) for statistical analysis and correlation analyses were performed using independent samples *t*-test. $P < 0.05$ was considered statistically significant.

RESULTS

All 1029 fetuses underwent autopsy following TOP between 11 and 33 weeks' gestation. Mean maternal age was 29.2 (range, 16–45) years and median gestational age at TOP was 19.0 (range, 11–33) weeks. The gender differentiation was 51.4% (529/1029) of females and 48.4% (498/1029) of males. It was not possible to determine the gender in two cases.

Table 1 shows an overview of the congenital anomalies identified at autopsy among 1029 fetuses terminated between 11 and 33 weeks. The dominating primary diagnoses were central nervous system (CNS) anomalies (34.4%, 354/1029), followed by cardiovascular system anomalies (18.2%, 187/1029), urinary system anomalies (13.1%, 135/1029) and fetal hydrops/cystic hygroma (9.4%, 97/1029). In addition to the primary diagnosis that led to TOP, 46.1% (474/1029) of all fetuses had a secondary diagnosis. In this study, 3.3% (34/1029) of cases had normal morphology but were terminated due to chromosomal anomalies. Table 2 gives an overview of the karyotype of the terminated pregnancies. Karyotype was normal in 59.5% of cases and unknown in 10.1%. Thirty percent (313/1029) of all cases had an abnormal karyotype. Trisomy 18 (8.7%, 90/1029) was the most common abnormal karyotype, followed by trisomy 21 (8.3%, 85/1029).

Table 3 demonstrates the distribution of primary diagnoses according to gestational age at TOP; 13.7%

Table 1 Congenital anomalies diagnosed at autopsy in 1029 fetuses terminated between 11 and 33 weeks during 1985–2014

	Primary diagnosis			
Diagnosis	*Total (n = 1029)*	*Abnormal karyotype (n = 313)*	*Secondary diagnosis (n = 816)*	*Total (n = 1845)*
Chromosomal anomalies with normal morphology	34 (3.3)	34 (100)	0 (0)	34 (1.9)
Central nervous system anomaly	354 (34.4)	66 (18.6)	66 (8.1)	420 (22.8)
Cardiovascular system anomaly	187 (18.2)	95 (50.8)	133 (16.3)	320 (17.3)
Respiratory system anomaly	6 (0.6)	2 (33.3)	35 (4.3)	41 (2.2)
Diaphragmatic/abdominal wall defect	55 (5.3)	26 (47.3)	52 (6.4)	107 (5.8)
Gastrointestinal system anomaly	7 (0.7)	4 (57.1)	102 (12.5)	109 (5.9)
ARS/LBWC	33 (3.2)	0 (0)	1 (0.1)	34 (1.9)
Urinary system anomaly	135 (13.1)	9 (6.7)	135 (16.5)	270 (14.6)
Genital system anomaly	0 (0)	0 (0)	29 (3.6)	29 (1.6)
Skeletal anomaly*	11 (1.1)	3 (27.3)	146 (17.9)	157 (8.5)
Skeletal dysplasia†	67 (6.5)	4 (6.0)	0 (0)	67 (3.6)
Arthrogryposis including LMPS	32 (3.1)	2 (6.3)	0 (0)	32 (1.7)
Facial defect	5 (0.5)	2 (40.0)	66 (8.1)	71 (3.9)
Fetal hydrops, cystic hygroma	97 (9.4)	66 (68.0)	51 (6.3)	148 (8.0)
Conjoined twins	6 (0.6)	0 (0)	0 (0)	6 (0.3)

Data are given as *n* (%). *Skeletal anomaly includes malposition, isolated limb anomaly, vertebral anomaly, clubfeet, polydactyly, syndactyly. †Skeletal dysplasia includes osteochondrodysplasia such as thanatophoric dysplasia, achondrogenesis, osteogenesis imperfecta. ARS, amnion rupture sequence; LBWC, limb–body wall complex; LMPS, lethal multiple pterygium syndrome.

Table 2 Fetal karyotype among 1029 fetuses terminated between 11 and 33 weeks during 1985–2014

		Associated primary diagnosis			
Karyotype	*Total (n = 1029)*	*CNS anomaly (n = 354)*	*Cardiovascular anomaly (n = 187)*	*Urinary system anomaly (n = 135)*	*Fetal hydrops/ cystic hygroma (n = 97)*
Normal	612 (59.5)	256 (72.3)	82 (43.9)	98 (72.6)	22 (22.7)
Unknown*	104 (10.1)	32 (9.0)	10 (5.3)	28 (20.7)	9 (9.3)
Abnormal	313 (30.4)	66 (18.7)	95 (50.8)	9 (6.6)	66 (68.0)
Trisomy 13	36 (3.5)	18 (5.1)	12 (6.4)	0 (0)	1 (1.0)
Trisomy 18	90 (8.7)	23 (6.5)	37 (19.8)	1 (0.8)	4 (4.1)
Trisomy 21	85 (8.3)	4 (1.1)	33 (17.6)	2 (1.5)	20 (20.6)
Triploidy	13 (1.2)	8 (2.3)	1 (0.5)	1 (0.7)	1 (1.0)
Turner syndrome	39 (3.8)	1 (0.3)	0 (0)	0 (0)	37 (38.2)
Klinefelter syndrome	3 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)
Other chromosomal aberration	47 (4.6)	12 (3.4)	12 (6.4)	5 (3.7)	3 (3.1)

Data are given as *n* (%). *Not karyotyped or karyotyping unsuccessful. CNS, central nervous system.

(141/1029) of fetuses were terminated between 11 + 0 and 15 + 6 weeks (early TOP), 79.0% (813/1029) between 16 + 0 and 21 + 6 weeks (intermediate TOP) and 7.3% (75/1029) between 22 + 0 and 33 + 6 weeks (late TOP). The incidence of the anomalies at different gestational ages (early *vs* intermediate *vs* late TOP) was almost constant for cardiovascular system anomalies (17.7% *vs* 18.3% *vs* 17.3%) and CNS anomalies (31.9% *vs* 34.7% *vs* 36.0%), but the rate of fetal hydrops or cystic hygroma declined with increasing gestational age (14.2% *vs* 9.2% *vs* 2.7%). Figure 1 shows the rates of early, intermediate and late TOP among 1029 fetuses, in 5-year periods between 1985 and 2014. Throughout the 30-year period, there was an increase in the number of early TOPs, whereas the number of late TOPs decreased.

Table 4 describes the correlation between prenatal ultrasound findings and those seen at autopsy in 1029 fetuses terminated between 1985 and 2014. In the total study group of fetuses terminated between 11 and 33 weeks, there was full agreement between ultrasound and autopsy findings in 88.1% (907/1029), and the main diagnosis was correct in 97.9% (1007/1029).

Figure 2 demonstrates the number of TOPs in each correlation category, grouped in 5-year periods throughout the 30-year period. When comparing the 15-year periods of 2000–2014 with 1985–1999, the difference in rates of agreement was statistically significant, with $P = 0.003$ for full agreement and $P = 0.008$ for agreement of the main diagnosis.

By differentiating the groups by gestational age, we found full agreement in 86.5% of early TOPs, 88.8% of intermediate TOPs and 84.0% of late TOPs, respectively. However, there were non-significant differences in the rates of full agreement ($P = 0.43$) and agreement of the main diagnosis ($P = 0.66$) between early and intermediate TOP groups. Further, minor and major autopsy findings that were not detected at ultrasound occurred in 9.7% (100/1029) and 0.9% (9/1029), respectively, of the total cases. There was no case in Category 4, the correlation of none of the autopsy findings being suspected on

Table 3 Distribution of primary diagnoses according to gestational age at termination, between 11 and 33 weeks, among 1029 fetuses terminated during 1985–2014

	Detection rate (n *(%))* *at:*			
Primary diagnosis	*11 + 0 to 15 + 6 weeks* (n = *141)*	*16 + 0 to 21 + 6 weeks* (n = *813)*	*22 + 0 to 33 + 6 weeks* (n = *75)*	*11 + 0 to 33 + 6 weeks* (n = *1029)*
Chromosomal anomaly with normal morphology	5 (3.6)	29 (3.6)	0 (0)	34 (3.3)
Central nervous system anomaly	45 (31.9)	282 (34.7)	27 (36.0)	354 (34.4)
Cardiovascular system anomaly	25 (17.7)	149 (18.3)	13 (17.3)	187 (18.2)
Respiratory system anomaly	1 (0.7)	5 (0.6)	0 (0)	6 (0.6)
Diaphragmatic/abdominal wall defect	11 (7.8)	36 (4.4)	8 (10.7)	55 (5.3)
Gastrointestinal system anomaly	0 (0)	7 (0.9)	0 (0)	7 (0.7)
ARS/LBWC	7 (5.0)	25 (3.1)	1 (1.3)	33 (3.2)
Urinary system anomaly	11 (7.8)	111 (13.6)	13 (17.3)	135 (13.1)
Genital system anomaly	0 (0)	0 (0)	0 (0)	0 (0)
Skeletal anomaly*	2 (1.4)	8 (1.0)	1 (1.3)	11 (1.1)
Skeletal dysplasia†	3 (2.1)	58 (7.1)	6 (8.0)	67 (6.5)
Arthrogryposis including LMPS	9 (6.4)	21 (2.6)	2 (2.7)	32 (3.1)
Facial defect	0 (0)	4 (0.5)	1 (1.3)	5 (0.5)
Fetal hydrops/cystic hygroma	20 (14.2)	75 (9.2)	2 (2.7)	97 (9.4)
Conjoined twins	2 (1.4)	3 (0.4)	1 (1.3)	6 (0.6)

Data are given as *n* (%). *Skeletal anomalies include malposition, isolated limb anomaly, vertebral anomaly, clubfeet, polydactyly, syndactyly. †Skeletal dysplasia includes osteochondrodysplasia such as thanatophoric dysplasia, achondrogenesis, osteogenesis imperfecta. ARS, amnion rupture sequence; LBWC, limb–body wall complex; LMPS, lethal multiple pterygium syndrome.

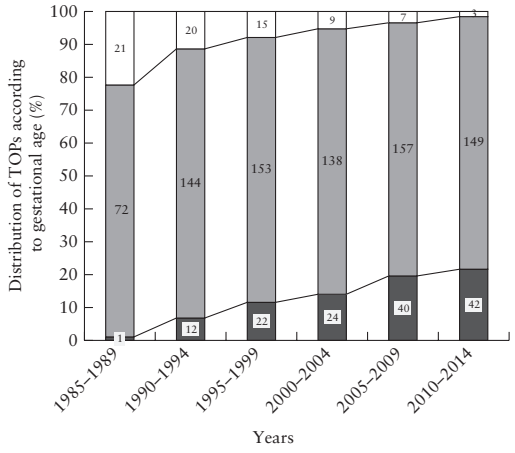

Figure 1 Distribution of terminations of pregnancy (TOP) at different gestational ages among 1029 fetuses terminated between 1985 and 2014. Numbers in each column represent numbers of TOP at each gestational age. ■, early TOP (11+0 to 15+6 weeks); ▒, intermediate TOP (16+0 to 21+6 weeks); □, late TOP (22+0 to 33+6 weeks).

ultrasound. In 1.3% (13/1029) of the pregnancies, ultrasound findings other than those leading to termination were not confirmed at autopsy. There was no false-positive diagnosis leading to TOP throughout the 30-year period.

Table 5 demonstrates the correlation between prenatal ultrasound findings and those identified at autopsy according to the primary diagnosis. The correlation rate of full agreement was high among cases with skeletal dysplasia (92.5%, 62/67), CNS anomalies (90.1%, 319/354) and urinary system anomalies (87.4%, 118/135), slightly lower for cardiovascular system anomalies (83.4%, 156/187) and significantly lower ($P = 0.01$) for diaphragmatic/abdominal wall defects (76.4%, 42/55) (Category 1 in Table 5). Table S1 describes the nine cases in Category 3, for which major autopsy findings were not detected on prenatal ultrasound. The discrepant findings in this category particularly involved CNS anomalies (occipital myelocele), cardiovascular anomalies (ventricular septal defect (VSD)) and urinary system anomalies (renal agenesis and cystic dysplastic kidneys). Moreover, in Case 3, limb–body wall complex was interpreted as a large gastroschisis on prenatal ultrasound.

