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

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Keywords:	Central nervous system, Fetal anomalies, Ultrasonography, Termination of pregnancy, Postmortem examination, Correlation ultrasound autopsy
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 (NCFM), 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 (WHO). 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 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.

Autopsy findings of central nervous system (CNS) anomalies in **intact** fetuses following termination of pregnancy (TOP) 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 (NCFM), 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 (WHO).

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 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.

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 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 80-90% 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 three-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 Struksnæs 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 liveborn infants between 1985 and 1994.

The cases resulted in TOP following approval by an abortion committee. Termination of pregnancy 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 17-18 week routine scan by measurement of biparietal diameter (BPD) and/or femur length (FL). In early pregnancies, BPD or crown-rump length (CRL) was used (21). In cases in which the anomaly affected fetal size, gestational age 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 to 2004 two 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 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 25.0 (SPSS Inc., Chicago, Ill., USA) in the statistical analyses, and correlation analyses were performed using Independent samples t-test. $P<0.05$ 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 gestational age was week 18.5 (range: 11-33). There were 51.0 % females (n=214) and 49.0 % males (n=206). The study included one 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. 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). 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 (80.0%, 16/20).

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 karyotype. Half of the population (49.8%, 209/420) had one or more associated organ system anomalies; of these 129 TOPs with normal 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 one case in category 3, no cases in category 4, and three cases where prenatal 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 explains the disagreement between US and autopsy in all cases in category 2, 3 and 5. In category 2, six of nine cases were from the first 15 years (1985-1999). In two cases (2.2 and 2.4, table 6) with anencephaly and cervical rachischisis, this rachischisis was not described at US. In one case (2.9, table 6) with holoprosencephaly and microcephaly, holoprosencephaly was miscategorized and microcephaly not described at US. In the one case in category 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 three cases in category 5, two cases with Dandy-Walker malformation and one hydrocephalus were not confirmed. However, in two of these cases the brain was macerated/autolytic. Figure 2 and 3 illustrate cases with lobar holoprosencephaly and Dandy-Walker malformation.

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 Struksnæs 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 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 category 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 1-2%, 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 one 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, i.e. 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 same event occurring early in pregnancy (44). In our study 19.6% (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 (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 four 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 seven 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 one 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, Dandy-Walker malformation 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 week (51). Prenatal diagnosis can be challenging in mild cases, and in the syndromic form of DWS, anomalies of the heart, face, limbs or gastrointestinal system may be present (52). Concerning the three cases in category 5, two cases with DWS and one with hydrocephalus were not confirmed. However, in two 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 two 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 one 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, choroid plexus cysts (CPC) are usually easy to detect at US (23, 57), but often difficult to confirm at autopsy because they collapse. This study includes some CPC detected at US, but they were not possible to verify at autopsy. All 16 fetuses with CPC 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).

Termination of pregnancy can be a serious result of prenatal diagnosis. In the present 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. (2004) the percentage of fetuses that underwent autopsy fell from 84% to 67% throughout the 90s (63). 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. 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 (2010-14), 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, neural tube defects 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

The authors declare that there is no conflict of interest.

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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

Table 2. Central nervous system anomalies categorized in subgroups in 420 fetuses terminated between week 11 and 33

ICD 10 Code	Subgroup	ICD 11 Code	Week 11+0 to 33+6			Week 11+0 to 15+6		Week 16+0 to 21+6		Week 22+0 to 33+6	
			n	N	%	n	%	n	%	n	%
Q00 Anencephaly and similar malformations	Anencephaly (incl. acrania) With cervical rachischisis With craniorachischisis	LA00	107 21 18	**107**	**22.4**	24	22.4	77	72.0	6	5.6
Q01 Encephalocele	(Meningo-)encephalocele*	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 Other (incl. unspecified) Dandy-Walker malformation	LA04 LA06.0	25 48 12	**85**	**17.8**	2	2.3	70	82.4	13	15.3
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 Alobar Semilobar Lobar	LA05.2	46 26 5 15	**46**	**9.6**	7	15.2	36	78.3	3	6.5
	Other reduction anomalies incl. cerebellar hypoplasia	LA05.5 LA06.1	40 21	**40**	**8.4**	2	5.0	33	82.5	5	12.5
	Cerebral cysts incl. choroid plexus cysts	LA05.7	20 16	**20**	**4.2**	1	5.0	18	90.0	1	5.0
Q05 Spina bifida	Cervical and/or thoracic With A-C malformation type II Lumbar and/or sacral With A-C malformation type II	LA02 + LA03 LA02 + LA03	9 5 97 82	**106**	**22.2**	- 7	- 6.6	9 86	8.5 81.1	- 4	- 3.8
Other	Miscellaneous **			**6**	**1.3**	1	16.7	4	66.6	1	16.7
Total				**477**	**100**	**57**	**11.9**	**383**	**80.3**	**37**	**7.8**

