# Study of Neural Tube Defects at Al-Diwaniyah Province / Iraq

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## Abstract

**Background:** The Neural tube defects NTDs refers to defect ocurr at birth resulting from defect in closure of the neural tube during early intra uterine life after conception; these anomalies are usually divided into cephalic and spinal forms. They include three main type , anencephaly, spina bifida and encephalocele , These NTDs are considered important causes of morbidity and mortality in infancy, childhood, and even young adulthood .

**Objective:** The aim of study is to study the type and incidence of the neural tube defect and it is it is risk factors and other associated variable.

Methods : This descriptive prospective study was carried on 120000 lived newborns from December 201 3 to December 2015 in al diwaniya teaching hospital , neurosurgical department and pediatrics hospital in al diwaniya province in south west Iraq ,the questionnaire include all the information's case were defined as women residing in the al diwaniya government , delivered live or still born with neural Tube defect . important feature related to the neonates and their parents like gender ,date of birth , type of neural tube defect ,father and mother age ,consanguineous marriage, drug take during pregnancy ,maternal diseases ,previous history of neural tube defect .

**RESULTS** : During a period of three years 2013-2015, there were (120,768 total ) birth ; the number of total births registered during the 3 years was 41761 in 2013, 39353 in 2014, and 39652 in 2015 . Among this sample population,112 women had fetus or newborn with NTD ( 1.078 per 1000birth ), An encephaly {3 (2.7%)} , spina bifida {103(92%)}, Encephalocele{6(5.3%)} Meningocele {20(17.9%)},Meningomyelocele {76 (67.9%)}, myeloschiasis {7 (6.2%)}, The age of 112 women that her babies affected NTDs , 30(26.8%) had 16-25 years , 55 (49.1%) had 26-35 years while 27 (24.1%) had above 35 years .

**Conclusion:** This study showed that folate deficiency are very important in reducing the NTDs occurrences consanguineous marriage is not important risk factor for NTDs.

Key word: Neural tube defect, risk factor, Iraq

## Introduction:

The term “Neural tube defects” NTDs means a collection of birth defects resulting from defective development of the neural tube during early fetal life after conception [1]This defect can occur at different levels of spinal cord , from cephalic to the caudal end, and to a variable degree. This results in abnormalities of the meninges, the vertebrae or skull, with a variable impact on the nervous tissue [2]. There are two main malformations of NTDs cephalic and spinal forms and they include firstly anencephaly and spina bifida and lastly encephalocele [3]. These diseases are considered an important causes of morbidity and

mortality in infancy & childhood & in young adulthood also.[4]Each year in the US , the spina bifida and anencephaly are the two most common form of NTDs, occurring in 1/4000 pregnancies.[5]. The NTDs range from a very simple and often subclinical small opening in the posterior vertebral canal, to a loss of closure of the whole tube, producing the most severe type of neural defect, the craniorachischisis. Spina bifida is classified into spina bifida cystica, aperta, and occulta. The incidence of NTDs ranges from ten to one hundred per 10,000 births with similar frequencies of spina bifida and anencephaly [6]. Incidence of NTDs has been reported as slightly more than nine to 14.6/ 10 000 births in the US, twelve in Ireland [7] , more than seventeen in England, fifteen in Turkey [8]& about thirty in Iran [9] . NTDs occur more frequently in the white color population and female sex affected commonly than male. In more than eighty percent of NTDs the lumbo-sacral region is site of defect . With myelomeningocele, the external sac is filled with cerebrospinal fluid (CSF)&spinal cord& nerves roots that have pulging through a defect . With meningocele, the defect contains meninges and cerebro- spinal fliud, and may or may not lead to symptoms. When the defect is opened & exposed called spina bifida aperta, while anencephaly involves the absence of the skull bone, and the cerebral hemispheres are completely lossed or malformed or reduced.[10]Anencephaly is a common CNS anomalies in the Western counteries, and seen in more than thirty five times more frequently in females than in males[11] Exposure to certain drugs like chemotherapy, anticonvulsant, maternal diabetes, fever, low economic state, and folate deficiency have been shown to increase the risk of NTDs .[12,13,14, 15,16,17,18,19,20,21] Hereditary causes are believed to be important.[12] The prevalence of NTD at birth varies considerably by countries, family descent and ranges of incidence is variable , as high as 1 /100 births in certain area of China , to approximately 1/5000 or less in some Scandinavian regions . important related factors for NTDs have been reported as past history of NTDs; age of the mother less than twenty or more than thirty five ; multipara; poor nutritional status and poor both maternal and father educational levels; low maternal folic acid; low B12 and serum zinic ; high copper; racial differences; higher levels of benzene; radiation; maternal hyperthermia & infection and use of medications before and during pregnancy ; and poor antenatal care [22,23,24,25,26,27,28,29 ] . during pregnancy the NTDs could be diagnosed by serum alphafetoprotein level between the 15th and 18th week of gestation. Confirmation requires amniotic fluid analysis and ultrasonic study. Without treatment, only up to thirty percent of myelomeningocele patients survive infancy but with treatment, eighty five percent of infants survive.Degree of disability in treated NTDs children varies highly from very simple to sever neurological disability with different system disability. 1/3 of the live cases are mentally deficient or learning disability . Studies have shown that very severely affected child who are not treated during the neonatal period ;die in the first few months after birth[30].

