Epidemiology of neural tube defects

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ABSTRACT

الأهداف: لمعرفة معدل انتشار عيوب الأنبوب العصبي (NTDs) ومقارنة النتائج مع المعطيات المتوافرة محلياً و دولياً وتسليط الضوء على أهمية تناول حمض الفوليك وتدعيم الطحين بحمض الفوليك لمنع العيوب الخلقية في الأنبوب العصبيNTDs.

الطريقة: أجريت دراسة استرجاعية للمعلومات المستقاة من السجلات الطبية للمواليد المصابين بعيوب الأنبوب العصبي والذين تم قبولهم في وحدة العناية المركزة لحديثي الولادة في مستشفى قوى الأمن بمدينة الرياض، المملكة العربية السعودية خلال 14 عام من 1996م إلى 2009م. تم وصف حمض الفوليك لكل النساء الحوامل في أول زيارة لعيادة الرعاية الأولية إما بجرعة 0.5 ملغ أو جرعة 5 ملغ (في حالة وجود قصة عائلية للإصابة بأحد عيوب الأنبوب العصبي). قورن معدل انتشار عيوب الأنبوب العصبي قبل مرحلة تدعيم الطحين بمعدلها بعد مرحلة تدعيم الطحين بحمض الفوليك سواء قبل أو بعد استثناء الأسباب الصبغية والجينية والمتلازمات. وقورنت كذلك النتائج مع تلك التقارير الصادرة من مناطق أخرى في المملكة العربية السعودية والعالم والموجودة في محرك البحث MEDLINE.

النتائج: خلال فترة الدراسة كان معدل انتشار عيوب الأنبوب العصبي 1.2 لكل 1000 مولود حي. وكان معدل الانتشار 1.46 لكل 1000 مولود حي وذلك قبل تدعيم الطحين وبعد تدعيم الطحين بلغ معدل الانتشار 1.05 لكل 1000 مولود حي p=0.103. وبعد استبعاد الأسباب الصبغية والجينية والمتلازمات لوحظ انخفاض معدل انتشار عيوب الأنبوب العصبي ولوحظ انخفاض معدل الانتشار بشكل مميز من 1.46 إلى 0.81 لكل 1000 مولود حي (p=0.0088). وقد حددت الأسباب الصبغية والجينية والمتلازمات في 20 حالة من بين الحالات (19.4%). تناول 2% من الأمهات حمض الفوليك قبل مرحلة الإلقاح و10% فقط تناولن حمض الفوليك خلال الأسابيع الأربعة الأولى من الحمل.

الخاتمة: بالرغم من تطبيق تدعيم الطحين بحمض الفوليك منذ 2001م إلا أن معدل انتشار عيوب الأنبوب العصبي مازال مرتفعاً في المملكة العربية السعودية. ويعزى ذلك إلى أسباب الدور الوراثي، والمتلازمي، والكروموسومات لعيوب الأنبوب العصبي والتي لا يمكن الوقاية منها عن طريق حمض الفوليك، وعوامل أخرى تلعب دوراً مميزاً مثل الحمل غير مخطط، وقلة الوعي بدور حمض الفوليك في منع الأسباب غير المتلازمي.

Objectives: To find the prevalence of neural tube defects (NTDs), and compare the findings with local and international data, and highlight the important role of folic acid supplementation and flour fortification with folic acid in preventing NTDs.

Methods: This is a retrospective study of data retrieved from the medical records of live newborn infants admitted to the Neonatal Intensive Care Unit (NICU), Security Forces Hospital (SFH), Riyadh, Saudi Arabia with NTDs spanning 14 years (1996-2009). All pregnant women on their first antenatal visit to the primary care clinic were prescribed folic acid 0.5 mg daily, or 5 mg if there is a family history of NTD. The pre-fortification prevalence is compared to post-fortification, before and after excluding syndromic, genetic, and chromosomal causes. The results were compared with reports from other parts of Saudi Arabia and internationally, through a literature search using MEDLINE.

