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ORIGINAL PAPER

Decreased incidence of myelomeningocele at birth: effect of folic acid recommendations or prenatal diagnostics?

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Abstract
Purpose In Denmark, prevention to reduce the spina bifida birth rate has focused on two areas: folic acid supplementation (1997) and changes in the national ultrasonography screening programme (2004). Myelomeningocele (MMC) is the most severe malformation among the spina bifidas. Taking into consideration the potential negative effect of high-dose folic acid consumption, we found a need to look into the effectiveness of these two strategies in our complete MMC population.
Methods All spina bifida patients born in the western part of Denmark are differentiated into proper subgroups based on MR imaging, giving us a unique chance to study a true MMC population. The total number of the group of MMC children since 1983 is 121. One hundred and eight (89%) parents answered a questionnaire.
Results Following the changes in the prenatal ultrasonography screening programme in 2004, a significant decline of 60% live birth MMC per year was noted, incidence rate ratio (IRR)=40% (22–73%), p=0.3%. We found no change in MMC birth rate after introduction of folic acid supplementation, IRR=121% (81–181%), p=36%.
Conclusion Our findings demonstrate no effect of folic acid recommendation due to lack of compliance among women of reproductive age in Denmark. However, we found an improved early detection rate of prenatal MMC by high-quality ultrasonography. Subsequent early termination of pregnancy has led to a significant reduction of birth rate of babies with MMC.

Keywords Myelomeningocele · Screening programme · Ultrasonography · Folic acid · Recommendations

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Introduction

Neural tube defect is a general term for the congenital malformation of the central nervous system with a worldwide incidence ranging from 1 to 10 per 1,000 births with almost equal frequencies between two major categories: anencephaly and spina bifida (SB). SB is also a broad term that encompasses several subgroups of defects, the absolute majority and the most serious deformity being myelomeningocele (MMC). Despite years of intensive epidemiological, clinical and experimental research, the exact aetiology of SB remains complex and poorly understood with genetic components interacting with multifactorial environmental factors [5, 15, 23, 24, 29].

The only effective risk reduction known in neural tube defects is periconceptional consumption of folic acid [1, 2, 8, 9, 18, 25]. Several strategies have been made, the fortification of common foods being reported to be the most effective; however, it is not sufficient to result in complete abolishment [3, 26]. The negative side effect of especially high-dose folic acid has been debated, and the thoughts of a protective role of folic acid against carcinogenesis have lately been questioned [6, 16]. Recent data indicate that an excessive intake of synthetic folic acid (from high-dose supplements or fortified foods) may increase maternal cancer risk [11]. Still, most countries recommend high-dose folic acid in high-risk pregnancies even though the ultrasonographic screening programme lately has improved in many countries [24].

Data from animal models, human intervention trials and analyses of cancer incidence suggest that the consumption of synthetic folic acid may induce growth of cancer cells [7, 11, 14, 19, 21, 22]. Recent findings from several large-scale human observational or placebo-controlled intervention trials indicate that the consumption of folic acid increases risk of overall cancer mortality and cancer at several sites: breasts, colon, lungs and prostate [7, 12, 13, 20, 27, 28].

An analysis of cancer statistics in the USA suggests that augmenting synthetic folic acid intake through mandatory fortification has increased colon cancer risk. A similar effect has been described in Chile [17]. The potential detrimental effects of high-dose synthetic folic acid intervention remain to be established.

Taking the potential negative effect of high-dose folic acid consumption into consideration, we found a need to look into the effectiveness of folic acid consumption in comparison with the modern national ultrasonography screening programme to reduce MMC birth rate, as MMC is the most severe deformity and a well-defined subgroup.

The Danish National Board Of Health has made official recommendations on folic acid intake of 0.4 mg folic acid from planned pregnancy until 3 months after fertilization, and in high-risk pregnancy, they recommend 5 mg folic acid from planned pregnancy until 2 months after fertilization (1997) and established changes in the national prenatal screening programme (2004). Before 2004, all women having a risk of 1% or more for severe genetic or other fetal diseases should be offered prenatal information, counselling and diagnostics. This included an offer of amniocentesis or chorion villus sampling for aneuploidy to all women at 35 years or more, but the recommendations did not include ultrasound screening for fetal anomalies. According to the national recommendations from 2004, all women should be offered a second trimester anomaly scan (in weeks 18–19) including assessment of the following fetal structures: head shape and intracranial structures, including the lateral ventricles, cerebellum and spinal cord.

