**CEOG** Clinical and Experimental Obstetrics & Gynecology

# The outcome and course of pregnancies complicated with fetal neural tube defects

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**Summary**

*Purpose:* The objectives of this study were as follows: to present the course and outcome of pregnancies complicated with neural tube defects, determine the association between prenatal ultrasound diagnoses, and definitive diagnoses after autopsy. *Matherial and Methods:* The survey was designed as a retrospective study and included 24 pregnant women who were attending a regular ultrasound examinations at the Department of Gynecology and Obstetrics, Clinical Center of Serbia, or patients who were referred from other institutions in Serbia. *Results:* Neural tube defects are divided into five subgroups: spina bifida, meningocele, myelomeningocele, acranius, and anencephaly. The most frequent in the present study was spina bifida with 67%. All pregnancies complicated with neural tube defects were terminated. *Conclusion:* Their clinical severity and uncertain cause make them priorities for further research, whether to better target primary preventive measures, to improve in-utero surgery for prenatal repair, or to identify the causative genes to provide an objective basis for individual genetic counselling.

*Key words:* Neural tube defects; Fetus; Outcome; Pregnancy.

## Introduction

The incidence of neural tube defects is two in 1,000 newborns that ranks this anomaly among the most common congenital malformations. The incidence of female children is four times higher than for male. Most of these malformations occur sporadically and are considered to be of multifactorial origin Anencephaly and spina bifida are the most common neural tube defects [1]. It has long been pointed to the foliate deficiency in pregnant women with neural tube malformations, which is why supplementation with folic acid is recommended for all women who plan to become pregnant during the three months before conception until 12 weeks of gestation. Also as risk factors for the development of these abnormalities are known folic acid antagonists such as methotrexate, valproic acid, vitamin A, diabetes, obesity, hyperthermia [2, 3]. However, 90% of children born with neural tube defects do not have any of the known risk factors. In recent years there has been a downward trend in the prevalence of neural tube defects which can be explained by successfully supplementation with folic acid, as well as improved prenatal sonographic diagnosis, and the use of screening protocols that imply the determination of alpha-fetoprotein in human serum [4]. Open neural tube defects increase the concentration of this glycoprotein in amniotic fluid and maternal serum. Since closed lesions do not increase the level of alpha-fetoprotein, screening in this case is not efficient. Serum alpha-fetoprotein varies with gestation, therefore it is expressed by the median. Cutoff value that is considered as a positive result in monofetal pregnancy is 2.5 MOM. Given this, the detection rate for anencephaly is over 95%, for open neural tube defects between 65% and 80%, and the false positive rate is between 1% and 3% [5]. Several studies, designed by the type of meta-analysis, suggested the fact that low mother serum vitamin B12 may be an important risk factor in the development of neural tube defects, therefore the authors recommend supplementation with synthetic vitamin B12 to the existing recommendations on the intake of folic acid [6].

The objectives of this study were as follows: to present the course and outcome of pregnancies complicated with fetal neural tube defects, to determine the association between prenatal ultrasound diagnoses, and definitive diagnoses after autopsy and additional analysis.

## Matherial and Methods

*Time and place of study implementation*

The research was conducted at the Department of Gynecology and Obstetrics, Clinical Center of Serbia in the period from January 2002 until December 2012.

