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MAGNITUDE OF CENTRAL NERVE SYSTEM CONGENITAL ANOMALIES NEURAL TUBE DEFECTS AND ASSOCIATED RISK FACTORS IN KARBALA GOVERNORATE

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ABSTRACT

Background: Neural tube defects (NTDs), a prevalent kind of central nervous system anomaly, are an important issue for the public. Some factors related to the environment, such as excessive heat, some medicines (especially folic acid antagonists), pesticides, excessive levels of radiation during the periconceptional period, and cigarette smoking, can cause neural tube abnormalities (NTDs). **Aim:** The aim of the present study was to determine the prevalence and possible risk factors responsible of NTDs (Neural Tube Defects) in Karbala governorate. **Patients and methods:** a case - control study was conducted in the intensive care unit of the neonates in Kerbala teaching hospital for children in Karbala / Iraq. The research was established over 6years period from January 1, 2018 to December 31, 2023, included 600 case -control group and115 patient group. **Results:** the most prevalent Type of congenital anomaly was Spina bifida (30.4%) and Congenital hydrocephalus (28.7%). 71.3% among cases had Maternal exposures (fever, radiation while only 40% had (Maternal exposures (fever, radiationregarding to the .(,use of unprescribed medications28.7% among the cases used unprescribed medications. only 37.4 of cases recievedPreconception folic acid supplementation while 87.0% among control received Preconception folic acid supplementation with statistical significant difference between the two groups. **Conclusion:** Spina bifida cystica was the most prevalent CNS defect observed in the current study, and the majority of mothers of the affected children did not receive folic acid supplementation during periconception ($P < 0.05$). Measures are needed to improve knowledge and implement suitable preventative health education measures, such as perinatal folic acid supplementation. and providing conventional prenatal care to moms of children at risk.

KEYWORDS: Central nervous system, neural tube defects, neonates, congenital anomalies, prevalence, predisposing factors.

INTRODUCTION

The knowledge of the development of the central nervous system (CNS) has been transformed by recent developments in medical genetics and molecular biology. This has allowed for the exact categorization of congenital defects in the CNS based on the developmental stage at which they occurred.[1]

Congenital anomalies are structural or functional abnormalities (For example, metabolic abnormalities) that appear during intrauterine life and can be diagnosed during pregnancy, at birth, or sometimes later in infancy. Congenital simply means existing at birth or prior to it.[2] Furthermore, additional systemic anomalies have been observed to coexist with CNS anomalies, with some studies indicating up to 7% in infants diagnosed with congenital heart defects and the majority of such children face elevated morbidity and death consequences.[3]

After congenital heart disease, CNS abnormalities are the second frequent cause of congenital defects. Major CNS aberrations have been identified and categorized through numerous investigations. CNS malformations include mild, moderate, or severe ventriculomegalies; neural tube defects, spinal cord malformations (myelomeningocele, meningocele, and encephalocele), and cavum septi pellucidi; posterior fossa abnormalities; porencephalic cysts; hydranencephaly and cancers.[3&4]

Typically, the neural tube closes during both the third and fourth weeks of intrauterine development. Each year, an estimated 300,000 newborns are born with NTDs throughout the world.[2] As regard to the World Health Organization (WHO), congenital abnormalities caused about 270,000 newborn fatalities over the world in 2010, with NTDs representing one of among the most dangerous and prevalent.[4] Spinal bifida, encephalocele, and anencephaly are significant subsets of these birth-related conditions.[5]

Prenatal screenings are designed to minimize mortality as well as morbidity while also enabling parents to make educated decisions about reproduction as well as plan for optimal healthcare during pregnancy as well as delivery.[5] As a consequence of this, the incidence of NTD in industrialized nations has declined throughout the past thirty years.[5-7]

Congenital central nervous system abnormalities occur in one to two occurrences per one thousand births,[1] and their prevalence is affected by environmental and genetic variables, as indicated by regional differences in frequency.[2]

The majority of the reasons of congenital abnormalities are unknown. However, data indicates that in around 25% of instances when the reasons are known, they appear to be caused by multiple factors, including a complex combination of genetic and environmental variables.[5] Morphogenesis mistakes have been connected to various well-known genetic factors, such as particular single gene mutations and teratogenic activity. A lack of folate increases the likelihood of neural tube abnormalities.[8]

