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ABSTRACT

Objectives

A prenatal ultrasound examination together with a postmortem examination provide the

basis for correct diagnosis in fetuses terminated due to congenital anomalies. The aim of

this study is to correlate fetal anomalies detected by ultrasound examination with

autopsy findings following termination of pregnancy (TOP) over a 30-year period, and

to evaluate the correlation rate at different gestational ages.

Methods

The study group consists of **1029 TOPs carried out over a 30-year period from 1985

to 2014.** The gestational age spans between 11 and 33 weeks. The ultrasound

examinations were performed at the National Center for Fetal Medicine (NCFM), St.

Olavs Hospital, Trondheim. **The 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 the TOPs, and the main diagnosis was correct in 97.8% (1007/1029). When

comparing the 15-year period 2000-2014 with the previous period, 1985-1999, the

differences in detection rate were statistically significant for full agreement and for

main diagnosis. In 1.3% (13/1029) of the cases, the US 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, while late TOPs have declined.

Conclusions

Our study demonstrates that there is a clear correlation between ultrasound and autopsy

findings; this correlation is continuously improving. In spite of this high correlation,

there is reason to continue the practice of validation to ensure the safety of the

diagnostic process leading to termination of pregnancy. The trend towards performing

earlier termination emphasises the necessity of such a practice.

INTRODUCTION

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

The Norwegian routine second trimester ultrasound (US) scan at 17-18 gestational weeks includes a survey of the fetal anatomy (16-18). Detection rates of the 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 sonographically detected as early as during the embryonic period at 7 to 8 weeks of gestational age based on the last menstrual period. A scan at the end of the first trimester at 11-13 weeks, can detect numerous types of anomalies (24).

Throughout the years of ultrasound diagnostics, detection by ultrasound has improved, especially due to increasing expertise of the ultrasonographers and higher quality of the ultrasound equipment (25). However, ultrasound diagnostics of congenital anomalies at earlier gestational age and the presence of more subtle conditions challenge the verification of congenital anomalies and require other pre- and postmortem examination methods (26).

This study is a quality control on TOPs carried out as a consequence of sonographically diagnosed fetal anomalies**.** The aim is to correlate fetal anomalies detected by ultrasound examination with autopsy following termination of pregnancy (TOP) throughout a 30-year period, and to evaluate the correlation rate at different gestational ages.

METHODS

The study is 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 includes cases from the non-selected area 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 termination of pregnancy between gestational weeks 11 and 33 **following approval by an abortion committee**, and an autopsy performed at the Department of Pathology at St. Olav's Hospital or a collaborating hospital.

According to Norwegian law from 1975 with later revisions, a fetus considered viable outside the mother's womb can not be terminated (27). The limit for viability was initially assumed to be approximately 23+6 weeks until the nineties and later gradually restricted. Since 2001, the upper limit for termination of a viable fetus is 21+6 weeks. A fetus with a lethal condition may be terminated later in pregnancy. **A total of 1029 terminated fetuses fulfilled the inclusion criteria during a 30-year period from 1985 to 2014.**

All cases were over time prospectively registered in a database at the NCFM and continuously validated. 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", while 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 (BPD) and femur length (FL). In early pregnancies, BPD or crown-rump length (CRL) is used (28). In cases where the anomaly affected fetal size, gestational age was based on the best estimate of clinical data. The termination of pregnancy was performed as soon as possible, preferably the day after the decision for termination was made. In cases where anomalies were detected as early as week 9 to 10, the termination of pregnancy was delayed 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 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 in order to minimize trauma. **Ultrasound reports were available to the pathologist at the postmortem examination.**

Correlations between US 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
5. Ultrasound findings not confirmed or not possible to confirm at autopsy

We used **SPSS 21.0** (SPSS Inc., Chicago, Ill., USA) in the statistical analysis, and correlation analyses were performed using Independent samples t-test. $P<0.05$ was considered statically significant.

The study was approved by the Regional Ethics Committee (REC).

RESULTS

All 1029 fetuses underwent autopsy following termination of pregnancy between weeks 11 and 33. The mean maternal age was 29.2 years (range 16-45 years). The median gestational age was week 19.0 (range 11-33). The gender differentiation included 51.4% females (529/1029) and 48.4% males (498/1029). It was not possible to determine the gender in two cases.

Table 1 shows an overview of congenital anomalies among 1029 autopsies of fetuses

terminated between weeks 11 and 33. The dominating primary diagnoses were 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 leading to termination of

pregnancy, 46.1 % (474/1029) of all fetuses had a secondary diagnosis. In this study,

34/1029 (3.3%) cases with normal morphology were terminated due to chromosome

anomalies. Table 2 gives an overview of the karyotype of the terminated pregnancies.