**Objective:** The aim of study is to study the type and incidence of the neural tube defect and it is it is risk factors and other associated variable .

**Patients and method**

this descriptive study was carried on 120000 lived newborns from

December 2013 to December 2015 in al diwaniya teaching hospital , neurosurgical department and pediatrics hospital in al diwaniya province in south west Iraq , the questionnaire include all the information's case were defined as women residing in the aldiwaniya government , delivered live or still born with neural Tube defect . Demographic characteristic of the neonates , and their parents such as sex ,date of birth , type of neural tube defect, site of lesion and any associated abnormalities ,father and mother age ,consanguineous marriage, rural or urban ,folate intake& other like drug take during pregnancy ,maternal diseases ,previous history of neural tube defect . The data was analyzed use SSPS program.

**Results:**

During a period of three years 2013-2015, there were (120,768 total ) birth ; the number of total births registered during the 3 years was 41761 in 2013, 39353 in 2014, and 39652 in 2015 .

Among this sample population,112 women had fetus or newborn with NTD ( 1.078 per 1000birth ), An encephaly {3 (2.7%)} , spina bifida {103(92%)}, Encephalocele{6(5.3%)}. Meningocele {20(17.9%)}, Meningomyelocele {76 (67.9%)}, myeloschiasis {7 (6.2%)}, as shows below by Table-1 -Types of NTD .

Regading the gender among 112 affected NTDs 64 (57.2%) were female and 48 (42.8%) were male, this difference is statically significant ($p<0.05$). Figure-1 shows the sex distribution of NTDs.

**Table-1 -Types of NTD**

| Type | Total no&% | | Male | Female |
|---|---|---|---|---|
| **Spinabifida** : | 103 | (92 ) | | |
| 1-meningomylocele | 76 | (67.9) | 34 | 42 |
| 2-Meningocele | 20 | (17.9) | 8 | 12 |
| 3-myeloschiasis | 7 | ( 6.2) | 2 | 5 |
| **Anencephalus** | 3 | (2.7 ) | 1 | 2 |
| **Encephalocele** | 6 | (5.3) | 3 | 3 |
| **total** | **112** | **( 100)** | **48** | **64** |

The site of the spina bifida depend on the level of the spinal cord involvement at which neural tube closure was incomplete. The lesion is location in our study the lumbosacral & dorsolumber region represent nearly the most common site of the cases 27.2% , 49.5 % while the cervical and

dorsal regions are the least common sites 3.9% & 4.9% respectively ; other few cases in all the cases of anencephaly and encephaly were excluded . **Table-2 NTD According To Site**