A-C, Arnold Chiari
* Syndromes with encephalocele: Meckel-Gruber (7), Cerebro-oculo-muscular syndrome (COMS) (2)
** Miscellaneous: Microphthalmos (1), Krabbe disease (1), Fraser syndrome (1), Apert syndrome (2), ependymoblastoma (1)

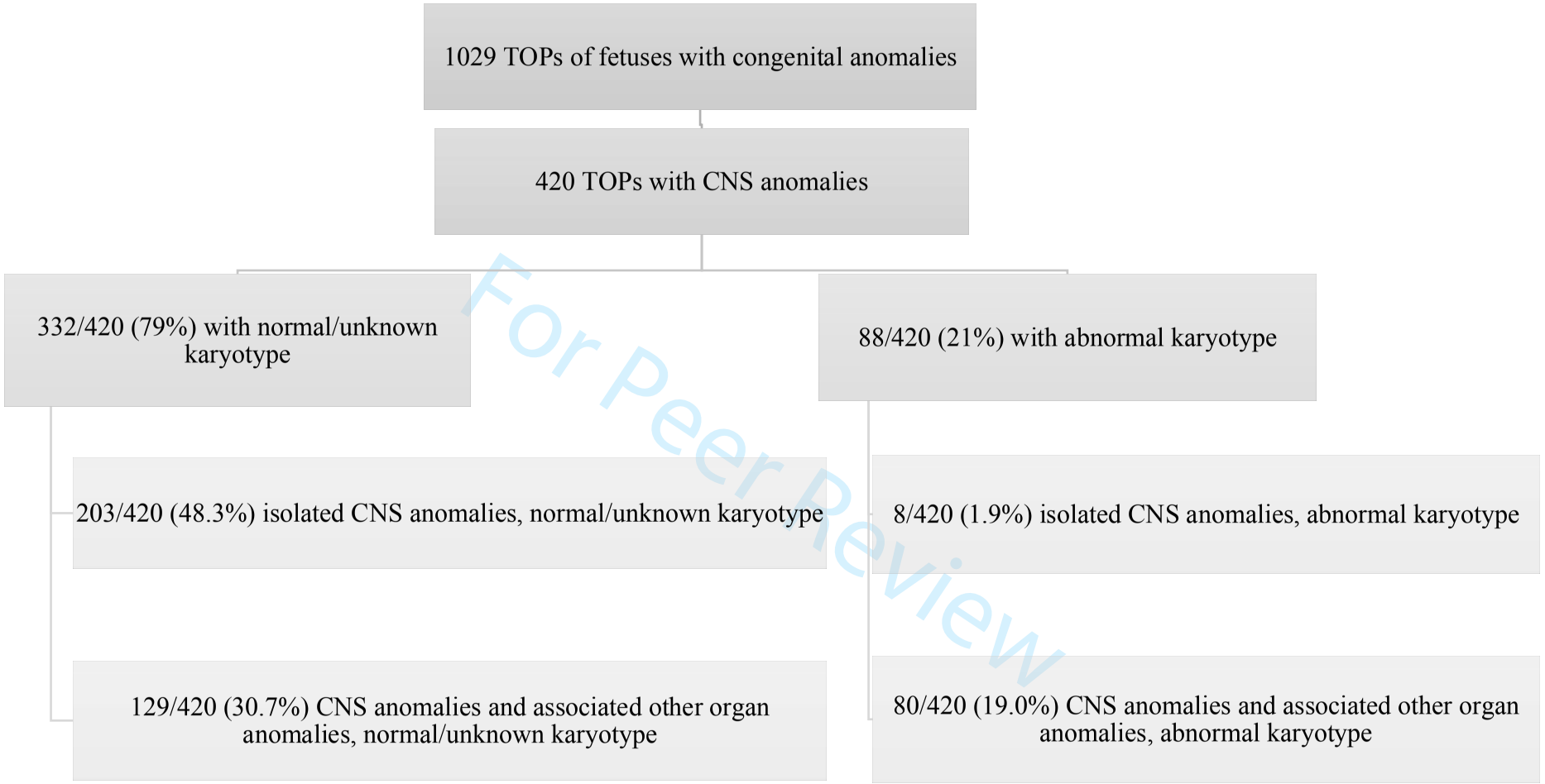

Figure 1. Distribution of karyotype and associated organ anomalies in autopsies of 420 fetuses aborted because of central nervous system anomalies (TOP/termination of pregnancy)

