Neural tube defects among neonates delivered in Al-Ramadi Maternity and Children's Hospital, western Iraq

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ABSTRACT

الأهداف: تحديد معدل انتشار وأنواع وأماكن تشوهات الأنبوب العصبي الخلقية (NTDs) ودراسة المتغيرات المتعلقة بالأم والبيئة.

الطريقة: تم فحص جميع المواليد الخدج ومكتملي الوزن في مستشفى النساء والأطفال – الرمادي – محافظة الأنبار – غرب العراق خلال الفترة من 1 نوفمبر 2007 حتى 1 نوفمبر 2008 للتأكد من الجنس، و عمر الجنين عند الولادة، وجود تشوهات الأنبوب العصبي، والتشوهات الخلقية المصاحبة الأخرى. تم جمع كافه البيانات المتعلقة من أمهات الأطفال المصابين بعد الولادة والتي تشتمل عن عمر الأم وعدد الأطفال، درجة القرابة من الأب، التحصيل الدراسي، الرعاية الصحية قبل الولادة، الأمراض السابقة ووجود ولادة سابقه مصابة بتشوهات الأنبوب العصب NTDs، وتناول الفولك أسيد والتشخيص بالأمواج فوق الصوتية أثناء الحمل.

النتائج: أظهرت نتائج الدراسة إن 33 طفل ولدوا مصابين بتشوه الأنبوب العصبي NTDs وبمعدل 3.3 لكل 1000ولادة وأن الغالبية من الحالات كانت من نوع التشوه الشوكي السحائي وانعدام الدماغ وأغلبية الحالات كانت في المنطقة الصدرية القطنية ثم في المنطقة القطنية العجزية. أثبتت النتائج إن ثلثي حالات تشوه الأنبوب العصبي NTDs كانت من زواج الأقارب وأن 12 من الأمهات قد تناولن ماده الفولك أسيد خلال فترة الحمل ولكن لم تتناوله أيا منهن في فترة ما حول الحمل. وأن 3 أمهات أنجبن ولادة سابقه لطفل مصاب بتشوه الأنبوب العصبي NTDs وتشكل الأمهات ما بين 34–25 عام أغلب حالات تشوه الأنبوب العصبي NTDs مقارنه بالأعمار الأخرى.

خاتمة: نسبة تشوهات الأنبوب العصبي NTDs لا تزال عالية في هذه الدراسة عند مقارنتها بتلك التي في الدول المتقدمة و بعض الدول النامية وأن زواج الأقارب يشكل نسبة عالية وكافه الأمهات 100% لم يتناولن ماده الفولك أسيد في فترة الحمل.

Objectives: To study the incidence, types, and sites of neural tube defects (NTDs) and its associated maternal and environmental variables.

Methods: All preterm and full term live and stillborn babies delivered at Al-Ramadi Maternity and Children's Hospital, Al-Anbar Governorate, Iraq, from the 1st of November 2007 to the 1st of November 2008 were examined for gender, gestational age, NTDs, and associated congenital malformations. Mother's data included age, parity, consanguinity, education, antenatal care, previous medical illnesses, other NTDs history, folic acid supplementation, and diagnostic ultrasound. Incidence was calculated per 1000 births.

Results: During the study, 33 infants were delivered with NTDs, giving an incidence of 3.3/1000 births. Most were of myelomeningocele and anencephaly types, and thoracolumbar and lumbosacral sites. Two-thirds of the cases found were from consanguineous marriage, 12 NTD's mothers took folic acid during their pregnancy, while none of them received the drug during the periconceptional period. Three mothers had another NTD affected babies before, and mothers 25-34 years old produced most of the NTD deliveries than any other age groups.

Conclusion: The NTDs incidence is still high compared with developed, and some developing countries. High consanguinity marriage and 100% lack of periconceptional folic acid intake needs further study considerations to reduce such morbid and mortal anomalies.

