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RISK FACTORS OF NEURAL TUBE DEFECTS IN MOSUL CITY - A CASE CONTROL STUDY

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ABSTRACT

Background: Neural tube defects (NTDs) are the second most common severe disabling human congenital defects in the world in which an opening in the spinal cord or brain remains from early stage in human development. **Aim:** To identify the epidemiological risk factors of neural tube defect in Mosul city by taking specific objectives such as history of antenatal care of mother & if she was taken folic acid, Age, parity, Residency, education & gender of the neonates. **Patients and Methods:** This study done in neonatal care unites in Mosul hospitals for neonates from 1st of January 2016 to the end of the June 2016. The number of neonates with neural tube defects was (60) neonates, & during the same period another (60) healthy neonatesfrom the same hospitals was taken for comparison. The information s was collected through interview of the mothers. **Results:** This study revealed that neonates with low birth weight, from low socioeconomic status are more prone to have NTDs with (OR=3.2, 3), also mothers with frequent visit to antenatal care during pregnancy revealed protective factor against NTD with (OR=3.5). The study shows a significant association between residence and occurrence of NTD were mothers' lives in rural area 3 times more prone to deliver baby with NTD than lives in urban areas. The occurrence of NTDs are higher in mothers who had family history of the disease (P=0.007). There is a great role for vitamins especially folic acid in preventing or decreasing NTDs when taken before or during the first months of pregnancy (P=0.00, OR=5.3), also mothers who had hyperthermia in the first months of pregnancy are more prone to had neonate with neural tube defects. **Conclusions:** The present study concluded that there is significant association of mothers lived in low socioeconomic state, rural areas, poor ANC in 1st trimester and small gestational age less than 37 weeks with increase risk of born baby with neural tube defect, also mothers who had born baby with NTD previously and have family history of NTD, and mothers who develop hyperthermia during pregnancy was more prone to deliver baby with NTD. On other hand mother who had frequent visit to ANC and who receive folic acid and vitamins during 1st trimester of pregnancy protect against deliver baby with NTD.

1. INTRODUCTION

1.1 Neural tube defects (NTDs)

Neural tube defects (NTDs) are the second most common severe disabling human congenital defects in the world in which an opening in the spinal cord or brain remains from early stage in human development.[1]

The prevalence of NTDs has decreased in the last three decades, some of the decline has been due to antenatal diagnosis, multivitamin and folic acid supplementations, but some are unexplained.[2]

1.2 Embryology of neural tube

The human nervous system originates from the primitive ectoderm that also develops into the epidermis. The ectoderm, endoderm, and mesoderm by the 3rd weeks. The endoderm particularly the notochordal plate and the intra embryonic mesoderm, induces the overlying ectoderm to develop the neural plate during the 3rd week of development. Failure of normal induction is responsible for most of the neural tube defects.[3] The neural plate is formed at stage 8 (days 17- 19), the neural fold occurs at stage 9 (days 19 – 21) and the fusion of the neural folds occurs at stage 10 (days 21- 23), any disruptions during stages 8-10 (i.e. When the neural plate

begins its first fold and fuses to form the neural tube) can cause craniorachischisis, the most severe form of NTD.[4] Mylomeningocele is a result of abnormality of stage 12 (day 26-30), closure of the caudal neuropore.[5]

Risk factors of NTDs

1 The sex variation, race, age of mother, Geographic, and social class

1. The incidence is higher in females versus males.[6]
2. The risk is approximately doubled for infants born to Hispanic women compared with white women. The risk seems lower in Ashkenazi Jews than in whites of European descent.[6]
3. Some populations with frequent consanguineous matings have an increased risk.[7]
4. The risk for African-Americans and Asians is lowest (but the incidence in northern China is higher: 5-6 in 1000 births)
5. The risk is increased in infants of particularly young or particularly older mothers of lower socioeconomic class This increase may be related to nutritional factors, those least likely to consume a vitamin preparation containing folic acid were women 18-24 years old, those who did not attend college, and those with annual incomes <$25,000.[8]