Table S2 shows TOPs with prenatal ultrasound findings that were not confirmed or not possible to confirm at autopsy ($n = 13$). In Cases 2, 3 and 5, the ultrasound findings were not possible to confirm at autopsy due to maceration or traumatization of the fetus. In all 13 cases, the unconfirmed findings did not affect the decision to terminate as there were other serious findings present. The discrepant findings of CNS anomalies (Cases 1–3) included Dandy–Walker anomaly and hydrocephaly. The discrepant findings of the cardiovascular system (Cases 4–8) were atrioventricular septal defect, VSD, double-outlet right ventricle and over-riding aorta. The discrepant findings of the urinary system (Cases 9–12) were cystic dysplastic kidneys. In Case 13, the sonographic findings of dwarfism with short limbs and disproportionately large head were confirmed at autopsy. Finally, in cases with hydrops and cystic hygroma seen on prenatal ultrasound, it was not always possible to confirm the findings at autopsy due to desiccation and they were not included as a discrepant.

Table 4 Correlation between prenatal ultrasound (US) findings and those seen at autopsy, according to gestational age at termination, between 11 and 33 weeks, in 1029 fetuses terminated during 1985–2014

	Detection rate (n *(%)) at:*			
Correlation	*11 + 0 to 15 + 6 weeks* (n = *141*)	*16 + 0 to 21 + 6 weeks* (n = *813*)	*22 + 0 to 33 + 6 weeks* (n = *75*)	*11 + 0 to 33 + 6 weeks* (n = *1029*)
Category 1: Full agreement between US and autopsy findings	122 (86.5)	722 (88.8)	63 (84.0)	907 (88.1)
Category 2: Minor autopsy findings not seen or recorded at US	17 (12.1)	75 (9.2)	8 (10.7)	100 (9.7)
Categories 1 and 2: Correct main diagnosis	139 (98.6)	797 (98.0)	71 (94.7)	1007 (97.9)
Category 3: Major autopsy findings not detected at US	1 (0.7)	5 (0.6)	3 (4.0)	9 (0.9)
Category 4: None of the autopsy findings suspected at US	0 (0)	0 (0)	0 (0)	0 (0)
Category 5: US findings not confirmed at autopsy	1 (0.7)	11 (1.4)	1 (1.3)	13 (1.3)

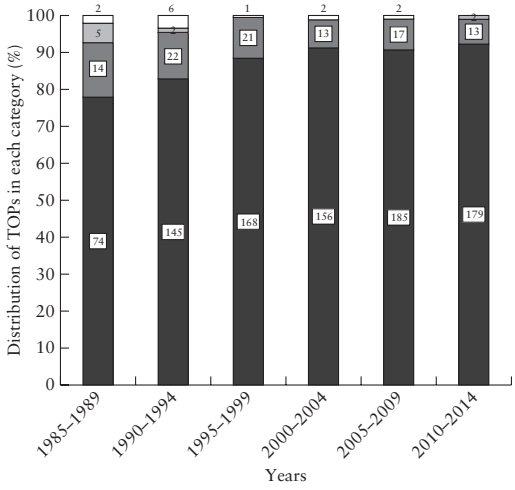

Figure 2 Distribution of terminations of pregnancy (TOP) in different categories of correlation between ultrasound (US) and autopsy findings, among 1029 fetuses terminated between 1985 and 2014. Numbers in each column represent numbers of TOP in each category. ■, Category 1: full agreement between US and autopsy findings; ■, Category 2: minor autopsy findings not seen or recorded at US; ■, Category 3: major autopsy findings not detected at US; □, Category 5: US findings not confirmed at autopsy. There were no fetuses in Category 4 (no autopsy findings suspected on US).

DISCUSSION

Over the 30-year period, there was full agreement between ultrasound and autopsy findings in 88.1% (907/1029) of terminated fetuses, and the main diagnosis was correct in 97.9% (1007/1029) (Table 4). In 1.3% (13/1029) of cases, the ultrasound findings were not confirmed at autopsy. The present validation showed that no termination was based on an ultrasound finding that retrospectively turned out to be a false-positive diagnosis. Considering the extensive use of ultrasound in prenatal diagnosis and the serious consequences the diagnosis may have, this particular finding represents the most important basis for continuing to rely on ultrasound in the diagnostic evaluation of the fetus. This validation also demonstrates the progress in diagnostic development that has taken place over 30 years[25,29]. The routine ultrasound examination has been the most important tool to assess the fetal anatomy since 1985. Interestingly, Figure 1 shows that the gradual reduction in the relatively late diagnoses of anomalies has been paralleled by a similar increase in anomaly detection at 11–14 weeks.

Figure 2 shows a gradual increase in the rate of full agreement between findings on ultrasound examination and at autopsy (Category 1) in 5-year intervals during the 30-year period. There were significant differences in the rate of full agreement and agreement of the main diagnosis when comparing the 15-year period of 2000–2014 with the previous period of 1985–1999. Skeletal dysplasia and CNS anomalies had high correlation rates, whereas the correlation rate in diaphragmatic/abdominal wall defects was significantly lower than the average in the present study (88.1%, Table 5). However, the correlation rates for full agreement improved throughout the study period for both diaphragmatic and abdominal wall defects. Throughout the 30-year period, a small group of fetal medicine experts have been responsible for most of the ultrasound examinations at the center. As found in other studies, ultrasound examinations performed at tertiary centers were more accurate than examinations performed in non-specialized departments[3,4,8,10,30]. Additionally, our policy has been to search for all anomalies present, including in cases in which a dominant serious finding leads to the decision to terminate a pregnancy.

Many studies have documented discrepancies between ultrasound and autopsy findings[2–15,30–34]. Table S3 summarizes 10 studies addressing TOP during the last decade (2006–2015). For Category 1, there is a range of 44.0–88.1% (mean, 58.2% (95% CI, 46.6–69.8)) across the studies. The series before ours were relatively small, presenting an average of 146 terminations, ranging from 52 to 328. Based on the evaluation of cases with full agreement (Category 1) and those with additional findings at autopsy (Categories 2 and 3) in these 10 studies, it seems that the higher proportion of full agreement in the present study and that by Rodriguez *et al.*[3] might be due to a better detection of minor anomalies, e.g. small VSD, horseshoe kidney, clubfoot and polydactyly.

For Category 5 (ultrasound findings not confirmed at autopsy), there is a range of 0–17.0% (mean, 8.9 (95%

Table 5 Correlation between prenatal ultrasound (US) findings and those seen at autopsy, according to primary diagnosis, in 1029 fetuses terminated during 1985–2014

	*Detection rate (*n *(%)) of correlation category:*				
Diagnosis	*1*	*2*	*3*	*4*	*5*
Chromosomal anomaly with normal morphology	34 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Central nervous system anomaly	319 (90.1)	27 (7.6)	5 (1.4)	0 (0)	3 (0.9)
Cardiovascular system anomaly	156 (83.4)	25 (13.4)	1 (0.5)	0 (0)	5 (2.7)
Respiratory system anomaly	5 (83.3)	1 (16.7)	0 (0)	0 (0)	0 (0)
Diaphragmatic/abdominal wall defect	42 (76.4)	11 (20.0)	1 (1.8)	0 (0)	1 (1.8)
Gastrointestinal anomaly	6 (85.7)	1 (14.3)	0 (0)	0 (0)	0 (0)
ARS/LBWC	29 (87.9)	4 (12.1)	0 (0)	0 (0)	0 (0)
Urinary system anomaly	118 (87.4)	15 (11.1)	1 (0.7)	0 (0)	1 (0.7)
Genital anomaly	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Skeletal anomaly*	8 (72.7)	1 (9.1)	1 (9.1)	0 (0)	1 (9.1)
Skeletal dysplasia†	62 (92.5)	4 (6.0)	0 (0)	0 (0)	1 (1.5)
Arthrogryposis including LMPS	32 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Facial defect	5 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Fetal hydrops/cystic hygroma	86 (88.7)	10 (10.3)	0 (0)	0 (0)	1 (1.0)
Conjoined twins	5 (83.3)	1 (16.7)	0 (0)	0 (0)	0 (0)
Total	907 (88.1)	100 (9.7)	9 (0.9)	0 (0)	13 (1.3)

Correlation category: 1, full agreement between US and autopsy findings; 2, minor autopsy findings not seen or recorded at US; 3, major autopsy findings not detected at US; 4, none of the autopsy findings suspected at US; 5, US findings not confirmed at autopsy. *Skeletal anomalies include malposition, isolated limb anomaly, vertebral anomaly, clubfeet, polydactyly, syndactyly. †Skeletal dysplasia includes osteochondrodysplasia such as thanatophoric dysplasia, achondrogenesis, osteogenesis imperfecta. ARS, amnion rupture sequence; LBWC, limb–body wall complex; LMPS, lethal multiple pterygium syndrome.

CI, 5.4–12.4); Table S3) across the studies. We have distinguished between whether or not the unconfirmed findings at autopsy implied wrong management of the pregnancy. In 10/13 cases in our study, other major findings were confirmed at autopsy (Tables S2 and S3), whereas in 3/13 cases, confirmation of the prenatal diagnosis was not possible due to fetal maceration (Tables S2 and S3). However, in all 13 cases, confirmation of other serious findings indicated that the pregnancy was not mismanaged. The unconfirmed findings primarily involved CNS, cardiovascular system and renal anomalies (Table S2). Concerning the CNS, ventriculomegaly and small posterior fossa abnormalities such as Dandy–Walker anomaly can collapse during autopsy and therefore be difficult to verify[35,36]. Imaging methods such as postmortem magnetic resonance imaging may better verify the findings[37,38]. Traditionally, anomalies in the cardiovascular system, e.g. small VSDs, are more difficult to examine by ultrasound, but the detection rate improves when a specialist in fetal echocardiography performs the heart examination[39–41]. Further, renal anomalies often cause difficulties because of oligohydramnios[42,43].

There are limitations concerning both ultrasound and autopsy, and they are therefore often considered as complementary techniques. Both methods are dependent on the skills and knowledge of the sonographer and pathologist. Factors such as fetal position, gestational age, amount of amniotic fluid and maternal obesity influence visualization during ultrasound examination[44,45]. Ultrasound reports were available to the pathologist at the postmortem examination and might introduce bias in the evaluation of autopsy findings[9]. Fetal maceration is a factor that may hinder the accuracy of the autopsy, especially autolysis of the brain.

Improvement of ultrasound technology and diagnostic skills has led to earlier diagnosis of anomalies, with a detection rate of fetal anomalies of around 40–50% during the first trimester[24,46–49]. In the present study, there was full agreement between ultrasound and autopsy findings in 86.5% of early TOP and 88.8% of intermediate TOP (Table 4). However, very early diagnoses of anomalies during the embryonic period may lead to relatively early TOPs, possibly resulting in traumatic destruction of the conceptus, making verification impossible. Therefore, we tried to delay the final sonographic diagnosis to approximately 12–13 weeks. Early diagnosis of anomalies with an early TOP has fewer medical and surgical complications[50]. However, earlier autopsies represent additional challenges for the perinatal pathologist. Abortion of increasingly smaller fetuses necessitates new methods of postmortem examination, and a dissecting microscope or magnifying lenses are often necessary to discern features not visible to the naked eye, for example in cases with a small VSD. Photographic documentation is especially useful when examining small fetuses and, when possible, genetic testing may verify certain syndromes[51]. The progress in ultrasound diagnostics has resulted in a diagnostic shift towards 'chromosomal markers'[24,52,53], which have proven to be of great help in the early detection of an underlying anatomical abnormality and in its verification.

In conclusion, fetal autopsy remains a quality control of ultrasound findings resulting in TOP. Our study demonstrates that the correlation between the two methods of assessment is continuously improving. However, we believe it is necessary to continue the validation practice, due, in particular, to the challenges of validating diagnoses made very early in pregnancy.

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SUPPORTING INFORMATION ON THE INTERNET

Tables S1–S3 may be found in the online version of this article.