Revised manuscript accepted for publication November 20, 2013

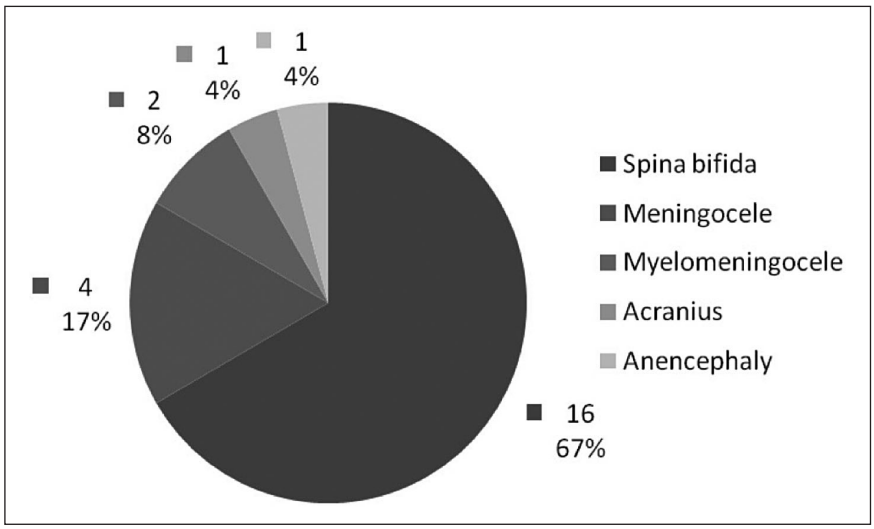


Figure 1. — Classification of neural tube defects.

*Respondents - monitoring units*

The study included 24 pregnant women who were attending a regular ultrasound examinations at the Department of Gynecology and Obstetrics, Clinical Center of Serbia, or patients who were referred from other institutions in Serbia. The criteria for inclusion in this study were visualized neural tube defect by ultrasound and insight into the histopathological diagnosis if the pregnancy was terminated. Criteria for exclusion from the study were non-disclosure in the histopathologic diagnosis. Two patients were excluded from the study, because the authors did not have access to histopathologic diagnosis.

*Clinical methodology*

If during a routine ultrasound examination there was suspected neural tube defect, it was advisable to review patient by a multidisciplinary Consilium for fetal anomalies which consist of the perinatologist, child neurologist, neurosurgeon, and geneticist who followed the further course of pregnancy. In addition to the ultrasound examination, some examinees were advised additional diagnostic methods and analysis to determine the precise diagnosis and etiology of diseases, such as screening for infections toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus (TORCH), karyotyping, and magnetic resonance imaging (MRI).

*Statistical methodology*

The survey was designed as retrospective study. Information during pregnancy and their outcomes were collected from Consilium for fetal anomalies reports and fetal autopsy reports Observation characteristics that we followed were: maternal age, parity history, history of similar or other congenital anomalies in a family or in previous pregnancies, weeks of gestation at which women first was shown Consilium for fetal anomalies, the total number of consultative examination, karyotype, MRI findings, mothers' comorbidities, prenatal sonographic diagnosis of abnormalities, the diagnosis at autopsy or postnatal diagnosis after birth, institution where birth took place, way of delivery (vaginal delivery or cesarean section), child's sex, and psychomotor development.

In order to determine the correlation between prenatal and final diagnosis, the authors divided them into three groups. In group 1 were pregnancies where the prenatal diagnosis and the final diagnosis after birth or autopsy fully matched, regardless of whether they were isolated or associated anomalies. Group 2 included pregnancies in which diagnosis at birth or after an autopsy confirmed prenatal diagnosis, but in which were discovered cerebral and extracerebral anomalies that were not seen by ultrasound. Group 3 classified anomalies that prenatally could not be diagnosed, so the diagnosis was made after the birth or autopsy or wrong diagnosed malformations.

Statistical analysis included descriptive statistics (integers, percentages of proportion, mean, and standard deviation). The results are presented as figures and in tabular form.

## Results

Neural tube defects are divided into five subgroups: spina bifida, meningocele, myelomeningocele, acranius, and anencephaly, which is represented in Figure 1.

The total number of fetuses with spina bifida was 16 (67% of the total number of all diagnosed neural tube defects). The average age of mothers whose pregnancies were complicated with existence of spina bifida was 25.7 years (range 18-40 years). Among them, there were eight (50%) multiparous and it is important to note that none of the respondents had previous pregnancy complicated with anomalies of the central nervous system. The patients were examined by the Consilium team average in the 28$^{th}$ week of gestation. The earliest was sent for examination in the 18$^{th}$ week of gestation, and at the latest in the 37$^{th}$ week. Most of the pregnant women surveyed, 12 (75%), had only one medical consultations, and only one was not at all anticipated in the examinations. Karyotyping was performed in only two patients and the results of one respondent are known to the authors, in which were normal. MRI was performed in three patients, and two findings coincided with ultrasound, while the results of the third one is unknown. Three pregnancies were twin, one after artificial fertilization procedure, whereby findings of the central nervous system of the second twin was normal in both pregnancies.