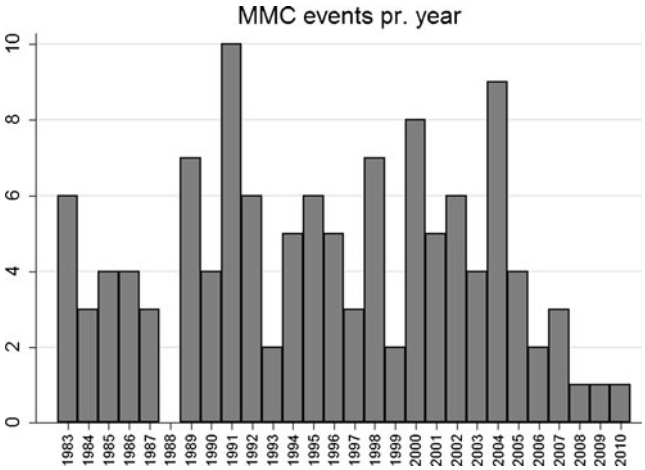

Fig. 1 MMC birth rate during the period 1983–2010. The Danish National Board of Health has made official recommendations on folic acid intake (1997) and established changes in the national prenatal screening programme (2004), marked with *different shades of grey*. Note the implementation delay after 2004; the last department in Denmark meeting the guidelines was in autumn 2006

The changes included screening of all pregnant women of all age groups, practically and theoretically educated ultrasonographic personnel (evaluated by demands and tests) and improved hard- and softwares now connected to the Fetal Medicine Foundation.

Methods

All children with SB born in the western part of Denmark are admitted to and followed at the Neurosurgical Department at Aarhus University Hospital. Only patients diagnosed with true MMC are included in this study. All parents since 1983 were asked to fill out a questionnaire together with either the first or the last author during their child's visit in the outpatient clinic. The questionnaire contained uniform questions about vitamin intake at the time of conception and ultrasonography during pregnancy. In

Table 1 Maternal average age divided by MMC number in the sibling's row

	Mother average age (years)
1. Child (*N*=43)	26
2. Child (*N*=38)	28
3. Child (*N*=20)	32
4. Child (*N*=3)	29
5. Child (*N*=1)	37
6. Child (*N*=1)	36

The national screening guidelines before 2004 only included mothers over the age of 35 years. Today, all pregnant women are included in the prenatal screening programme

Table 2 The Danish National Board of Health has made official recommendations on folic acid intake (1997)

	Before folic acid recommendation (–1997) (%)	After folic acid recommendation (1998–) (%)	Change
Use of prophylactics	57	92	62
Use of prophylactics before pregnancy	17	48	178

The table demonstrates the differences in folic acid supplementation before and after 1997

addition, data about maternal age and parity were collected. Background information regarding birth rate in the Danish population was derived from Statistics Denmark. Data were analysed in the Poisson regression model.

Results

The total number of the group of true MMC children is 121 from 1983 to 2010. One hundred and eight (89%) parents answered the questionnaire.

The mean MMC birth rate is 4.5 with considerable variation (0–10) (Fig. 1). The average maternal age is 28 years (range, 20–39) (Table 1). Parity is visualised (Fig. 1).

Mothers report an overall increase of 62% of folic acid supplementation after the changes in national recommendations in 1997 and an increase of 178% of correct folic acid intake before commencing the pregnancy (Table 2). These changes lead to an insignificant, but lower, incidence of MMC after 1998 (incidence rate ratio, IRR=82% (57–118%), p=28%). However, when we correct the incidence for the marked decrease after the changes in screening programme in 2004, we actually find an insignificantly increased incidence of MMC after the folic acid recommendations (IRR=121% (81–181%), p=36%). Corrections for the slight increase in the national birth rate (from Statistics Denmark) over the study period induce no conclusive changes to the above.

Following the introduction of new prenatal screening recommendations in 2004, including an 18–21-week anomaly scan to all pregnant women in Denmark, and subsequent termination, a decline of 60% live birth MMC per year was noted (Fig. 1). A corresponding IRR of 40% (22–73%) is clearly significant (p=0.3%). Correction for the observed incidence increase, following the folic acid recommendations, in fact entails an even lower IRR of 35% (18–68%); however, the mentioned increase appears intuitively unreasonable to model. The percentage of prenatally diagnosed live-born MMC children tripled after the changes in screening programme (Table 2).

Discussion

The recommendation of high-dose folic acid originates from the Medical Research Council Vitamin Study, a multicenter trial involving seven countries. The study described women with high-risk pregnancy and found a significant (72%) reduced neural tube defect incidence in the 4-mg folic acid-supplemented group and an insignificant (20%) reduction in the vitamin supplement group (without folic acid) compared with a placebo group (no vitamins). Unfortunately, the study contained no low-dose folic acid group. As a consequence, most countries issued a recommendation of high-dose folic acid (4 mg) daily during the periconceptional period and multivitamins containing folic acid (0.4 mg) before planning the next pregnancy to high-risk pregnancies. Later studies have pointed towards similar risk reduction (19–70%) with low and moderate folic acid doses [1, 2, 8, 9, 18, 25]. Consumption above 1 mg has not shown additional benefits [7, 11, 13, 19, 30].

