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MATERNAL-FETAL MEDICINE

Termination of pregnancy after prenatal diagnosis of spina bifida: a German perspective

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Abstract
Purpose To analyze fetal cases with spina bifida undergoing termination of pregnancy according to chromosomal analysis and further diagnosed sonographic findings.
Methods Retrospective analysis of cases with spina bifida leading to termination of pregnancy in a tertiary referral center from 2002 to 2011.
Results In the study period, 246 cases of spina bifida were diagnosed in our center and 157 parents chose termination of pregnancy. The time of diagnosis was on average 2 days before the first presentation at our department (22 + 3, range: 12 + 3 − 33 + 3 weeks of gestation). Among 157 pregnancies with spina bifida and termination of pregnancy, further malformations could be detected in 46 (29.3 %) cases. An abnormal karyotype could be found in 13 (18.1 %). Severe ventriculomegaly or mild/moderate ventriculomegaly was present in 109 (69.4 %) and 29 (18.5 %) of the cases, respectively, while banana sign was detectable in 153 cases (97.5 %). In the majority, the upper lesion level was lumbar (71.3 %). In 67 cases (42.7 %), termination of pregnancy took place in or after the 24th week of gestation.
Conclusion Direct and indirect signs of spina bifida were detectable in nearly all cases independent of the gestational age. Therefore, the diagnosis could have been made in all cases with late termination. Implementation of a uniform prenatal care including first-trimester scan with potential signs for open spina bifida and second-trimester anomaly scan with indirect intracranial findings and direct detection of spinal lesion could lead to an earlier diagnosis and help to reduce late termination of pregnancy in neural tube defects.

Keywords Spina bifida · Termination of pregnancy · Neural tube defect · Ultrasound

Introduction

Risk of neurological impairment due to structural malformations is the main reason for late termination of pregnancy (TOP). Neural tube defects (NTD), such as anencephaly, cephalocele, spina bifida and other rare spinal fusion disorders, represent the largest group [1].

In the past, the level of maternal serum alpha-fetoprotein assessment served as a screening test for open spina bifida in the second trimester [2, 3]. Until 2011, the German guidelines of prenatal diagnostics included only measurements of the biparietal diameter and head circumference. Current screening consists solely of sonographic findings in the first (not visible/not typical intracranial translucency, thickened brainstem and larger brain stem occipital distance ratio) and the second trimester anomaly scan (examination of posterior fossa and alterations in size and appearance of the brain structure) [2]. Herniation of cerebellum (Chiari Malformation II) is the most specific and sensitive indirect finding for prenatal diagnosis of spina bifida [2].

While anencephaly is more likely to be diagnosed early in pregnancy [4, 5], spina bifida was formerly detected later and only in three of four cases [4]. Today, detailed ultrasound examination during the second trimester detects up

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to 100 % of neural tube defects [4, 6, 7]. Magnetic resonance imaging, as a useful additional tool to ultrasound, can confirm suspected findings and exclude additional central nervous system abnormalities [6–9].

Spina bifida in contrast to anencephaly is per se not lethal and morbidity strongly depends on the size and level of the lesion. Almost all cases with spina bifida are associated with lifelong handicaps and morbidity as well as mortality [10–12].

The morbidity varies, but a large part of the children have a normal neurodevelopment and are more or less able to walk [11, 12]. Generally, morbidity depends on the level of spinal lesion, need for ventriculoperitoneal shunting and associated shunt complications. Although in utero repair of myelomeningocele (fetoscopic or open repair technique) has been shown to improve neurological outcome, so far postnatal surgery is still the worldwide standard treatment of neural tube defects [11–15].

Despite today's enhanced prediction of prognosis and improved therapies, a substantial proportion of women still opt for TOP. The rate of TOP varies internationally, from 56 % in cases of isolated open spina bifida [16] to an overall rate of 70–81 % in cases with neural tube defects [4, 17].

This analysis focuses on TOP in cases with fetal spina bifida in a single tertiary referral center. Our study comprises sensitivity of ultrasonographic signs, associated malformations, time of diagnosis and TOP.