**Figure- 2 sex distribution of NTD**

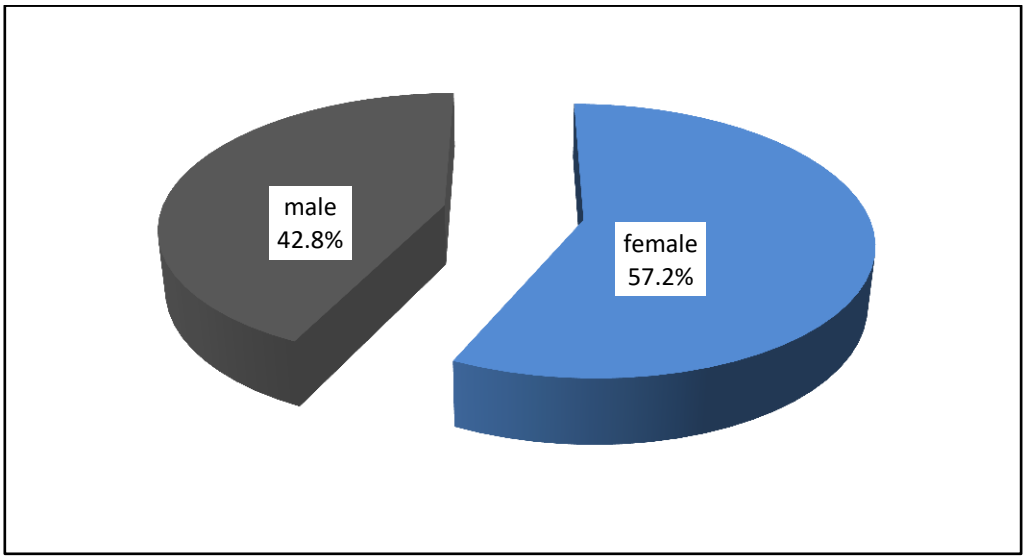


**Table-2 NTD According To Site**

| site | Total no&% | | male | female |
|---|---|---|---|---|
| cervical | 4 | 3.9 | 1 | 3 |
| dorsolumber | 51 | 49.5 | 21 | 30 |
| lumbosacral | 28 | 27.2 | 13 | 16 |
| dorsal | 5 | 4.9 | 2 | 3 |
| lumber | **15** | **14.5** | **7** | **8** |

Regarding the associated anomalies with NTDs, in our study the Hydrocephalus is the common associated congenital malformations of the brain represent 61 (59.2 % )in patients with spina bifida and 4 ( 66.6% ) in patients with encephalocele .the orthopedic anomalies like club foot 28 ( 27 % ) , congenital hip dislocation 14 (13.6% ) commonly occur in the pateints with spina bifida and not reported with anencephaly and encephalocele in current study .

The other associated problems with NTDs like bladder and bowel control problems, including incontinence, and abnormal eye movement and seizure present in few percent mainly in spine bifida cases 11.6 % . **Table-3 common ascociated anomalies and problems with NTDs .**

## Table-3- Associated anomlies

| Associated anomaly | Total | male | female | Spina bifida NTDs(N=103) | | Anencephaly NTDs(N=3 | | Encephalocele NTDs(N=6) | |
|---|---|---|---|---|---|---|---|---|---|
| hydrocephalus | 65 | 30 | 35 | 61 | 59.2 % | | | 4 | 66.6% |
| Club foot | 28 | 12 | 16 | 28 | 27% | | | | |
| DDH | 14 | 5 | 9 | 14 | 13.6% | | | | |
| others | 14 | 7 | 7 | 12 | 11.6% | 2 | 66.6% | | |

Regarding the Mother variable associated with NTDs in this study, 62.5% and 37.5% of parents with affected newborns lived in rural and urban areas, respectively, and our results also shows that there is no significant relation between consanguineous marriage of parents and NTDs in which conseguinity avialable in 40.2% and not present in 59.8% .

This study show that no folic acid supplementation during pregnancy in 82 (73.2%) of cases of NTDs and no intake in about 30 (26.8% ) statistically significant result.