The karyotype was normal in 59.5% of the cases, unknown among 10.1%. Thirty

percent (313/1029) of all cases had an abnormal karyotype. Trisomy 18 was the most

common abnormal karyotype (8.7%, 90/1029), thereafter trisomy 21 (8.3%, 85/1029).

Table 3 demonstrates the distribution of primary diagnoses among 1029 terminated

fetuses: 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). The rate of congenital

anomalies at different gestational ages was almost constant for cardiovascular system

anomalies (17.7% - 18.3% - 17.3%) and CNS anomalies (31.9% - 34.7% - 36.0%), but

the rate of fetal hydrops and cystic hygroma declined with increasing gestational age

(14.2% - 9.2% - 2.7%). Figure 1 shows the rate of terminations in weeks 11+0 to 15+6,

weeks 16+0 to 21+6 and weeks 22+0 to 33+6, over five-year periods between 1985 and

2014 for 1029 fetuses. There is an increase in the number of early TOPs, while the

number of late TOPs decreases throughout the 30-year period (Figure 1).

Table 4 describes the correlation between prenatal ultrasound findings and autopsy

findings in 1029 terminated fetuses between 1985 and 2014. In the total study group

between week 11 and 33, there was full agreement between ultrasound and autopsy

findings in 88.1% (907/1029), and the main diagnosis was correct in 97.8%

(1007/1029). When comparing the 15-year period 2000-2014 with the previous period

1985-1999, the differences in detection rate were statistically significant, with p=0.003

for full agreement and p=0.008 for main diagnosis. By differentiating the groups by

gestational age, we found full agreement in the three groups in 86.5% (weeks 11+0 to

15+6), 88.8% (weeks 16+0 to 21+6) and 84.0% (weeks 22+0 to 33+6), respectively.

However, there were non-significant differences in the correlation rate for full

agreement (p=0.43) and main diagnosis (p=0.66) between first gestational group (weeks

11+0 to 15+6) and second gestational group (weeks 16+0 to 21+6). Further, minor and

major autopsy findings not detected at ultrasound, constituted 9.7% (100/1029) and

0.9% (9/1029) respectively, of the total material. There were no cases in category 4. In

1.3% (13/1029) of the pregnancies, ultrasound findings other than those leading to

termination, were not confirmed at autopsy. There were no false-positive diagnoses

leading to TOP throughout the 30-year period.

Table 5 demonstrates the correlation between prenatal ultrasound examination and

autopsy findings according to primary diagnosis in 1029 terminated fetuses between

1985 and 2014. **The correlation rates for full agreement were high among skeletal**

dysplasia (92.5%, 62/67), CNS anomalies (90.1%, 319/354) and urinary system

anomalies (87.4%, 118/135) and slightly lower for cardiovascular system anomalies

(83.4%, 156/187), but significantly lower (p = 0.01) for diaphragmatic/abdominal

wall defects (76.4%, 42/55) (Category 1, Table 5). Figure 2 demonstrates the number of TOPs in each correlation category grouped in five-year periods throughout the 30-year period. Table 6 describes the cases in category 3, major autopsy findings not detected at prenatal ultrasound, among 9 terminated fetuses. The discrepant findings in this category involve particularly CNS anomalies (occipital myelocele), cardiovascular anomalies (VSD) and urinary system anomalies (renal agenesis and cystic dysplastic kidneys). Moreover, in case number 3, limb-body-wall complex was interpreted as a large gastroschisis at US.

Table 7 shows all TOPs with ultrasound findings not confirmed or not possible to confirm at autopsy among 13 terminated fetuses. **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 termination decision since there were other serious findings present.** The discrepant findings in CNS (nr. 1-3) include **Dandy-Walker anomaly** and hydrocephaly. The discrepant findings in the cardiovascular system (nr. 4-8) are atrioventricular septal defect (AVSD), ventricular septal defect (VSD), double outlet right ventricle and overriding aorta. The discrepant findings in the urinary system (nr. 9-12) are cystic dysplastic kidneys. In case number 13, sonographic findings of dwarfism were confirmed at autopsy. Finally, cases with hydrops and cystic hygroma at ultrasound were not always possible to confirm at autopsy due to desiccation and they were not included as discrepant.