Furthermore, research suggests that some genetic factors (such as changes in folate-responsive or folate-dependent processes) have a negative impact on CNS development. Environmental variables such as excessive heat, some medicines (Especially folic acid antagonists), pesticides, excessive levels of radiation during the periconceptional period, and cigarette smoking can cause neural tube abnormalities (NTDs).[6] Additional variables that increase risk include parental consanguinity, older maternal and paternal ages, preterm delivery, and maternal metabolic abnormalities.[8]

The prognosis for CNS abnormalities has improved as a result of prenatal diagnosis, categorization, and determination. Most children born with congenital defects who survive infancy suffer physical, emotional, or social consequences and are at a higher risk of morbidity.[9-11]

In high-income nations, Specifically, the neonatal rate and the general prevalence of NTD have decreased during the previous 30 years.[10] Research demonstrates that the decrease in NTD birth prevalence has been mainly due to premature cessation of pregnancy after serum alpha-fetoprotein assessments that was done routinely were implemented, as well as advances in the use of ultrasound decisions for in utero early identification and cessation of affected pregnancies.[11] Furthermore, advances in folic acid supplementation have contributed to a reduction in the overall incidence of NTDs.[4] As a study performed in Seattle, Washington, USA, the incidence of myelomeningocele was 5 per 10,000 newborns in 1981-1982, but had dropped to 0.5 in 2001.[12]

Compared to the industrialized world, the frequency of birth NTDs in poor nations remains high, with reported incidences of up to 130 per 10,000 births.[13] Despite the World Health Organization's resolution on birth defect surveillance, data on the incidence of NTDs are scarce in lower income countries.[14]

Such abnormalities are clinically noteworthy since they are associated with high rates of morbidity and mortality, as well as having an impact on survivors' neurocognitive and motor development, which may have long-term consequences. As a result, it is critical to assess the fetal CNS during the prenatal period in order to detect any changes in growth and provide appropriate pregnancy monitoring guidance to parents. Options for fetal treatments, delivering time and type, postnatal care, and prognosis.[9]

Several studies have shown that systematic in utero early detection and termination of afflicted fetuses reduces the frequency of NTDs. Furthermore, advances in folic acid availability have significantly reduced the frequency of NTDs.[7,14]

Factors connected with NTD in Karbala governorate have not been thoroughly researched, and the country lacks national prevention policies. Some researchers suggest prospective and cohort follow-up investigations to better understand the causes of neural tube abnormalities (7, 8). Therefore, this research attempted to evaluate the prevalence and possible risk factors responsible for NTDs (Neural Tube Defects) in Karbala governorate.

PATIENTS AND METHODS

Study Design and Setting

The case-control study (retrospective) design was performed among neonates admitted in the intensive care unit of neonates of Kerbala teaching hospital for children in Karbala / Iraq. The study was performed over 6years (from January 1, 2018 to December 31, 2023), in the neonatal intensive care unit.

Study population

The research population consisted of all neonates born at the intensive care unit of neonates the between January 1, 2018 and December 31, 2023, as determined by an examination of mother medical records. NTDs cases include congenital hydrocephalus, spinal bifida, myelomeningocele, Anencephaly and encephalocele, which can occur alone or in conjunction with other congenital deformities, while controls are newborns who do not have NTDs.

Eligibility criteria
The study included all moms giving birth in intensive care unit of neonates in Karbala teaching hospital for children in Karbala / Iraq with complete records of patient's information; cases with incomplete medical records were excluded from the study.

Sample size Calculation and Sampling technique
The sample included in the study was 600 cases in control group and115 in patient group.

Data collection tools
The data was gathered from health records using a checklist. The structured checklist was based on similarly conducted research (14-15). The checklist was designed to gather data on sociodemographic, parental, and other factors that increase the risk for neural tube anomalies.

An independent academic translator developed the checklists in English first, then translated them to Arabic and returned to English to ensure language accuracy.