The age of 112 women that her babies affected NTDs , 30(26.8%) had 16-25 years , 55 (49.1%) had 26-35 years while 27 (24.1%) had above 35 years .**Table-4- shows the Mother variable associated with NTDs**

**figure -2 - relation of parental age with ntd**

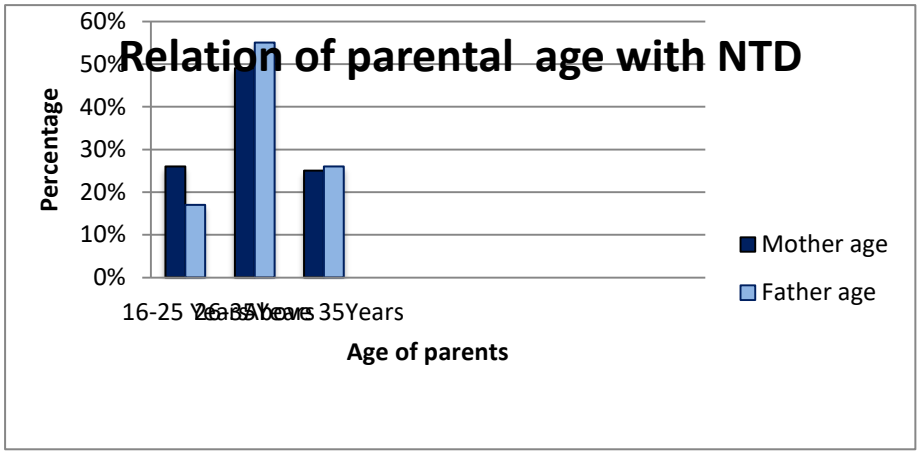

**Table-4- Mother variable associated with NTD**

| VARIABLE | NO | % |
|---|---|---|
| Residency: | | |
| Rural | 70 | ( 62.5) |
| Urban | 42 | ( 37.5) |
| Consanguinity: | | |
| Yes | 45 | ( 40.2) |
| No | 67 | ( 59.8) |
| Parity: | | |
| Primi gravida | 30 | ( 26.8) |
| Multipara | 82 | ( 73.2) |
| Antenatal care: | | |
| Booked | 50 | ( 44.6) |
| Unbooked | 62 | (55.4 ) |
| Folic acid: | | |
| Taken | 82 | (73.2) |
| Not taken | 30 | (26.8) |
| Previous sibling: | | |
| Yes | 8 | (7.2 ) |
| no | 104 | (92.8) |
| maternal disease during 1st trimester | | |
| yes | 5 | (4.5 ) |
| no | 107 | (95.5) |

**Discussion :**

In the current study prevalence equal to 1.078 per 1000 which is differ from that and in the United States , before 1980 the prevalence of meylomeningocele in the united states was 11,02 per 1000 live birth more recently , prevalence has declined to 0.44 per 1000 live birth 20% to 30% of the declined this may be return to pregnancy termination after prenatal diagnosis and prenatal folate supplementation (31) the termination of pregnancy is prohibited in our society belong to religious causes.

In other region there are small difference between own our study in the occurrence of NTDs in different region ; The united kingdom practically Ireland , has a higher prevalence of NTDs than to continentals Europe , U K 1.1 per 1000(36 ) , Canada 1.41 per 1000 (37 ) , study in France 1.4 per 1000( 36),study in turkey 1.5 per 1000(38), data in Saudi Arabia shows 1.3 per 1000 (39). In our study from 2013 to 2015 , the prevalence 1.078 per 1000 birth unlike other previous study in AL –Ramadi/Iraq ,3.3 per 1000. ( 32), and other study in Sulaimaniyah 2006-2010, incidence 3.5per 10000 ( 33).

Birth defects are the leading cause of infant mortality in developed countries and in current study the main cause of death associated with anencephalus and encephalocele which represent 8% of cases of NTDs in which differ to other study (34 ,35);. The Midwest had the highest rate of NTD-specific infant deaths among US regions (36 ) .