Results: The prevalence of NTDs during the period was 1.2 per 1000 live births. The pre-fortification of flour with folic acid prevalence was 1.46 per 1000 live births. The post-fortification prevalence was 1.05 (p=0.103). After excluding syndromic, genetic, and chromosomal causes from calculation of the prevalence, there was a significant reduction in the prevalence, from 1.46 to 0.81 per 1000 live births (p=0.0088). Syndromic, genetic, and chromosomal causes were identified in 20 cases (19.4%). Only 2% of mothers received preconception folic acid, and only 10% of them received it during the first 4 weeks of gestation.

Conclusion: Despite the implementation of fortification of flour with folic acid since 2001, the prevalence of NTDs in the Kingdom of Saudi Arabia is still high. This is due to the impact of genetic, syndromic, and chromosomal causes of NTD not preventable by folic acid. Other factors like unplanned pregnancy and lack of awareness of the role of folic acid in preventing nonsyndromic causes, play a significant role.

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Neural tube defects (NTDs) are serious birth defects, which result from the failure of the neural tube to close in the cranial region, or more caudally along the spine by the 28th day of gestation.[1] Infants born with anencephaly die within a few hours or days of birth, while those with spina bifida have lifelong disabilities with varying degrees of paralysis, hydrocephalus, requiring ventriculoperitoneal shunting, and neurogenic bladder and rectum with incontinence of urine and stools. According to the Neural Tube Defects Registry Cumulative Report 2000-2012 from multi-institutions in the Kingdom of Saudi Arabia (KSA),[2] more than half of the patients with spina bifida and encephalocele (51%) are handicapped and cannot move around, while 21% can walk independently. Spina bifida associated damage to the spinal cord produces severe disabilities requiring extensive medical, surgical, and multidisciplinary care. The prevalence of NTDs ranges from one to 10 per 1,000 births, being highest in some regions of China and lowest in Scandinavian countries.[3-7] Defects in the cranial region include anencephaly, encephalocele (meningocele, or meningomyelocele), craniorachischisis totalis, and congenital dermal sinus. Spinal presentations include: spina bifida aperta (cystic, myelomeningocele [MMC], meningocele), myeloschisis, congenital dermal sinus, lipomatous malformations (lipomyelomeningocele), split cord malformation, diastematomyelia, diplomyelia, caudal agenesis, and amniotic band disruption. Numerous risk factors have been identified for NTDs, like maternal exposure to teratogens (methotrexate, valproic acid, and aminopterin), maternal diabetes, hyperthermia, low socioeconomic status, and lack of folate, as well as genetic succeptibility.[8] The most common NTDs are spina bifida, anencephaly, and encephalocele. They may result in spontaneous abortion, stillbirth, or death in early infancy, or a lifetime of disability. The NTDs can be associated with syndromes and chromosome aberrations,[8] which are important to identify to differentiate them from non-syndromic multifactorial NTDs for sound genetic counseling. In this retrospective study, we aimed to find the prevalence of NTDs, and compare our results with local and international data. We also aimed to reinforce the role of folic acid supplementation and fortification of flour with folic acid, as major preventive measures for prevention of NTDs, and increase awareness of childbearing age women of the importance of folic acid consumption before, and during pregnancy.

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Methods. The study consisted of retrospective analysis of data, spanning a period of 14 years (1996-2009), retrieved from the medical records of newborn babies admitted to the neonatal intensive care unit (NICU) with NTDs and their mothers at the Security Forces Hospital (SFH), Riyadh, KSA, the main hospital serving the employees of the Ministry of Interior and their dependents throughout the Kingdom. All babies with NTDs were identified by checking delivery logbooks, NICU records with diagnosis of NTD, and monthly perinatal statistics including all birth defects. The prevalence was calculated by dividing the number of live born infants diagnosed to have NTD by the total number of live born infants during the study period (1996-2009), and multiplying by 1,000 to obtain the prevalence of NTD per 1,000 live born infants. The prevalence of NTDs pre-fortification of flour with folic acid (1996-2000) included the number of live born infants diagnosed to have NTDs divided by the total number of live born infants during the same period multiplied by 1000. The same method was used for post-fortification prevalence (2001-2009). To compare our results with reports from other parts of KSA, from the region and internationally, the literature was searched using a MEDLINE search and NTD registry cumulative report (2000-2012) from multi-institutions in KSA.[2] Fortification of flour with folic acid was mandated in the KSA in the year 2001. The population studied included live born babies with NTDs admitted to NICU at the SFH. Cases with spina bifida occulta were not included. As NTDs due to syndromic, genetic, and chromosomal defects are not preventable by folic acid, we adjusted the prevalence of NTDs pre- and post-fortification by excluding these cases from our calculations to ascertain the impact of these cases on the prevalence.