Statistical analysis
Statistical Analysis was performed to the data by using the IBM® SPSS statistical soft-ware 26. We used the one-sample Kolmogorov—Smirnov test to determine the normality of data and the data were normally distributed. Quantitative data was presented as means and standard deviations (SD) and qualitative data was presented as frequancy and percentage. Chi-squared test was used for the qualitative data. The level of significant was adopted at $p<0.05$.

RESULTS
In this study, a total of 715 newborns (115 cases and 600 controls) were included. Near to half (51.3% and 53%) of the mothers aged from 20 – 30 years among cases and control respectively. The majority of the studied participants were house wives (95.7% & 87.3% among cases and control respectively). Consanguinity presented 573.4% among the cases while only 35% among the control group (table 1). 56.5% & amp; 41.0% of the neonates were female. As regard to their weight, 58.6% of the patient weighted from 2.5 – 4 kg while 81.7% of the control group weighted from 2.5 – 4 kg (table 2). As regard to the Type of congenital anomaly of neural tube defect, Table (3) revealed that the most frequent type of congenital anomaly was Spina bifida (30.4%) and Congenital hydrocephalus (28.7%) while only 5.2% had Encephalocele. To study the most risk factors causing neural tube defect, Table (4) showed that 26.1% of the patients had family history of congenital anomalies while only 8.0% of the control group had family history of congenital anomalies with statistical significant differences between the two groups. There was statistical significant difference between the cases and control as regard to having still birth as 24.3% of the cases had still birth while only 3.3% of the control had still birth. As regard to Previous history of congenital abnormality, only 10.4% and 4% had a Previous history of congenital abnormality. 11.3% & 4.0% had Maternal chronic disease among cases and control respectively. There were statistical significant differences as regard to Maternal exposures (fever, radiation) as 71.3% among cases had Maternal exposures (fever, radiation) while only 40% had Maternal exposures (fever, radiation). regarding to the use of unprescribed medications, 28.7% among the cases used unprescribed medications. only 37.4 of cases recieved Preconception folic acid supplementation while 87.0% among control received Preconception folic acid supplementation with statistical significant difference between the two groups.

Table (1): Distribution of maternal and paternal information among the studied groups.

	Cases (n = 115)		Control (n = 600)		Test of sig.	P. value
	No.	%	No.	%		
Maternal age (Years)						
less than 20 year	22	19.1	102	17.0		
20-30 year	59	51.3	318	53.0	**X^2 = 0.08**	**0.77**
30-40 year	33	28.7	132	22.0		
more than 40 year	1	0.9	48	8.0		
Residence						
Rural	48	41.7%	204	34%	**X^2 = 1.35**	0.47
Urban	67	58.3%	396	66%		
Mother Occupation						
Housewife	110	95.7%	524	87.3%	**X^2 = 1.74**	0.34
Employee	5	4.3%	76	12.7%		
Father occupation						
Wage earner	83	72.2%	507	84.5%	**X^2 = 1.96**	0.54
Employee	32	27.8%	93	15.5%		
Consanguinity					**X^2 = 2.24**	**0.08**

Present	66	57.4%	210	35%		
Absent	49	42.6%	390	65%		

Table (2): Demographic data of the infants among different studied groups.

	Cases (n = 115)		Control (n = 600)		Test of sig.	P. value
	No.	%	No.	%		
Gander	50	43.5	354	59.0%	X^2 = 1.87	0.07
Male	65	56.5	246	41.0%		
Female						
Weight(kg)					X^2 = 3.29	0.042*
<kg 2.5	40	34.8	108	18.0%		
2.5 – 4 kg	67	58.3	490	81.7%		
>4kg	8	7.0	2	0.3		

χ2: Chi square test

Table (3): Distribution of central nerve system congenital anomalies among the studied cases.

	Cases (n = 115)	
	Frequency	Percent
Type of congenital anomaly		
Congenital hydrocephalus	33	28.7%
Spina bifida	35	30.4%
Encephalocele	6	5.2%
Spina bifida with Inchudes; menindgocele (Spinal) myelocele	1	0.9%
Anencephaly and similar malformations	3	2.6%
Other Congenital malformations of nervous system	37	32.2%
ICD		
Q00	3	2.6%
Q01	6	5.2%
Q03	33	28.7%
Q04	21	18.3%
Q05	36	31.3%
Q07	16	13.9%

Table (4): Distribution of Associated Risk Factors related to Neural Tube Defects of the study participants among the studied groups.