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Neural tube defects (NTDs) account for most congenital anomalies of the central nervous system (CNS), and result from the failure of the neural tube to close spontaneously between the third and fourth week of intrauterine development. Many factors including radiation, drugs, malnutrition, chemicals, and genetic determinants (mutations in folate-responsive, or folate-dependent pathways), may adversely affect the normal development of the CNS from the time of conception.[1] These NTDs are considered important causes of morbidity and mortality in infancy, childhood, and young adulthood.[2] Each year in the United States alone, spina bifida and anencephaly are the 2 most common form of NTDs, occurring in 1/4000 pregnancies.[3] Pathologically, NTDs range from a very uncomplicated and often subclinical small opening in the posterior vertebral canal, to a lack of closure of the whole neural tube, producing the most severe type of defect, the craniorachischisis. The lesions of NTDs include spina bifida, anencephaly, encephalocele, and dermal sinus. Spina bifida is classified into spina bifida cystica, aperta, and occulta. Spina bifida cystica is further subclassified into myelomeningocele, and meningocele. With myelomeningocele, the external sac is filled with cerebrospinal fluid (CSF), spinal cord, and nerves roots that have herniated through a defect in the vertebral arches and dura. With meningocele, the sac contains only meninges and CSF, and may produce no neurological symptoms. When the defect is opened and exposed to the environment it is called spina bifida aperta, while anencephaly involves the absence of the skull calvaria, and the cerebral hemispheres are completely missed or reduced.[4] Anencephaly is the most common CNS malformation in the Western world, and seen 37 times more frequently in females than in males.[5] It is believed that the most common types of NTDs are multifactorial in origin, which occur when there is a genetic predisposition to malformation triggered by environmental risk factors, including socioeconomic status, parental occupation, maternal nutritional status, and folic acid deficiency, which have been shown to play a very powerful role in the occurrence of these defects.[6,7] Anticonvulsants, particularly valproic acid given in the first trimester of pregnancy were shown to increase a woman's risk for spina bifida in her offspring up to 1-2%.[8] Racial, ethnic, and geographical zones have considerable effect on the prevalence of NTDs at birth. The prevalence may be as high as 1/100 births in some regions of China, to approximately 1/2000 or less in some Scandinavian countries. In many countries, the prevalence is approximately 1/1000 births.[9-12] In Western countries, NTDs form a large but diminishing proportion of all major congenital malformations.[7,13,14] The recurrence risk for couples having one child with isolated NTD and no family history is 2-5%, depending on the baseline population risk.[15] Neural tube defects may lead to spontaneous abortion, still birth, and early infant death from ascending CNS infections, or to life long crippling disabilities, ranging from lower paralysis and loss of sensation, to stool and urine incontinence, hydrocephalus, mental, and physical retardation. Still, such morbid and mortal anomalies compose an important part of congenital anomalies noticed in Al-Anbar Governorate, Iraq. The aim of this study is to estimate its recent incidence, types, sites, and its associated causative factors, in Al-Ramadi Maternity and Children Hospital, which is the main gynecology and pediatrics hospital in Al-Anbar Governorate, west of Iraq.

Methods. This is a descriptive cross-sectional study of the incidence of NTDs and its types among live and stillborn babies, delivered at Al-Ramadi Maternity and Children Hospital, Al-Anbar Governorate, west of Iraq, in a one-year study period from the 1st of November 2007 to the 1st of November 2008. The hospital covers Al-Ramadi city (the center of the Governorate [450,000 populations]) pediatric and obstetric cases, and serves as a referral hospital for pediatrics and gynecology cases from other districts of the governorate. The daily hospital range of deliveries is 25-50 births. All live preterm, full term, and stillborn hospital deliveries were examined for their gestational age, gender, NTD types, sites, and associated congenital anomalies. Out of hospital delivered NTD cases were excluded from the study. Mothers of affected babies were interviewed regarding their age, residence, consanguinity, date of delivery, parity, level of education, antenatal care, nutritional status, medical illnesses (hypertension and diabetes mellitus), smoking, exposure to radiation, history of periconceptional, or during pregnancy folic acid supplementation, and for the prenatal ultrasound (U/S) examination. The NTD associated hydrocephalus is diagnosed when the baby's occipitofrontal circumference measured more than 3 standard deviations above the mean for age and gender, supported by the CT scan examination of the brain. Rates were calculated per 1000 births. This research was approved by the Research Approval committee of the Al-Anbar Medical College.

Results. During the study period, there were 10,016 hospital births, with 5206 males, and 4810 females. The number of babies born with NTDs was 33 (11 males and 22 females), giving an overall incidence of 3.3/1000 live births with a male to female ratio of 1:2. **Table 1** shows the number and incidence of each type of NTD recorded in the study. Most of them had spina bifida, followed by anencephaly, and encephalocele