Statistical analysis. All prevalence rates are given per 1000 live births. Categorical data were summarized with absolute numbers and percentages while continuous data were summarized with means and standard deviations (SD). To compare the prevalence rate before and after fortification, we used the exact rate ratio test, assuming poison counts. Comparison among different groups was performed using Chi-square test for categorical variable and analysis of variance (ANOVA) for continuous variable. All analysis was performed using the Statistical Package for Social Sciences version 17 (SPSS Inc., Chicago, IL, USA), and R software version 2.11.1 (GNU General Public License, Boston, MA, USA).

Results. During the study period of 14 years (1996-2009), the total number of live borns was 85,672 infants, of whom 103 live born infants (58 females, 45 males) had NTDs; thus, the prevalence of NTD was 1.2 per 1000 live births. This prevalence is similar to that reported from other regions in KSA and Gulf Cooperation Council (GCC) countries, lower than reports from other Arab and Islamic countries, but higher than that found in USA and Western countries (**Tables 1, 2, & 3**). All babies with obvious NTDs were admitted to the NICU, others with mild forms like spina bifida occulta were admitted to the normal nursery, and were not included in analysis. Stillborn babies with NTDs were also not included, as well as termination of pregnancies. All deliveries were registered in the delivery ward records. Pre-fortification (before 2001) prevalence was 1.46 per 1000 live borns and did not

Table 1 - Prevalence of neural tube defects in different regions of Saudi Arabia.

Authors	Region, city	Study period	Prevalence/1000	
			Pre-fortification	Post-fortification
El-Awad & Sivasankaran[12]	Southwest (Asir)	1987 - 1990	0.82	-
Asindi & Al-Shehri[13]	Southwest (Asir)	1995 - 1998	0.78	-
Murshid[10]	Al Madina	1996 - 1997	1.09	-
Thaliji et al[11]	Eastern Province	-	1.6	-
Safdar et al[9]	Jeddah	1997 - 2000 2001 - 2005	1.9	 0.76
Hakami & Majeed-Saidan[14]	Central (Riyadh)	2001 - 2010	-	0.44
Present study	Central (Riyadh)	1997 - 2000 2001 - 2005	1.46 -	- 1.04

Table 2 - Prevalence of neural tube defects in different Arab/Islamic countries.

Authors	Country, city	Study period	Prevalence/1000	
			Pre-fortification	Post-fortification
Masri[23]	Jordan	1993 - 2002	1.1	-
Samson[15]	United Arab Emirates (Abu Dhabi)	1992 - 1999	1.23	0.29
Rajab et al[16]	Sultanate of Oman		1.25	-
Golalipour et al[20]	Iran	1998 - 2003	2.87	-
Elsheik[21]	Sudan	2003 - 2004	3.84	-
Salih[22]	Sudan	1999 - 2004 (Review)	2.4 - 3.84	
Dudin[18]	Palestine	1986 - 1993	5.49	-
Houcher et al[19]	Algeria	2004 - 2006	7.5	-

Table 3 - Prevalence of neural tube defects in other countries.

