Follow-up studies in prenatal medicine

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CHAPTER 4

Outcome of children with prenatally diagnosed central nervous system malformations

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Abstract

Objective To study the outcome of pregnancies with a prenatally diagnosed central nervous system (CNS) malformation.

Methods Leiden University Medical Center is a tertiary referral center for fetal ultrasound and invasive prenatal diagnosis. Maternal and neonatal records of prenatally diagnosed CNS malformations were retrospectively reviewed over a 6-year period (1993–1998). Information on current development of surviving children was obtained by contacting the care-giving pediatric neurologist.

Results During the study period 124 fetuses were diagnosed with a CNS malformation. Data on pregnancy and delivery were available for 118 pregnancies Additional malformations were present in 47% of fetuses (55/118). A total of 46% of pregnancies (54/118) were terminated, and 15% (18/118) ended in spontaneous intrauterine death. A total of 39% of pregnancies (46/118) resulted in live birth, and 29 of the infants were still alive at the age of 3 months. One child was lost to follow-up, one infant died at the age of 4 months, and two children died at the age of 3 years. Psychomotor development of the remaining 25 children was normal for five, slightly disabled for seven, moderately disabled for five and severely disabled for eight.

Conclusion Due to the high rate of termination of pregnancy and to the frequent association with other anomalies, the survival rate of pregnancies in which a CNS defect had been diagnosed prenatally was only 25%. More than 50% of surviving children were moderately or severely disabled.

Introduction

Congenital central nervous system (CNS) malformations are relatively common and account for a substantial proportion of miscarriages, stillbirths and infant deaths.[1,2] Moreover, these malformations are an important cause of long-term morbidity in children. Prenatal detection of CNS malformations has substantially improved in the last decade. After diagnosing a CNS anomaly prenatally, sonographers and obstetricians have to counsel the parents, who, after receiving the bad news, are confronted with difficult decisions, which may involve the option of terminating the pregnancy.[3-7] In order to give clinicians some guidance during counselling, we aimed to review the number and type of CNS anomalies that were detected prenatally in our center and to describe the outcome of these pregnancies. We also wanted to know which factors influenced the decisions made by the parents (for example, gestational age at the time of diagnosis, type of CNS malformation and whether or not additional anomalies were found). Furthermore, we wanted to evaluate the accuracy of ultrasound examination in our center. Finally, we were interested in the long-term outcome of survivors, because such information may be particularly helpful in counselling future parents.

Methods

In The Netherlands, fetal anomaly scans are not part of routine prenatal care. Detailed ultrasonography is only performed when there is an increased risk of fetal anomaly based on family history, maternal illness or medication, or complications during pregnancy. Leiden University Medical Center is a tertiary referral hospital for prenatal anomaly scanning. All prenatal ultrasound examinations in this hospital are performed by experienced sonographers and reported in a database. We reviewed this database for all pregnancies with CNS malformations detected between 1 January 1993 and 31 December 1998. We excluded 19 cases with choroid plexus cysts, because these cysts either disappeared spontaneously before birth (n = 15) or the fetus died due to other causes (n = 4). The remaining malformations were classified into seven groups: (1) spina bifida, (2) anencephaly, (3) encephalocele, (4) hydrocephaly, (5) holoprosencephaly, (6) Dandy-Walker malformation and (7) other CNS anomalies.

Malformations were also classified as: (a) isolated, (b) associated with a chromosomal disorder or (c) associated with other anomalies but with a normal karyotype. Isolated malformations included cases with abnormalities developing in sequence from the primary malformation. For example, spina bifida with hydrocephaly and pes equinovarus or holoprosencephaly with facial abnormalities were classified as isolated malformations. We reviewed clinical records of both

mother and child for information on pregnancy, delivery and neonatal period. If extra information was required, we contacted the referring gynecologist in order to complete our data. A clinical geneticist routinely examined all infants as well as fetuses after termination of pregnancy (TOP) or intrauterine death after 16 weeks. Current clinical information at the time of completion of this study was obtained by contacting the pediatric neurologists involved in the care of the surviving children. We based our estimation of mental and motor development on medical information and for some of the older children on their school performance. Because of the large variation in age between the children and the frequency of serious abnormalities, we could not perform a standardized test.