DISCUSSION

Seen over the 30-year period, there was full agreement between ultrasound and autopsy

findings in 88.1% (907/1029), and the main diagnosis was correct in 97.8%

(1007/1029) (Table 4). In 1.3% (13/1029) of the cases, the US findings were not

confirmed at autopsy. The present validation showed that none of the terminated

pregnancies were based on an ultrasound finding which 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 import basis for continuing to rely on ultrasound diagnosis in the

diagnostic evaluation of the fetus. This validation also demonstrates the progress in the

diagnostic development that has taken place over 30 years (25,29). Since 1985, the

routine ultrasound examination has been the most important tool to assess the fetal

anatomy. Interestingly, figure 1 shows that the gradual reduction in the relatively late

diagnosis of anomalies has been paralleled with a similar increase in anomaly detection

during weeks 11-14.

Figure 2 shows a gradual increase in the rate of full agreement between ultrasound

examination and autopsy (category 1) over five-year intervals during the 30-year period.

There were significant differences in the full agreement and main diagnosis when

comparing the 15-year period 2000-2014 with the previous period 1985-1999. **Skeletal**

dysplasia and CNS anomalies had high correlation rates, while correlation rate in

diaphragmatic/abdominal wall defects was significantly lower than average in the

present study (88.1%, Table 4). 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 other studies state, US examinations performed at tertiary centers turn out to be 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, also in cases where a dominant serious finding leads to the decision to terminate a pregnancy.**

Many studies have documented discrepancies between ultrasound and autopsy findings (2-15,30,40-43). **Table 8 shows 10 studies addressing TOP during the last decade (2006-2015). 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; they present an average of 146 terminations, range 52 to 378. Based on the evaluation of the full agreement cases (category 1) and the additional findings by autopsy (categories 2 and 3) for the ten series, 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.**

In category 5, there is a range between 0-17.0% (mean 8.9, 95% CI: 5.4,12.4) (Table 8). We have distinguished between whether or not the unconfirmed findings at autopsy implied wrong management of the pregnancy. In 10/13 cases (1.0%) in our study, other major findings were confirmed by autopsy (Table 7, Table 8 *), while in 3/13 (0.3%) cases, confirmation of the prenatal diagnosis was not possible due to fetal maceration (Table 7, Table 8 †). However, in all 13 cases, the confirmation of other serious findings indicated that the pregnancy was not

mismanaged. The unconfirmed findings involved especially CNS anomalies,

cardiovascular system anomalies and renal anomalies (Table 7). Concerning CNS,

ventriculomegaly and small post posterior fossa abnormalities such as Dandy-

Walker anomaly can collapse during autopsy and therefore be difficult to verify

(31, 32). Imaging methods such as postmortem magnetic resonance imaging (MRI)

may better verify the findings (33,34). 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 (35-37). Further, renal anomalies often cause difficulties because of

oligohydramnios (38,39).

There are limitations concerning both ultrasound and autopsy and therefore they are

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 between 40-50%

during the first trimester (24, 46-49). In the present study, there was full agreement

between US 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 to 13 weeks. Early diagnosis of anomalies

with 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. Photo 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 has proven to

be of great help in early detection of an underlying anatomical abnormality and in their

verification.

In conclusion, fetal autopsy remains a quality control of the ultrasound findings

resulting in termination of pregnancy. Our study demonstrates that the correlation is

continuously improving. However, we believe it is necessary to continue the validation

practice, in particular due to the challenges of validating diagnosis made very early in

pregnancy.

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Table 1. Congenital anomalies in 1029 autopsies of fetuses terminated between weeks 11 and 33

Diagnoses	Primary diagnosis				Secondary diagnosis		Total diagnoses	
			Abnormal karyotype					
	n	%	n	%	n	%	n	%
Chromosomal anomalies with normal morphology	34	3.3	34	100	-	-	34	1.9
Central nervous system anomalies	354	34.4	66	18.6	66	8.1	420	22.8
Cardiovascular system anomalies	187	18.2	95	50.8	133	16.3	320	17.3
Respiratory system anomalies	6	0.6	2	33.3	35	4.3	41	2.2
Diaphragmatic/abdominal wall defects	55	5.3	26	47.3	52	6.4	107	5.8
Gastrointestinal system anomalies	7	0.7	4	57.1	102	12.5	109	5.9
ARS/LBWC	33	3.2	0	0	1	-	34	1.9
Urinary system anomalies	135	13.1	9	6.7	135	16.5	270	14.6
Genital system anomalies	-	-	-	-	29	3.6	29	1.6
Skeletal anomalies *	11	1.1	3	27.3	146	17.9	157	8.5
Skeletal dysplasia †	67	6.5	4	6.0	-	-	67	3.6
Arthrogryposis, including LMPS	32	3.1	2	6.3	-	-	32	1.7
Facial defects	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	-	-	6	0.3
Total	1029	100	313	30.4	816	100	1845	100

ARS, Amnion rupture sequence; LBWC, Limb-body-wall complex; LMPS, Lethal multiple pterygium syndrome

*   Skeletal anomalies include malposition, isolated limb anomalies, vertebral anomalies, clubfeet, polydactyly, syndactyly, etc.