Authors	Country, region	Study period	Prevalence per 1000	
			Pre-fortification	Post-fortification
Nazer & Cifuentes[29]	Chile	1999 - 2009	1.70	0.96
Alembik et al[26]	France	1979 - 1992	1.094	-
Buccimazza et al[28]	South Africa	20 years	1.74 - 0.63	-
Rankin et al [27]	North of England	1984 - 1996	1.79 (+ termination) 0.56 (birth)	-
De Wals et al[7]	Canada, Québec	1992 - 2000	1.89	1.28
Hendricks et al[3]	USA	1993 - 1995	0.95 - 1.51	-
Tuncbilek et al[30]	Turkey	1993 - 1994	3.01	-
Centers for Disease Control and Prevention[25]	USA	1995 - 2005	0.25	0.19
Klusmann et al[24]	Germany	1996 - 2003	1.05	0.68
Li et al[5]	China, Shanxi Province	2003 - 2004	13.9	-

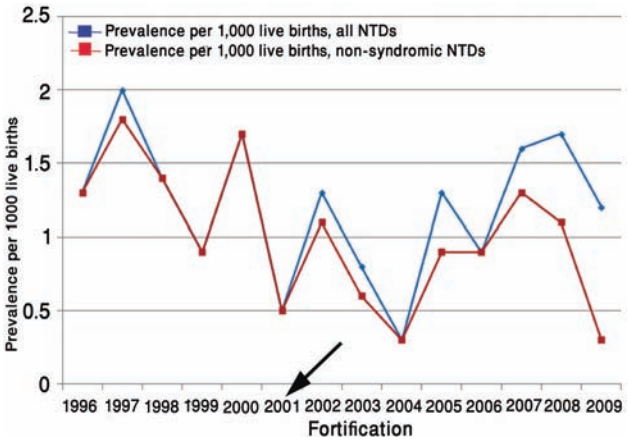

Figure 1 - Comparison between pre-fortification (1996-2000) and post-fortification (2001-2009) prevalence of neural tube defects with, and without syndromic causes.

differ significantly from the post-fortification prevalence of 1.04 (p=0.103). When the syndromic causes of NTD were excluded from calculation, the pre-fortification prevalence was 1.43 and post-fortification was 0.81, with a significant p=0.0088 (**Tables 4 & 5, Figure 1**). The mean maternal age for all NTDs was 29.45 (±7.31) years. Of the 103 cases of NTDs 51 (49.5%) were MMC, 29 (28.15%) anencephaly, 18 (17.5%) encephalocele, 2 (1.9%) lipomeningocele, 2 (1.9%) sacral agenesis, and one (0.97%) amniotic band syndrome. There is female predominance especially for encephalocele with a M:F ratio of 0.45, and 0.66 for anencephaly, and 0.77 for all NTDs. Other reports from the literature also showed a high prevalence of NTDs in females. The site of spinal defects: lumbosacral in 42.6%, lumbar 25.9%, dorsolumbar 18.5%, sacral 9.3%, and 1.85% for cervical, and dorsal. A similar distribution was also found in other reports. The majority (85%) of NTDs were detected antenatally by ultrasound scan.

Associated syndromes and anomalies with MMC included omphalocele, multiple congenital anomalies (MCA), Waardenburg syndrome, Walker-Warburg syndrome, and bilateral choanal atresia. Syndromes associated with encephalocele included 5 cases of Meckel-Gruber, and 2 cases of Joubert syndrome. Chromosome defects included one case of inverted Y (X inv Y) associated with dorsolumbar MMC, and one case 45, XY, der (13,14) (q10 q10) with large encephalocele who died a few hours after birth. The mortality rate was 48.5% of all NTDs. Morbidities included paraplegia in 70%, neurogenic bladder (81%), and hydrocephalus requiring ventriculo-peritoneal shunt in 63%. These children are followed up in the newborn high-risk clinics, pediatric neurology clinics, and neurosurgery outpatient clinic.

Table 4 - Comparison between pre-fortification (1996-2000) and post-fortification (2001-2009) prevalence of different types of neural tube defects (NTDs).