Table 6. Category 3 – Major autopsy findings not detected at prenatal ultrasound among 9 terminated fetuses between 1985 and 2014

Case n=9	Year	Mat. age	Sex	GA	Indication for TOP	Final diagnosis after autopsy	Major autopsy findings not detected at ultrasound
1	1986	31	M	23	Cystic dysplastic kidneys	Meckel-Gruber syndrome with cystic dysplastic kidneys, occipital myelocele and polydactyly	Occipital myelocele, polydactyly
2	1986	25	F	23	Cystic dysplastic kidneys (anhydramnios), short extremities, small thorax	VSD and common ventricle, lung hypoplasia, cystic dysplastic kidneys, micrognathia, cleft palate, short extremities. Possible Saldino-Noonan syndrome (radiology not performed)	VSD and common ventricle, micrognathia, cleft palate
3	1986	34	F	21	Corpus callosum agenesis, gastroschisis, scoliosis and pelvic deformity	LBWC, corpus callosum agenesis, scoliosis and pelvic deformity	LBWC interpreted as large gastroschisis at US
4	1988	21	M	22	Hydrocephalus	Hydrocephalus, left renal agenesis, bilateral radial aplasia with missing thumb	Left renal agenesis, bilateral radial aplasia with missing thumb
5	1988	22	M	18	Oligohydramnion, lung hypoplasia, vertebral deformities, clubfeet	Renal agenesis, anal atresia, lung hypoplasia, vertebral deformities, clubfeet	Renal agenesis (adrenals interpreted as kidneys by US), anal atresia
6	1992	26	F	21	Triploidy, IUGR, holoprosencephaly, lumbosacral bifid spine, left renal agenesis and cystic dysplastic right kidney	Triploidy, IUGR, holoprosencephaly, lumbosacral bifid spine, omphalocele, left renal agenesis and cystic dysplastic right kidney, VSD, syndactyly right hand	VSD, omphalocele, syndactyly right hand
7	1993	29	M	18	Alobar holoprosencephaly, urethral and anal atresia, cleft lip and palate	Alobar holoprosencephaly, cystic dysplastic kidneys, urethral and anal atresia, cleft lip and palate	Cystic dysplastic kidneys
8	2012	34	M	19	Lumbosacral myelomeningocele, Arnold Chiari malformation, left clubfoot	Lumbosacral myelomeningocele, Arnold Chiari malformation, left clubfoot, right renal agenesis and double left ureter.	Right renal agenesis and double left ureter
9	2013	24	F	13	Thoracal scoliosis, dysplastic right lower limb with missing fibula	Thoracal scoliosis, dysplastic right lower limb with missing fibula, cystic dysplastic right kidney and hydronephrosis left kidney, esophageal atresia with tracheoesophageal fistula, anal atresia and persistent cloaca	Cystic dysplastic right kidney and hydronephrosis left kidney, esophageal atresia with tracheoesophageal fistula, anal atresia and persistent cloaca

Mat. age, maternal age; IUGR, intrauterine growth restriction; LBWC, limb-body-wall complex; VSD, ventricular septal defect

Table 7. Category 5 – Prenatal ultrasound findings not confirmed or not possible to confirm at autopsy among 13 terminated fetuses between 1985 and 2014

Discrepant anomalies	Case n=13	Year	Mat. age	Sex	GA	Indication for TOP	Final diagnosis after autopsy	US findings not confirmed or not possible to confirm
CNS (n=3)	1	1991	28	F	23	Microcephaly, IUGR, Dandy-Walker anomaly	Microcephaly, IUGR	Dandy-Walker anomaly
	2	1992	35	F	22	Hydrocephaly, IUGR	IUGR	Hydrocephaly (not confirmed due to fetal maceration)
	3	1996	30	F	19	Trisomy 13, Tetralogy of Fallot, Dandy-Walker anomaly and cerebellar hypoplasia, bilateral cleft lip and palate	Trisomy 13, Tetralogy of Fallot, bilateral cleft lip and palate, cerebellar hypoplasia	Dandy-Walker anomaly (brain was autolytic)
CHD (n=5)	4	1991	41	M	19	Trisomy 21, AVSD	Trisomy 21, possible ASD and VSD	Not AVSD at autopsy
	5	1992	41	M	13	Trisomy 18, AVSD	Trisomy 18	AVSD (not confirmed due to traumatised fetus)
	6	2003	33	F	18	Trisomy 18 (FISH), VSD and double outlet right ventricle, bilateral cleft lip and palate, bilateral claw hand	Trisomy 18, aortic coarctation, bilateral cleft lip and palate, bilateral claw hand	VSD and double outlet right ventricle
	7	2005	39	M	21	Trisomy 18 (FISH), small VSD and overriding aorta, choroid plexus cyst, vertebral deformities, syndactyly left foot	Trisomy 18, choroid plexus cyst, vertebral deformities, syndactyly left foot	Small VSD and overriding aorta
	8	2005	32	M	20	Trisomy 13, VSD, double outlet right ventricle and overriding aorta, left cleft lip and palate, polydactyly	Trisomy 13, left cleft lip and palate, polydactyly, arhinencephaly (not seen at US)	VSD, double outlet right ventricle and overriding aorta
Urinary system (n=4)	9	1987	26	F	18	Cystic dysplastic kidneys (oligohydramnios)	Renal agenesis	Cystic dysplastic kidneys
	10	1993	26	M	19	Trisomy 18, IUGR, cystic dysplastic kidneys, VSD, fetal hydrops/cystic hygroma, limb contractures (possible arthrogryposis)	Trisomy 18, IUGR, VSD, fetal hydrops/cystic hygroma, limb contractures	Cystic dysplastic kidneys
	11	2001	36	M	22	Trisomy 18, omphalocele, AVSD, unilateral cystic dysplastic kidney, bilateral cleft lip and palate, claw hands	Trisomy 18, omphalocele, AVSD, bilateral cleft lip and palate, claw hands	Unilateral cystic dysplastic kidney
	12	1990	34	F	18	Turner syndrome, fetal hydrops and cystic hygrom, cystic dysplastic kidneys	Turner syndrome, fetal hydrops and cystic hygrom	Cystic dysplastic kidneys
Skeletal dysp. (n=1)	13	1987	17	F	23	Lethal dwarfism	Short limbs and large head in relation to extremities. Hypoplastic lungs.	Lethal dwarfism

CHD, congenital heart defects; Mat. age, maternal age; IUGR, intrauterine growth restriction; LBWC, limb-body-wall complex; VSD, ventricular septum defect; AVSD atrioventricular septum defect; FISH, fluorescence in situ hybridization

Table 8. Studies of TOP during the last decade (2006-2015) comparing prenatal ultrasound examination and autopsy findings

Study	**Year**	**TOP** (n)	**Full agreement** Category 1 (%)	**Additional findings by autopsy** Category 2-3 (%)	**Disagreement** Category 5 (%)	**Gestational age** (weeks)
Struksnæs et al.	2015	1029	88.1	10.6	1.3 (1.0*, 0.3†)	11-33
Rodriguez et al.	2014	151	86.0	4.6	9.1 (1.9*, 7.2†)	11-24
Vimercati et al.	2012	144	49.0	34.0	17 (13.0*, 4.0†)	12-24
Hauerberg et al.	2012	52	46.0	44.0	9.6 (7.7*, 1.9†)	12-25
Lomax et al.	2012	71	44.0	46.0	10 (8.6*, 1.4†)	16-22
Antonsson et al.	2008	112	44.6	40.2	15.2 (11.6*, 3.6†)	Second trimester
Akgun et al.	2007	107	51.0	42.0	0	13-28
Kaasen et al.	2006	274	58.4	31.4	9.9*	12-24
Amini et al.	2006	328	53.4	37.8	8.8 (7.0*, 1.8†)	11-24
Ramalho et al.	2006	76	61.1	33.6	5.3†	7-35

* Proportion of TOPs with ultrasound findings that were not confirmed by autopsy. These findings came in addition to other findings that were confirmed by autopsy, and they did not affect the clinical indication for terminating the pregnancy.
† Proportion of TOPs where the clinical indication for terminating the pregnancy, based on specific ultrasound findings, could not be supported by the autopsy findings. The disagreements between prenatal US and autopsy findings were often due to the presence of prenatally oligo/anhydramnion and/or postmortem fetal maceration/autolysis.

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Autopsy Findings of Central Nervous System Anomalies in Intact Fetuses Following Termination of Pregnancy After Prenatal Ultrasound Diagnosis

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Abstract

Objectives: Central nervous system (CNS) anomalies are the second most frequent category of congenital anomalies after congenital heart defects (CHDs). In this study, the aim was to investigate the distribution of different CNS anomalies with associated anomalies and karyotype in a fetal autopsy population of terminated pregnancies over a 30-year period and to correlate the ultrasonographic diagnoses of CNS anomalies with autopsy findings.

Materials and Methods: This study includes 420 intact fetuses with CNS anomalies terminated at gestational ages 11^{+0} to 33^{+6} over a 30-year period from 1985 to 2014. An ultrasound (US) examination was performed at the National Centre for Fetal Medicine, St. Olavs Hospital, Trondheim. The autopsies were performed at the Department of Pathology at the same hospital or a collaborating hospital. The anomalies were subcategorized according to the classification by the World Health Organization.

Results: Neural tube defects such as anencephaly (22.4%, 107/477) and spina bifida (22.2%, 106/477) constituted the most common CNS anomalies, followed by congenital hydrocephalus (17.8%, 85/477). In total, the karyotype was abnormal in 21.0% of all termination of pregnancies (TOPs), with trisomy 18 as the most frequent abnormal karyotype. CHDs, skeletal anomalies, and urinary anomalies were the most common associated organ anomalies. Throughout the study period, there was full agreement between US and postmortem findings of CNS anomalies in 96.9% (407/420) of TOPs.

Conclusion: In this study of autopsy findings of CNS anomalies in intact fetuses terminated after prenatal US diagnosis, neural tube defects were most common. About half of the fetuses had isolated serious CNS anomalies, while the other half were CNS anomalies associated with structural and/or chromosomal anomalies. The prenatal US diagnoses were in good concordance with autopsy findings. In particular, due to challenges of diagnoses made early in pregnancy, it is necessary to continue the validation practice.

Keywords

central nervous system, correlation ultrasound autopsy, fetal anomalies, postmortem examination, termination of pregnancy, ultrasonography

Introduction

Central nervous system (CNS) anomalies are the second most frequent category of congenital anomalies after congenital heart defects (CHDs),[1,2] and neural tube defects (NTDs) are the most common of severe anomalies of the CNS.[3] Major structural CNS anomalies are easily diagnosable by prenatal ultrasound (US) examination.[4,5] The detection of serious CNS anomalies at US scan may result in termination of pregnancy (TOP), and around 30% of TOPs performed after the 12th gestational week

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have been reported to be due to CNS anomalies.[6] A detailed postmortem neuropathological examination is important in verification of US findings in terminated fetuses and may also give a more detailed diagnosis.[7] Pre- and postmortem magnetic resonance imaging (MRI) has lately become an additional valuable tool in the diagnosis and verification of suspected brain and spine abnormalities,[8–10] especially helpful after the 20th week of gestation.[11–15]

During the last decades, first trimester scan has evolved,[16–20] and specialized protocols for detecting CNS anomalies exist.[21–23] About 45% of CNS anomalies are detected in the first trimester in several first trimester studies.[19] NTDs were among the first to be reported diagnosed during first trimester with 80% to 90% detection rates,[24] with later improvement to 100% and 84% for anencephaly and spina bifida, respectively.[25] The corpus callosum and the cerebellum are not sufficiently developed to allow complete assessment in the first trimester US. First trimester US markers have been identified, but the diagnosis of certain anomalies can often not be confirmed in the first trimester because the structures do not become sonographically apparent until second and third trimester.[23] It is important to have insight in normal neurodevelopment in order to be able to properly detect fetal brain anomalies during first trimester, and 3-dimensional (3D) US plays an increasing role in the evaluation of brain anomalies as it may obtain planes not easily obtainable with conventional 2D US.[26] The gestational age (GA) at TOP is often related to the type of anomaly, such as earlier terminations in cases of NTDs compared to later terminations of vermian anomalies as Dandy–Walker malformation (DWM).[27–29]

There are few studies focusing on CNS anomalies in perinatal autopsy populations.[2–4,28–31] In this study, the aim was to investigate the distribution of CNS anomalies with associated anomalies and karyotype in an autopsy material of terminated fetuses over a 30-year period and to correlate the prenatal ultrasonographic diagnoses of CNS anomalies with autopsy findings.