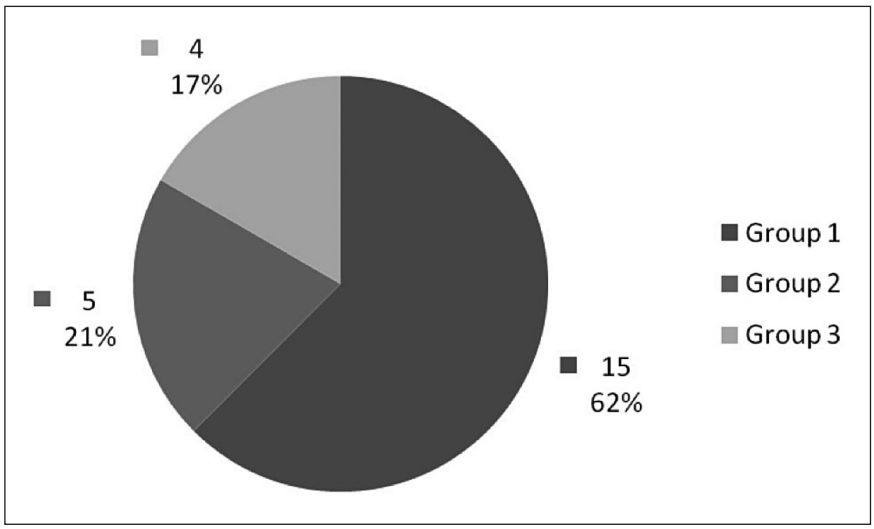


Figure 2. — Matching prenatal and final diagnosis.
± Group 1 - pregnancy in which the prenatal diagnosis and the final diagnosis after birth or autopsy fully matched; Group 2 pregnancy in which the birth or after an autopsy confirmed prenatal diagnosis but were diagnosed with associated cerebral and extracerebral anomalies which were not seen by ultrasound; Group 3 pregnancies with anomalies prenatally either could not be diagnosed or only after birth or autopsy diagnosis or wrongly diagnosed.

Table 1. — *Associated anomalies with neural tube defects.*

| Associated anomalies | Number |
|---|---|
| Ventriculomegaly | 19 |
| Corpus callosum agenesis | 2 |
| Cerebellum herniation | 3 |
| Lissencephaly | 1 |
| Talipes equinovarus | 2 |
| Hypertelorism | 1 |
| Hepatomegaly | 2 |
| Ventricular-septal defect | 1 |
| Kidney agenesis | 1 |
| Splenomegaly | 1 |
| Total | 33 |

One respondent mother had hypertension. Spina bifida was isolated in only two (13%) cases, while the remaining 14 (87%) fetuses were diagnosed with associated anomalies (Table 1) wherein internal hydrocephalus was diagnosed in all cases. Only one spina bifida was cervicothoracal.

All 16 pregnancies complicated by the presence of spina bifida were terminated (Table 2) and after termination autopsy was conducted. In the majority of fetuses, 14 (88%), autopsy confirmed the presence of spina bifida, while in two fetuses (12%), spina bifida was not seen; hence the authors can conclude that prenatal ultrasound diagnosis and postnatal final diagnosis were fully matched in ten cases (63%) (Figure 2). Three cases (18%) after autopsy presented associated anomalies such as talipes equinovarus in two fetuses and agenesis of corpus callosum in one fetus, but these anomalies would not have had a significant impact on decision making on further continuation of the pregnancy, as spina bifida anomaly dominates the findings, and in one fetus (6%) prenatal central nervous system anomalies was identified as Dandy Walker malformation, and after the final autopsy diagnosis, it was spina bifida associated with internal hydrocephalus.