NTD type	Pre-fortification per 1000 live births	Post-fortification per 1000 live births	(% reduction)
Spina bifida	0.76	0.56	(26.3)
Anencephaly	0.43	0.26	(39.5)
Encephalocele	0.27	0.19	(29.6)
All NTDs	1.46	1.01	(30.8) p=0.103
Syndromic excluded	1.43	0.81	(43.4) p=0.008

Table 5 - Comparison between pre-fortification (1996-2000) and post-fortification (2001-2009) prevalence of neural tube defects (NTDs) with and without syndromic causes.

Year	Prevalence per 1000 livebirth all NTDs	Prevalence per 1000 live births non-syndromic NTDs
1996	1.3	1.3
1997	2.0	1.8
1998	1.4	1.4
1999	0.9	0.9
2000	1.7	1.7
2001	0.5	0.5
2002	1.3	1.1
2003	0.8	0.6
2004	0.3	0.3
2005	1.3	0.9
2006	0.9	0.9
2007	1.6	1.3
2008	1.7	1.1
2009	1.2	0.3

Table 6 - Effect of fortification of flour with folic acid on the prevalence of neural tube defects (NTDs).

Author	Place of study	Prevalence of NTD per 1000 pre-fortification	Prevalence of NTD per 1000 post-fortification
Present study	Riyadh	1.46	1.04
Safdar et al 2007[9]	Jeddah	1.90	0.76
Alasfoor et al[35]	Oman	2.17	0.78
Cortes et al 2012[36]	Chile	1.71	0.86
Mills & Signore 2004[37]	USA	0.50	0.34
Chen et al 2004[38]	Costa Rica	9.70	6.30

Discussion. *Prevalence of NTDs.* From the analysis of our data at SFH, spanning 14 years (1996-2009), the prevalence of NTDs was 1.2 per 1,000 live borns.

This is comparable (**Table 1**) to the prevalence reported by Safdar et al[9] in Jeddah (1.3/1000), Murshid[10] in Al Madina (1.09/1000), and Thaliji et al[11] in the Eastern Province (1.6/1000); but much higher than the reports from the Southwest Asir area in 1992 (0.82/1000),[12] and in 2001 (0.78/1000).[13] Both studies from Asir[12,13] were conducted during the pre-fortification of flour with folic acid, which was mandated in Saudi Arabia in 2001, and no mother in their studies received preconceptional folic acid supplementation. Their reports were likely to be an underestimation of the true prevalence since infants with anencephaly were not referred from peripheral hospitals to their main referral hospital (Asir Central Hospital) as stated by Asindi et al.[13] Hakami and Majeed-Saidan[14] reported from Riyadh in the Central Region a prevalence of 0.44/1000 post-fortification (2001-2010). However, they excluded from analysis 8 cases of dysraphism occurring as part of specific syndromes. Our prevalence is similar to those found in GCC countries: United Arab Emirates (1.14/1000);[15] Oman (1.25/1000);[16] and Kuwait (1.19/1000).[17] Compared with other Arab and Islamic countries (**Table 2**) the prevalence in Saudi Arabia is much lower than Palestine (5.49/1000),[18] Algeria (7.5/1000),[19] Northern Iran (2.87/1000),[20] and Sudan (2.4-3.48/1000),[21,22] but similar to Jordan (1.1/1000).[23] Compared with other countries worldwide (**Table 3**), our prevalence is similar to reports from Canada (1.28-1.89/1000),[7] Germany (1.05/1000),[24] and the USA (0.95-1.51/1000).[3] According to the Centers for Disease Control and Prevention 2009 report,[25] the prevalence in the USA pre-fortification was 0.204/1000, and post-fortification was 0.19/1000. Hendricks et al's[3] report was from the Texas-Mexico border being influenced by Hispanics with high rates of NTDs. Our reported prevalence is also similar to that in France (1.09/1000),[26] but lower than reports from the North of England (1.79/1000, including terminations),[27] South Africa (1.74/1000),[28] Chile (pre-fortification 1.70/1000, post-fortification 0.96/1000),[29] Turkey (3.01/1000),[30] and China with the highest rates in the world (6-14.9/1000).[4] Shanxi province in Northern China has one of the highest reported prevalence rates of NTD in the world of 14.9/1000 births.[4,5] The gender distribution in our study showed a female predominance (male to female ratio 0.77 for all NTDs) especially for encephalocele (M:F - 0.45), and anencephaly (0.66). These findings are similar to other studies that reported higher prevalence in females.[20,31,32] The mortality rate (48.5%) was found to be high in our study, which includes all forms of NTDs, but all deaths were due to lethal conditions: Meckel-Gruber syndrome (5 cases), anencephaly (29 cases), Walker-Warburg syndrome, and other associated congenital malformations.