†   Skeletal dysplasia includes osteochondrodysplasias such as thanatophoric dysplasia, achondrogenesis, osteogenesis imperfecta, etc.

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Table 2. Fetal karyotype among 1029 pregnancies terminated between weeks 11 and 33

Karyotype		Total		CNS anomalies		Cardiovascular anomalies		Urinary system anomalies		Fetal hydrops, cystic hygroma	
		n	%	n	%	n	%	n	%	n	%
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	-	-	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	-	-	-	-	37	38.2
	Klinefelter syndrome	3	0.3	-	-	-	-	-	-	-	-
	Other chromosomal aberrations	47	4.6	12	3.4	12	6.4	5	3.7	3	3.1
Total		1029	100	354	100	187	100	135	100	97	100

* Unknown: not karyotyped or karyotyping unsuccessful

Table 3. Distribution of primary diagnoses among 1029 terminated pregnancies between weeks 11 and 33

Primary diagnosis	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	
	n	%	n	%	n	%	n	%
Chromosomal anomalies with normal morphology	5	3.6	29	3.6	-	-	34	3.3
CNS anomalies	45	31.9	282	34.7	27	36.0	354	34.4
Cardiovascular system anomalies	25	17.7	149	18.3	13	17.3	187	18.2
Respiratory system anomalies	1	0.7	5	0.6	-	-	6	0.6
Diaphragmatic/abdominal wall defects	11	7.8	36	4.4	8	10.7	55	5.3
Gastrointestinal system anomalies	-	-	7	0.9	-	-	7	0.7
ARS/LBWC	7	5.0	25	3.1	1	1.3	33	3.2
Urinary system anomalies	11	7.8	111	13.6	13	17.3	135	13.1
Genital system anomalies	-	-	-	-	-	-	-	-
Skeletal anomalies *	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 defects	-	-	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
Total	141	100	813	100	75	100	1029	100

ARS, Amnion rupture sequence; LBWC, Limb-body-wall complex; LMPS, Lethal multiple pterygium syndrome

*   Skeletal anomalies include malposition, isolated limb anomalies, vertebral anomalies, clubfeet, polydactyly, syndactyly, etc.

†   Skeletal dysplasia includes osteochondrodysplasias such as thanatophoric dysplasia, achondrogenesis, osteogenesis imperfecta, etc.

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Table 4. Correlation between prenatal ultrasound (US) and autopsy findings in 1029 terminated fetuses between 1985 and 2014

Correlation	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	
	n	%	n	%	n	%	n	%
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 detected at US	17	12.1	75	9.2	8	10.7	100	9.7
Category 1 + 2 (Correct main diagnosis)	139	98.6	797	98.0	71	94.7	1007	97.8
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
Category 1-5: Total	141	100	813	100	75	100	1029	100

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Table 5. Correlation between prenatal ultrasound examination and autopsy findings according to primary diagnosis in 1029 terminated fetuses between 1985 and 2014

Diagnoses	Categories									
	1		2		3		4		5	
	n	%	n	%	n	%	n	%	n	%
Chromosomal anomalies with normal morphology	34	100	0	0	0	0	0	0	0	0
Central nervous system anomalies	319	90.1	27	7.6	5	1.4	0	0	3	0.9
Cardiovascular system anomalies	156	83.4	25	13.4	1	0.5	0	0	5	2.7
Respiratory system anomalies	5	83.3	1	16.7	0	0	0	0	0	0
Diaphragmatic/abdominal wall defects	42	76.4	11	20.0	1	1.8	0	0	1	1.8
Gastrointestinal anomalies	6	85.7	1	14.3	0	0	0	0	0	0
ARS/LBWD	29	87.9	4	12.1	0	0	0	0	0	0
Urinary system anomalies	118	87.4	15	11.1	1	0.7	0	0	1	0.7
Genital anomalies	-	-	-	-	-	-	-	-	-	-
Skeletal anomalies *	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 defects	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

ARS, Amnion rupture sequence; LBWC, Limb-body-wall complex; LMPS, Lethal multiple pterygium syndrome

*   Skeletal anomalies include malposition, isolated limb anomalies, vertebral anomalies, clubfeet, polydactyly, syndactyly, etc.