In the current study anencephaly represent 2.7 % from all NTDs , while in the united states anencephaly occurs in about 1 out of every 10,000 births.(37) the average rate are high among Africans populations with like Nigeria estimated about 3/10,000 in 1990 & in Ghana estimated at eight per / 10,000 in 1992 .(38) data from China are estimated at five per /10,000 (38) in general ,average of the incidence of anencephaly in the US during previous century have change from 0.3 to 7 per 1000 births.(35)

Encephalocele present in 5.3 % in our study , but the control of disease centre report 1/ 12,200 babies born in the United States each year will have encephalocele. This means that more than three hundred U.S. babies are born with this disease every year.(39)

Regarding the site of spinal lesion , the cervical and thoracic regions are the least sites to be involved , and lumbar and lumbosacral regions commonest area for these lesions.The manifestations of the spina bifida depend on the level of the spinal cord involvement at which neural tube closure was defected. The lesion is located in lumbosacral area in more than eighty percent of the cases(40) while in our study the lumbosacral and dorsolumber region represent the most common of the cases 27.2,49.5 % respectively while the cervical and thoracic regions are the least common sites 3.9% & 4.9% respectively.

Regarding the associated anomalies with NTDs, in our study the Hydrocephalus is the common associated congenital malformations of the brain represent 59.2 % in patients with spina bifida and 66.6% in patients with encephalocele also these not in line with other study in the US in which hydrocephalus present at birth in 85-95% of cases as shown by ultrasonography (40,41)

The Orthopedic anomalies like club foot 27 %, hip dislocation 13.6% commonly occur in the pateints with spina bifida and not reported with anencephaly and encephalocele in current study ,also differ from other study (42)

The other associated problems with NTDs like Bladder and bowel control(sphinictors) problems, including incontinence, urinary tract infections(UTI), and abnormal eye movement and seizure present inform of 11.6% in spina bifida and 66.6% in anencephalus unlike other study( 43,44). Seizures may occurred in up to seventeen percentof the children with meningomyelocele and commonly occur in hydrocephalus (45).

Abnormalities of the central nervous system(CNS) are the most common birth anomalies and NTDs represent the commonest part of it (40). In our work, malformations of the nervous system are the most frequent and the first neural tube defects. Only nutritional factors are related factors on which it is possible to prevent (41).

This study show that no folic acid supplementation in 73.2% of cases of NTDs and no intake in about 26.8% , so the folic acid may decrease the disease and similar to the study current and should be used for women before and during pregnancy [46] .

In this study, 62.5% and 37.5% of parents with affected newborns found in rural and urban areas . the mother reside in urban that showed a higher incidence in rural localities.This result was similar to a study was reported from Texas (47)

Regarding our results, there was no clear relation between consanguinity and NTDs. Various reports considered consanguineous marriage have attributed to higher incidence of NTDs to consanguinity (48-49). A study in India reported that NTDs was statistically significantly higher between babies born to parents of consanguineous marriages ($P < 0.01$) (50) .

This study showed that there was significant difference between mothers' ages and NTDs, the higher incidence occur between the age( 26 – 35 )years in which reach 49.1% whereas maternal age of more than 40 years in a study at Texas (51) and maternal age of over 30 years in Russia (52) were associated with NTDs. In Turkey (53), so a significant association between mothers' ages and NTDs was found.

Mothers of nineteen years old or less have a higher risk for having a child with spina bifida in other study(54) .

We observed a significant female predominance in our NTD cases, 57.2% female with 42.8% a male, which similar to the sex difference consistent in many studies. This female predominance in Canada study in both still & live births (55) , and differs from other studies in Iran (56) and not in line with China study (57) .

