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# Neural tube defects in Switzerland from 2001 to 2007: are periconceptual folic acid recommendations being followed?

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## Summary

**Background:** Neural tube defects (NTDs) are common congenital anomalies. Their aetiology is complex, with both genetic and environmental factors implicated. The present study was performed to analyse the birth prevalence of NTD in Switzerland from 2001 to 2007 and to identify possible risk factors.

**Methods:** Diagnosed cases of NTD in all paediatric units in Switzerland and four prenatal centres were reported to the Swiss Paediatric Surveillance Unit from January 2001 to December 2007. Patient, mother, and NTD characteristics were assessed prospectively with a questionnaire.

**Results:** Data of 140 newborns and foetuses with NTD were studied. The major group suffered from myelomeningocele (70%), followed by anencephaly (16%) and encephalocele (14%). The prevalence of NTD in live born children between 2001 and 2007 was 0.13‰, corresponding

to 9–10 affected newborns each year. About the same number of pregnancies was terminated annually. Correct periconceptual folic acid supplementation was taken by 5% of the women. Remarkably, 39% of the women with an affected pregnancy were not Swiss citizens – almost twice the proportion of foreigners living in Switzerland.

**Conclusions:** NTDs remain a frequent problem in Switzerland. Although correct periconceptual folic acid supplementation is effective in reducing the prevalence of NTD, women still do not follow these recommendations. Possible reasons are lack of awareness and communication problems. Consequently, only a public health policy that includes folic acid fortification of food is likely to result in significant prevention of NTD.

**Key words:** neural tube defects; myelomeningocele; encephalocele; anencephaly; folic acid supplementation

## Introduction

Neural tube defects (NTDs) are common and serious congenital malformations. About 1–2 per 1000 pregnancies are affected, both in the US and in the European Union [1, 2]. The most frequent open NTDs are myelomeningocele (MMC) [3] and anencephaly [4]. MMC occurs due to the failed closure of the caudal end of the neural tube, which results in dysplasia of the spinal cord, nerve roots, and meninges. Thereby MMC often leads to irreversible neurological, urological, and orthopaedic impairments causing life-long disabilities. Anencephaly results from a failed closure of the rostral end of the neural tube. It is characterised by a total or partial absence of the brain and the overlying skull, and the outcome is always lethal. However, encephalocele represents a post-closure NTD. It is characterised by a membrane-covered protrusion of the brain through an abnormal opening in the skull [5, 6]. The prognosis

of this defect is variable; syndromic forms are often lethal.

There is ample evidence that periconceptual folic acid supplementation can significantly reduce the risk of NTD [7]. Consequently, health organisations worldwide issue recommendations for women to take 0.4 mg of synthetic folic acid daily (4 mg daily to prevent NTD recurrence). Supplementation is recommended starting at least four weeks before conception continued until the end of the first trimester. In Switzerland these recommendations were formulated in 1996 and are currently supported by the Federal Office of Public Health, the Swiss Nutrition Council, the Swiss Paediatric Society, and the Swiss Society of Gynaecology and Obstetrics [8]. Since 2000, information on folic acid use has been widely available to women of childbearing age. Due to a lack of the necessary regulations, at present only

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AP and TA contributed equally to this work.

voluntary fortification of food is allowed in Switzerland.

In 2001 the Swiss Paediatric Surveillance Unit (SPSU) began a detailed analysis of the reported cases of NTD in newborns. Additionally, four foetal-maternal medicine centres were in-

cluded. The aim of the present study was to assess NTD birth prevalence in Switzerland. Further aims were to evaluate any trend in prenatally diagnosed NTD, possible risk factors, the impact of periconceptual folic acid supplementation, and pregnancy outcome with NTD.

## Methods

The period of NTD surveillance was from January 1 2001 to December 31 2007. Ours was a cross-sectional observational study. Before the start of the surveillance, all 38 paediatric and neonatal units in Switzerland received information about the project as well as the study protocol. All the information was ascertained with a questionnaire completed by physicians on a voluntary basis. The mothers remained anonymous and could not be contacted later. All the paediatric or neonatal units, which were confronted with a NTD case, participated in the study. To detect any trend in prenatally diagnosed NTD, four foetal-maternal medicine centres (University Hospitals at Basle, Geneva, and Zurich, and the centre in Lucerne) were also included. It has been estimated that these centres cover about 59% of the Swiss population [9]. Hence we included all newborns with NTD and were able to detect major trends in prenatal diagnosis. It was not possible to include all prenatally diagnosed NTD, because at present a comprehensive surveillance system is not available in Switzerland.