Table 3 Total live birth rate of MMC before and after the changes in the national prenatal screening programme from 1983–2010

	Before changed prenatal screening (1983–2004)	After changed prenatal screening (2004–2010)	Change (%)
MMC birth rate (based on all known 121 patients)	5	2.0	−60
Prenatally diagnosed MMC	9%	27%	200
Scanned patients (N=95)	84 (88%)	11 (100%)	
Scanned 1st trimester	33 (39.3%)	5 (45.5%)	16
Scanned 2nd trimester	40 (47.6%)	6 (54.5%)	15
Scanned 3rd trimester	8 (9.5%)	0 (0%)	−100
Scanned unknown period	3 (36%)	0 (0%)	

Changes in prenatal life born diagnosed with MMC are shown as well as the total number of scanned mothers. The fourth column illustrates the percentage change

In our institute, we have a complete population of SB, born in the western part of Denmark. Of the MMC parents, 108 (89%) answered the questionnaire. All children are differentiated into proper subgroups on the basis of their MR imaging, giving us a unique chance to make a population-based true MMC study. Most other studies published include a mixture of neural tube defects even though the malformations differ both in risk factors prenatally, prognosis and neural dysfunctions.

Surprisingly, we found no effect on birth rate in true MMC after the national folic acid recommendations. A bias could be found in the study setup, as we gathered information from 2000–2010, and hence, the questionnaires before year 2000 are based on recall. Further, there is a compliance problem, similar to other pregnant women in DK, with only 48% correct folic acid intact after 1997 [24]. This study does not reject an effect of folic acid; however, we question an overall effect on MMC birth rate following the introduction of the national folic acid recommendations without high compliance.

The most severe cases of myelomeningocele can be diagnosed at the time of the first trimester risk assessment (nuchal translucency scan), noting irregularities of the bony spine or a bulging within the posterior contour of the fetal back. From the early second trimester (weeks 15–16), other ultrasound markers appear, reflecting the intracranial effect of the MMC: a “lemon shaped” cranium and “banana shaped” cerebellum [4]. When a severe fetal anomaly, as MMC, is diagnosed, termination of pregnancy before neonatal viability is an option in many countries, including Denmark. The majority of parents in Denmark opt for termination in the case of severe MMC, in agreement with the experience in France [10].

We found a highly significant decrease in the incidence after the national change in screening programme in 2004 even without corrections for the implementation delay; the last department in Denmark meeting the guidelines was in autumn 2006. Prior to these changes, ultrasonography screening was offered only to mothers above 35 years, in case of abnormalities during the pregnancy or in high-risk pregnancies. After 2004, an 18–21-week anomaly scan is offered to all pregnant women, the quality of the ultrasound equipment has improved, and increased focus on training, certification and quality assurance were also a consequence of the new recommendations for prenatal screening. This has significantly increased the detection rate of classic MMC signs. These changes might explain the reduced birth rate, since the majority of mothers were below 35 years and therefore had no routine scan before 2004 (Table 1). Surprisingly 88% of the women did have an ultrasonography scan before the changes in 2004; however, only 9% live-born infants were diagnosed prior to birth (Table 3). This might reflect that many of the prenatal ultrasound scans performed before 2004 was not a part of a systematic review of the fetal anatomy, but performed on indications like vaginal bleeding, decreased fetal movements, etc.

After 2004, 100% of the mothers in our study had a second trimester ultrasound screening, the birth rate significantly decreased close to eradication, and 27% of the live birth MMC was detected before birth. These mothers however decided to keep the fetus.This underlines the importance of the national guidelines for prenatal screening, proper training of the sonographers and doctors performing the screening, and high-quality ultrasound equipment.

The reduction of neural tube defects in the literature seems similar in high-dose and low-dose folic acid consumption. In addition, several papers indicate no additional benefits from folic acid consumption above a 1-mg daily intake [7, 11, 13, 19, 30]. Adding to this, papers report a potential risk of inflicting a cancer disease with consumption of high-dose folic acid. In this group of high-risk pregnancies, we find no effect of introducing national folic acid recommendations without high compliance. Most European countries are reluctant to introduce food fortified with FA due to the report of a possible cancer risk. Still, there is a recommendation of high-dose FA intake for high-risk pregnancies.

In conclusion, our findings demonstrate no effect of folic acid recommendation due to lack of compliance among women of reproductive age in Denmark. However, we found an improved early detection rate of prenatal MMC by a high-quality ultrasonography. Subsequent early termination of pregnancy has led to a significant reduction of the birth rate of babies with MMC.

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