## Conclusion:

This study showed that Folate deficiency are very important in reducing the occurrences of NTDs, considered that the consanguineous marriage is not important predisposing factor for NTDs , the disease is common in rural area , multipara womens with poor antenatal care . In our opinion, folate supplements are appropriate to prevent recurrence of NTD in infants of high–risk women but this required specific isolated study. Further studies should be carried out with large sample size to verify the cause-effect relationship of paternal factors ,other nutritional factors and vitamins deficiency with NTDs.

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## References :


1- Moore, K.L. and Persaud, T.V.N. (1998) The Developing Human. Clinically Oriented Embryology. WB Saunders Company, Toronto.

2- Cabaret, A.S. (2004) Les malformations du tube neural: Ethiopathogénie et facteurs pronostiques: A partir de 83 cas du centre pluridisciplinaire du diagnostic prénatal de Rennes [Thèse]. Université de Rennes, Rennes.

3- Elwood, M., Elwood, H. and Little, J. (1992) Epidemiology and Control of Neural Tube Defects. Oxford UniversityPress, Oxford .

4- Wen SW, Liu S, Joseph KS, Rouleau J, Allen A. Patterns of infant mortality caused by major congenital anomalies. Teratology 2000; 61: 342-346.

5- Centers for Disease Control and Prevention (CDC). Neural
tube defect surveillance and folic acid intervention--Texas- Mexico border, 1993-1998. MMWR Morb Mortal Wkly Rep 2000; 49: 1-4.

6- Au KS, Ashley-Koch A, Northrup H. Epidemiologic and genetic aspects of spina bifida and other neural tube defects. Developmental disabilities research reviews 2010;16:6-15.

7- McDonnell RJ, Johnson Z, Delaney V, Dack P. East Ireland 1980-1994: epidemiology of neural tube defects. J Epidemiol Community Health 1999;53:782- 788

8- Mandiracioglu A, Ulman I, Luleci E, Ulman C. The incidence and risk factors of neural tube defects in Izmir, Turkey: a nested case-control study. Turk J Pediatr 2004;46:214-220.

9- Golalipour M, Mansourian R, Keshtkar A. Serum Copper concentration in newborns with neural tube defects in Northern Iran; A case control study. Iran J Ped 2009;19:5.

10 Tolmie J. Neural tube defects and other congenital malformations
of the central nervous system. In: Emery AEH, Rimoin DL, editors. Principles and practice of Medical Genetics. 3rd ed. New York (NY): Churchill Livingstone; 1997. p. 2145-2176.

11- Ellenbogen R. Neural tube defects in the neonatal period.
EMedicine Journal 2002, volume 3, issue 4. Updated 30 January 2009. Accessed 19 October 2009. Available from URL: http://www.emedicine.com/ped/topic2805.htm.

12- Gucciardi E, Pietrusiak MA, Reynolds DL, Rouleau J. Incidence of neural tube defects in Ontario 1986-1999.CMAJ 2002; 167: 237-240.

13- Nau H. Valproic acid – induced neural tube defects. In: Bock G, Marsh J, editors. Neural tube defects. Chichester (UK):John Wiley & Sons Ltd; 1994. p. 144-160.

14- Warkany J. Aminopterin and methotrexate: folic acid deficiency. Teratology 1978; 17: 353-358. 5. Shaw EB. Fetal damage due to maternal aminopterin ingestion. Am J Dis Child 1972; 124: 93-94.

15- Holmes LB. Spina bifida: anticonvulsants and other maternal
influences. In: Bock G, Marsh J, editors. Neural tube defects. Chichester (UK): John Wiley & Sons Ltd; 1994. p. 332-338.

16- Mills JL, Baker L, Goldman S. Malformations in infants of diabetic mothers occurs before the seventh gestational week. Diabetes 1979; 28: 292-293.

17- Elwood JM, Little J, Elwood JH. Epidemiology and control of neural tube defects. Oxford (UK): Oxford University Press; 1992.

18- Milunsky A, Ulcickas M, Rothman KJ, Willett W, Jick SS, Jick H. Maternal heat exposure and neural tube defects. JAMA 1992; 268: 882-885.