Materials and methods

This was a retrospective cohort study (retrospective analysis of prospectively collected data) in a single tertiary referral center over a 10-year period from 2002 to 2011. Cases were identified by searching the database (ViewPoint 5.6.23.59; ViewPoint Bildverarbeitung GmbH, Weßling, Germany) in the Department of Obstetrics and Prenatal Medicine, University Hospital Bonn, Germany. The inclusion criteria were singletons with isolated and non-isolated spina bifida. Gestational age was calculated based on the last menstrual period and confirmed by the crown–rump length measurement at 11–13 weeks of gestation. The cases were divided into two groups based on the gestational age at the time of TOP ($\leq 23 + 6$ or $\geq 24 + 0$ weeks of gestation).

Multiple pregnancies and TOPs due to other reasons were excluded from the final analysis.

All TOPs were conducted according to German law §218a. Written consent was obtained by each woman. Patients above 20 weeks of gestation received a feticide by hyperosmolar potassium chloride administration (1 mol KCl, 7.46 %) into fetal circulation. Labor was routinely induced with misoprostol or with gemeprost after a previous cesarean section.

We provided for quantitative variables, either the sample median or mean. Statistical dispersion was reported by giving either the range or the standard deviation (SD). Categorical data were summarized by their absolute and relative frequencies. These descriptive statistics were reported for both the complete sample and for each subgroup.

Results

From 2002 to 2011 we identified 12.698 live births, out of which 63 newborns (0.5 %) had a spinal dysraphism. 211 TOPs out of the 1017 registered in our database were performed due to a neural tube defect. We excluded 29 cases with anencephaly and 25 with cephalocele, leaving 157 cases for the final analysis. Only one case with spina bifida occulta (<24 weeks of gestation), detected by tethered cord, was included in the analysis.

Gestational age at the time of diagnosis was on average 2 days before the first presentation at our department ($22 + 3$, range $12 + 3$–$33 + 3$ weeks of gestation). Time lapse between the first diagnosis and TOP was at median 12 days (range 4–47 days) in the group $\leq 23 + 6$ weeks of gestation and 15 days (range 4–36 days) in the group ≥ 24 weeks of gestation. Forty percent ($n = 27$) of TOP ≥ 24 weeks of gestation were discovered firstly $\leq 23 + 6$ weeks of gestation.

Women's demographic data are displayed in Table 1. Isolated spina bifida was identified in 63 (70.0 %) and non-isolated spina bifida in 27 pregnancies (30.0 %) $\leq 23 + 6$ weeks of gestation and ≥ 24 weeks of gestation in 48 cases (71.6 %) and 19 cases (28.4 %), respectively. The characteristics of non-isolated spina bifida cases are displayed in Table 2.

Banana sign was detectable in 153 of 157 cases (97.5 %). The banana sign was not present only in three cases $\leq 23 + 6$ weeks of gestation, out of which one presented with occult spina bifida and two with sacral lesions, and one case $\geq 24 + 0$ weeks of gestation presented with lumbar lesion. Mild to moderate ventriculomegaly (10–15 mm) and severe ventriculomegaly (>15 mm) were diagnosed in 29 and 109 cases (18.4 and 69.4 %), respectively.

We identified 26 fetuses with thoracic spina bifida (16.6 %), 112 with lumbar (71.3 %) and 16 with a sacral lesion (10.2 %) (Fig. 1). Most of the cases with upper lesion level $\geq$L3 were detected earlier in pregnancy (Fig. 2).

Severe ventriculomegaly was detected in 76.6 % in cases with isolated spina bifida and in 52.2 % in the non-

Table 1 Women's demographics

Characteristics	All patients $n = 157$	Patients ≤23 + 6 weeks $n = 90$	Patients ≥24 + 0 weeks $n = 67$
Age (years) (mean)	30.1 ± 5.8	31.3 ± 5.8	28.6 ± 5.3
Gravidity (median)	2 (1–11)	2 (1–11)	2 (1–6)
Parity (median)	1 (0–8)	1 (0–8)	1 (0–5)
Gestational age (weeks) (median)	23 (13 + 2–33 +6)	22 (13 +2–23 + 6)	26 (24 + 0–33 + 6)
Consanguinity	3	2	1
Prior cesarean section (≥1)	27	17	10
Body mass index (kg/m^2) (mean)	27.1 ± 5.4	27.0 ± 5.4	27.0 ± 5.6