Materials and Methods

The study included a total of 420 intact fetuses with CNS anomalies terminated at GA 11^{+0} to 33^{+6} weeks over a 30-year period between 1985 and 2014. Inclusion criteria were a prenatal US examination performed at the National Center for Fetal Medicine (NCFM), which is a referral center for pregnant women from all over Norway, and an autopsy performed at the Department of Pathology at St. Olavs Hospital, University Hospital of Trondheim, or a collaborating hospital. Of the total population, 158 fetuses came from the center's local population and 262 fetuses were referred from other hospitals. All cases are part of the material of 1029 TOP cases with congenital anomalies in Struksnaes et al.[32] Of the 420 terminated fetuses fulfilling the inclusion criteria, 125 TOPs were part of the general autopsy population of 140 cases with CNS anomalies presented by Isaksen et al. in 1998,[4] which in addition to TOPs included spontaneous abortions, intrauterine fetal deaths, and live-born infants between 1985 and 1994.

The cases resulted in TOP following approval by an abortion committee. TOP was performed as soon as possible; preferably the day after the decision for termination was made. According to Norwegian law from 1975, with later revisions, a fetus considered viable outside the mother's uterus cannot be terminated.[33] Until the 1990s, the limit for viability was assumed to be approximately 23^{+6} weeks, and since 2001, the upper limit for termination of a fetus has been set to 21^{+6} weeks. However, a fetus with a lethal anomaly can be terminated later in pregnancy.

When pregnancies are terminated because of serious fetal anomalies, verification of these anomalies is crucial for both the diagnostician and the patient. All abortions were induced medically to preserve the completeness of the specimen, in order to make the verification possible. In the early 1990s, terminations of pregnancy were performed by using prostaglandin analogues (gemeprost) alone, which were applied in the vagina. Since the end of the 1990s, all TOPs were performed by using a combination of anti-progesterone (mifepristone) with prostaglandin analogues (gemeprost, later misoprostol).

Fetal medicine experts were responsible for most of the US examinations at the NCFM. Structures evaluated on the basic US examination of the fetal CNS include head size and shape, lateral ventricles, choroid plexus, cavum septi pellucidi, thalami, cerebellum, cisterna magna, and spine.[34] Pregnancy length and expected day of delivery were determined at the 17- to 18-week routine scan by measurement of biparietal diameter (BPD) and/or femur length. In early pregnancies, BPD or crown-rump length was used.[21] In cases in which the anomaly affected fetal size, GA was based on the best estimate of clinical data. All fetuses were prospectively registered in a database at the NCFM with several variables including maternal age, obstetric history, congenital anomalies, and results of fetal invasive procedures. US reports were available to the pathologist before the postmortem examination. Doctors in training, supervised by a senior pathologist, performed the autopsies between the years 1985 to 1990 and 2005 to 2014, while between the years 1991 and 2004, 2 consultant pathologists with experience in perinatal pathology were responsible for all the autopsies. A neuropathologist was consulted in difficult cases, particularly in cases where microscopy was crucial.

The final diagnosis at the last US examination and the autopsy findings were documented. CNS anomalies were subcategorized according to the classification by the

World Health Organization (WHO), Clinical Modification codes (ICD-10) under the group, ''Congenital malformations of the nervous system'' (Q00–Q07) (Table 1).[35] The new classification of CNS anomalies in ICD-11 is also illustrated in Table 2.[36]

Correlations between US findings and autopsy findings were categorized, in accordance with a modification of the method described by Isaksen et al.[4]

1. Full agreement between US and autopsy findings.
2. Minor autopsy findings not seen or recorded at US examination.
3. Major autopsy findings not detected at US examination.
4. None of the autopsy findings suspected at US examination.
5. US findings not confirmed or not possible to confirm at autopsy.

We used SPSS 25.0 (SPSS Inc., Chicago, IL, USA) in the statistical analyses, and correlation analyses were performed using independent samples t test. $P < .05$ was considered statistically significant.

Results

Throughout the 30-year period, 420 intact fetuses had one or more CNS anomalies at autopsy. Of these, 12% (50/420) were terminated before week 16^{+0}, 80% (338/420) terminated between week 16^{+0} to 21^{+6} and 8% (32/420) terminated between week 22^{+0} to 33^{+6}. The mean GA was week 18.5 (range: 11–33). There were 51.0% females (n = 214) and 49.0% males (n = 206). The study included 1 conjoined twin. The mean maternal age was 28.5 years (range: 16–44).

Table 2 shows the distribution of different subgroups of CNS anomalies in 420 fetuses, categorized according to the WHO categorization (Table 1). There are in total 477 anomalies. Of all 477 diagnoses, 92.2% (440/477) were detected in fetuses terminated before week 22^{+0}, and 11.9% (57/477) of the diagnoses were detected during the first trimester. NTDs such as anencephaly (22.4%, 107/477) and spina bifida (22.2%, 106/477) constituted the most common CNS anomalies, followed by congenital hydrocephalus (17.8%, 85/477). Other anomalies were different types of holoprosencephaly (9.6%, 46/477) and (meningo-) encephalocele (7.1%, 34/477). Most encephaloceles were occipital (79.4%, 27/34), and also categorized under encephalocele (Q01) were 7 fetuses with Meckel-Gruber syndrome and 2 fetuses with cerebro-oculo-muscular syndrome. There were 17 cases with microcephaly, mainly associated with encephalocele (47.1%, 8/17) or holoprosencephaly (29.4%, 5/17). Half of all reduction anomalies were cerebellar hypoplasia (52.5%, 21/40), and most cerebral cysts were choroid plexus cysts (CPCs; 80.0%, 16/20).

Table 1. WHO Classification of Congenital Malformations of the Nervous System (CNS), ICD-10 Codes.

ICD 10 Code	Congenital Malformations of the Central Nervous System
Q00	Anencephaly and similar malformations
Q01	Encephalocele
Q02	Microcephaly
Q03	Congenital hydrocephalus
Q04	Other congenital malformations of brain
Q05	Spina bifida
Q06	Other malformations of spinal cord
Q07	Other malformations of nervous system

Figure 1 shows the distribution of karyotype and associated organ anomalies among the 420 TOPs. Almost 80% (332/420) of all TOPs had a normal or unknown karyotype. About half of the population (48.3%, 203/420) consisted of TOPs with one or more isolated CNS anomalies and normal or unknown karyotype. Half of the population (49.8%, 209/420) had one or more associated organ system anomalies; of these, 129 TOPs with normal or unknown karyotype and 80 TOPs with abnormal karyotype. In cases with abnormal karyotype, 90% (80/88) had other organ system anomalies. Trisomy 18 was the most common abnormal karyotype (9%, 38/420) followed by trisomy 13 (5%, 21/420) (Table 3). CNS anomalies in the subgroup ''Other congenital malformations of brain'' (Q04) were most frequently associated with abnormal karyotype at 44.3% (54/122), in which 20 (43.5%) of the 46 cases with holoprosencephaly had trisomy 13. Most cases with anencephaly, encephalocele, microcephaly, congenital hydrocephalus, or spina bifida had a normal karyotype.

Table 4 demonstrates the distribution of associated structural organ anomalies. The most frequent associated findings were CHDs (21.9%, 82/374), skeletal anomalies (19.5%, 73/374), and urinary system anomalies (16.3%, 61/374). Table 4 also shows the association between other organ anomalies and different subgroups of CNS anomalies. For instance, spina bifida was most often associated with urinary system anomalies (31.1%, 33/106). Almost 84% (89/106) of cases with spina bifida and almost 70% (73/107) of cases with anencephaly were associated with other organ system anomalies, in contrast to only 23.5% (4/17) of cases with microcephaly.

Table 5 shows the correlation between prenatal US findings and autopsy findings of CNS anomalies in 420 terminated fetuses. In the whole study group between week 11^{+0} and 33^{+6}, there was full agreement between US and autopsy findings in 96.9% (407/420). The overall main diagnosis was correct in 99.1% (416/420) and 100% correct in the first trimester. There was 1 case in category 3, no cases in category 4, and 3 cases where prenatal

Table 2. Central Nervous System Anomalies Categorized in Subgroups in 420 Fetuses Terminated Between Weeks 11 and 33.

ICD 10 Code	Subgroup	ICD 11 Code	Week 11^{+0} to 33^{+6} n	Week 11^{+0} to 33^{+6} N	Week 11^{+0} to 33^{+6} %	Week 11^{+0} to 15^{+6} n	Week 11^{+0} to 15^{+6} %	Week 16^{+0} to 21^{+6} n	Week 16^{+0} to 21^{+6} %	Week 22^{+0} to 33^{+6} n	Week 22^{+0} to 33^{+6} %
Q00 Anencephaly and similar malformations	Anencephaly (including acrania)	LA00	107	107	22.4	24	22.4	77	72.0	6	5.6
	With cervical rachischisis		21								
	With craniorachischisis		18								
Q01 Encephalocele	(Meningo-)encephalocele[a]	LA01		34	7.1	8	23.5	25	73.6	1	2.9
Q02 Microcephaly	Microcephaly	LA05.0		17	3.6	4	23.5	13	76.5	–	–
Q03 Congenital hydrocephalus	Malformations of Sylvian aqueduct	LA04	25	85	17.8	2	2.3	70	82.4	13	15.3
	Other (including unspecified)		48								
	Dandy–Walker malformation	LA06.0	12								
Q04 Other congenital malformations of brain	Agenesis of corpus callosum	LA05.3		16	3.4	1	6.2	12	75.0	3	18.8
	Holoprosencephaly	LA05.2	46	46	9.6	7	15.2	36	78.3	3	6.5
	Alobar		26								
	Semilobar		5								
	Lobar		15								
	Other reduction anomalies	LA05.5	40	40	8.4	2	5.0	33	82.5	5	12.5
	including cerebellar hypoplasia	LA06.1	21								
	Cerebral cysts	LA05.7	20	20	4.2	1	5.0	18	90.0	1	5.0
	including choroid plexus cysts		16								
Q05 Spina bifida	Cervical and/or thoracic	LA02	9	106	22.2	–	–	9	8.5	–	–
	With A–C malformation type II	+LA03	5			7	6.6	86	81.1	4	3.8
	Lumbar and/or sacral	LA02	97								
	With A–C malformation type II	+LA03	82								
Other	Miscellaneous[b]			6	1.3	1	16.7	4	66.6	1	16.7
Total				477	100	57	11.9	383	80.3	37	7.8

Abbreviation: A-C, Arnold Chiari.

[a]Syndromes with encephalocele: Meckel-Gruber (7), Cerebro-oculo-muscular syndrome (COMS) (2).

[b]Miscellaneous: Microphthalmos (1), Krabbe disease (1), Fraser syndrome (1), Apert syndrome (2), ependymoblastoma (1).

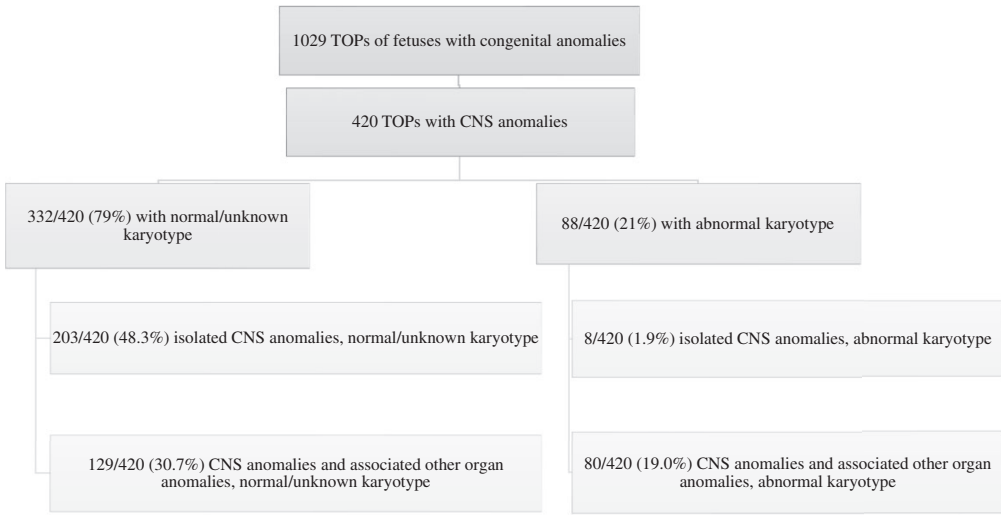

Figure 1. Distribution of karyotype and associated organ anomalies in autopsies of 420 fetuses aborted because of central nervous system anomalies (TOP/termination of pregnancy).