types. **Table 2** shows the anatomical distribution of the studied NTDs. Nine anencephalic cases were excluded, and from the 24 cases, the thoracolumbar was the most common site, followed by the lumbosacral sites. **Table 3** shows the distribution of the 51 recorded NTD associated anomalies. Twenty-six (78.7%) of these NTD cases had one, or more of these associated congenital anomalies. Most cases were clubbed foot, then hydrocephaly, followed by polydactyly, and other types of anomalies. **Table 4** shows the relation of these NTDs with certain maternal variables. **Table 5** shows the diagnostic results of NTDs by U/S. Only 29 out of the 33 mothers underwent U/S examination during their affected pregnancy, and from these 6 cases were prenatally diagnosed as having NTDs. The result also showed that 18 of our NTDs cases were associated with polyhydramnios, and 4 with oligohydramnios. **Figure 1** shows the distribution of these NTD cases in relation with maternal age. Twenty-two (66.6%) of the cases were from 25-34 years old mothers, 6 (18.2%) cases were above 34 years old, and 5 (15.1%) of the NTD cases were from mothers below 25 years old. **Figure 2** shows a waving pattern of the NTD incidence along the months of the study year. The incidence was increasing, and then decreases every 3-4 months, followed by a persistently high incidence in August, September, October, and November, the last Autumn, and early Winter months, of the study year.

Table 1 - Types of neural tube defects (NTDs).

Types of NTDs	n (%)	Incidence/1000 live births
Spina bifida (n=22)		2.2
Cystica (n=18)		
Meningomyelocele	15 (45.5)	
Meningocele	3 (9.1)	
Aperta	3 (9.1)	
Occulta	1 (3.0)	
Anencephaly	9 (27.2)	0.9
Encephalocele	2 (6.1)	0.2
Total	**33 (100)**	**3.3**

Table 2 - Sites of neural tube defects (NTDs) (n=24)*.

Sites	n	(%)
Thoracolumbar	9	(37.5)
Lumbosacral	8	(33.3)
Lumbar	4	(16.7)
Sacral	1	(4.2)
Temporoparietal	2	(8.3)

*Cases of anencephaly were excluded

Table 4 - Mother's variables related with neural tube defects.

Variables	n	(%)
Residency		
Rural	13	(39.4)
Urban	20	(60.6)
Consanguinity		
Yes	21	(63.6)
No	12	(36.4)
Education		
Illiterate	24	(72.7)
Primary school	4	(12.1)
Secondary school	2	(6.1)
Higher education	3	(9.1)
Parity		
Primigravida	5	(15.1)
Multipara	28	(84.9)
Antenatal care		
Booked	16	(48.5)
Unbooked	17	(51.5)
Folic acid		
Not taken	21	(63.6)
Taken during pregnancy	12	(36.4)
Smoking		
Maternal	0	(0)
Paternal	20	(60.6)

Table 3 - Neural tube defects (NTDs) associated congenital anomalies (N=51).

Anomalies	NTDs associated anomalies (n=51)		Spina bifida NTDs (n=22)		Anencephaly NTDs (n=9)		Encephalocele NTDs (n=2)	
				n (%)				
Clubbed foot	22	(43.1)	20	(90.9)	2	(22.2)	-	-
Hydrocephaly	20	(39.2)	19	(86)	-	-	1	(50)
Polydactyly	3	(5.9)	-	-	3	(33.3)	-	-
DDH*	2	(4.0)	2	(9.1)	-	-	-	-
Imperforated anus	2	(4.0)	-	-	1	(11.1)	1	(50)
Ectopia vesica	1	(1.9)	1	(5.0)	-	-	-	-
Gastroschisis	1	(1.9)	1	(5.0)	-	-	-	-
Total	**51**	**(100)**	**43**	**(84)**	**6**	**(11.7)**	**2**	**(3.9)**

DDH - developmental dysplasia of the hip joint

Discussion. The NTDs incidence is progressively decreasing now in all developed and some developing countries through the periconceptional folic acid supplementation, prenatal maternal serum alpha-feto protein screening and U/S diagnosis, and termination of affected pregnancies. These measures are not, or still partially applied in most main Iraqi hospitals, and the NTDs incidence is still high in Iraq and most developing countries. **Table 6** compares our overall spina bifida, and anencephaly incidence with the results of some Iraqi Governorates. All our incidences were lower than these results, except the spina bifida incidence of the Basrah Governorate.[16-18] **Table 7** compares our overall spina bifida, and anencephaly incidence with that of some near and far countries. All incidences are high compared with Turkey, Iran, Saudi Arabia, and Kuwait, and Israel, Italy, Ireland, UK, Canada, USA, and Australia.[9,12,19-30]

Table 5 - Amniotic fluid state, diagnosed and undiagnosed neural tube defects (NTDs) by ultrasound examination (n= 29).