Table 3. Distribution of karyotype in 420 fetuses with central nervous system anomalies

Karyotype		Distribution of 420 TOPs		Distribution in central system anomalies											
				Q00 Anencephaly and similar malformations n= 107		Q01 Ence-phalocele n=34		Q02 Microcephaly n=17		Q03 Congenital hydrocephalus n=85		Q04 Other congenital malformations of brain n=122		Q05 Spina bifida n=106	
		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**

T13, trisomy 13; T18, trisomy 18; T21, trisomy 21; Tripl, triploidy; 45X, Turner syndrome; Other, other chromosomal aberrations.

Table 4. Associated organ anomalies in 420 fetuses with central nervous system anomalies

Associated organ system anomalies	**Total diagnoses**		**Distribution in central system anomalies**											
			Q00 Anencephaly and similar malformations n=107		Q01 Ence-phalocele n=34		Q02 Microcephaly n=17		Q03 Congenital hydrocephalus n=85		Q04 Other congenital malformations of brain n=122		Q05 Spina bifida n=106	
	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*	**73**	**19.5**	12	11.2	5	14.7	-	-	19	22.4	18	14.8	17	16.0
Skeletal dysplasia †	**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**												

GI, gastrointestinal; 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.

Table 5. Correlation between prenatal ultrasound and autopsy findings in 420 fetuses with central nervous system anomalies

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	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**

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, 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, omphalocele	Arnold Chiari malformation, spinal defect, ASD, VSD, tricuspid atresia, 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, lip palate cleft	Acrania, LBWC, scoliosis, 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, cystic hygroma	Autopsy findings not detected at US: Occipital meningocele, 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, hypoplastic pulmonalis	Trisomy 18, VSD, DORV, hypoplastic pulmonalis, 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, polydactyly
5.1	1991	23	Microcephaly, IUGR, Dandy-Walker malformation	Microcephaly, IUGR	US findings not confirmed at autopsy: Dandy-Walker malformation
5.2	1992	22	Hydrocephaly, 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, cerebellar hypoplasia	Dandy-Walker malformation (brain was autolytic)