19- Botto LD, Yang A. Methylene tetrahydrofolate reductase (MTHFR) and birth defects. Am J Epidemiol 2000; 151:862-877.

20-Tuncbilek E, Boduroglo K, Alikasifoglu M. Neural tube defects in Turkey prevalence distribution and risk factors. Turk J Pediatrics 1999; 41: 299-305.

21- van der Put NM, Steegers–Theunissen RPM, Frosst P, Trijbels FJ, Eskes TK, van den Heuvel LP, et al. Mutated methylenetetrahydrofolate reductase as a risk factor for spina bifida. Lancet 1995; 346: 1070-1071.

22- Nili F, Jahangiri M. Risk factors for neural tube defects: a study at university-affiliated hospitals in Tehran. Arch Iran Med 2006;9:20-25.

23- Kumar A. Neural tube defects: a neglected problem. Indian pediatrics 2009;46:665-667.

24- van der Linden IJ, Afman LA, Heil SG, Blom HJ. Genetic variation in genes of folate metabolism and neural-tube defect risk. The Proceedings of the Nutrition Society 2006;65:204-215.

25- Lupo PJ, Symanski E, Waller DK, Chan W, Langlois PH, Canfield MA, Mitchell LE. Maternal exposure to ambient levels of benzene and neural tube defects among offspring: Texas, 1999-2004. Environ Health Perspect 2011;119:397-402.

26- Shiota K. Neural tube defects and maternal hyperthermia in early pregnancy: epidemiology in a human embryo population. Am J Med Genet 1982;12:281-288.

27- Blatter BM, van der Star M, Roeleveld N. Review of neural tube defects: risk factors in

parental occupation and the environment. Environ Health Perspect 1994;102:140-145.
28- 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.
29- Rashid BR. Risk factors of neural tube defects in Sulaimania Governorate Baghdad: Iraqi Board for Medical specialization, 2008.
30 -Humphreys R, Rengachary S. Spinal Dysraphysm. In: Humphreys R, ed. Neurosurgery. New York: McGraw-Hill, 1996.
31- youman text book of neurosurgery6th Ed2015.

32-Zaid R. Al-Ani, , Sahar J. Al-Hiali, FICMS, , Suhaib M. Al-Mehimdi, . Neural tube defects among neonates delivered in Al-Ramadi Maternity and Children's Hospital, western IraqSaudi Med J 2010; Vol. 31 (2).
33-Ari Sami Hussain Nadhim, Nasih Othman and Nabaz Mohammed Mustafa Neural tube defects in Sulaimaniyah, Iraqi Kurdistan: a descriptive study of 50 cases JSMC, 2014 (Vol 4) No.2.
34- Stevenson, R.E., Allen, W.P., Pai, G.S., Best, R., Seaver, L.H., Dean, J., et al. (2000) Decline in Prevalence of Neural
Tube Defects in a High-Risk Region of the United States. Pediatrics, 106, 677-683.
35- Barboza Argüello, M.L. and Umaña Solís, L.M. (2011) Impacto de la fortificación de alimentos con ácido fólico en los
defectos del tubo neural en Costa Rica. American Journal of Public Health, 30, 1-6.

36-Davidoff MJ , Petrini J, Damus K, Russell RB, Mattison D. Teratology. Neural tube defect-specific infant mortality in the US 2002;66 Suppl 1:S17-22.

37- Neural Tube Defects : From Origin to Treatment: From Origin to Treatment. Oxford University Press. 2005. pp. 125–126. ISBN 9780199775149.

38- Timson, J. (1970). "The sex ratio in anencephaly". Genetica. **41** (3): 457–65. doi:10.1007/BF00958926. PMID 4922971.
39- Parker SE, Mai CT, Canfield MA, Rickard R, Wang Y, Meyer RE, Anderson P, Mason CA, Collins JS, Kirby RS, Correa A. Updated national birth prevalence estimates for selected birth defects in the United States, 2004–2006. Birth Defects Res A Clin Mol Teratol. 2010 Dec 1;88(12):1008-16.