Results

In the 6-year study period, 4,470 pregnancies were screened for congenital anomalies in our center. Mean maternal age in the study group was 30 years. Indication for ultrasound was, first, an increased risk of fetal anomaly already known before the beginning of the pregnancy (Group 1: for example, a congenital anomaly in a previous child) or, second, an increased fetal risk because of pregnancy complications (Group 2: for example, polyhydramnios in the current pregnancy). The mean gestational age in Group 1 (n = 2,731) was 20 weeks, and in Group 2 (n = 1,739) 28 weeks. In 580 cases (116 in Group 1 and 464 in Group 2) a fetal anomaly was diagnosed. A CNS malformation was diagnosed in 2.8% of pregnancies (124/4,470), but we only had information on pregnancy and delivery for 118 cases. Ten of these 118 were multiple pregnancies (two triplets and eight twins) but in each of these pregnancies only one fetus had a congenital CNS malformation. The mean age of the 118 women at the time of delivery was 30 years (range, 18–43 years). Karyotyping was performed prenatally in 70 cases and postnatally in eight cases. In 40 cases the parents chose not to undergo karyotyping. A total of 46% of fetuses (54/118) were male and 49% were female (58/118). In six unkaryotyped cases, four with anencephaly, one with holoprosencephaly and one with encephalocele, the sex remained undetermined after TOP (five cases between 12 and 17 weeks) or fetal death (one case at 12 weeks). The mean gestational age at the time of diagnosis was 28 weeks (range, 12–42 weeks). A total of 43% of CNS malformations (51/118) were diagnosed before 24 weeks and 57% (67/118) after 24 weeks' gestation. When the CNS malformation was diagnosed before 24 weeks, only 24% of mothers (12/51) chose to continue the pregnancy, whereas 78% of mothers (52/67) continued their pregnancy when the malformation was diagnosed after 24 weeks.

Table 1 lists the CNS malformations diagnosed at the time of ultrasound examination. Closure defects of the neural tube (spina bifida, anencephaly and

encephalocele) were the most common finding (51%), followed by hydrocephaly without spina bifida (26%). Holoprosencephaly (8%) and Dandy-Walker malformation (7%) were less common. Other malformations (the remaining 8%) were microcephaly (one diagnosed as Pena Shokeir syndrome) (n = 4), enlarged cisterna magna (n = 3), enlarged third ventricle in association with Pena Shokeir syndrome (n = 1) and isolated agenesis of the corpus callosum (n = 1). In 53% of fetuses (63/118), the CNS malformation appeared to be isolated. In the remaining 47% of fetuses (55/118) there were additional abnormalities: 17 chromosomal abnormalities (five trisomy 18, three trisomy 13, three translocations, two deletions, two triploidy, one tetrasomy and one Turner syndrome), six prenatally undetected CNS malformations and 32 other anatomical anomalies (e.g. anomalies of the heart, kidney, diaphragmatic hernia and syndromes such as Pena Shokeir syndrome, Goldenhar syndrome and Meckel–Grüber syndrome). None of the fetuses with a CNS malformation in combination with a chromosomal disorder survived longer than 3 months after birth. In the majority of cases (37/55) additional anomalies were so serious that they determined the outcome of pregnancy. Only 20% of fetuses (11/55) with a CNS malformation in combination with additional anomalies and only 30% of fetuses (18/63) with an isolated CNS malformation survived beyond 3 months after birth.