### Swiss Paediatric Surveillance Unit (SPSU)

The Swiss Paediatric Surveillance Unit (SPSU) was established in 1995 to assess the epidemiological features of selected childhood diseases leading to hospitalisation. Monthly, hospitals report occurring cases of the respective disease to the SPSU. Consequently the treating physician answers a questionnaire concerning the reported anonymous case. On this basis no case control or interventional studies are possible. The SPSU is operated under the auspices of the Swiss Paediatric Society and the Swiss Federal Office of Public Health.

### Case definition

The study population comprised newborns with NTD admitted to all paediatric units in Switzerland. Foetuses with NTD from four foetal-maternal medicine cen-

tres were also included. The main categories were MMC, anencephaly (including acrania, craniorachischisis, and exencephaly), and encephalocele. The data assessed included year of diagnosis, sex of the foetus, type of NTD, age and nationality of the mother, and folic acid supplementation (periconceptual, postconceptual, or no supplementation). Moreover the questionnaires addressed prenatal diagnosis, cases of recurrence, intake of possible teratogenic drugs such as antiepileptic drugs during the pregnancy, and outcome of the pregnancy (live birth, still birth/spontaneous abortion, or termination of pregnancy (TOP)). Folate receptor antibodies were analysed only in one case, because this analysis was not part of the study [10]. Supplementation is defined as periconceptual if starting at least four weeks before conception and continued until the end of the first trimester. Extracranial malformations were assessed with the aim of recognising possible syndromic NTD.

We excluded newborns and foetuses with closed spinal dysraphism, such as diastematomyelia, lipomeningocele, thickened filum terminale, caudal regression syndrome, intradural lipoma, and dermal sinus. This category of mainly caudal defects is probably independent of folate and embryologically distinct from MMC [11]. Most of them are diagnosed late, sometimes even in adulthood [12]. All cases with an unclear diagnosis, even if reported as NTD, were not evaluated.

### Statistics

The birth prevalence of NTD was calculated as the total of newborns with NTD divided by the total number of live births during the study period. The annual total number of Swiss births was obtained from the Swiss Federal Office of Statistics. This data base was also used as a source for the number of foreigners living in Switzerland and the Swiss population.

## Results

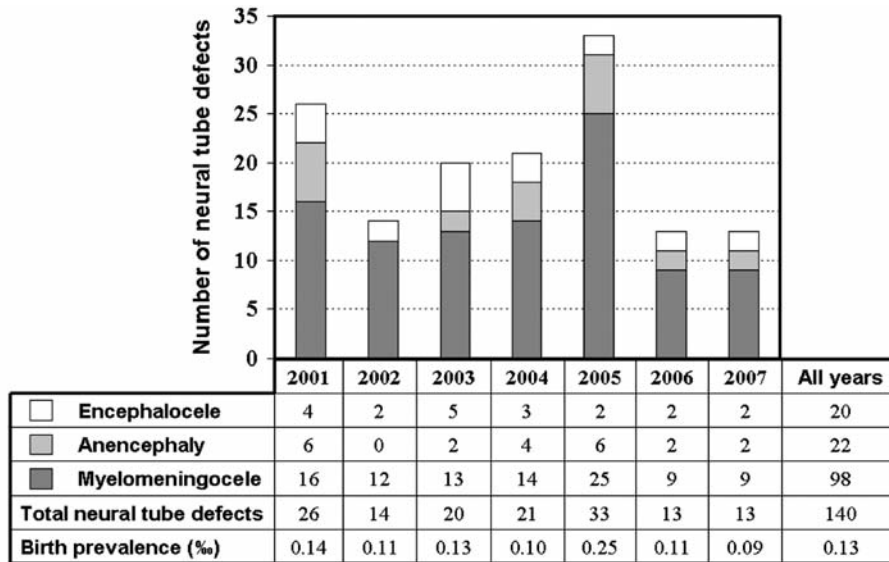
During the study period, 140 foetuses and newborns with NTD were identified. This corresponds to an average of about 20 cases each year. The distribution of NTD according to diagnostic category and year is shown in fig. 1 and epidemiological characteristics are listed in table 1. MMC was the most frequently recorded anomaly with 98 cases (70% of all subjects). Anencephaly was detected in 22 cases (16%) and encephalocele in 20 (14%). Sixty-seven of 140 foetuses were female (48%) and 56 were male (40%), whereas in 17 TOP the gender was not identified (12%). An affected sibling was reported in two families (0.01%).