	Cases (n = 115)		Control (n = 600)		Test of sig.	P. value
	No.	%	No.	%		
Family history					X^2 = 3.14	0.03*
yes	30	26.1%	48	8.0%		
no	85	73.9%	552	92.0%		
Previous history of Abortion					X^2 = 0.14	0.89
Present	20	17.4%	102	17.0%		
Absent	95	82.6%	498	83.0%		
Stillbirth history					X^2 = 4.54	0.02*
Yes	28	24.3%	20	3.3%		
No	86	74.8%	580	96.7%		
Previous history of congenital abnormality					X^2 = 1.852	0.06
Present	12	10.4	24	4.0%		
Absent	103	89.6	576	96.0%		
Maternal chronic disease					X^2= 1.95	0.06
Present	13	11.3%	24	4.0%		
Absent	102	88.7%	576	96.0%		

Maternal exposures (fever, radiation(					X^2 = 2.35	0.031*
Present	82	71.3%	564	40%		
Absent	33	28.7%	36	60%		
Cigarette smoking					X^2= 1.35	0.16
Yes	9	7.8%	18	3.0%		
No	106	92.2%	582	97.0%		
Use of medication					X^2 = 4.54	0.001*
Yes	33	28.7%	24	4.0%		
No	82	71.3%	576	96.0%		
Preconception folic acid supplementation					X^2 = 3.41	0.001*
Yes	43	37.4	522	87.0%		
No	72	62.6	78	13.0%		

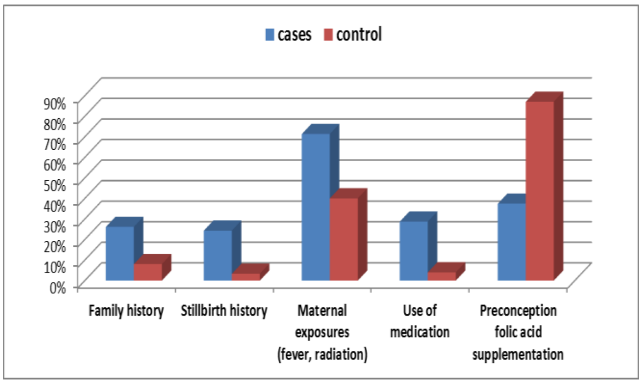

Fig. 1: Associated Risk Factors related to Neural Tube Defects of the study participants among the studied groups.

DISCUSSION

Neural tube abnormalities continue to be a major public health concern because they cause morbidity and death in neonates and babies. As a result, the current study was done to determine the factors that cause NTDs (Neural Tube Defects) among infants in Karbala governorate.

Women who did not receive FA before and throughout the first three months of pregnancy, as well as women who were exposed to fever or radiation, all had a substantial correlation with NTD.

Spina bifida (30.4%) and congenital hydrocephalus (28.7%) were among the prevalent CNS anomalies in the current study. Additionally, a research conducted over thirty-five years previously in Enugu, South East Nigeria[13] and in Ibadan, South West Nigeria[14] found that hydrocephalus was the most prevalent CNS abnormality.

The age of the mother is a significant risk factor in the birth of a child with a congenital abnormality. Therefore, Females over 35 should have more thorough examinations due to the increased chance of birthing a congenitally deformed baby.[15]

In this study, approximately 28.7% of the mothers were between the ages of 30 and 40. Research indicates a link between maternal age and the prevalence of congenital abnormalities, with a lower frequency among those under 20 years old.[15,16] Mohamed et al. found a correlation between maternal age and the occurrence of congenital abnormalities. The incidence was lower for those under the age of 20 and higher for those aged 20-35.[17] In Brazil, the highest risk factor for birth abnormalities is advanced mother age (>35 years).[18]

A history of paternal consanguinity was found among the research participants. This demonstrated that consanguineous marriages increase the incidence of congenital abnormalities because some uncommon recessive genes can easily appear.[19] Shama et al. demonstrated that consanguinity was a significant risk factor.[19] fortunately the current investigation found that maternal consanguinity was an important cause of most abnormalities. In addition, Nath et al.[20] Mehrabi et al., and Bromiker[21,22] demonstrated that the consanguinity for deformed newborns was elevated, although there was no significant association between abnormalities and the degree of relatives of the parents.