Table 1. Classification of 118 pregnancies with prenatally diagnosed central nervous system malformations

Main CNS malformation on prenatal ultrasound	Isolated CNS malformation	In combination with abnormal karyotype	In combination with other malformations	Total
Spina bifida	16*	3	7	26
Anencephaly	24†	-	-	24
Encephalocele	1	1	8	10
Hydrocephaly	11	5	15	31
Holoprosencephaly	3	4	3	10
Dandy - Walker	4	3	1	8
Other	4	1	4	9
Total	63	17	17	118

*All fetuses with isolated spina bifida had associated anomalies (e.g. hydrocephaly, hindbrain herniation, pes equinovarus) or ultrasonographic markers ('lemon' or 'banana' sign).[20]
†Three fetuses with anencephaly also had spina bifida. CNS, central nervous system.

Table 2 lists the outcome of the 118 pregnancies according to the type of CNS malformation. TOP was performed in 46% of pregnancies (54/118). In 13% of pregnancies (15/118) TOP was performed after 24 weeks, because it was decided that the fetus had an abnormality that was not compatible with life or would cause severe handicap with inhumane suffering. All these fetuses, except those with anencephaly and one fetus with rachischisis totalis, had serious additional (non-CNS) anomalies. Spontaneous intrauterine death occurred in 15% of pregnancies (18/118). Eventually, 46 pregnancies resulted in live births and 25% of the infants were still alive at the age of 3 months (45% of all pregnancies without TOP). Of the 17 infants who died in the first 3 months after birth, 14 died in spite of therapeutic interventions. In three cases (diagnosed with spina bifida, hydrocephaly and Pena Shokeir syndrome, respectively) the parents declined therapeutic interventions.

Table 2. Classification of 118 pregnancies with prenatally diagnosed central nervous system malformations

	TOP		Intrauterine death		Live born		
Ultrasound findings	**<24 weeks**	**>24 weeks**	**Ante-partum**	**Intra-partum**	**Died <3 months**	**Alive after 3 months**	**Total**
Spina bifida	8	3	2	1	4	8	26
Anencephaly	13	6	1	1	3	--	24
Encephalocele	7	1	1	--	--	1	10
Hydrocephaly	8	2	3	1	2	15	31
Holoprosencephaly	2	1	3	2	2	-	10
Dandy - Walker	1	2	1	-	3	1	8
Other	--	--	1	1	3	4	9
Total (n (%))	39(33%)	15(13%)	12(10%)	6(5%)	17(14%)	29(25%)	118(100%)

TOP, termination of pregnancy.

In 12 cases, listed in **Table 3**, diagnosis after birth differed from prenatal ultrasound diagnosis. In nine cases the abnormalities turned out to be more extensive than prenatally suspected, whereas in three cases they turned out to be less extensive. In all cases the medical intervention (if any) remained justified. Difficulties in the prenatal diagnosis of CNS malformations occurred predominantly with spina bifida, with posterior fossa anomalies and with corpus callosum agenesis.

Table 3. Data from 12 children in whom antepartum diagnosis differed from postpartum diagnosis