Amniotic fluid state by ultrasound	Diagnosed NTDs	Undiagnosed NTDs
	n (%)	
Normal	1 (3.4)	6 (20.7)
Oligohydramnios	0 (0)	4 (13.8)
Polyhydramnios	5 (17.2)	13 (44.8)
Total	**6 (20.7)**	**23 (79.3)**

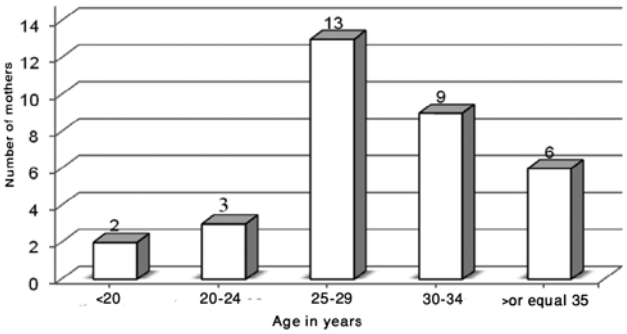

Figure 1 - Relation of maternal age with neural tube defects.

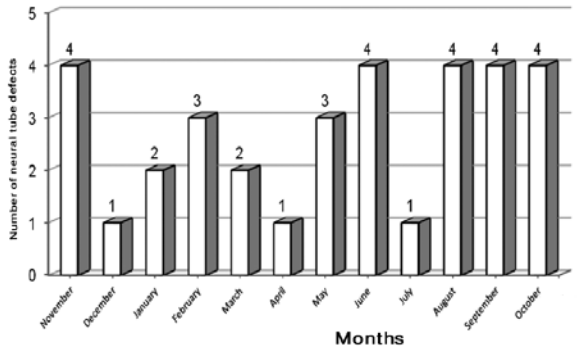

Figure 2 - Monthly incidence variations of neural tube defects.

In this study, the incidence was higher for spina bifida, followed by anencephaly, and then encephalocele. Such a pattern was similar to that noticed in the USA,[9] Turkey,[25] China,[19] Algeria,[20] India,[22] Iran,[23]while it was different from the incidence of other studies.[21,28] These incidence variations could be due to the influence of the genetic, nutritional, socioeconomic, and geographical factors, as well as the effect of the type of sample collection (referral hospitals were expected to have higher rates), and the criteria of diagnosis. We observed a significant female predominance in our NTD cases, with a male to female ratio of 1:2. Others had reported 0.58,[16] 0.70,[20] 0.60,[22] 0.78,[23,31] 0.85,[32] or even a male predominance of 1.07,[33] and 1.1[27] male to female ratios.

In Western countries, anencephaly was the most common type of NTD.[34] This was different from our results, which showed that spina bifida was much more frequent than the anencephalic NTDs anomalies. Anencephaly was particularly reported more prevalent in communities with high rates of consanguinity.[35] Regarding the NTD sites, the thoracolumbar was the most common site noticed in our NTD cases. This was in agreement with the Western pattern for site distribution,[13] but was in contrast to the North

Table 6 - Incidence of neural tube defects (NTDs) in some Iraqi Governorates.

Governorate	All NTDs	Spina bifida	Anencephaly	Encephalocele
Al-Anbar (current study)	3.3	2.2	0.9	0.2
Diwaniah[16]	8.4	3.7	2.3	2.4
Basrah[17]	4.34	1.13	1.74	-
Najaf[18]	27.0	9.0	10.4	7.0

Table 7 - All neural tube defects (NTDs), spina bifida and anencephaly incidences of other countries.

Country	All NTD rates*	Spina bifida rate†	Anencephaly rate†
China[19]	13.9	-	-
Algeria[20]	7.5	4.2	2.4
Jordan[21]	6.5	5.89	0
India[22]	5.7	3.1	1.8
Iraq (current study)	3.3	2.2	0.9
Iran[23]	2.87	1.6	1.1
Kuwait[24]	1.6	0.26	0.38
Turkey[25]	1.5	1.05	0.11
USA[9]	1.46	0.7	0.64
Canada[12]	1.41	0.47	0.47
France[26]	1.4	0.15	0.10
Saudi Arabia[27]	1.3	1.04	0.02
Israeli Jews[28]	1.15	0.46	0.53
United Kingdom[26]	1.1	0.36	0.7
Ireland (Dublin)[26]	1	0.51	0.36
Italy[26]	0.5	0.23	0.07
Australia[29]	0.46	0.3	0.11

*All NTDs incidences were arranged in descending pattern.
†rates per 1000 births[30]

American pattern that showed higher predominance of the lumbosacral site.[36]