Table 2 Anomalies in non-isolated spina bifida cases

Structural anomalies	Pregnancies ≤23 + 6 weeks $n = 25$ (27.8 %)	Pregnancies ≥24 + 0 weeks $n = 19$ (28.4 %)
Cerebral[a]	1	4
Congenital heart defect	2	2
Urinary tract and kidneys	3	2
Soft tissue	2	1
Other isolated morphological anomalies	7	8
Multiple other malformations	10	2

[a] Other than spina bifida-associated anomalies (hydrocephalus, Chiari II malformation, microcephaly)

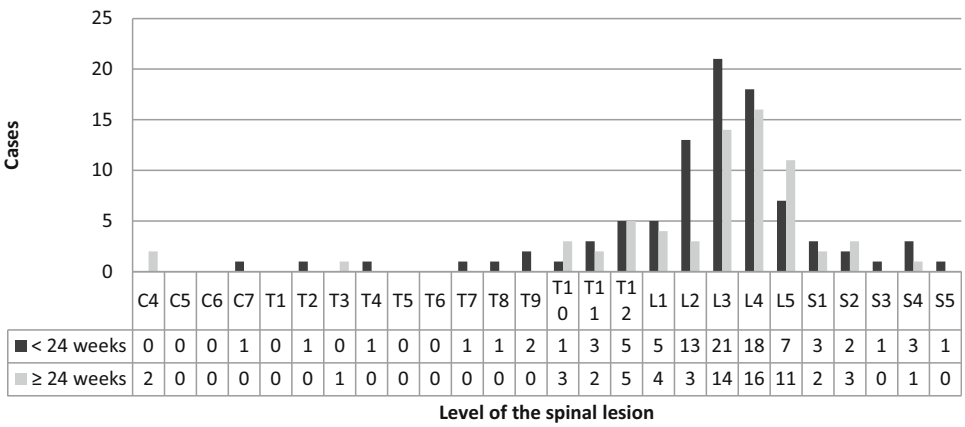

Fig. 1 Distribution of the upper level of the spinal lesion

isolated cases, while the width of the lateral ventricles was normal in 4.5 and 30.4 %, respectively (Table 3). There was no difference in cases with isolated and non-isolated spina bifida regarding the time of first presentation at our tertiary center, 22 + 3 (range 13 + 5–33 + 2) weeks of gestation) and 22 + 4 (range 12 + 3–33 + 3) week of gestation, respectively.

Fetal karyotyping was carried out in 72 cases (45.9 %) (Table 4). Chromosomal defects were registered in 18.1 %, although only 15.4 % in cases with isolated spina bifida. 42.7 % of TOP following prenatal diagnosis of spina bifida took place at ≥24 weeks of gestation.

Within 48 h, stillbirth was achieved in 94.3 % of fetuses ($n = 148$). Fetal data are summarized in Table 5.

Discussion

In this retrospective analysis, we investigated 157 terminated pregnancies with fetal spina bifida in a single tertiary care center from 2002 to 2011.

The mean gestational age at diagnosis was 22 weeks. This corresponds to published data from the EUROCAT registry from 17 European countries [18].

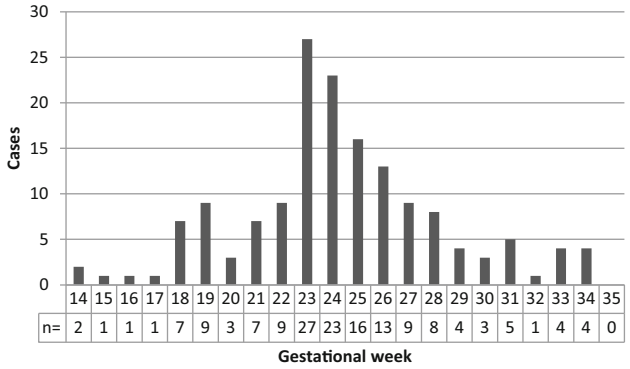

Fig. 2 Distribution of the gestational age

Sonographic cerebellar signs, which often trigger suspicion of spinal lesions, have been found to be the most reliable diagnostic markers [16]. In the detection of spina bifida the banana sign was present in 97.5 % of cases. These findings confirm observations of previous studies that reported the presence of one or more intracranial markers in nearly all affected cases [4, 19]. Our distribution of the upper level of the defect is nearly identical to data from Belgium and the Netherlands [20].