Gestational age at diagnosis (weeks)	**Diagnosis before birth**		**Diagnosis after birth**		
	CNS anomaly	***Other anomalies***	***CNS anomaly***	***Other anomalies***	***Outcome***
23	Spina bifida (S3-S4)	Growth restriction	Spina bifida not confirmed	Low-set ears, abnormal appearance	Intrauterine death at 25 weeks
25	Microcephaly, encephalocele	Large VSD, single umbilical artery, unbalanced translocation (46,XX;t(1;3))	Microcephaly, epidermal cyst	Tetralogy of Fallot, unbalanced translocation (46,XX;t(1;3))	TOP
19	Hydrocephaly	Growth restriction, oligohydramnios triploidy (69,XXX)	Spina bifida (L3-L4)	Triploidy (69,XXX), micrognathia, cheilo-gnathopalatoschisis, polydactyly, horseshoe kidney, pes equinovarus	Intrauterine death at 27 weeks
30	Hydrocephaly	None	Hydrocephaly	Walker Warburg syndrome Lissencephaly, eye and skeletal malformations, muscle dystrophy	Died at 3 years due to pneumonia
33	Hydrocephaly, agnesis of the corpus callosum. Suspicion of spina bifida and pes equinovarus	None	Hydrocephaly	None	Alive
34	Hydrocephaly	None	Hydrocephaly	Goldenhar syndrome: palatoschisis, anal atresia, deafness	Alive
40	Hydrocephaly	None	Spina bifida (cervical myelo-meningocele)	None	Alive
25	Suspicion of Dandy-Walker malformation	VSD with overriding aorta, trisomy 13, growth restriction	Holoprosencephaly	VSD with overriding aorta, trisomy 13, palatoschisis, abnormal hands and feet	TOP (severe maternal pre-eclampsia)
32	Dandy-Walker malformation or arachnoidal cyst	Fluid collection in the neck	No Dandy-Walker malformation or cyst	Hydrops fetalis	Died 3 weeks after birth
34	Suspicion of Dandy-Walker malformation	Hyperechogenic kidneys, possibly polycystic kidney disease	Dandy-Walker malformation not confirmed	Hyperechogenic kidneys, trisomy 13	Died 2 days after birth
34	Dandy-Walker malformation, partial vermis aplasia	None	Hypoplasia right cerebellar hemisphere	None	Alive
31	Agenesis of the corpus callosum	None	Head circumference > 98th percentile	None	Alive

CNS, central nervous system; TOP, termination of pregnancy; VSD, ventricular septal defect.

Table 4. Outcome of 29 children who survived the first 3 months after birth

Gestation at diagnosis (weeks)	Diagnosis postpartum	Gestation at birth (weeks)	Age at follow-up (years)	Mental disabilities	Motor disabilities
35	Spina bifida (L3-S2)	37	6	+ (Special school)	++ (Wheelchair-bound)
27	Spina bifida (occipital meningocele)	35	5.5	N	+ (Walks independently)
39	Spina bifida (L2-S2)	40	4	+++	+++
29	Spina bifida (L2-S2)	37	4	+	+++ (Wheelchair-bound)
37	Spina bifida (Th12-L1)	41	4	N	+++ (Wheelchair-bound)
40	Spina bifida (cervical myelomeningocele. Prenatally diagnosed as hydrocephaly)	40	3	N	+++ (Wheelchair-bound)
17	Spina bifida (L5-S2 (fetal valproate syndrome)	40	3	+	+ (walks independently) with callipers)
24	Spina bifida (L5-S1)	37	2	N	+ (Walks independently)
15	Spina bifida (L5-S1)	39	1	N	N
20	Encephalocele	35	Died at 3 years (cause unknown)	+++	+++
33	Hydrocephaly	37	7	N	+ (Walks independently)
35	Hydrocephaly	40	5	++ (severe deafness)	N
34	Hydrocephaly (Goldenhar syndrome)	38	4	++ (severe deafness)	++ (Walks with aid a few steps)
39	Hydrocephaly, camptodactyly	39	4	+++	+++ (Tetraparesis)
30	Hydrocephaly (Walker Warburg syndrome)	38	Died at 3 years due to pneumonia	+++	+++
39	Hydrocephaly	40	3	N	N
29	Hydrocephaly	35	3	N	+++ (Diplegia)
34	Hydrocephaly, corpus callosum agenesis	37	2.5	+	+ (Walks independently)
30	Hydrocephaly	31	2.5	N	+ (Walks independently)
27	Hydrocephaly, partial corpus collosum	33	2	+++ (Blind)	+++
36	Hydrocephaly	37	2	N	N
26	Hydrocephaly, partial corpus callosum	37	2	++ (Severe deafness)	+ (Walks independently)
31	Hydrocephaly, anal atresia, syndactyly	36	Died at 4 months due to pneumonia	+++	+++
26	Enlarged cisterna magna prenatally normalizing and postpartum not confirmed	40	7	N	N
30	Microcephaly	40	3	+++	+++
30	Microcephaly	39	2	++	++
34	Hypoplasia right cerebellar hemisphere (prenatally diagnosed as Dany-Walker malformation)	37	1.5	+	+
31	Head circumference >98th percentile (prenatal suspicion of corpus callosum agenesis)	38	0.5	N	N
30	Hydrocephaly		37	Lost to follow-up	

N, normal development; +, slightly disabled; ++, moderately disabled; +++, severely disabled.