In the present study, there were detected four (17%) fetuses with meningocele. The average age of women whose pregnancies were complicated with this malformation was 29.5 years, with the youngest respondent being 21-years-old and the oldest 38 years. Three respondents were nulliparous, and one in the second pregnancy had a history of previous pregnancy complicated with central nervous system anomaly. One respondent was first presented to Consilium in the 29$^{th}$ week of gestation, two in the 32$^{nd}$, and one in 33$^{th}$ week. Two respondents were presented to Consilium once, and the other two had two consultative examination, where only one out of four of them did not carry out all planned examinations. Fetal karyotype analysis was performed in none of the cases. MRI was performed in three respondents, while the result was known for two: in one fetal ultrasound fully coincided with the findings of MRI, while the second MRI showed the existence of corpus callosum agenesis that was not visualized by ultrasound. In only one fetus (25%), meningocele was isolated, and in the remaining three (75%) it was associated with other cerebral and extracerebral anomalies (Table 1). Three fetuses had ventriculomegaly and one fetus also had lissencephaly and cerebellum herniation, the second one had agenesis of corpus callosum body, and the third had agenesis of kidney and ureter. All four pregnancies complicated with meningocele were terminated with all the autopsies performed. Prenatal and postnatal diagnoses were fully matched in two respondents; the third after an autopsy, was diagnosed with agenesis of kidney and ureter, and in the fourth cerebellum herniation (Arnold Chiari type II) and lissencephaly (Figure 2).

This survey included two (13%) fetuses with myelomeningocele. One respondent was 26-years-old and the first and only time she was presented to the Consilium was in the 34$^{th}$ week of gestation. The third pregnancy had no previous complicated by the existence of anomalies of the central nerv-

Table 2. — *Outcome of pregnancies complicated with neural tube defects.*

| Anomalies | Number (percentage) | Pregnancy termination | | Anomaly confirmed | |
|---|---|---|---|---|---|
| | | Yes | No | Yes | No |
| Neural tube defects | 24 (16.8) | 24 (100) | 0 | 22 (92) | 2 (8) |
| • Spina bifida | 16 | 16 | 0 | 14 (88) | 2 (12) |
| • Meningocele | 4 | 4 | 0 | 4 | 0 |
| • Myelomeningocele | 2 | 2 | 0 | 2 | 0 |
| • Acranius | 1 | 1 | 0 | 1 | 0 |
| • Anencephaly | 1 | 1 | 0 | 1 | 0 |

ous system. Fetal karyotype analysis was not done and the patient was not referred to MRI. Mother had epilepsy. This pregnancy was terminated. Prenatally, moderate lumbosacral myelomeningocele with moderate ventriculomegaly was diagnosed, and after an autopsy, the presence of hepatosplenomegaly and mild facial dysmorphy were also discovered. Fetus was male. Another respondent was 32-years-old, it was a second child, and her previous pregnancy proceeded without complications. The first and only time she was presented to the Consilium in the 37th week of gestation. Neither fetal karyotyping nor MRI was performed. This pregnancy was also terminated. Prenatally, anomaly was identified as teratoma associated with moderate ventriculomegaly. After the autopsy, the diagnosis was myelomeningocele with moderate ventriculomegaly. This fetus was female.

One fetus (4.5%) in the present study was diagnosed with acranius. The woman was 32-years-old with normal previous pregnancies. The first time she was presented to the Consilium in 16th gestational week, and it was also the last time. Karyotyping of the fetus was not done, and the women had not been sent to MRI. It was twin pregnancy, with normal findings of other twin central nervous system. The pregnancy was also terminated. Prenatal and postnatal findings were matched and it was an isolated acranius.

The research include also one fetus (4.5%) with anencephaly. It was the patient's first baby and she was 22-years-old and was presented only time to the Consilium in 18th week of gestation. Fetal karyotyping was not performed, and MRI coincided with ultrasound findings. Pregnancy was also terminated. After the autopsy, the diagnosis was anencephaly with choloanencranius. The fetus was a female.