Table 3. Distribution of Karyotype in 420 Fetuses With Central Nervous System Anomalies.

			Distribution in Central System Anomalies											
	Distribution of 420 TOPs		Q00 Anencephaly and Similar Malformations (n = 107)		Q01 Encephalocele (n = 34)		Q02 Microcephaly (n = 17)		Q03 Congenital Hydrocephalus (n = 85)		Q04 Other Congenital Malformations of Brain (n = 122)		Q05 Spina Bifida (n = 106)	
Karyotype	N	%	n	%	n	%	n	%	n	%	n	%	n	%
Normal	293	69.8	83	77.6	30	88.2	13	76.5	59	69.4	59	48.4	80	75.5
Unknown	39	9.3	15	14.0	4	11.8	3	17.6	7	8.2	9	7.4	6	5.7
Abnormal	88	20.9	9	8.4	–	–	1	5.9	19	22.4	54	44.3	20	18.9
T13	21	5	–	–	–	–	–	–	3	3.5	23	18.9	1	0.9
T18	38	9	7	6.5	–	–	–	–	4	4.7	18	14.8	15	14.2
T21	5	1.2	–	–	–	–	–	–	4	4.7	2	1.6	0	–
Tripl	8	1.9	–	–	–	–	–	–	3	3.5	2	1.6	4	3.8
45,X	2	0.5	1	0.9	–	–	–	–	1	1.2	1	0.8	–	–
Other	14	3.3	1	0.9	–	–	1	5.9	4	4.7	8	6.6	–	–
Total	420	100	107	100	34	100	17	100	85	100	122	100	106	100

Abbreviations: Other, other chromosomal aberrations; T13, trisomy 13; T18, trisomy 18; T21, trisomy 21; Tripl, triploidy; 45X, Turner syndrome; TOPs, termination of pregnancies.

findings were not confirmed at autopsy (category 5). In all cases in category 5, other serious organ anomalies were confirmed that justified the management of the pregnancy.

Table 6 shows the disagreement between US and autopsy in all cases in categories 2, 3 and 5. In category 2, 6 of 9 cases were from the first 15 years (1985–1999). In 2 cases (2.2 and 2.4, Table 6) with anencephaly and cervical rachischisis, this rachischisis was not described at US. In 1 case (2.9, Table 6) with holoprosencephaly and microcephaly, holoprosencephaly was miscategorized and microcephaly not described at US. In 1 case in category

Table 4. Associated Organ Anomalies in 420 Fetuses With Central Nervous System Anomalies.

			Distribution in Central System Anomalies											
	Total Diagnoses		Q00 Anencephaly and Similar Malformations (n = 107)		Q01 Encephalocele (n = 34)		Q02 Microcephaly (n = 17)		Q03 Congenital Hydrocephalus (n = 85)		Q04 Other Congenital Malformations of Brain (n = 122)		Q05 Spina Bifida (n = 106)	
Associated Organ System Anomalies	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Cardiovascular system anomalies	82	21.9	12	11.2	1	2.9	1	5.9	20	23.5	31	25.4	17	16.0
Respiratory system anomalies	12	3.2	2	1.9	1	2.9	–	–	1	1.2	4	3.3	3	2.8
Diaphragmatic/ abdominal wall defects	35	9.4	12	11.2	–	–	–	–	5	5.9	13	10.7	5	4.7
GI system anomalies	35	9.4	3	2.8	3	8.8	–	–	5	5.9	14	11.5	10	9.4
ARS/LBWD	14	3.7	8	7.5	1	2.9	1	5.9	–	–	1	0.8	3	2.8
Urinary system anomalies	61	16.3	13	12.1	6	17.6	1	5.9	12	14.1	26	21.3	33	31.1
Genital system anomalies	5	1.3	1	0.9	–	–	–	–	–	–	4	3.3	–	–
Skeletal anomalies[a]	73	19.5	12	11.2	5	14.7	–	–	19	22.4	18	14.8	17	16.0
Skeletal dysplasia[b]	11	2.9	–	–	–	–	–	–	1	1.2	10	8.2	–	–
Arthrogryposis with LMPS	4	1.1	–	–	–	–	–	–	–	–	4	3.3	–	–
Facial defects	33	8.8	9	8.4	2	5.9	1	5.9	6	7.1	11	9.0	–	–
Fetal hydrops, cystic hygroma	9	2.4	1	0.9	1	2.9	–	–	–	–	6	4.9	1	0.9
Total	374	100												

Abbreviations: ARS, amnion rupture sequence; GI, gastrointestinal; LBWC, limb-body-wall complex; LBWD, limb-body-wall defect; LMPS, lethal multiple pterygium syndrome.
[a]Skeletal anomalies include malposition, isolated limb anomalies, vertebral anomalies, clubfeet, polydactyly, and syndactyly.
[b]Skeletal dysplasia includes osteochondrodysplasias such as thanatophoric dysplasia.

Table 5. Correlation Between Prenatal Ultrasound and Autopsy Findings in 420 Fetuses With Central Nervous System Anomalies.

	Detection rate at different GAs							
	Week 11^{+0} to 15^{+6}		Week 16^{+0} to 21^{+6}		Week 22^{+0} to 33^{+6}		Week 11^{+0} to 33^{+6}	
Correlation	n	%	n	%	n	%	N	%
Category 1: Full agreement between US and autopsy findings	48	96.0	328	97.0	31	96.9	407	96.9
Category 2: Minor autopsy findings not seen or recorded at US examination	2	4.0	7	2.1	–	–	9	2.2
Category 1 + 2 (Main diagnosis)	50	100	335	99.1	31	96.9	416	99.1
Category 3: Major autopsy findings not detected at US examination	–	–	–	–	1	3.1	1	0.2
Category 4: None of the autopsy findings suspected at US examination	–	–	–	–	–	–	0	0
Category 5: US findings not confirmed or not possible to confirm at autopsy	–	–	3	0.9	–	–	3	0.7
Category 1–5: Total	50	11.9	338	80.5	32	7.6	420	100

Abbreviations: GA, gestational age; US, ultrasound.

Table 6. All Cases With Disagreement Between Ultrasound and Postmortem Findings of Central Nervous System Anomalies in 420 Fetuses.

Category Case	Year	GA	Indication for TOP	Final Diagnosis After Autopsy	Comments
2.1	1989	20	Thanatophoric dysplasia	Thanatophoric dysplasia and hydrocephalus	Autopsy findings not detected at US: Hydrocephalus
2.2	1992	18	Anencephaly	Anencephaly with cervical rachischisis	Autopsy findings not detected at US: Cervical rachischisis
2.3	1992	16	Arnold Chiari malformation, ASD, VSD, tricuspid atresia, and omphalocele	Arnold Chiari malformation, spinal defect, ASD, VSD, tricuspid atresia, and omphalocele	Autopsy findings not detected at US: Spinal defect
2.4	1994	20	Anencephaly	Anencephaly with cervical rachischisis	Autopsy findings not detected at US: Cervical rachischisis
2.5	1994	11	LBWC, scoliosis, and lip palate cleft	Acrania, LBWC, scoliosis, and lip palate cleft	Autopsy findings not detected at US: Acrania
2.6	1999	18	Right cystic dysplastic kidney and agenesis left kidney	Right cystic dysplastic kidney and agenesis left kidney, occipital meningocele, and cystic hygroma	Autopsy findings not detected at US: Occipital meningocele and cystic hygroma
2.7	2001	19	Acrania	Microcephaly and parietal encephalocele	Microcephaly and parietal encephalocele was interpreted as acrania at US
2.8	2002	14	T18, VSD, DORV, and hypoplastic pulmonalis	Trisomy 18, VSD, DORV, hypoplastic pulmonalis, and sacrococcygeal meningomyelocele	Autopsy findings not detected at US: Sacrococcygeal meningomyelocele
2.9	2012	19	Semilobar holoprosencephalon	Lobar holoprosencephalon and microcephaly	Autopsy findings not detected at US: Microcephaly
3.1	1986	23	Cystic dysplastic kidneys	Meckel-Gruber syndrome with cystic dysplastic kidneys, occipital myelocele, and polydactyly	Autopsy findings not detected at US: Occipital myelocele and polydactyly
5.1	1991	23	Microcephaly, IUGR, and Dandy–Walker malformation	Microcephaly and IUGR	US findings not confirmed at autopsy: Dandy–Walker malformation
5.2	1992	22	Hydrocephaly and IUGR	IUGR	Hydrocephaly (not confirmed due to fetal maceration)
5.3	1996	19	T13, Tetralogy of Fallot, Dandy–Walker malformation, cerebellar hypoplasia, cleft lip, and palate	Trisomy 13, Tetralogy of Fallot, cleft lip and palate, and cerebellar hypoplasia	Dandy–Walker malformation (brain was autolytic)

Abbreviations: ASD, atrial septal defect; DORV, double outlet right ventricle; GA, gestational age; IUGR, intrauterine growth restriction; LBWC, limb-body-wall complex; T13, trisomy 13; T18; trisomy 18; TOP, termination of pregnancy; US, ultrasound; VSD, ventricular septal defect.

3 with Meckel-Gruber syndrome, cystic dysplastic kidneys were detected at US, though because of anhydramnios, occipital myelomeningocele and polydactyly were not detected. Concerning the 3 cases in category 5, 2 cases with DWM and 1 hydrocephalus were not confirmed. However, in 2 of these cases, the brain was macerated/autolytic. Figures 2 and 3 illustrate cases with lobar holoprosencephaly and DWM.

Discussion

Throughout the 30-year period, 40.8% (420/1029) of terminated intact fetuses in the total material of 1029 TOP cases with congenital anomalies in Struksnaes et al. had one or more CNS anomalies at autopsy. About half the population of 420 fetuses were terminated due to isolated serious CNS anomalies, while the rest were CNS

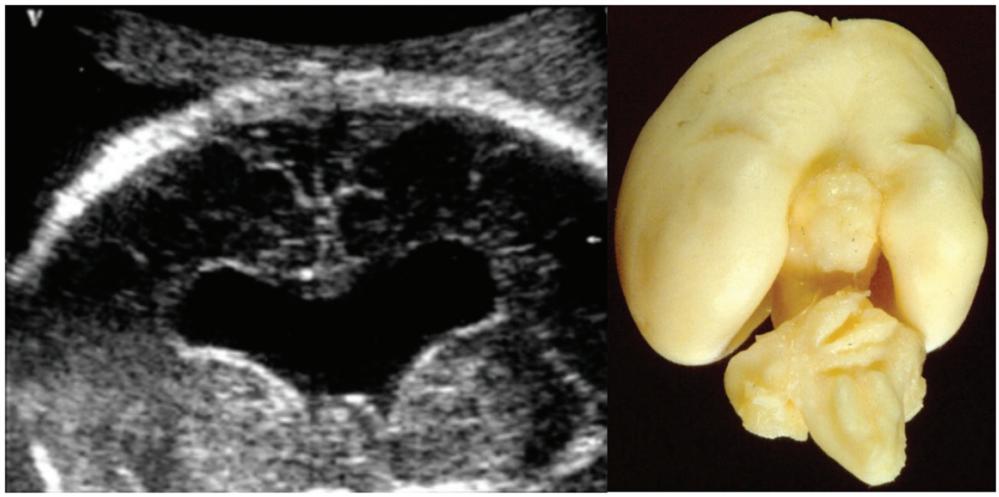

Figure 2. Ultrasound image and postmortem photography of an 18-week fetus with lobar holoprosencephaly, 1993. The ultrasound image is a coronal section through the brain with open connection between the lateral ventricles. There is no corpus callosum and no septi pellucidi. Associated anomalies: premaxillary agenesis, polycystic kidneys, and cloacal agenesis.