The role of folic acid. Both observational and interventional studies including randomized controlled trials revealed that adequate consumption of folic acid periconceptionally can prevent 50-70% of NTDs.[33,34] Fortification of flour with folic acid resulted in a significant decline in the prevalence of NTDs as reported by many studies (**Table 6**).[9,35-38] Our study revealed an apparent decline in the prevalence of NTDs in the post-fortification period (2001-2009), with a reduction of 30% (**Table 4 & 5**). This is further augmented when the syndromic causes, in which associated NTDs are not preventable by folic acid, are excluded from calculations, 44.5% reduction, the adjusted prevalence was 0.81/1000 live births, post-fortification compared with 1.43/1000 pre-fortification (p=0.0088). The syndromic causes constitute around 20% of all NTDs. This is due to the high incidence of genetic disorders of autosomal recessive inheritance as a result of a high rate of consanguineous marriages in KSA. On the other hand, the role of preconception folic acid supplementation is hampered by the fact that most of the pregnancies are unplanned, and almost all pregnancies are diagnosed after the first 4 weeks of gestation, the critical period for prevention, in addition to the poor levels of awareness of the importance of folic acid supplementation among childbearing age females, 88% of females in one study from KSA are not aware of the importance of folic acid.[39]

In our study, only 2% of women with an NTD affected child took preconception folic acid, while only 10% received folic acid within the first 4 weeks. Our study demonstrates that NTDs pose a significant public health problem in KSA calling for population-wide educational campaigns on folic acid, and its role in preventing NTDs. We also suggest fortification of the staple diet, which is rice with folic acid, and encourage consumption of foods rich in folic acid like vegetables, beetroot, asparagus, spinach, kidney beans, lentils, and fruits like melons and strawberries. With advances in molecular genetics and diagnostic tools, genetic and syndromic causes of NTD can be prevented utilizing preimplantation genetic diagnosis (PGD), or early detection of these cases by chorionic villous sampling and by high resolution early antenatal ultrasound scan and offer early termination of pregnancy and sound counseling for the family.

Limitations of the study. Limitations of our study include a retrospective study and only live born infants

are included, thus missing significant numbers of stillbirths, and termination of pregnancies due to lethal syndromes associated with NTD like Meckel-Gruber syndrome and other conditions.

In conclusion, the prevalence of NTDs (1.2 per 1000 live births) in the present study is similar to that reported from other regions of Saudi Arabia and GCC countries, lower than reports from other Arab and Islamic countries, but higher than that found in the USA and Western countries. The reduction (30%) was not statistically significant (p=0.1030) between pre-fortification prevalence and post-fortification prevalence. Syndromic, genetic, and chromosomal defects were remarkable and constituted around 20% of total NTDs. This could be the reason why the prevalence of NTD did not change significantly post-fortification as these cases are not preventable by folic acid fortification and supplementation. It is suggested that all women capable of becoming pregnant to take periconceptional (namely, 2-3 months before and until 3 months after conception) 0.5 mg folic acid or folic acid-containing multivitamin supplementation, and 5 mg if there is family history of NTD. This can be augmented by establishing a network of preconception or periconception care within the primary health care, and a national campaign to raise awareness of NTDs and the importance of folic acid in its prevention, utilizing the public, and social media. There is also a need to consider fortification of rice, which constitutes one of the main staple foods for the Saudi population. Genetic causes of NTDs can be prevented by preimplantation genetic diagnosis, or by early termination of pregnancy if such cases are detected early in pregnancy.