In 84 of 98 cases (86%) the MMC was isolated, whereas in 14 cases (14%) MMC was part of a syndrome such as trisomy 13 or 18. Nineteen cases of anencephaly occurred in isolation (86%), only three were syndromic (14%). Out of 20 encephaloceles, eight cases were syndromic (40%). Four of them represented part of the Meckel-Gruber syndrome.

The mean age of the mothers at the time of delivery was 30 years (median 31, range 15-45 years). Eighty-two mothers were Swiss (59%) and 54 were foreigners (39%). In the remaining four cases the nationality of the mothers was not reported. Most foreign mothers originated from

**Figure 1**

Neural tube defects according to diagnostic category and year.



**Table 1**

Epidemiological data according to the neural tube defects (n = 140).

		Anencephaly	Myelomeningocele	Encephalocele	Total NTD
Total number		22	98	20	140
Sex*	male	5	43	8	56
	female	7	51	9	67
Age of the mothers (years)**	median (range)	34 (21–45)	30 (15–37)	31.5 (19–43)	31 (15–45)
Nationality of the mothers***	Swiss	11	60	11	82
	foreign	11	34	9	54

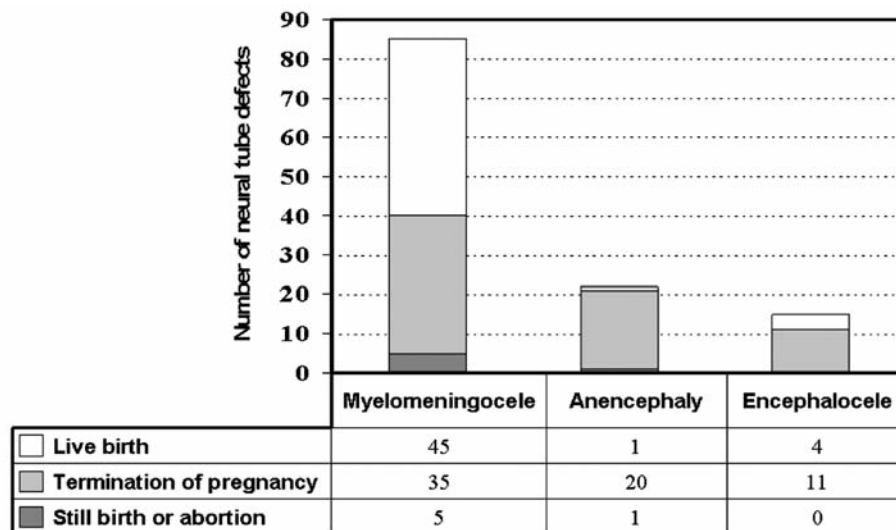
\* In 17 cases of termination of pregnancies the sex was not specified

\*\* In 6 cases the age of the mother was not specified

\*\*\* In 4 cases the nationality of the mother was not specified

**Figure 2**

Pregnancy outcome of neural tube defects after prenatal diagnosis according to category.