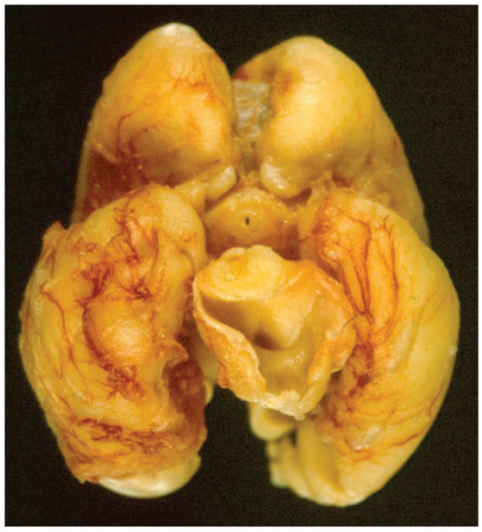

Figure 3. Postmortem photograph of a 15-week fetus with Dandy–Walker malformation, 1997. Associated anomaly: atrioventricular septal defect.

anomalies associated with other structural and/or chromosomal anomalies. NTDs including anencephaly and spina bifida constituted 45% of all CNS anomalies (213/477). CHDs were the most common associated organ anomalies, and abnormal karyotype was only present in about 1/5 of all TOPs. In 10% of cases, karyotyping was not available, often due to tissue culture failure. A total of 69% (27/39) of all cases with unknown karyotype were TOPs from the first half of the 30-year period. Throughout the study period, there was full agreement between US and postmortem findings of CNS anomalies in 96.9% of TOPs. In the 13 cases in categories 2, 3, and 5 with disagreement between US and autopsy findings (Table 6), confirmation of other serious findings justified TOP.

NTDs were most common, in accordance with the literature.[4,37–39] Stevenson et al. state that about 20% of NTDs have anomalies in other organs.[40] In our study, 38.4% (94/245) of fetuses with NTDs had one or more associated organ anomalies. Moreover, earlier studies show that in isolated NTDs, the incidence of chromosome anomalies is 1% to 2%, though when major CNS anomalies are associated with other organ system anomalies, the incidence is much higher, up to 20%.[41,42] This is in agreement with our findings. Moreover, more than 20% (24/107) of all cases with anencephaly were detected during the first trimester, and the overall correlation rate was good. In 1 case (2.5, Table 6) with acrania and limb-body-wall complex, acrania was not detected at US. Acrania is seldom isolated and it is disputed whether anencephaly is a result of acrania, that is, when the brain is not protected, it disintegrates in the amniotic fluid.[23,43] In LBWC, the combination of limb defects, abdominal wall defect, and acrania is the result of the

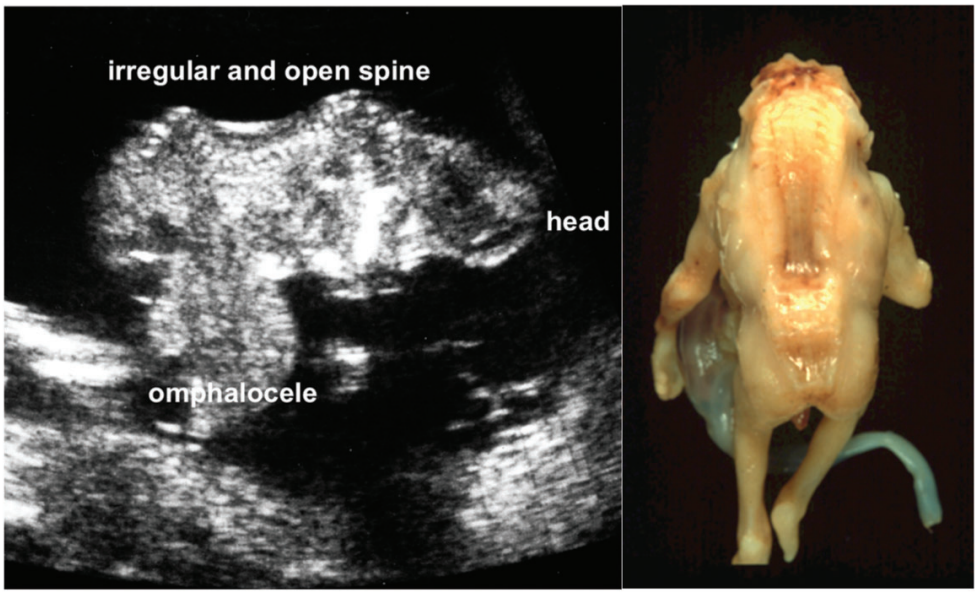

Figure 4. Ultrasound image and postmortem photography of a 14-week fetus with craniorachischisis, 1996. The ultrasound image shows a sagittal section through the body with irregular and open spine, abnormal head pole, and a large body wall defect—omphalocele. Associated anomalies: trisomy 18, omphalocele, and horseshoe kidney.

same event occurring early in pregnancy.[44] In our study, 19.6% (21/107) of cases with anencephaly had associated cervical rachischisis, and in 2 of these cases, the rachischisis was not described in the US report (2.2 and 2.4, Table 6). Anencephaly occurring together with rachischisis totalis (craniorachischisis) is a rare condition.[45,46] In our study, there were 18 cases with craniorachischisis, in which 4 cases had trisomy 18 and omphalocele. Figure 4 illustrates a fetus with craniorachischisis.

Occipital encephalocele in addition to bilateral polycystic kidneys and postaxial polydactyly is known as the classic triad of Meckel-Gruber syndrome. There were 7 cases with this syndrome in the total material. These abnormalities may be difficult to visualize when renal dysfunction results in severe oligohydramnios. It is important to be aware that kidney dysplasia in Meckel-Gruber can be associated with other CNS anomalies than occipital encephalocele. In our study, in 1 case in category 3 (3.1, Table 6), US did not detect the occipital myelocele and polydactyly. Since Meckel-Gruber syndrome is autosomal recessive, the distinction from sporadic occurring dysplastic kidneys is important.[47]

Congenital hydrocephalus is a common CNS anomaly, with several possible etiologies.[48,49] It can be caused by x-linked stenosis of the Sylvian aqueduct, but also infections like cytomegalovirus and toxoplasmosis may block the aqueduct by creating inflammatory tissue.[50] Melcer et al. and Domrose et al. focused on CNS anomalies in late TOPs and found that hydrocephalus was the most common anomaly, which can be explained by the fact that hydrocephalus usually develops during second or early third trimester.[28,29] In our study, in addition to agenesis of corpus callosum, there were more late TOPs with hydrocephalus (15.3%, 13/85) compared to the other main groups of CNS anomalies (Table 2). According to the WHO classification, DWM is part of "Congenital hydrocephalus" (Q03, Table 2) and refers to a failure of the normal closure of the fourth ventricle with persistence of Blake's pouch that occurs at the 13th to 18th weeks.[51] Prenatal diagnosis can be challenging in mild cases, and in the syndromic form of DWM, anomalies of the heart, face, limbs, or gastrointestinal system may be present.[52] Concerning the 3 cases in category 5, 2 cases with DWM and 1 with hydrocephalus were not confirmed. However, in 2 cases (5.2 and 5.3, Table 6), the brain tissue was macerated.

The holoprosencephaly sequence develops from failure of the prosencephalon (forebrain) to differentiate into 2 cerebral hemispheres and lateral ventricles.[53] The first brain structures can be identified not before the end of week 6, based on the last menstrual period (LMP) by using high-frequency transvaginal US, when the cavity

of the rhombencephalon becomes visible. During LMP-based week 7, all brain vesicles are detectable including the lateral hemispheres.[23] In contrast to hydrocephalus, this anomaly can be diagnosed early in pregnancy and the alobar type can be detected as early as the end of week 7.[54] Almost half of the cases with holoprosencephaly in the study were associated with trisomy 13, which is in accordance with the literature and is a strong indicator for performing karyotyping/genetic examinations. In our study, in 1 case (2.9, Table 6) with microcephaly and holoprosencephaly, the microcephaly was not described at US, and the lobar holoprosencephaly at autopsy was miscategorized as semilobar at US. Microcephaly is a condition where the head size is smaller compared to other fetuses of the same age and sex, and according to WHO, the best possibility of diagnosing microcephaly is made at the end of the second trimester or in the third trimester.[55]

Postmortem examination of first trimester fetuses represents a challenge in the verification of US detected anomalies.[56] The brain is small and vulnerable and may be traumatized during the process of removing it during autopsy. In our department, it is removed under water in order to minimize trauma and then fixed in a zinc-formalin solution to make it firmer. Alternatively, it can be submerged in absolute alcohol for 24 hours before slicing. For instance, CPCs are usually easy to detect at US,[23,57] but often difficult to confirm at autopsy because they collapse. This study includes some CPCs detected at US, but they were not possible to verify at autopsy. All 16 fetuses with CPCs had other organ system anomalies leading to TOP, and 75% (12/16) were associated with an abnormal karyotype. In such cases, particularly in small fetuses and in macerated/traumatized fetuses, postmortem MRI would have been of help in verifying prenatal findings.[8,10,58,59]

TOP can be a serious result of prenatal diagnosis. In this study, all TOPs were based on severe and/or lethal anomalies of the CNS, which were confirmed by autopsies. Fetal autopsy has been regarded as quality control in diagnosing and verifying congenital anomalies detected at US.[2,56,60–62] Cooperation between ultrasonographers and pathologists is of great value. However, studies show that autopsy rates are low,[28,29] and according to Boyd et al.,[63] the percentage of fetuses that underwent autopsy fell from 84% to 67% throughout the 90s. We found in our study an average autopsy rate of 88.8% during the 30-year period, in which 1029 of 1157 fetuses with congenital anomalies were examined postmortem after TOP. From the beginning of the study in 1985, the rate increased from 92.3% to 96.8% in 1999. Then the rate started falling, and in the last 5-year period (2010–2014), the rate was 81.5%. Some studies have discussed possible causes, including cultural and religious beliefs,[29,63] and postmortem MRI has become a possible alternative to traditional postmortem examination in verification of anomalies.[58,59,64]

In this 30-year study of autopsy findings of CNS anomalies in intact fetuses terminated after prenatal US diagnosis, NTDs were most common, followed by congenital hydrocephalus. About half of the fetuses had serious CNS anomalies that were not associated with other structural or chromosomal anomalies. Even though the correlation between prenatal US and postmortem findings of CNS anomalies was high, it is necessary to continue the validation practice, in particular due to the challenges of validating diagnoses made early in pregnancy.

Declaration of Conflicting Interests

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Paper III

Original Investigation

Postmortem Assessment of Isolated Congenital Heart Defects Remains Essential Following Termination of Pregnancy

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Abstract

Objectives: To investigate the correlation between prenatal ultrasound (US) and autopsy findings in pregnancies terminated due to isolated congenital heart defects (CHDs), including CHDs associated with heterotaxy syndrome.

Materials and methods: The material consists of 67 fetuses with prenatally detected isolated CHDs or CHDs associated with heterotaxy syndrome at a tertiary center in Norway between 1985 and 2014. The main CHDs were categorized into subdiagnoses of CHDs in accordance with ICD-10. The US and autopsy findings were categorized according to degree of concordance.

Results: Gestational age at termination was 12 + 0–22 + 6 weeks. Hypoplastic left heart syndrome was the most common main diagnosis among the 67 fetuses (32.8%). There was full agreement between US and autopsy findings in 97.4% (222/228) of all subdiagnoses. The discrepant findings in three fetuses had no influence on the decision to terminate the pregnancy.

Conclusions: The correlation was high between prenatal US and postmortem findings in fetuses with isolated CHDs. Meticulous assessment of cardiac anatomy is particularly necessary when the decision to terminate relies on isolated CHDs. The trend of earlier termination challenges verification of diagnoses at autopsy. Consequently, the fetus should be examined at a tertiary center with fetal medicine specialists, pediatric cardiologists and perinatal pathologists.

Keywords

prenatal ultrasound, autopsy, anomalies, isolated fetal heart defects, heterotaxy syndrome, termination of pregnancy

Introduction

A systematic assessment of the fetal anatomy at the second trimester ultrasound (US) examination has become an essential part of the prenatal examinations to locate disorders which may influence the care of the pregnancy. In certain cases, disorders detected are of such a severe nature that termination of the pregnancy (TOP) may be an option for the parents. It is then of utmost importance that the US diagnosis is correct.