Considering the WHO's periconceptional folic acid fortification guidelines, studies have indicated that many females, particularly those from poor socioeconomic backgrounds, do not follow them.[23] In the present research, mothers who neglected to take FA supplements were around threefold more probable to have infants with NTDs than mothers who received folic acid prior to and throughout being pregnant, which might explain the elevated prevalence of neural tube abnormalities in the research group.

The finding of the present study is consistent with research undertaken in Northwestern Ethiopia,[24] Addis Ababa (25), the Bales zone,[26] and England and Wales[27] This might be explained by the fact that folic acid is essential for the synthesis of nucleic acids, lipids, and proteins necessary for cell division. Furthermore, iron folate/folic acid aids in the metabolism of amino acids required for DNA and RNA production, as well as serving as an important antioxidant. As a result, it should be accessible to all women before to and during pregnancy.[24] Furthermore, research has indicated a link with several genetic factors (such as changes in folate-responsive or folate-dependent pathways), that may have a deleterious effect on CNS development beginning with conception.[14]

Folate deficiency has been linked to teratogenicity, which raises the chance of neural tube abnormalities.[19] Both observational and interventional studies have found that women who consume enough folate have a 50-70% lower risk of neural tube abnormalities.[29&30]

Maternal febrile sickness during early pregnancy, such as rubella infection, has been linked to an elevated the probability of congenital abnormalities. Some congenital malformations, notably affecting the cardiovascular system, such as tricuspid atresia and sepal defects, have been associated to maternal fever in the first trimester. In the current study, the CNS congenital anomalies were studied and it was found that almost one-third of the women had a history of febrile disorder in the first trimester of the pregnancy.[31]

The current study found that there were statistical significant differences as regard to Maternal exposures (fever, radiation (as 71.3% among cases had Maternal exposures (fever, radiation (while only 40% had Maternal exposures (fever, radiation).

Almost any medicine used by pregnant moms has the potential to be teratogenic. Approximately 28.7% of the mothers used prescribed drugs in the pregnancy. In our context, some moms believe that using particular herbal combinations can allow them give birth to "light" weight infants, preventing protracted obstructed labor and the necessity for a cesarean surgery. On contrary, some of the prospective moms may have been taking the herbal mixtures to cure one type of infertility or another without realizing until they became pregnant, exposing their babies to the harmful effects of such indigenous medicines.[32]

According to estimates, drug exposure causes around 2-3% of birth abnormalities.[32] Furthermore, the period of exposure during embryogenesis is critical since fetal brain development occurs long into the second and third trimesters of pregnancy. The influence of drug exposure during pregnancy and fetal life is a widespread issue. Some of the impacts may not be apparent until later in life.[33]

Because birth abnormalities are a cause that lead to death before the age of five, sufficient information from surveillance is required to establish effective preventative efforts. This is especially significant for birth malformations that may be avoided using well-established therapies.[34] Although many births in Karbala governorate in Iraq take place outside of health facilities, prevalence studies give some information about the prevalence and contributing factors for NTDs. Such findings can serve as a beginning point for nations with reduced resources to launch a NTD monitoring program, which could eventually expand to population-based surveillance.[35&36]

Study limitation

One limitation possibly present in the present study is recall and self-report bias. The study's limitations included the self-identified character of the source of income and other related variables. It is a hospital-based study and may have overlooked many births that happened outside of hospitals.

CONCLUSION

Spina bifida was the most prevalent CNS defect observed in the current study, and the majority of influenced mothers did not receive folic acid supplementation during periconception ($P < 0.05$). Measures are needed to elevate knowledge and implement appropriate preventive health education methods, such as periconceptional folic acid supplementation and providing access to conventional prenatal care to at-risk moms.