Table 4 lists the 29 infants surviving more than 3 months, classified according to diagnosis after birth. One child was lost to follow-up after 3 months. The duration of follow-up of the remaining 28 children varied from 6 months to 7 years. Two children with encephalocele and hydrocephaly, respectively, died at the age of 3 years, and one child with hydrocephaly died at the age of 4 months. Of the remaining 25 children, five had normal psychomotor development, seven were slightly disabled, five were moderately disabled, and eight were severely disabled. Normal development was seen in one child with sacral spina bifida, two with hydrocephaly, one with prenatally suspected corpus callosum agenesis and one with prenatally suspected posterior fossa anomaly. The two latter anomalies were, however, not confirmed after birth.

Discussion

We have described a cohort of fetuses diagnosed with CNS abnormalities at our center. More than half of the prenatal diagnoses were made after 24 weeks' gestation. This is a consequence of the fact that prenatal ultrasound screening for abnormalities is not routinely performed in The Netherlands. In 90% of cases prenatal ultrasound examination provided a complete and correct diagnosis. In 8% of cases additional, prenatally undetected, abnormalities were found after birth, and in 2% the abnormalities were found to be less extensive than prenatally suspected. In 51% of cases closure defects of the neural tube were found, and 26% of cases were diagnosed as hydrocephaly without spina bifida. CNS abnormalities are very frequently associated with secondary anomalies; in our study all spina bifida cases had hindbrain herniation, hydrocephaly, or pes equinovarus and many cases of holoprosencephaly had facial abnormalities. Moreover, 45% of fetuses with CNS abnormalities in our study were found to have additional anomalies, or an abnormal karyotype. After the diagnosis was made, 46% of pregnancies were terminated and another 29% resulted in fetal or neonatal death. None of the fetuses with an abnormal karyotype, anencephaly or holoprosencephaly survived. More than 50% of the surviving children remained moderately or severely disabled, and only 4% of the initial cohort had normal psychomotor development.

The major reasons for the low survival rate of fetuses with CNS anomalies in our study are the high rate of TOP as well as the frequent coexistence of additional anomalies. Previous studies have also found a high rate of additional (CNS or other) anomalies. Aletebi and Fung described 15 fetuses with posterior fossa anomalies, seven of which were found to have additional anomalies.[8] Ecker *et al.* found that 86% of fetuses with posterior fossa anomalies had additional malformations.[9] Den Hollander *et al.* found that 50% of fetuses with ventriculomegaly had additional anomalies.[10] Kölble *et al.* described ten fetuses

with prenatally diagnosed Dandy-Walker malformation.[11] Postnatally, Dandy-Walker malformation was confirmed in all cases, but additional malformations, not diagnosed prenatally, were found in seven cases.