Since the systematic examination of the fetal population was introduced in the eighties, the correlation between the prenatal US findings and autopsy results has been assessed over time with respect to the various organ groups.[1–6] Some fetuses may have multiple anomalies, often with chromosomal aberrations as the dominant condition. In fetuses with multiple structural or chromosomal anomalies, the decision to terminate a pregnancy may be based on a platform of several severe diagnoses. Congenital heart defects (CHDs)

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have traditionally been difficult to detect and relatively often anomalies associated with the CHDs are located first.[3,7]

As a consequence of the focus on increasing the prenatal detection rate of CHD in general, cases with isolated CHDs are also being detected.[8] If this leads to TOP being an option, detailed prenatal and postmortem assessment of the cardiac anatomy is essential since the diagnosis relies on an isolated CHD without any associated anomalies.

The aim of this study was to investigate the correlation between prenatal US diagnoses and autopsy findings over a 30-year period, in pregnancies terminated because of isolated CHDs, including CHDs associated with heterotaxy syndrome in the fetus.

Materials and Methods

Included in the study were data from pregnant women who, during the period from 1985 until and including 2014, had a prenatal US examination performed at the National Center for Fetal Medicine (NCFM) that was followed by termination of pregnancy and a subsequent autopsy at the Department of Pathology; both institutions are located at St. Olavs University Hospital in Trondheim, Norway. The selected material comprised pregnant women from the catchment area of the hospital as well as referrals from all over Norway, as NCFM is a national referral center.

In Norway, the second trimester US examination is performed at 18 gestational weeks by Certified Nurse-Midwives with one-year university based Postgraduate Certificate in Obstetric Ultrasound and includes a detailed examination of the fetal anatomy. At NCFM, the prenatal US data, along with several variables including maternal age, obstetric history, detailed outline of congenital anomalies including karyotype, and results of fetal invasive procedures are prospectively registered in an extensive database which was designed at the introduction of routine US in Norway in 1986 to track the consequences of the national program at our center.

From an autopsy series of 1029 TOP cases with congenital anomalies including chromosomal aberrations, there were 320 fetuses with CHDs.[5] From the latter group, we included 67 fetuses with isolated CHDs for detailed evaluation. Ten of these fetuses had CHDs combined with heterotaxy syndrome and were included as none of these had extracardiac anomalies except for the abnormal arrangement of internal organs; this anomaly did not influence the decision for TOP and allowed an additional 10 cases to be part of the study group. Fetuses with CHDs and extracardiac and/or chromosomal anomalies were not included since the associated anomalies in this heterogeneous group could have had an impact on the decision for TOP.

When the NCFM was established in 1990, a pathologist with experience in perinatal pathology was included in the team of experts, a practice which over time has been reinforced. Following termination of pregnancies, autopsies were classified according to affected organ groups. To facilitate a detailed comparison with the prenatally detected anomalies of the heart with the autopsy findings, each single anomaly, e.g. ventricular septal defect (VSD), and all subdiagnoses involved in a main diagnosis or syndrome, e,g. hypoplastic left heart syndrome (HLHS), were subcategorized and registered separately. The subcategorization of CHDs was based on the classification by the World Health Organisation, Clinical Modification codes (ICD-10) under the group, "Congenital malformations of the circulatory system" (Q20-Q26) (Table 1).[9]

Fetal medicine experts were responsible for the final US examinations at the NCFM. With few exceptions, a pediatric cardiologist was present during the US scans. Pregnancy length and expected day of delivery were mainly determined at the 18th week routine scan by measurement of biparietal diameter (BPD) in most fetuses or by femur length (FL) when BPD for various reasons could not be used. In early pregnancies, BPD or crown-rump length (CRL) was used.

For all 67 cases, TOP was approved by the regional abortion committee. According to Norwegian law from 1975, with later revisions,[10] the upper limit for termination was based on the earliest gestational age for possible survival of newborns. Until the 1990s, the upper limit was $23+6$ weeks, which, from 2001, was changed to $21+6$ weeks. Termination of pregnancy was preferably performed the day after the decision for termination was made. All abortions were induced medically to preserve the completeness of the specimen.

The pathologists had regular meetings with the fetal medicine experts, and the prenatal US reports were available to the pathologist before postmortem examination. From 1991, the autopsy protocol was

Table 1. WHO Classification of Congenital Malformations of the Circulatory System, ICD-10 Codes.[9]

Code	Congenital Malformations of the Circulatory System
Q20	Congenital malformations of cardiac chambers and connections
Q21	Congenital malformations of cardiac septa
Q22	Congenital malformations of pulmonary and tricuspid valves
Q23	Congenital malformations of aortic and mitral valves
Q24	Other congenital malformations of heart
Q25	Congenital malformations of great arteries
Q26	Congenital malformations of great veins

standardized to include whole-body radiography and photography, to document external and internal abnormalities. The heart was examined *in situ* before the arterial connections were cut. If more than one cardiac defect was found, the anomalies were classified according to the most serious defect.

CHDs were categorized as major or minor in accordance with Mitchell et al.[11] The heart defects were grouped as simple or complex. A simple heart defect was defined as one without additional cardiac defects, e.g. transposition of the great arteries (TGA) or atrioventricular septal defect (AVSD). A heart defect was defined as complex when additional heart defects were present, e.g. TGA with pulmonary atresia.

Correlations between US findings and autopsy findings were categorized in accordance with a modification of the method described by Isaksen et al.[12]

1. Full agreement between ultrasound and autopsy findings
2. Minor autopsy findings not seen or recorded at ultrasound examination
3. Major autopsy findings not detected at ultrasound examination
4. None of the autopsy findings suspected at ultrasound examination
5. Ultrasound findings not confirmed or not possible to confirm at autopsy

SPSS 25.0 (SPSS Inc., Chicago, Ill., USA) was used in the statistical analysis, and correlation analyses were performed using independent samples t-test. $P < 0.05$ was considered statistically significant.

The study was approved by the Regional Committee for Medical and Health Research Ethics in Norway (REK 2009/790). Since this is autopsy material, the Regional Ethic Committee gave dispensation from informed consent.

Results

The present study included data from a total of 67 terminated pregnancies, 38 from the catchment area of the NCFM and 29 from referring hospitals. The pregnancies were terminated at mean gestational age 19 + 0 weeks (range: 12 + 0 to 22 + 6 weeks). Eleven (16%) of the pregnancies were terminated between weeks 12 + 0 and 16 + 6. The sex distribution was 44.8% females and 55.2% males. The mean maternal age was 29 years (range: 21–41 years).

Table 2 shows the main diagnosis after autopsy in all 67 pregnancies terminated due to isolated CHDs. The dominating group comprising 22 (32.8%) of the total 67 fetuses was HLHS, which includes hypoplastic left ventricle, aortic and mitral atresia/stenosis and aortic arch hypoplasia. LAI was the second most common main diagnosis (8.9%, 6/67).

Table 2. Main Diagnosis Based on Autopsy Results in 67 Pregnancies Terminated due to Isolated CHDs.

Main Diagnosis	n	%
HLHS	22	32.8
Left atrial isomerism	6	8.9
DORV simple	5	7.4
Tricuspid atresia complex	5	7.4
Truncus arteriosus	4	6.0
TGA complex	3	4.5
DILV complex	3	4.5
HRHS	2	3.0
AVSD simple	2	3.0
TGA simple	2	3.0
Mitral atresia/stenosis simple	2	3.0
Pulmonary stenosis simple	2	3.0
Tricuspid atresia/stenosis simple	2	3.0
Right atrial isomerism	2	3.0
Other CHDs with heterotaxy	2	3.0
TGA, corrected	1	1.5
DIRV complex	1	1.5
Mitral atresia complex	1	1.5
Total	**67**	**100**

CHD, congenital heart defect; HLHS, hypoplastic left heart syndrome; DORV, double outlet right ventricle; TGA, transposition of the great arteries; DILV, double inlet left ventricle; HRHS, hypoplastic right heart syndrome; AVSD, atrioventricular septal defect; DIRV, double inlet right ventricle; simple, no additional cardiac defects; complex, with additional heart defects present.

Table 3 shows a detailed postmortem distribution of all subdiagnoses of CHDs among the 67 fetuses, altogether 228 CHDs, categorized according to ICD-10. Anomalies of the cardiac chambers and connections (Q20) comprised the largest category, 91/228 (39.9%), including TGA, 17/228 (7.5%) and double outlet right ventricle (DORV), 13/228 (5.7%). Hypoplastic right ventricle and hypoplastic left ventricle were also part of this category, comprising 11/228 (4.8%) and 38/228 (16.6%), respectively. Two of the 11 fetuses with hypoplastic right ventricle had hypoplastic right heart syndrome (HRHS), and 22 of 38 fetuses with hypoplastic left ventricle had HLHS.

Among the 10 fetuses with heterotaxy syndrome, there were six fetuses with left atrial isomerism (LAI), two fetuses with right atrial isomerism (RAI) and two fetuses defined as "Other CHDs with heterotaxy" (Table 2). Table 4 shows an overview of the 10 cases with heterotaxy syndrome after autopsy examination, including subdiagnoses of the CHDs. In the fetuses with LAI, heart defects such as AVSD, TGA and hemiazygos continuation were common, while both fetuses with RAI had hypoplastic left ventricle and DORV. Overall, five fetuses (50%) with heterotaxy syndrome had hypoplastic left or right ventricle.

Table 3. Detailed Postmortem Distribution of All Subdiagnoses of CHDs Among the 67 Terminated Pregnancies, According to ICD-10.[9]

ICD-10 Category	Subdiagnoses	n	%	N	%
Cardiac chambers and connections (Q20)	Truncus arteriosus	5	2.1	91	39.9
	DORV	13	5.7		
	DOLV	2	0.9		
	TGA complete	15	6.6		
	TGA corrected	2	0.9		
	DIRV	2	0.9		
	DILV	3	1.3		
	Hypoplastic right ventricle	11	4.8		
	Hypoplastic left ventricle	38	16.6		
Cardiac septa (Q21)	VSD	21	9.2	34	14.9
	ASD	2	0.9		
	AVSD	11	4.8		
Pulmonary and tricuspid valves (Q22)	Pulmonary atresia/stenosis	14	6.1	26	11.5
	Tricuspid atresia/stenosis	10	4.5		
	Tricuspid insufficiency	2	0.9		
Aortic and mitral valves (Q23)	Aortic atresia/stenosis	23	10.1	47	20.6
	Mitral valve stenosis	24	10.5		
The great arteries (Q25)	Coarctation of the aorta	1	0.4	19	8.3
	Overriding aorta	3	1.3		
	Atresia/hypoplasia of the aorta	10	4.5		
	Atresia/hypoplasia of the pulmonary artery	5	2.1		
The great veins (Q26)	Anomalous venous return	11	4.8	11	4.8
Total		**228**	**100**	**228**	**100**

DORV, double outlet right ventricle; DOLV, double outlet left ventricle; TGA, transposition of the great arteries; DIRV, double inlet right ventricle; DILV, double inlet left ventricle; VSD, ventricular septal defect; ASD, atrial septal defect; AVSD, atrioventricular septal defect.

Table 4. Overview of the 10 Cases With Heterotaxy Syndrome After Autopsy Examination, Including Subdiagnoses of the CHDs.