Despite the fact that almost all neonates born with an open spina bifida have evidence of hydrocephalus at the time of birth, only 70 % will develop hydrocephalus during fetal life. Our observed rates of hydrocephalus were similar to those reported by Nicolaides et al. [21] and Pilu et al. [22] (69.4 % compared to 75.9 %).

Although intracranial signs play a critical role in the diagnosis of spina bifida, characterizing the exact spinal lesion is essential for outcome prediction [16].

In line with current literature, cases with upper lesion level (≥L3) were diagnosed earlier in pregnancy, whereas most spinal and sacral lesions were typically discovered during the second-trimester anomaly scan [20].

It is widely known that chromosomal anomaly rates in cases with isolated spina bifida are low and range from 2.6 % [23] to 9.7 % [24], but could approach 16–25 % [12, 23, 25] if there are additional structural anomalies.

Table 3 Intracranial signs of spina bifida

	All fetuses				Pregnancies ≤23 + 6 weeks				Pregnancies ≥23 + 0 weeks			
	Isolated SB		Non-isolated SB		Isolated SB		Non-isolated SB		Isolated SB		Non-isolated SB	
	n = 111 (%)		*n* = 46 (%)		*n* = 63 (%)		*n* = 27 (%)		*n* = 48 (%)		*n* = 19 (%)	
Severe ventriculomegaly	85	76.6	24	52.2	45	71.4	11	40.7	40	83.3	13	68.4
Mild/moderate ventriculomegaly	21	18.9	8	17.4	15	23.8	4	14.8	6	12.5	4	21.1
None of both	5	4.5	14	30.4	3	4.8	12	44.5	2	4.2	2	10.5

SB spina bifida, Mild/moderate ventriculomegaly was defined as 10–15 mm

Table 4 Genetic data

Characteristics	All fetuses		Pregnancies ≤23 + 6 weeks		Pregnancies ≥24 + 0 weeks	
	n = 157 (%)		*n* = 90 (%)		*n* = 67 (%)	
Karyotype or genetic analysis	72	45.9	41	46.7	31	46.3
Chromosomal analysis						
Normal	59	81.9	31	78.0	28	90.3
With isolated spina bifida	38	64.4	20	64.5	18	64.3
With non-isolated spina bifida	21	35.6	11	38.7	10	35.7
Abnormal	13	18.1	10	24.4	3	9.7
With isolated spina bifida	2	15.4	0	0	2	66.7
With non-isolated spina bifida	11	84.6	10	70.0	1	33.3
Abnormal karyotypes						
Trisomy 13	3	23.1	2	20.0	1	33.3
Trisomy 18	3	23.1	3	30.0	0	0
Trisomy 21	1	7.7	1	10.0	0	0
69,XXX	3	23.1	2	20.0	1	33.3
No karyotype or genetic analysis	85	54.1	49	56.7	36	53.7

Further abnormalities <24 weeks one Mikrodeletion 22q11 and ≥24 weeks one 46XX,der(6) and one 46,XX,r(21)(31)/45,XX.-21

Table 5 Fetal data

Fetal characteristics	All fetuses $n = 157$	Pregnancies $\leq 23 + 6$ $n = 90$	Pregnancies $\geq 24 + 0$ $n = 67$
Weigth (g)			
Mean	649.7	410.3	971.3
Range	6–2140	6–775	213–2140
Length (cm)			
Mean	29.9	26.0	35.3
Range	6–48	6–35	26–48
Head circumference (cm)			
Mean	21.1	18.4	24.2
Range	11–33.5	11–28	19.5–33.5
Upper level of the defect			
≥L3	89 (56.7 %)	55 (61.1 %)	34 (50.8 %)
L4–L5	52 (33.1 %)	25 (27.8 %)	27 (40.3 %)
≤S1	16 (10.2 %)	10 (11.1 %)	6 (8.9 %)

In our collective, the observed rate of chromosomal defects in spina bifida (18.1 % overall) was in line with previous publications. On the contrary to the published results, specifically in our cases with isolated spina bifida higher rates were revealed (15.4 %),considering that chromosomal analysis was performed in only 45.9 % of our cases.