The Netherlands is one of two countries in the European Union where neither routine ultrasound screening for fetal anomalies nor maternal serum screening are implemented. A recent report from the Dutch Health Council again advised against prenatal ultrasound screening.[12] This restrictive policy clearly explains why so many CNS anomalies in our study were detected after 24 weeks. In the Netherlands, TOP is prohibited after 24 weeks' gestation, unless detected anomalies are considered to be incompatible with postnatal life or would cause severe handicap with inhumane suffering. The advanced gestational age at the time of detection probably explains why, compared to other European countries, a smaller percentage of pregnancies with CNS anomalies were terminated.[9,13-15] Forrester and Merz studied the various factors influencing the decision to perform TOP and found that 65% of pregnancies with prenatally diagnosed neural tube defects were terminated.[13] Hassed *et al.* reported on 25 families faced with a CNS anomaly that was considered lethal.[14] Only two of the families elected to continue the pregnancy. Ecker *et al.* described 99 pregnancies with prenatally diagnosed posterior fossa anomalies.[9] A total of 50% of these pregnancies were terminated. Cornel *et al.* also found that the percentage of TOP in prenatally diagnosed neural tube defects in The Netherlands was relatively low compared to other European countries.[15] Based on these studies, it seems likely that individual parents would benefit from the introduction of routine second-trimester fetal ultrasound in The Netherlands. Most of the discrepancies between prenatal and postnatal diagnosis in our study concerned non-CNS anomalies that were not detected with prenatal ultrasound. However, in two cases with multiple anomalies, closure defects of the neural tube were missed, and in two cases with hydrocephaly, prenatally suspected spina bifida was not confirmed after birth. Other false-positive diagnoses concerned posterior fossa anomalies and agenesis of the corpus callosum. Isaksen *et al.* reported reliability rates similar to those found in our study.[16] They compared prenatal ultrasound and postmortem findings in 124 fetuses and infants with CNS anomalies and found complete concordance in 89% of cases. Den Hollander *et al.* described 42 cases with prenatally diagnosed fetal ventriculomegaly and found complete concordance in 28 cases, more extensive anomalies in ten, and less extensive anomalies in four cases.[10]

Of course, the prognosis for surviving children depends on their specific anomaly. In our study the children most likely to survive were those with spina bifida and hydrocephaly. Out of nine survivors with spina bifida, five had normal mental development and four could walk independently. Their development depended mainly on the level of the lesion. Out of 13 survivors with hydrocephaly, five had normal mental development, and seven could walk independently.

Overall, the children with isolated hydrocephaly were less disabled than those with additional anomalies. Mulder *et al.* described the outcome of 67 fetuses with a CNS anomaly.[17] Only 1/25 fetuses with spina bifida survived, and this child was severely retarded at the age of 2 years. Out of three survivors with hydrocephaly, one child was moderately retarded and two developed normally. Den Hollander *et al*. found normal psychomotor development in 12/26 surviving children with prenatally diagnosed ventriculomegaly.[10] Lipitz *et al.* found normal neurological outcome for 25/26 fetuses with isolated, borderline unilateral ventriculomegaly.[18] Twining *et al.* studied 38 cases of fetal ventriculomegaly.[19] They found that fetuses with isolated ventriculomegaly had an 80% chance of survival and a 50% chance of normal development. Aletebi and Fung found some degree of cognitive, neurosensory or psychomotor delay at follow-up in 4/5 survivors with prenatally diagnosed posterior fossa abnormalities.[18] In general, our findings concur with those of previous studies.

Conclusion

We conclude that prenatal diagnosis of CNS malformations is fairly reliable and that the prognosis of affected fetuses is generally poor. Due to the high rate of TOP and to the frequent association with other anomalies, the survival rate was only 25% in our study. More than 50% of surviving children were moderately or severely disabled.