Heterotaxy Syndrome	Year	GA	Structural Defects
LAI	1998	20	Hypoplastic left ventricle, hypoplastic ascending aorta, pulmonary stenosis, azygos vein continuation of IVC, abdominal situs inversus (stomach right side, midline liver, polysplenia)
	2001	18	Pulmonary veins to right atrium, VSD, truncus arteriosus, pulmonary atresia, abdominal situs inversus (stomach, pancreas and descending colon right side, midline liver, polysplenia)
	2009	14	AVSD, complete TGA, azygos vein continuation of IVC
	2010	20	AVSD, hypoplastic left ventricle, DORV, complete TGA, pulmonary veins and both caval veins into left atrium, bilobed right lung, abdominal situs inversus (midline liver, malrotation of intestines)
	2011	16	AVSD, complete TGA with right aortic arch, pulmonary stenosis, hemiazygos vein continuation of IVC, abdominal situs inversus (stomach and two spleens right side, midline liver, coecum left side)
	2012	16	AVSD, bilobed lungs, azygos vein continuation of IVC
RAI	2009	20	Levocardia, ASD, VSD, hypoplastic left ventricle with hypoplastic mitral valve, DORV, complete TGA, pulmonary stenosis, IVC to left sided atrium and SVC to right sided atrium, bilobed lung right side and trilobed left side, abdominal situs inversus (spleen, pancreas and stomach right side, midline liver, coecum left side)
	2012	20	Hypoplastic left ventricle, AVSD, pulmonary atresia, DORV, infracardiac total anomalous pulmonary venous return to IVC, abdominal situs inversus (stomach right side, midline liver and coecum, asplenia)
Other CHDs with heterotaxy	1989	20	Dextrocardia, AVSD, single ventricle, hypoplastic right atrium, pulmonary atresia, total anomalous pulmonary venous return, abdominal situs inversus (stomach, spleen and pancreas right side, midline liver, coecum left side)
	2000	19	Dextrocardia, single atrium with SVC and pulmonary veins, AVSD, right aortic arch, functional left ventricle with double outlet, hypoplastic right ventricle, pulmonary atresia, abdominal situs inversus (spleen, pancreas and accessory spleen right side, coecum left side)

GA, gestational age; LAI, left atrial isomerism; IVC, inferior vena cava; VSD, ventricular septal defect; AVSD, atrioventricular septal defect; TGA, transposition of the great arteries; DORV, double outlet right ventricle; RAI, right atrial isomerism; ASD, atrial septal defect; SVC, superior vena cava; CHDs, congenital heart defects.

Table 5 demonstrates the correlation between prenatal US findings and autopsy findings in all 228 subdiagnoses of the CHDs amongst the 67 fetuses. There was full agreement between US and autopsy findings in 222 of the 228 CHDs (97.4%). The discrepant findings were found in three fetuses (Table 6). In the first fetus from 2004, a VSD was not seen at US (category 2: minor autopsy findings not seen or recorded at US examination) and a suspected truncus arteriosus at US was diagnosed at autopsy as a complete TGA, VSD and left ventricle outflow tract obstruction (LVOTO) (category 3: major autopsy findings not detected at US examination). In the second fetus from 2011, all US findings were verified at autopsy, except DORV (category 5: US findings not confirmed or not possible to confirm at autopsy, false positive). In the third fetus from 2014, prenatal findings were recategorized at autopsy. Overriding aorta and pulmonary artery smaller than aorta at US examination were not confirmed at autopsy (category 5, false positive). Moreover, postmortem findings of aortic stenosis, interrupted aortic arch and left subclavian artery rising from pulmonary artery were not seen at US (category 3: major autopsy findings not detected at US examination) (Table 6).

Table 5. Correlation Between Prenatal US and Autopsy Findings in All Subdiagnoses of CHDs in 67 Fetuses.

Categories	N	%
1: Full agreement between US and autopsy findings	222	97.4
2: Minor autopsy findings not seen or recorded at US examination	1	0.4
3: Major autopsy findings not detected at US examination	3	1.3
4: None of the autopsy findings suspected at US examination	–	–
5: US findings not confirmed or not possible to confirm at autopsy	2	0.9
1-5: Total	228	100

CHDs, congenital heart defects; US, ultrasound.

Discussion

When a pregnancy is terminated due to congenital anomalies detected by US, verification of those findings by autopsy is important.[5,13–15] In the present study, there was full agreement between US and autopsy findings in 97.4% of 228 subdiagnoses of the CHDs among 67 fetuses. Previous studies addressing the correlation between US findings and verification at autopsy have addressed multiple organ groups,[4,5,16–18] or included all cases with cardiac pathology, irrespective of the main cause of death.[19–21] We are not aware of other studies comparing prenatal US and postmortem findings in pregnancies terminated due to isolated CHDs or CHDs associated with heterotaxy syndrome. It is therefore difficult to compare our correlation rates with other studies.

If the cardiac diagnosis is a false positive finding when other lethal or serious extracardiac anomalies are present, the false positive diagnosis will not determine the management of the pregnancy in the same way as if the termination is performed based on a false positive isolated major CHD only.[4,5,13,14] In cases with isolated CHDs, high agreement is especially important as there

Table 6. Cases With Disagreement Between Ultrasound and Postmortem Findings.

Case	Year	GA	Ultrasound Diagnosis	Final Diagnosis After Autopsy	Disagreement
1	2004	18	Tricuspid atresia, hypoplastic RV, suspected truncus arteriosus	HRHS with tricuspid atresia, hypoplastic RV, complete TGA, VSD and LVOTO	VSD not seen at US (category 2). Suspected truncus arteriosus at US was diagnosed as complete TGA (category 3), VSD and LVOTO at autopsy (category 3)
2	2011	17	HLHS with mitral atresia, VSD, DORV, hypoplastic aorta with preductal coarctation	HLHS with mitral atresia, VSD, hypoplastic aorta with preductal coarctation	DORV not verified at autopsy (category 5, false positive)
3	2014	21	TOF with VSD, overriding aorta and pulmonary artery smaller than aorta. Suspected DORV variant	DORV, aortic stenosis, VSD, interrupted aortic arch, left subclavian artery rising from pulmonary artery	Aortic stenosis, interrupted aortic arch, left subclavian artery rising from pulmonary artery were not seen at US (category 3). Overriding aorta and pulmonary artery smaller than aorta were not confirmed (category 5, false positive)

GA, gestational age; RV, right ventricle; HRHS, hypoplastic right heart syndrome; TGA, transposition of the great arteries; VSD, ventricular septal defect; LVOTO, left ventricle outflow tract obstruction; US, ultrasound; HLHS, hypoplastic left heart syndrome; DORV, double outlet right ventricle; TOF, Tetralogy of Fallot.

are no other associated organ anomalies that would justify TOP.

The fetal heart is considered the most challenging organ to examine prenatally.[8] In a non-selected population, 51% of the CHDs will be isolated; this emphasizes the necessity of a verification of the prenatal diagnosis.[8] To validate the quality of the US examinations, we chose to divide each major CHD into subdiagnoses as these constitute the main diagnosis and may also be important for the prognosis. Despite the false positive subdiagnosis (category 5) in two cases in our study, both had other serious subdiagnoses confirmed at autopsy, thus management had not been affected by the false positive subdiagnoses. The false positives illustrate the complexity of isolated CHDs.

One factor for the high correlation in our study may be a result of improved detection of minor CHDs. Traditionally, conditions with hypoplastic heart chambers and large VSDs and AVSDs have been easier to detect than minor VSDs and atrial septal defects.[22–24] Even though minor anomalies do not change the management of the pregnancy with regard to TOP, detecting these minor findings is important as they may indicate the presence of a more serious anomaly and are essential in evaluating the severity of the CHD.[5,13] Another factor that may contribute to the high correlation rate in our study, is that all 67 fetuses were intact after medical abortion and were not macerated or traumatized prior to verification at autopsy.

HLHS was the most common main diagnosis among all pregnancies terminated due to isolated CHDs and was found in 22 of the 67 fetuses (Table 2). It is considered a serious or lethal condition constituting 1–2% of all major CHDs,[25] and generally occurs in children without other anomalies.[26] Previous studies have reported TOP in 60–80% of cases in which HLHS was detected prenatally.[25,27] In antenatally diagnosed cases, detailed parental counseling is important, with a discussion of options of termination or continuation of pregnancy, including the choice of postnatal interventions such as compassionate care and cardiac surgery.[28,29]

Anomalies of the aortic and mitral valves (Q23) together with anomalies of cardiac chambers and connections (Q20) comprised 60% of all 228 subdiagnoses of CHD (Table 3). Cardiac septal defects (Q21) are traditionally the most common CHDs, but in our study they constituted only 14.9%. This finding correlates with the literature, where most septal defects in autopsy populations are related to abnormal karyotype;[30,31] such cases were excluded from the present study.

All CHDs in the 10 cases with heterotaxy syndrome (Table 4) were major anomalies. CHD is an important component of heterotaxy syndrome, resulting in significant mortality.[32] However, the prognosis of patients with heterotaxy varies, as they represent a heterogeneous group, and surgery is often complex.[33] In these cases, the choice leading to termination of pregnancy was based on findings of serious/lethal CHDs while the abnormal arrangement of organs was of subordinate importance when deciding to terminate the pregnancy. However, when heterotaxy is suspected during prenatal examination, further search for other anomalies, including CHDs, is necessary.

The complexities of CHDs emphasize the necessity of a referral center with specialists in fetal medicine.[34] Collaboration with a pediatric cardiologist is of great value, particularly when there are no associated anomalies.[35] In Table 6, which shows the disagreement between US and postmortem findings, it should be noted that in addition to fetal medicine specialists, a pediatric cardiologist evaluated cases 2 and 3, but not case 1. When the fetal medicine specialist was not sure about the details in the cardiac diagnosis, the prenatal findings were defined as "suspected" (Table 6). The broad range of CHDs without associated anomalies is challenging for the prenatal detection of CHDs, also when the heart is evaluated in detail by experts in fetal medicine and pediatric cardiologists. Moreover, classifications and categorizations of CHDs have evolved during the last decades, resulting in differences in terminology.

Fetal autopsy is not mandatory in Norway, but the involved parents are informed about the value of autopsy and the importance of quality control in diagnosing and verifying congenital anomalies detected at US prior to termination of pregnancy. To terminate a pregnancy is a difficult decision for the parents and a verification of the prenatal findings may ease their grief.[36] The information parents gain can be a positive confirmation of the choice they have made and may also provide them with additional knowledge of recurrence in a future pregnancy.[37] Such verification is also essential for clinicians in order to provide proper counselling. Despite the high correlation between the prenatal findings and the autopsy findings in our study, we still believe an autopsy is of value. However, an autopsy is not an option in all cases, and it is then reassuring to be aware of the high expertise of the fetal medical examiner.

Even though studies have shown that autopsy helps to establish the cause of death and can provide additional clinically significant information, autopsy rates are falling in the western world.[37–39] Dislike for the invasiveness of traditional autopsy and cultural and religious beliefs have been raised as possible causes leading to falling autopsy rates.[40] However, alternatives to traditional invasive postmortem examination of congenital anomalies have been developed that include less-invasive methods and a variety of imaging modalities, that may alleviate this falling trend.[41] Postmortem magnetic resonance imaging has shown promising results in general, including fetal hearts.[40,42,43] Micro-focus CT imaging with virtual dissection of the fetal heart may become a good alternative to conventional autopsy;[44] postmortem two-dimensional US

may also be an alternative to invasive autopsy, although the results for the fetal heart still need to be improved.[45]

During the last decade there has been a move towards the use of US in the first trimester.[46,47] This has led to detection of congenital anomalies and, in selected cases, TOP at an earlier gestational age, making the verification of anomalies at autopsy difficult. The autopsy verification is particularly challenging when CHDs are the only prenatal finding leading to TOP. Opening the heart in situ and dissection with a stereomicroscope improves the visualization at autopsy[3] and requires an experienced perinatal pathologist. Postmortem imaging methods may be of particular help for the smaller fetuses. By performing medical abortion, the fetus is kept intact which makes the valuable verification at autopsy by a perinatal pathologist possible.

Conclusively, in this autopsy material of 67 fetuses with isolated CHDs, detailed prenatal assessment and postmortem examination revealed 228 subdiagnoses of CHDs, with 97.4% full agreement between prenatal US and autopsy findings. The two false positive subdiagnoses did not affect the basis for the TOP. Even though our study demonstrates a high degree of correct prenatal cardiac assessment, we cannot ignore the serious consequences of a misdiagnosis, especially when the decision to terminate a pregnancy is based on abnormalities in one organ only. We believe it is important to inform the parents of the option of autopsy given the benefit reassurance might represent for the couple. However, an autopsy is not an option in all cases, and we appreciate the expertise of fetal medicine specialists performing prenatal examinations with high accuracy. Consequently, the fetus should be examined at a tertiary medical center with fetal medicine specialists in collaboration with a pediatric cardiologist and an experienced perinatal pathologist.

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