†   Skeletal dysplasia includes osteochondrodysplasias such as thanatophoric dysplasia, achondrogenesis, osteogenesis imperfecta, etc.

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

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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

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| 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

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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	Ultrasound findings not confirmed or not possible to confirm at autopsy
CNS anomalies (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)
Cardiovascular system anomalies (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

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Urinary system anomalies (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 dysplasia (n=1)	13	1987	17	F	23	Lethal dwarfism	Short limbs and large head in relation to extremities. Hypoplastic lungs.	Lethal dwarfism

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

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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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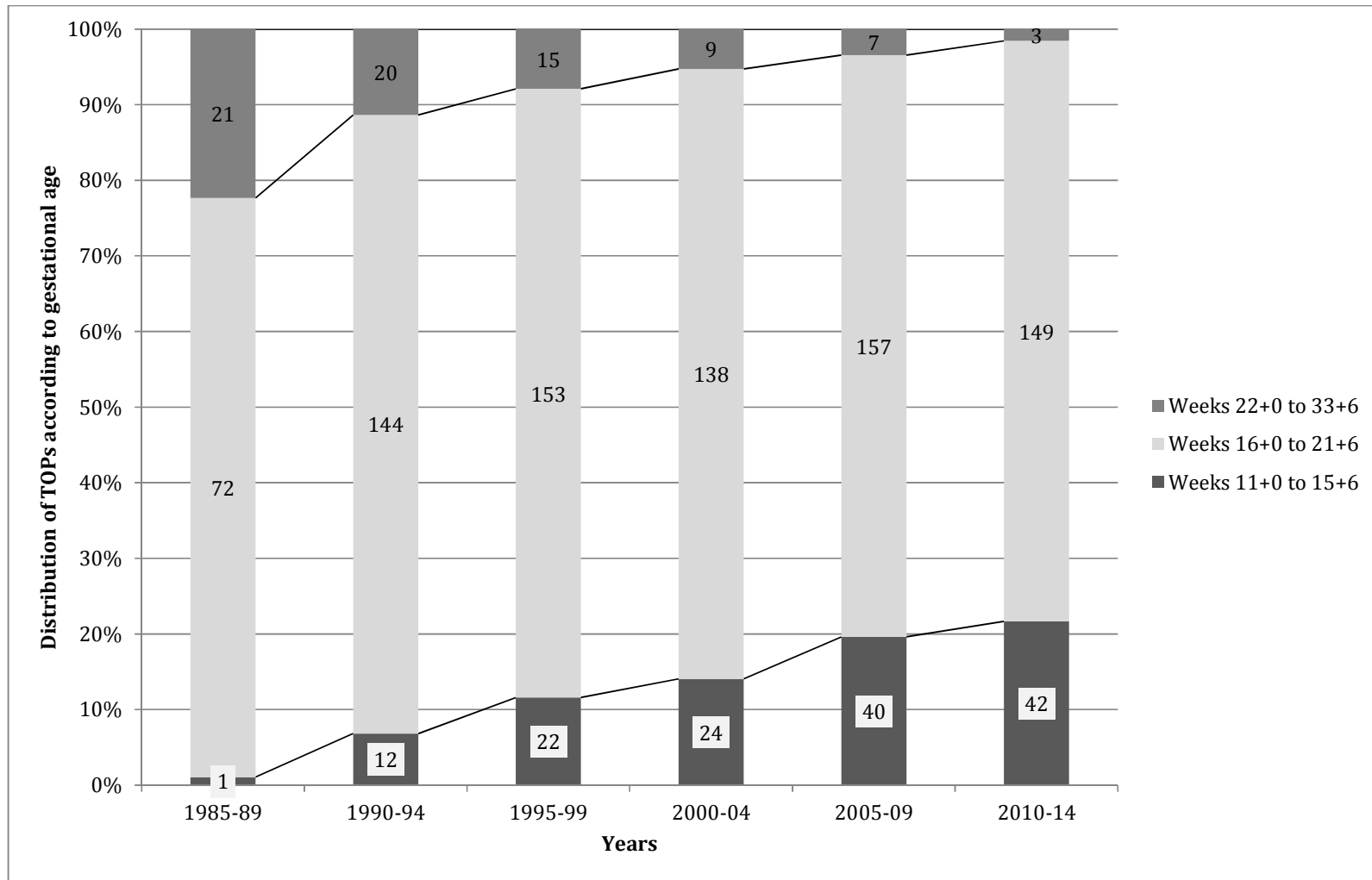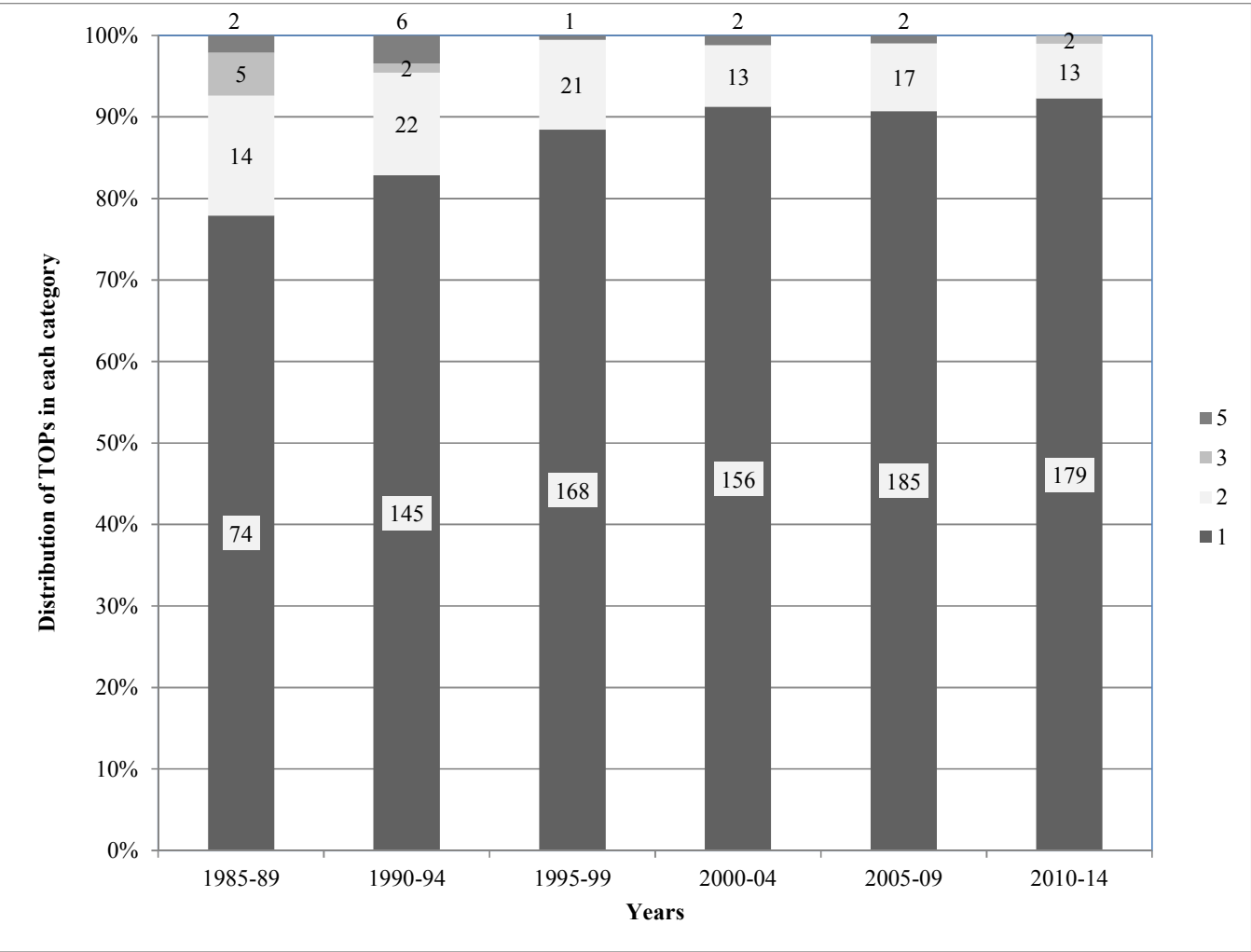24
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Figure 1. The rate of terminations in weeks 11+0 to 15+6 (early TOP), weeks 16+0 to 21+6 (intermediate TOP) and weeks 22+0 to 33+6 (late TOP) over five-year intervals between 1985 and 2014 for 1029 fetuses. The numbers in each column represents the number of TOPs.

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Figure 2. The distribution of TOPs in each correlation category 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.