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

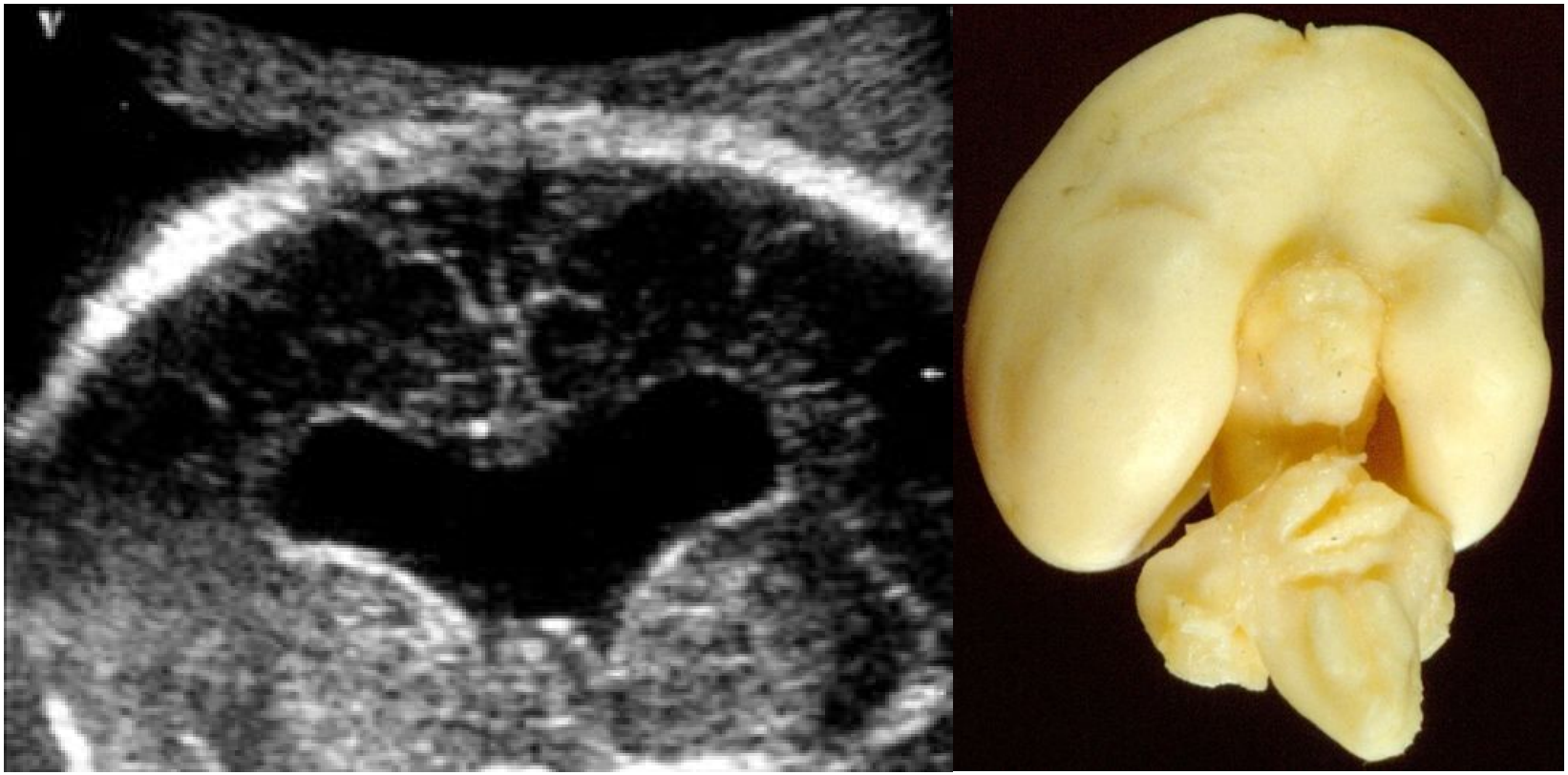

Figure 2. Ultrasound image and postmortem photography of 18 week fetus with lobar holoprosencephaly, 1993. The ultrasound image is a coronal section through the brain with open connection between the lateral ventricles. There is no corpus callosum and no septi pellucidi. Associated anomalies: premaxillary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

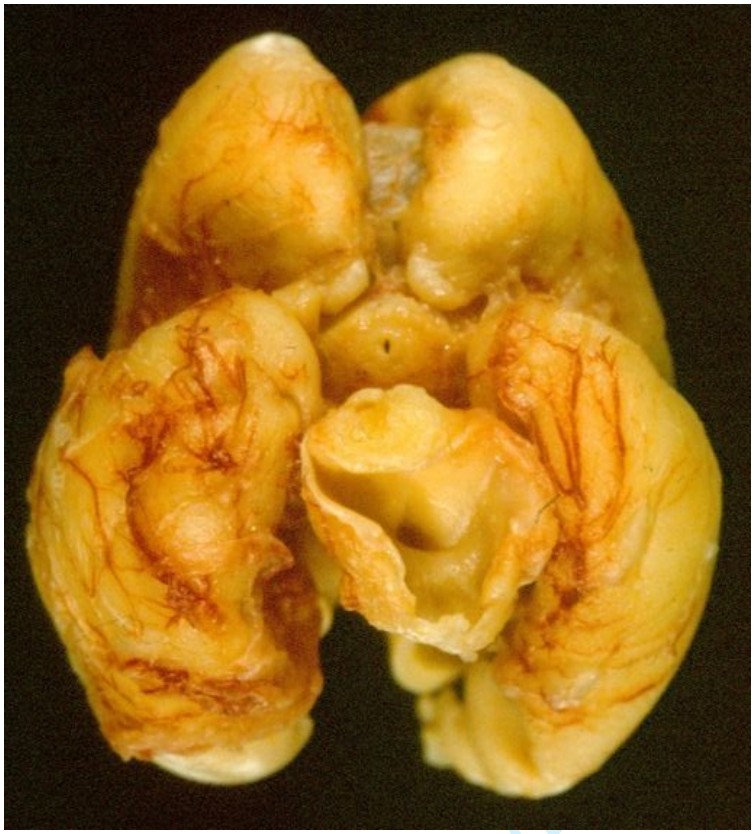

Figure 3. Postmortem photograph of 15 week fetus with with Dandy-Walker malformation, 1997. Associated anomaly: atrioventricular septal defect (AVSD).