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References

1. Copp AJ, Brook FA, Estibeiro JP, Shum AS, Cockroft DL. The embryonic development of mammalian neural tube defects. ***Prog Neurobiol*** 1990; 35: 363-403.
2. King Faisal Specialist Hospital & Research Centre. Neural Tube Defects Registry Cumulative Report 2000-2012. [Accessed 2013 February 12] Available from: http://rc.kfshrc.edu.sa/rcf/Reports/NTDR_AR_2012.pdf
3. Hendricks KA, Simpson JS, Larsen RD. Neural tube defects along the Texas-Mexico border, 1993-1995. ***Am J Epidemiol*** 1999; 149: 1119-1127.
4. Li Z, Ren A, Zhang L, Ye R, Li S, Zheng J, et al. Extremely high prevalence of neural tube defects in a 4-county area in Shanxi Province, China. ***Birth Defects Res A Clin Mol Teratol*** 2006; 76: 237-240.
5. Li Z, Ren A, Zhang L, Guo Z, Li Z. A population-based case-control study of risk factors for neural tube defects in four high-prevalence areas of Shanxi province, China. ***Paediatr Perinat Epidemiol*** 2006; 20: 43-53.
6. Jacobsen P. Regional variations in neural tube defects and alfa-fetoprotein screening in Denmark 1983-88. ***Acta Obstet Gynecol Scand*** 1996; 75: 620-623.
7. De Wals P, Rusen ID, Lee NS, Morin P, Niyonsenga T. Trend in prevalence of neural tube defects in Quebec. ***Birth Defects Res A Clin Mol Teratol*** 2003; 67: 919-923.
8. Chen CP. Syndromes, disorders and maternal risk factors associated with neural tube defects (II). ***Taiwan J Obstet Gynecol*** 2008; 47: 10-17.
9. Safdar OY, Al-Dabbagh AA, Abuelieneen WA, Kari JA. Decline in the incidence of neural tube defects after the national fortification of flour (1997-2005). ***Saudi Med J*** 2007; 28: 1227-1229.
10. Murshid WR. Spina bifida in Saudi Arabia: is consanguinity among the parents a risk factor? ***Pediatr Neurosurg*** 2000; 32: 10-12.
11. Thaliji AA, Abu Osba YK, Hann RW. Incidence of neural tube defects in the Eastern Province of Saudi Arabia. ***J KwT Med Assoc*** 1996; 20: 99-104.
12. El-Awad Mel-H, Sivasankaran S. Neural tube defects in Southwestern region of Saudi Arabia. ***Ann Saudi Med*** 1992; 12: 449-452.
13. Asindi A, Al-Shehri A. Neural tube defects in the Asir Region of Saudi Arabia. ***Ann Saudi Med*** 2001; 21: 26-29.
14. Hakami WS, Majeed-Saidan MA. The incidence and spectrum of central nervous system malformations in newborns over a decade (2001-2010) in the Central Region of Saudi Arabia. ***Saudi Med J*** 2011; 32: 1137-1142.
15. Samson GR. The Incidence and Demographic of Neural Tube Defects in Abu Dhabi, United Arab Emirates (1992-1999). ***J Trop Pediatr*** 2003; 49: 256-257.
16. Rajab A, Vaishnav A, Freeman NV, Patton MA. Neural tube defects and congenital hydrocephalus in the Sultanate of Oman. ***J Trop Pediatr*** 1998; 44: 300-303.
17. Teebi AS, al Saleh QA, Odeh H. Meckel syndrome and neural tube defects in Kuwait. ***J Med Genet*** 1992; 29: 140.
18. Dudin A. Neural tube defect among Palestinians: a hospital-based study. ***Ann Trop Paediatr*** 1997; 17: 217-222.
19. Houcher B, Bourouba R, Djabi F, Houcher Z. The prevalence of neural tube defects in Setif University Maternity Hospital, Algeria. 3 years Review (2004-2006) ***Pteridines*** 2008; 19: 12-18.
20. Golalipour MJ, Mobasheri E, Vakili MA, Keshtkar AA. Epidemiology of neural tube defects in northern Iran, 1998-2003. ***East Mediterr Health J*** 2007; 13: 560-566.
21. Elsheikh GEA. Neural tube defects: pattern and incidence in Omdurman Maternity Hospital, Sudan. [dissertation]. Khartoum (Sudan): University of Khartoum; 2004.
22. Salih MAM. Genetic Disorders in Sudan. In: Teebi AS, editor. Genetic Disorders Among Arab Populations. 2nd ed. New York (NY): Springer; 2010. p. 575-612.
23. Masri AT. Neural tube defects in Jordan. A hospital based study. ***Journal of Pediatric Neurology*** 2006; 4: 245-249.