2 Folic acid deficiency

Folate (vitamin B_9) and vitamin B_{12} are very important in reducing the occurrences of NTDs.[9] Folate is required for the production and maintenance of new cells, for DNA synthesis and RNA synthesis. Folate is needed to carry one carbon groups for methylation and nucleic acid synthesis. It has been hypothesized that the early human embryo may be particularly vulnerable to folate deficiency due to differences of the functional enzymes in this pathway during embryogenesis combined with high demand for post translational methylations of the cytoskeleton in neural cells during neural tube closure.[10] Vitamin B_{12} is also an important receptor in the folatebiopathway such that studies have shown deficiency in vitamin B_{12} contributes to risk of NTDs as well.[11]

3- Chromosome abnormalities: including trisomies 13 and 18, triploidy, unbalanced translocations, and ring chromosomes.[12]

4 – Drugs(13)

a-antifolates like aminopterin, methotrexate, primidone.

b- Anticonvulsants including carbamazepine and valproic acid phenytoin, phenobarbital acid are also associated with an increased risk of neural tube defects. Valproic acid appears to have a propensity for causing lumbo-sacral defects.

c-The fertility drugs such as clomiphene are associated with NTDs remains *controversial.*

d- Lead and glycol ethers have also been suspected to be associated with NTDs.

5- Maternal diabetes. Diabetic women face a risk of neural tube defects that is up to 20 times greater than the general population risk. This can be reduced by achieving tight glycemic control prior to conception and maintaining it through the first trimester of pregnancy.[12]

6- Family history: one type of malformation puts other family members at risk of all types of defect. The recurrence risk is as follows

a. Two to three percent with one affected sibling. Some types of NTDs may be folic acid resistant, and even with folic acid treatment, a residual risk of-1% remains.[13]

b. Approximately 4-6% with two affected siblings; higher if other associated findings suggest a syndrome/condition with possible Mendelian inheritance.[14]

7- Maternal hyperthermia: has been implicated as a risk factor in neural tube defects and this is likely risk factor hen the fever is high 39 C^0 and prolong more than 24 hours.[15]

Prevention of NTDs

N**e**ural tube defects are multifactorial, so there is no any known way to prevent it entirely. However, many studies have shown that dietary supplementation with folic acid (folate) has been helpful in preventing NTDs.[16]

Aim of study

To identify the epidemiological risk factors of neural tube defect in Mosul city by taking specific objectives such as history of antenatal care of mother & if she was taken folic acid, Age, parity, Residency, education & gender of the neonates.

2. PATIENTS AND METHODS

2.1 Study setting

The present study is conducted in the neonatal care unite at Al- Batool, Al-Khansaa & Al-Salam Teaching hospitals in Mosul city.

These NCU are staffed by Pediatric specialists with the assistance of senior house officers and they deliver services to about 60 patients daily, they receive cases directly from the delivery ward.

2.2 Study design

Case control design was adopted in order to achieve the objectives of the present study. In order to examine the possible association between exposure to a certain risk factors and the development of NTDs, a group of neonate with NTDs 60 (cases) and another group of neonate without NTDs 60 (controls) were taken Both cases & controls were randomly collected during the study period.

2.3 Study period

It has been planned to collect data approximatly six months period from the 1st of January 2016 to the end of June 2016.

2.9 Analysis of data

Analysis were carried out by using Pentium four computer through the use of SYSTAT 12.

A two by two table will be assigned as follow

	Cases	Controls	Total
Present	a (cases exposed)	b (controls exposed)	a + b
Absent	c (cases not exposed)	d (controls not exposed)	c + d
	a + c	b + d	a + b + c + d

Odd ratio will be calculated as a measure of association between risk factors and the disease.

The interpretation of the value of OR will be as follow
OR = 1 (The exposure is not related to the NTDs)
OR > 1 (The exposure is positively related to the NTDs)
OR < 1 (The exposure is negatively related to the NTDs)
95% confidence interval (CI) of the results will be calculated, it quantifies the uncertainty in measurement, it's usually reported as 95% CI, which is the range of values within which we can be 95% sure that the true value for the whole population lies. Chi squared (x^2) test was used to find the statistical association.

3. RESULTS

3.1 Gestational age

Table 3.1: Gestational age and occurrence of NTDs.