In agreement with a similar study,[37] our NTD cases were associated with different congenital anomalies, and some patients had more than one associated congenital anomaly that reflects the polymorph nature of such anomalies. Clubbed foot was the most common associated skeletal defect, and was observed in 66.6% of the NTD cases. The same anomaly was the most frequently noticed in several other studies.[37,38] Hydrocephaly was associated with 20 (60.6%) of our NTD cases. This was close to the result of other studies,[21,22,37] but it is less than the international figure of 85-90% reported NTDs hydrocephalus associated anomalies.[13,36] It was seen that all patients with thoracic and most patients with lumbosacral spina bifida are at increased risk for hydrocephaly.[33] In general, patients with spina bifida, excluding anencephaly and encephalocele, will have an 80-85% chance of developing associated hydrocephalus anomalies.[39]

Our study showed that 60.6% of the mothers reside in urban areas. This was similar to the Diwaniah study in Iraq,[16] but was different from other studies that showed a higher incidence in rural localities.[19,23] Various authors considered consanguineous marriage an important predisposing factor for NTDs. Relatives of children with NTDs face a higher risk of having a child with NTD than the general population.[40] In our study, 63.6% of NTD cases were the result of consanguineous marriage, compared to the 50% in Saudi Arabia,[27] 13% in Algeria,[20] 70% in Jordan,[21] 33% in India,[22] and 43% in Iran.[23] The risk for NTDs was seen inversely related to the level of maternal education, with women who had primary school education or less, having more than 2-fold risk of developing NTD births when compared to those with higher education.[19] This in part is due to diet pattern, socioeconomic status, and lack of awareness for the potential benefit of folic acid supplements in preventing NTDs among women with low education.[41] This was consistent with our study, which showed the highest NTD prevalence among illiterate, and low education mothers compared with those of higher education.

Concerning parity, 84.8% of the NTD mothers were multipara. This was consistent with the results recorded in the Diwaniah governorate (74%),[16] and Jordan (93.9%),[21] and with that of other studies,[42,43] but it differs from studies[7,11] that showed a U-shaped pattern, with the risk being highest in mothers having both low and high number of deliveries. Although 48.4% of NTD producing mothers in our study had regular antenatal care, most of them attended the antenatal care after the first month of pregnancy when the neural tube malformation has been completed, and folic acid has lost its desired effect to prevent these anomalies. Folic acid supplementation before conception and during the first trimester of pregnancy is one of the few public health interventions that is effective in reducing the risk of NTDs.[14,44-47] Food fortification with folic acid became mandatory in 1998 in the USA,[14] in 2000 in the UK,[48]and 2001 in Saudi Arabia.[49] In Iraq, folic acid fortification is still not applied, and our women are not aware of the importance of this drug in the prevention of this morbid and mortal anomaly, and in this study only 36.4% of the mothers received the drug during their pregnancy, and none of them received it during their periconceptional period.

The NTDs are an example of a disorder that has a multifactorial inheritance, including environmental factors, such as tobacco smoking, which is considered an important teratogenic agent producing NTDs.[50] Recent studies reported that cigarette smoking reduces the fetal serum level of folic acid.[51] Other studies centers on the carbon monoxide effect, which was found to reduce the oxygen carrying capacity to the fetal tissue and the nicotine which crosses the placenta, and reduces the uterine blood flow, affecting fetal oxygenation, and the acid-base balance leading to such anomalies.[52] In the Najaf governorate study,[18] they found that the incidence of NTDs among the active and passive smoking mothers was higher than those who are non-smokers. This was consistent with our results where we found 60.6% of the NTDs cases are associated with the maternal passive smoking from their smoking husbands, but none of them were smokers.

Our research showed an inversed U-shape NTD incidence in relation to the maternal age, in which the highest rate was found in mothers aged 25-34 years old. This observation was different from other studies that showed a U-shaped curve, with higher rates among young mothers,[53] and those over 35 years,[9] and from the Golalipour study[23] that showed a linear relation between the NTD rates and the increasing maternal age. Six out of our 33 NTD cases were prenatally diagnosed by U/S examination, but for religious and social causes, none of these pregnancies were terminated after the diagnosis. In this study, a waving pattern with a 3-4 monthly up and down NTD incidence variation was seen, which is followed by a persistent high incidence in September, October, November, and December, the last Autumn, and early Winter months of the studied year. This pattern was comparable to the Golalipour study[23] that showed increased incidence from October to December and January to March of the Autumn and Winter months in their studied year.

During the study period, hospital abortions and the out of hospital and midwife deliveries were excluded from the study, which reduced the total sample size of

the studied deliveries and therefore, our results may be underestimated.

To evaluate the whole country, recent NTD incidence and its associated risk factors, another multicenter case-control study is required, and the broadcasting, magazine, and medico-social facilities must be used to educate the mothers on the well-known importance of the periconceptional folic acid supplementation to reduce the risk of these dangerous anomalies.

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