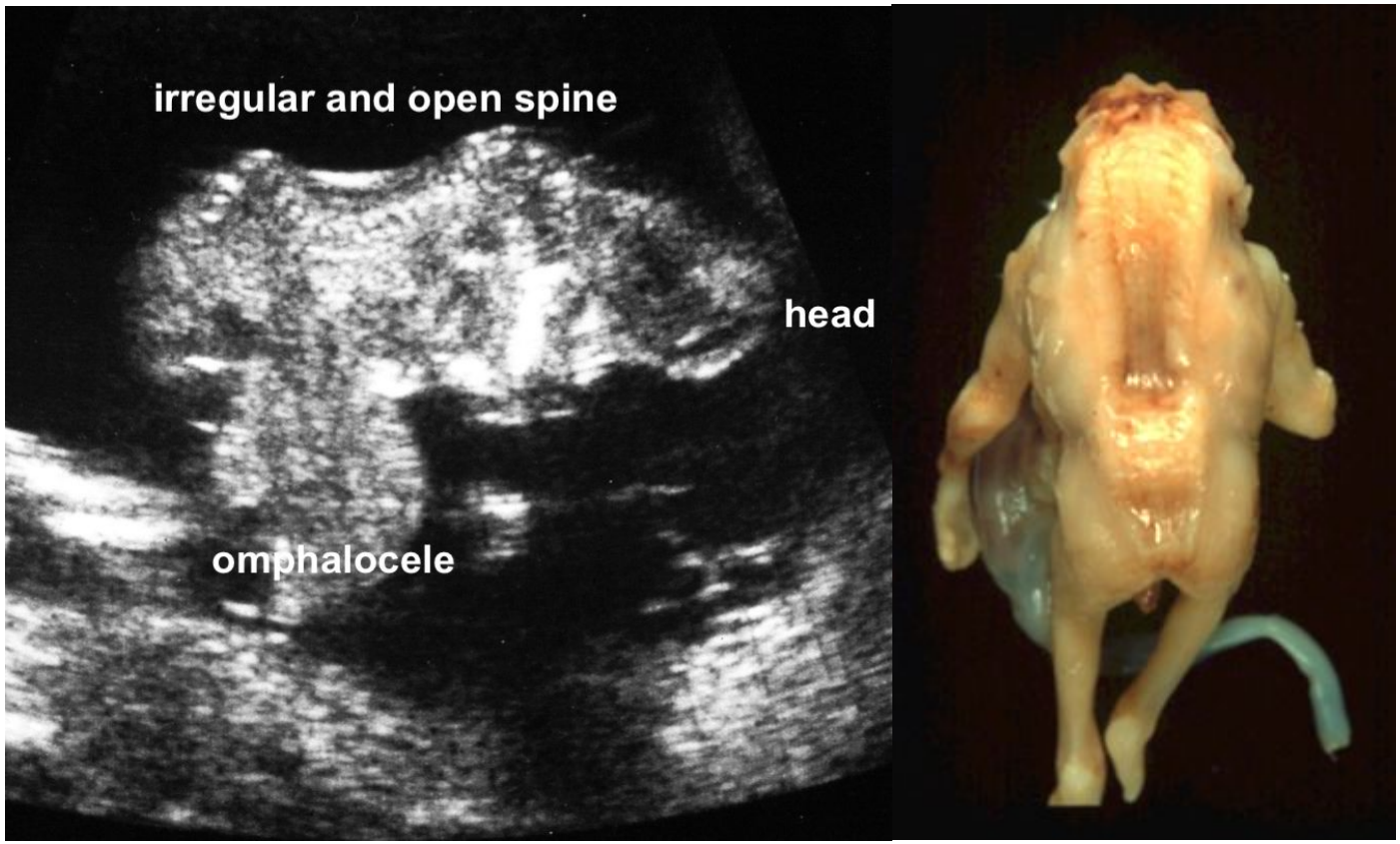

Figure 4. Ultrasound image and postmortem photography of 14 week fetus with craniorachischisis, 1996. The ultrasound image shows a sagittal section through the body with irregular and open spine, abnormal head pole and a large body wall defect – omphalocele. Associated anomalies: trisomy 18, omphalocele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