24. Klusmann A, Heinrich B, Stöpler H, Gärtner J, Mayatepek E, Von Kries R. A decreasing rate of neural tube defects following the recommendations for periconceptional folic acid supplementation. ***Acta Paediatr*** 2005; 94: 1538-1542.
25. Centers for Disease Control and Prevention. Racial/Ethnic Differences in the Birth Prevalence of Spina Bifida. United States, 1995-2005. ***MMWR Morb Mortal Wkly Rep*** 2009; 57: 1409-1413.
26. Alembik Y, Dott B, Roth MP, Stoll C. Prevalence of neural tube defects in northeastern France, 1979-1992 impact of prenatal diagnosis. ***Ann Genet*** 1995; 38: 49-53.
27. Rankin J, Glinianaia S, Brown R, Renwick M. The changing prevalence of neural tube defects: a population-based study in the north of England, 1984-96. Northern Congenital Abnormality Survey Steering Group. ***Paediatr Perinat Epidemiol*** 2000; 14: 104-110.
28. Buccimazza SS, Molteno CD, Dunne TT, Viljoen DL. Prevalence of neural tube defects in Cape Town, South Africa. ***Teratology*** 1994; 50: 194-199.
29. Nazer HJ, Cifuentes OL. [Effects of wheat flour fortification with folic acid on the prevalence of neural tube defects in Chile]. ***Rev Med Chil*** 2013; 141: 751-757. Spanish
30. Tunçbilek E, Boduroğlu K, Alikaşifoğlu M. Neural tube defects in Turkey: prevalence, distribution and risk factors. ***Turk J Pediatr*** 1999; 41: 299-305.
31. Lary JM, Paulozzi LJ. Sex differences in the prevalence of human birth defects: a population-based study. ***Teratology*** 2001; 64: 237-251.
32. Rittler M, López-Camelo J, Castilla EE. Sex ratio and associated risk factors for 50 congenital anomaly types: clues for causal heterogeneity. ***Birth Defects Res A Clin Mol Teratol*** 2004; 70: 13-19.
33. MRC Vitamin Study Research Group. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. ***Lancet*** 1991; 338: 131-137.
34. Blencowe H, Cousens S, Modell B, Lawn J. Folic acid to reduce neonatal mortality from neural tube disorders. ***Int J Epidemiol*** 2010; 39 Suppl 1: 110-121.
35. Alasfoor D, Elsayed MK, Mohammed AJ. Spina bifida and birth outcome before and after fortification of flour with iron and folic acid in Oman. ***East Mediterr Health J*** 2010; 16: 533-538.
36. Cortés F, Mellado C, Pardo RA, Villarroel LA, Hertrampf E. Wheat flour fortification with folic acid: changes in neural tube defects rates in Chile. ***Am J Med Genet A*** 2012; 158: 1885-1890.
37. Mills JL, Signore C. Neural tube defect rates before and after food fortification with folic acid. ***Birth Defects Res A Clin Mol Teratol*** 2004; 70: 844-845.
38. Chen LT, Rivera MA. The Costa Rican experience: reduction of neural tube defects following food fortification programs. ***Nutr Rev*** 2004; 62: S40-S43.
39. Kari JA, Bardisi ES, Baitalmal RM, Ageely GA. Folic acid awareness among female college students. Neural tube defects prevention. ***Saudi Med J*** 2008; 29: 1479-1751.