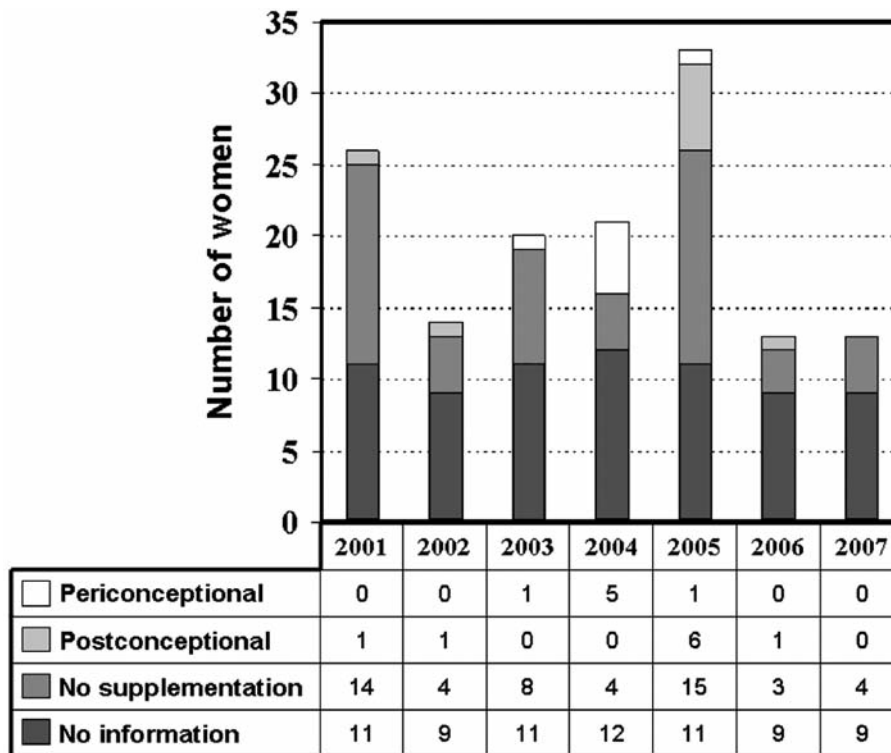
Southern Europe (n = 23, 43%), especially from the Balkans (n = 19).

NTD was diagnosed prenatally in 122 cases (87%), whereas 16 cases (11%) were only detected at birth. Eleven of those were MMCs and five were encephaloceles. In two MMCs we do not know whether they were diagnosed prenatally. However, all anencephalic foetuses were detected prenatally by ultrasound. Twenty of the 22 pregnancies (91%) affected by anencephaly were

terminated following this diagnosis. However, the TOP rate for encephalocele (73%) and MMC (41%) was lower (fig. 2). Sixty-eight of 140 foetuses were born alive (48%), corresponding to a mean value of about 9–10 cases each year and to a Swiss annual NTD birth prevalence of about 0.13%. At birth, MMC was the most frequently recorded NTD with 58 cases (85% of total newborns), whereas only nine were affected by encephalocele (13%) and one by anencephaly (2%).

**Figure 3**

Folic acid supplementation according to year.



Two foetuses with MMC and one with anencephaly were stillborn. Maternal periconceptual folic acid supplementation was correct in only seven cases (5%) (fig. 3). In one of these cases NTD was reported as syndromic. Additionally, in one case the pregnant woman received antiepileptic therapy with valproic acid [13] and in another

case autoantibodies against folate receptors were found subsequently in the maternal serum [10]. However, in 52 cases (37%) no folic acid supplementation was taken and in nine cases it was only taken postconceptionally (7%). In the majority of cases (51%), information about folic acid supplementation was not reported.

## Discussion

The NTD birth prevalence did not decline substantially during the past decade either in Europe [2, 14] or in Switzerland, as our study shows. A total of 140 NTD were reported to the SPSU from 2001 to 2007, corresponding to about 20 cases each year. Because almost 40% of them were born, the Swiss annual NTD birth prevalence was about 0.13‰, which signifies that 1–2 newborns in 10'000 births are affected by NTD each year. Comparable published series in other countries as USA, UK, and Sweden show a prevalence between 0.2–0.3‰ [15–17].

Prenatal diagnosis has improved during the last 30 years. In this report, the prenatal diagnosis rate is 87% and corresponds to other published series, which range from 82 to 98% [18, 19]. After the prenatal diagnosis of NTD, about half of the pregnancies were terminated. In comparison to interruption rates of 60–83% published in similar studies, the rate in this analysis is lower [17, 20]. Only four foetal-maternal centres were included, therefore a significant number of TOP was certainly missed. Consequently, the percentage of born MMC (59%) is above the ranges shown in the literature (20–52%) [20, 21].