For parental counseling, a precise characterization of the spinal defect as well as the detection of further anomalies and the fetal karyotype is mandatory. With the help of this information, the outcome can be explained to the parents based on existing clinical data.

Also, our rate of TOP coincides with published observations [4, 17]. Forty-three percent of terminated pregnancies in our cohort occurred beyond 24 weeks of gestation. The high rate most likely relates to a non-detection of spina bifida in routine screening. In this context, it is important to emphasize that effective screening tools even in first-trimester screening have been introduced [10, 26–29].

The former German guideline for pregnancy care only comprised assessment of the biparietal diameter and "noticeable abnormalities" in the first trimester and in the second trimester only the biparietal diameter, head circumference and the body contour as potential indicators for open spina bifida. In the revised guideline of 2014 [30], abnormalities of head shape, ventricle, cerebellum (visible: yes or no) and body contour are now issues that have to be communicated to each patient. Though late detection is a common problem, often moderate or severe ventriculomegaly becomes apparent at the end of second or early third trimester, as in Germany the third ultrasound screening is performed between $28 + 0$ and $31 + 6$ weeks of gestation.

In general, most German women attend the above-mentioned routine screening. Only in high-risk pregnancies or due to own concerns patients are assigned or present themselves at their own costs to a specialist for prenatal ultrasound. Unfortunately, in Germany, there is no general screening performed by an experienced sonographer in the first and second trimester. A survey in 12 countries showed detection of neural tube defects roughly 1 week earlier than in Germany [31].

Generally, open and fetoscopic fetal surgery are available for prenatal treatment of spina bifida. The optimal gestational age for fetal surgery, to preserve neuromotor function, reverse hindbrain herniation, and avoid the need for postnatal ventriculoperitoneal shunting, seems to be before 26 weeks of gestation [13]. Open fetal surgery seems to be associated with lower rates of procedure-related complications (e.g., premature rupture of membranes) compared to the endoscopic approach, but present high rates of hysterotomy scar complications [32]. However, we believe that minimally invasive techniques using fewer ports of smaller diameters, tissue engineering and other new technologies, which can be applied earlier in pregnancy, could be the first treatment choice in the near future.

Despite major progress achieved in prevention, prenatal diagnosis and intervention, spina bifida remains a main reason for morbidity and mortality [31]. It is difficult to predict at the moment whether these promising strategies, with uncertain risk-to-benefit ratio, will modify the predominantly negative attitude of gynecologists and parents toward TOP after prenatal diagnosis of open spina bifida [17].

Limitations

All investigated cases have been referred to our tertiary care center, which implies that we cannot provide the exact gestational age at diagnosis and also explains why the cases

with closed spina bifida are underrepresented in our study. One further limitation is the retrospective nature of the study. Beyond that, patients were assigned to our tertiary care center for second opinion or further diagnosis, which may explain a referral bias in the patient's collection. The reason for the time lapse between diagnosis and TOP cannot be analyzed in this retrospective study. Factors for delay are various, e.g., referral for a second opinion, psychosocial and medical interdisciplinary counseling and finally the difficulty of parents to come to a decision.

Conclusion

European countries operate within different legal frameworks giving the option of TOP and especially late TOP for fetal anomaly. In our opinion, implementation of a uniform prenatal care including first-trimester ultrasound examination with potential signs for open spina bifida and second-trimester anomaly scan with indirect intracranial findings and direct detection of spinal lesion would lead to an earlier diagnosis and help to reduce late TOP in neural tube defects.

Compliance with ethical standards

All procedures were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.
For this type of study, formal consent is not required.

Conflict of interest The authors declare that they have no conflict of interest.

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