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References

1. Rosano A, Botto LD, Botting B, Mastroiacovo P. Infant mortality and congenital anomalies from 1950 to 1994: an international perspective. *J Epidemiol Community Health 2000;54:660-6.*
2. Brett EM. Hydrocephalus and congenital anomalies of the nervous system other than myelomeningocele. In Paediatric Neurology, Brett EM (ed.). *Churchill Livingstone: London, UK. 1991;467-509.*
3. Vos JMI, Offringa M, Bilardo CM, Lijmer JG, Barth PG. Sensitive and specific screening for detection of spina bifida by echography in the second trimester; systematic review and meta-analysis. *Ned Tijdschr Geneeskd 2000;144(36):1736-41.*
4. Limb CJ, Holmes LB. Anencephaly: changes in prenatal detection and birth status, 1972 through 1990. *Am J Obstet Gynecol 1994;170:1333-8.*
5. Lai TH, Chang CH, Yu CH, Kuo PL, Chang FM. Prenatal diagnosis of alobar holoprosencephaly by two-dimensional and three-dimensional ultrasound. *Prenat Diagn 2000;20:400-3.*
6. Van Dorsten JP, Hulsey TC, Newman RB, Menard MK. Fetal anomaly detection by second-trimester ultrasonography in a tertiary center. *Am J Obstet Gynecol 1998;178:742-9.*
7. Grandjean H, Larroque D, Levi S. Eurofetus Study Group. The performance of routine ultrasonographic screening of pregnancies in the Eurofetus Study. *Am J Obstet Gynecol 1999;181:446-54.*
8. Aletebi FA, Fung Kee Fung K. Neurodevelopmental outcome after antenatal diagnosis of posterior fossa abnormalities. *J Ultrasound Med 1999;18:683-9.*
9. Ecker JL, Shipp TD, Bromley B, Benacerraf B. The sonographic diagnosis of Dandy-Walker and Dandy-Walker variant: associated findings and outcomes. *Prenat Diagn 2000;20:328-32.*
10. Den Hollander NS, Vinkesteijn A, Schmitz- van Splunder P, Catsman-Berrevoets C, Wladimiroff YW. Prenatally diagnosed fetal ventriculomegaly; prognosis and outcome. *Prenat Diagn 1998;18:557-66.*
11. Kölble N, Wisser J, Kurmanavicius J, Bolthauser E, Stallmach T, Huch A, Huch R. Dandy-Walker malformation: prenatal diagnosis and outcome. *Prenat Diagn 2000;20:318-27.*
12. Health Council of the Netherlands. Prenatal Screening: Down's Syndrome, Neural Tube Defects, Routine Ultrasonography, *Publication No. 2001/11. The Hague: Health Council of the Netherlands, 2001.*
13. Forrester MB, Merz RD. Prenatal diagnosis and elective termination of neural tube defects in Hawaii, 1986-1997. *Fetal Diagn Ther 2000; 15:146-51.*
14. Hassed SJ, Miller CH, Pope SK, Murphy P, Quirk JG Jr, Cunniff C. Perinatal lethal conditions: the effect of diagnoses on decision making. *Obstet Gynecol 1993;82:37-42.*
15. Cornel MC, Leurquin P, de Walle HEK, Staal-Schreinemachers AL, Beekhuis JR. Epidemiology of prenatal diagnosis and selective pregnancy termination because of fetal neural tube defects in The Netherlands in comparison to other European countries.

Ned Tijdschr Geneeskd 1997;141:2239-44.

16. Isaksen CV, Eik-Nes SH, Blaas HG, Torp SH. Comparison of prenatal ultrasound and postmortem findings in fetuses and infants with central nervous system anomalies. *Ultrasound Obstet Gynecol 1998;11:246-53.*
17. Mulder T, Boer K, Wolf H, Zondervan HA, Kok JH. Poor prognosis in children with ultrasonographically diagnosed abnormalities of the central nervous system. *Ned Tijdschr Geneeskd 1996;140:609-12.*
18. Lipitz S, Yagel S, Malinger G, Meizner I, Zalel Y, Achiron R. Outcome of fetuses with isolated borderline unilateral ventriculomegaly diagnosed at mid-gestation. *Ultrasound Obstet Gynecol 1998;12:23-31.*
19. Twining P, Jaspan T, Zuccollo J. The outcome of fetal ventriculomegaly. *Br J Radiol 1994; 67: 26-31.*
20. Nicolaides KH, Campbell S, Gabbe SG, Guidetti R. Ultrasound screening for spina bifida: cranial and cerebellar signs. *Lancet 1986;12:72-4.*