40 - Jacobs RA. Myelodysplasia. In: Wolraich ML (ed). Disorders of Development and Learning, 2nd edition. 1996, St. Louis: Mosby, pp. 213-261 .

41- Dias MS, Li V. Pediatric Neurosurgical Disease. Pediatr Clin North Am 1998;45(5):1539-1578.

42-Mitchell, L. E.; Adzick, N. S.; Melchionne, J.; Pasquariello, P. S.; Sutton, L. N.; Whitehead, A. S. (2004). "Spina bifida". *Lancet*. **364** (9448): 1885–1895

43- Mitchell, L. E.; Adzick, N. S.; Melchionne, J.; Pasquariello, P. S.; Sutton, L. N.; Whitehead, A. S. (2004). "Spina bifida". Lancet. **364** (9448): 1885–1895. doi:10.1016/S0140-6736(04)17445-X. PMID 15555669.

44-Juranek, J; Salman MS (2010). "Anomalous development of brain structure and function in spina bifida myelomeningocele". Developmental Disabilities. 1. **16** (1): 23–30. doi:10.1002/ddrr.88.

45. Ashwal S. Congenital structural defects. In: Swaiman KF, Ashwal S (eds). Pediatric Neurology: Principles & Practice, 3rd edition. 1999, St. Louis: Mosby, pp. 234-300.

46-De-Regil LM, Peña-Rosas JP, Fernández-Gaxiola AC, Rayco-Solon P. Effects and safety of periconceptional oral folate supplementation for preventing birth defects. Cochrane Database Syst Rev 2015; :CD007950.

47- Luben TJ, Messer LC, Mendola P, Carozza SE, Horel SA, Langlois PH. Urban-rural residence and the occurrence of neural tube defects in Texas, 1999-2003. Health Place. 2009;15(3):848–54. doi: 10.1016/j.healthplace.2009.02.006.

48-Murshid WR. Spina bifida in Saudi Arabia: is consanguinity among the parents a risk factor? Pediatr Neurosurg. 2000;32(1):10–2.

49- Al-Ani ZR, Al-Hiali SJ, Al-Mehimdi SM. Neural tube defects among neonates delivered in Al-Ramadi Maternity and Children's Hospital, western Iraq. Saudi Med J. 2010;31(2):163–9.

50 -Mahadevan B, Bhat BV. Neural tube defects in Pondicherry. Indian J Pediatr. 2005;72(7):557–9

51- Canfield MA, Marengo L, Ramadhani TA, Suarez L, Brender JD, Scheuerle A. The prevalence and predictors of anencephaly and spina bifida in Texas. Paediatr Perinat Epidemiol. 2009;23(1):41–50. doi: 10.1111/j.1365-3016.2008.00975.x.

52-Petrova JG, Vaktskjold A. The incidence of neural tube defects in Norway and the Arkhangelskaja Oblast in Russia and the association with maternal age. Acta Obstet Gynecol Scand. 2009;88(6):667–72.

53- Onrat ST, Seyman H, Konuk M. Incidence of neural tube defects in Afyonkarahisar, Western Turkey. Genet Mol Res. 2009;8(1):154–61.

54 - Vieira AR, Castillo Taucher S. Maternal age and neural tube defects: Review. Spanish Rev Med Chil. 2005 Jan;133(1):62-70.

55- De Wals P, Tairou F, Van Allen MI, et al. Reduction in neural-tube defects after folic acid fortification in Canada. *N Engl J Med*. 2007 Jul 12. 357(2):135-42.

56- 12. Behrooz A, Gorjizadeh MH. Prevalence and Correlates of Neural Tube Defect in South West Iran: Retrospective analysis. Sultan Qaboos Univ Med J. 2007;7(1):31–4.

57- Yin Z, Xu W, Xu C, Zhang S, Zheng Y, Wang W, et al. A population-based case-control study of risk factors for neural tube defects in Shenyang, China. Childs Nerv Syst. 2011;27(1):149–54. doi: 10.1007/s00381-010-1198-7.