Conflicts of interest

The writers have indicated that they have no conflicts of interests.

Authors' contributions

Every author participated equally in the present investigation.

REFERENCES

1. Bitew ZW, Worku T, Alebel A, Alemu A. Magnitude and associated factors of neural tube defects in Ethiopia: a systematic review and meta-analysis. Global pediatric health, 2020; 7.
2. Mashuda F, Zuechner A, Chalya PL, Kidenya BR, Manyama M. Pattern and factors associated with congenital anomalies among young infants admitted at Bugando medical centre, Mwanza, Tanzania. BMC Res Notes, 2014; 7: 195.
3. Abebe S, Gebru G, Amenu D, Mekonnen Z, Dube L. Risk factors associated with congenital anomalies among newborns in southwestern Ethiopia: A case-control study. PloS one, 2021; 28, 16(1): e0245915.

4. Obu HA, Chinawa JM, Uleanya ND, Adimora GN, Obi IE. Congenital malformations among newborns admitted in the neonatal unit of a tertiary hospital in Enugu, South-East Nigeria – A retrospective study. BMC Res Notes, 2012; 5: 177.
5. Cui M, Lu XL, Lyu YY, Wang F, Xie XL, Cheng XY, Zhang T. Knowledge and intake of folic acid to prevent neural tube defects among pregnant women in urban China: a cross-sectional study. BMC pregnancy and childbirth, 2021; 21, 21(1): 432.
6. Lee KS, Choi YJ, Cho J, Lee H, Lee H, Park SJ, Park JS, Hong YC. Environmental and genetic risk factors of congenital anomalies: an umbrella review of systematic reviews and meta-analyses. Journal of Korean medical science, 2021; 7: 36(28).
7. Shi QY, Zhang JB, Mi YQ, Song Y, Ma J, Zhang YL. Congenital heart defects and maternal fever: Systematic review and meta-analysis. J Perinatol, 2014; 34: 677–82.
8. G. Sorri and E. Mesfin, "Patterns of neural tube defects at two teaching hospitals in Addis Ababa, Ethiopia a three years retrospective study," Ethiopian Medical Journal, 2015; 53, 3: 119–126.
9. "International statistical classification of diseases and related health problems, 10th revision. Geneva: World Health Organization; 2010," http://apps.who.int/classifications/icd10/browse/2010/en.
10. Mohammed YA, Shawky RM, Soliman AS, Ahmed MM. Chromosomal study in newborn infants with congenital anomalies in Assiut University hospital: Cross-sectional study. Egyptian Journal of Medical Human Genetics, 2011; 12(1).
11. Ebrahimi S, Esfahani SA, Bagheri F. Prevalence of neural tube defects in Yasuj, South West Iran. Shiraz E-Medical Journal, 2013; 14(1): 54-62.
12. Al-Ani ZR, Al-Haj SA, Al-Ani MM, Al-Dulaimy KM, Al-Maraie AK, Al-Ubaidi BK. Incidence, types, geographical distribution, and risk factors of congenital anomalies in Al-Ramadi Maternity and Children's Teaching Hospital, Western Iraq. Saudi Med J, 2012; 1, 33(9): 979-89.
13. Adeloye A, Odeku EL. Congenital malformations of the central nervous system in Nigeria. West Afr Med J Niger Med Dent Pract, 1972; 21: 73–7.
14. Ohaegbulam SC, Saddeqi N. Congenital malformations of the central nervous system in Enugu, Nigeria. East Afr Med J, 1979; 56: 509–13.
15. Eke CB, Uche EO, Chinawa JM, Obi IE, Obu HA, Ibekwe RC. Epidemiology of congenital anomalies of the central nervous system in children in Enugu, Nigeria: A retrospective study. Annals of African medicine, 2016; 1, 15(3): 126-32.
16. SinghA. Ravinder K. and Jammu S. Pattern of Congenital Anomalies in Newborn : A Hospital Based Prospective, Jammu(J&K)- India, 2009; 11: 34-36.
17. Mohamed A., Mohamed M., Ahmed E.and Wael B.. Dysmorphogenesis, Clinical Study Ass. Univ.,Assiut Med. J, 2007; 30: 159- 84.
18. Silvana G., Maria d. Congenital malformations in Rio de Janeiro, Brazil: prevalence and associated factors Cad. Saúde Pública, Rio de Janeiro, 2006; 22: 2423-31.
19. Shama M., Salva N., Nadya A. The Accuracy of Ultrasound in the Diagnosis of Congenital Abnormalities JPMA, 2006; 56.
20. Nath A, Patil C, Naik V. Prevalence of consanguineous marriages in a rural community and its effect on pregnancy outcome. Indian Journal of community Medicine, 2004; 29: 41-43.
21. Mehhrabi A, Zeyghami B. The effect of consanguineous marriage on congenital malformation. Journal of Research in Medical Sciences, 2005; 10: 298-301.
22. Bromiker R, Baruch M. Association of parental consanguinity with congenital malformations among Arab newborns in Jerusalem. Clinical Genetics, 2004; 66: 63.
23. Branum AM, Bailey R, Singer BJ. Dietary supplement use and folate status during pregnancy in the United States. The Journal of nutrition, 2013; 1, 143(4): 486-92.
24. Seyoum G, Adane F. Prevalence and associated factors of birth defects among newborns at referral hospitals in Northwest Ethiopia. Ethiopian J Health Dev, 2018; 32: 1–7.
25. Taye M, Afework M, Fantaye W, Diro E, Worku A. Factors associated with congenital anomalies in Addis Ababa and the Amhara Region, Ethiopia: a case-control study. BMC Pediatr, 2018; 18: 142. doi: 10.1186/s12887-018-1096-9
26. Atlaw D, Worku A, Taye M, Woldeyehonis D, Muche A. Neural tube defect and associated factors in Bale zone hospitals, southeast Ethiopia. J Pregnancy Child Health, 2019.
27. Morris J, Wald N. Quantifying the decline in the birth prevalence of neural tube defects in England and Wales. J Med Screen, 1999; 6: 182–5. doi: 10.1136/jms.6.4.182
28. Murphy ME, Westmark CJ. Folic acid fortification and neural tube defect risk: analysis of the food fortification initiative dataset. Nutrients, 2020; 18, 12(1): 247.
29. Atta CA, Fiest KM, Frolkis AD, Jette N, Pringsheim T, St Germaine-Smith C, Rajapakse T, Kaplan GG, Metcalfe A. Global birth prevalence of spina bifida by folic acid fortification status: a systematic review and meta-analysis. American journal of public health, 2016; 106(1): e24-34.
30. 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 of systematic reviews, 2015(12).
31. Shi QY, Zhang JB, Mi YQ, Song Y, Ma J, Zhang YL. Congenital heart defects and maternal fever:

Systematic review and meta-analysis. J Perinatol, 2014; 34: 677–82.
32. Attia QA, Al-Obeidi RA. Risk Factors for Congenital Heart Disease Among Infants In Mosul City. Mosul Journal of Nursing, 2020; 1, 8(2): 177-86.
33. “International Clearinghouse for Birth Defects Surveillance and Research. Annual report 2011 with data for 2009. Rome, Italy: The Centre of the International Clearinghouse for Birth Defects Surveillance and Research, 2011”.
34. Cortes MS, Chmait RH, Lapa DA, Belfort MA, Carreras E, Miller JL, Samaha RB, Gonzalez GS, Gielchinsky Y, Yamamoto M, Persico N. Experience of 300 cases of prenatal fetoscopic open spina bifida repair: report of the International Fetoscopic Neural Tube Defect Repair Consortium. American journal of obstetrics and gynecology, 2021; 1, 225(6): 678-e1.
35. Yin Z, Xu W, Xu C, Zhang S, Zheng Y, Wang W, Zhou B. A population-based case-control study of risk factors for neural tube defects in Shenyang, China. Child's Nervous System, 2011; 27: 149-54.
36. Gandy K, Castillo H, Rocque BG, Bradko V, Whitehead W, Castillo J. Neurosurgical training and global health education: systematic review of challenges and benefits of in-country programs in the care of neural tube defects. Neurosurgical Focus, 2020; 1, 48(3): E14.