## Discussion

The greatest number of pregnancies complicated with the existence of open spina bifida were terminated. In 2008, the European Surveillance of Congenital Anomalies (EUROCAT) conducted an analysis of 12 European countries and came to the conclusion that the termination rate of pregnancies complicated with all neural tube defects was 88% [6]. In the study of Biggio *et al.*, 38% of patients whose pregnancies were complicated with open spina bifida of fetus were terminated. In 75% of the patients whose pregnancies were terminated had lumbosacral spina bifida, and 25% thoracic spina bifida. In most cases, 65% were diagnosed with meningomyelocele and meningocele in 5% of the patients; the remaining 30% were myeloschisis. Talipes was diagnosed in 25% of cases where the pregnancy was terminated. The average width of the lateral ventricles where ventriculomegaly was associated with spina bifida was 11 ± 3 mm. The incidence of neural tube defects was four times higher in male than in female fetuses [7]. Ghi *et al.*, showed that all the subjects in their study with open spina bifida had a banana and lemon sign, while they were absent in closed anomalies, so they concluded that on the basis of altered cranial anatomy, it is possible to differentiate open and closed neural tube defects [8]. Cameron *et al.* in their study showed that the 'lemon' and 'banana' sign were present in 97% of fetuses with spina bifida and in 75% of cases with ventriculomegaly [9]. Research shows that some fetuses with open spina bifida have a better prognosis, and it would be useful to select them prenatally based on sonographic findings [1, 7]. The most important single predictor of postnatal psychomotor development is the lesion level. High lesions have a worse prognosis and may have a lethal outcome. Neonatal mortality in high lesions is about 13%. In the first five years after surgical management of spina bifida, mortality was 35%. The best prognosis is seen in defects at the sacral and lumbosacral levels. Spinal lesions at higher levels are associated with more severe ventriculomegly. The largest number of lethal outcome occurs as a result of surgical complications or as a result of herniation of the cerebellum. In addition to the level of lesion and presence of ventriculomegaly, as a potential predictor it is also mentioned with talipes, which is associated with open spina bifida in 50% of cases, but so far did not prove a significant correlation with postnatal prognosis [8]. It is important to note that if ventriculomegaly develops after 24 weeks of gestation, the degree of expansion of the lateral ventricles is smaller. According to the literature, ventriculomegaly is associated with open spina bifida in 80% to 95% of cases [10]. It was also observed that the ventriculomegaly degree has significant impact on intellectual and motor development, with this development marred in severe forms of dilated ventricles, but it is not possible to set a limit to the width of the ventricle, which can safely be an indicator of proper psychomotor development. In addition, complications that arise as a result of ventriculo-peritoneal shunt, such as obstruction or infection, can significantly affect the intellectual development than the ventriculomegaly degree [11, 12]. It is known that a large number of patients with open spina bifida have some degree of dysfunction of the sphincters. Only 17% of children do not have problems with urination. Paraplegia is present in 25%, severe paraparesis in 25%, and about 25% of children with no significant extremity dysfunction [13]. If a previous pregnancy was complicated with spina bifida, the risk of its recurrence is ten times higher [6, 14, 15].

The present survey included two (13%) fetuses with myelomeningocele and four (17%) with meningocele. There were only three cases (14%) with isolated spina bifida, meningocele, and myelomeningocele. The remaining 19 (86%) were associated with cerebral and extracerebral anomalies. In all 19 fetuses ventriculomegaly was also present and in 17 (90%) it was hydrocephalus, and the remaining 10% ventriculomegaly was of moderate type. Beside ventriculomegaly, the following malformations were associated: cerebellar herniation in three (16%) fetuses, corpus callosum agenesis, hepatomegaly, and talipes in two (11%), and one fetus (5%) was associated with hypertelorism, lissencephaly, facial dysmorphy, ventricular septal defect, and agenesis of the kidney and ureter. Irish authors have shown that 18% of cases were diagnosed with aneuploidies and that in almost every fetus presented associated structural anomalies. In the present study, all the fetuses had a neat karyogram [16].

## Conslusion

The present study showed that all pregnancies complicated with neural tube defects were terminated, but it is important to mention that majority of them were associated with other structural abnormalities.

Neural tube defects provide a multifaceted challenge to epidemiologists, clinicians, and developmental biologists alike. Although their imminent eradication was predicted when prenatal diagnosis was introduced, and again after the discovery of the preventive effects of folic acid; in fact neural tube defects remain one of the commonest categories of birth defects worldwide. Their clinical severity and uncertain cause make them priorities for further research, whether to better target primary preventive measures, to improve in-utero surgery for prenatal repair, or to identify the causative genes to provide an objective basis for individual genetic counselling.

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