The aetiology of NTD is complex and consists of genetic and environmental factors. Embryonic genetic factors include chromosomal abnormalities such as trisomy 13 and 18 and syndromes such as Meckel-Gruber. In our study, about 5% of NTDs were associated with a syndrome, corresponding to other published series (2–17%) [22]. Differentiation of syndromic NTD from isolated forms is important in terms of pathogenesis, genetic counseling, and prognosis.

It is known that folate is important for regular cell synthesis, especially when the cellular proliferation rate is high such as during embryonal and foetal growth [23]. The high density of folate carriers in the neural tube suggests a critical role for folate during neural-tube closure around the 28<sup>th</sup> day of pregnancy [24, 25]. Delivery of folate to the embryo depends on maternal folate intake, absorption, metabolism, folate transport across the placenta, and embryonal folate uptake [26]. Mutated folate pathway genes such as methylenetetrahydrofolate reductase (MTHFR) and folate receptor genes cause NTDs via both maternal and embryonic genotypes [27, 28]. Possible environ-



mental factors in the development of NTDs include low folic acid intake, autoantibodies against the folate receptor, and drugs influencing the folate metabolism such as valproic acid, as shown in our study [10, 13, 29].

A low folate diet is the main factor in open, non-syndromic NTD and can easily be influenced. Therefore many health organisations have recommended periconceptual supplementation by 0.4 mg folic acid daily [2, 7]. Although consistent supplementation reduces the risk of NTD by 40 to 80% [20, 30–32], a non-declining birth prevalence of NTD is of concern to Switzerland as well as to many other countries worldwide [2, 14]. This indicates that the recommendations alone are not sufficiently effective. In fact, only 5% of the women in our study took folic acid in the correct manner and half of the treating doctors were not properly informed about the patients' intake of folic acid. The birth of a newborn with an open NTD is very stressful for parents. Therefore paediatricians obviously have a tendency not to ask about folic acid supply in order to avoid provoking feelings of guilt and self criticism. Many women of childbearing age obviously remain unaware of the need to take folic acid, especially because many pregnancies are unplanned [2]. In Switzerland, this proportion is estimated by the Swiss Society of Gynaecology and Obstetrics around 50%, which is comparable to French data [33]. Youngsters, less educated individuals, and immigrants are particularly vulnerable groups [7]. Indeed, in our study the percentage of foreign women bearing a pregnancy with NTD is two-fold higher than the proportion of foreigners living in Switzerland. This finding is important and probably represents communication difficulties both of treating doctors and public health campaigns. Therefore, special attention should be paid to language, cultural barriers, and also illiteracy [34]. However, despite public health campaigns, ignorance of periconceptual folic acid supplementation remains and only half of the women of childbearing age follow the recommendations [7]. The only way to address women at risk might be through folic acid fortification of food [35]. Among other strategies, this is already performed in the USA and Canada and has improved the folate status considerably [20, 36]. It has thus led to a significant additional reduction of the NTD prevalence by 20 to 50% [15, 21, 37].

We are aware of limitations in our study. Firstly, only four prenatal centres (covering only

about 59% of the Swiss population) were included, resulting in missing several aborted pregnancies (about one third to half). Secondly, many report forms were only partially completed, especially regarding folic acid supplementation. This limits the robustness of our conclusion, since complete information is necessary for its confirmation and in understanding why periconceptual folic acid recommendations are not being followed. Thirdly, this study uses a descriptive approach limiting statistical analysis.

In summary, this study shows that the birth prevalence of NTD in Switzerland has not significantly decreased over the last 7 years. NTD remains a frequent congenital defect and a serious medical and public health problem. Although the protective role of periconceptual folic acid supplementation is clear, women of childbearing age still do not follow the recommendations. Possible reasons are a lack of awareness and communication problems. Providing information on the effect of folic acid supplementation does not have enough impact on the folic acid intake of women at risk. Consequently, only a public health policy that includes folic acid fortification of food is likely to result in significant prevention of NTD.

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