Gestational age in weeks	Case		Control		O.R.	95% Conf. Interval	P value
	No.	%	No.	%			
≤37WKs	56	93.3	47	78.3			
>37WKs	4	6.7	13	21.7			
Total	60	100	60	100	3.872	65.928-4.397	0.023

^{2}=4.386

This table revealed the association of gestational age with neural tube defect occurrence, which is shows that preterm neonates are more prone to have NTDs than term neonate by> 3 times(OR=3.8).

3.2 Birth weight

Table 3.2: Birth weight and occurrence of NTDs.

Birth weight	Case		Control		O.R.	95% Conf. Interval	P value
	No.	%	No.	%			
<2.5Kg	16	26.7	6	10			
>2.5Kg	44	73.3	54	90			
Total	60	100	60	100	3.27	33.3-3.11	0.06

^{2}= 3.842

This table define the association of birth weight with NTDs. the following results illusterates that neonates with low birth weight less than 2.5kg are prone 3 times to develop NTDs which indicates that low birth weight is a risk factor for NTDs.

3.3 Gender influence

Table 3.3: Influence of gender on the occurrence of NTDs.

Birth weight	Case		Control		O.R.	95% Conf. Interval	P value
	No.	%	No.	%			
Female	34	56.7	35	58.3			
Male	26	43.3	25	41.7			
Total	60	100	60	100	0.934	0.45-1.919	0.853

The results above show the association of gender with NTDs occurrence. There was not significant difference between male and female & that it does not considered a risk factor for NTDs.

3.4 Parity of the mother

Table 3.4: Parity of the mother and NTDs.

Parity	Case		Control		2	P value	O.R.	95% Conf. Interval
	No.	%	No.	%				
Prime	21	35	24	40	0.320	0.572	0.808	0.387-1.685
Second	9	15	14	23.3	1.345	0.246	0.580	0.234-1.441
Third	12	20	8	13.3	0.960	0.327	1.625	0.625-4.213
Fourth and above	18	30	14	23.3	0.682	0.409	1.408	0.630-3.147
Total	60	100	60	100				

In this study the highest percentage of NTDs were in the first pregnancy. From the total 60 cases (21 cases), (35%) were prime, then declined in the second and third pregnancy, then further increased as the parity became fourth and above . In 18 cases 30% the parity were fourth and above. In comprise with the control the sequences of labour have no significant influence on the occurrence of NTDs.

3.5 Maternal age

Table 3.5: Maternal age and occurrence of NTDs.

Maternal age/ years	Case		Control		2	P value	O.R.	95% Conf. Interval
	No.	%	No.	%				
< 20	6	10	5	8.3	0.100	0.752	1.222	0.372-4.010
20-29	34	56.7	38	63.3	0.556	0.456	0.757	0.366-1.568
30-39	16	26.6	14	23.5	0.178	0.673	1.195	0.527-2.705
>40	4	6.7	3	5	0.152	0.697	1.357	0.323-5.674
Total	60	100	60	100				

This table show that the mother of <20 years age and >40 years more risky to born baby with NTU with (OR1.22,1.4) respectively.

3.6 Residency

Table 3.6: Parents residency and NTDs.

Residency	Case		Control		O.R.	95% Conf. Interval	P value
	No.	%	No.	%			
Rural	40	66.7	21	35			
Urban	20	33.3	39	65			
Total	60	100	60	100	3.74	9.805-7.77	0.001

According to this study there is a significant association between rural residency and the occurrence of NTDs, mothers who lived in rural areas are 3 times prone to have a baby with NTD than those lived in urban areas.

3.7 Socioeconomic status

Table 3.7: Socioeconomic status and NTDs.

Socioeconomic status	Case		Control		2	P value	O.R.	95% Conf. Interval
	No.	%	No.	%				
Low	42	70	23	38.3	12.117	0.000	3.754	1.766-7.978
Moderate	16	26.7	26	43.3	3.663	0.056	0.476	0.222-1.018
High	2	3.3	11	18.3	6.988	0.008	0.154	0.037-0.654
Total	60	100	60	100				

This study found that mothers who lived in low socioeconomic state were prone 3 times to NTDs than those in moderate and high socioeconomic state.

3.8 Family history of NTDs

Table 3.8: Family history of NTDs.

Family history	Case		Control		O.R.	95% Conf. Interval	P value
	No.	%	No.	%			
Yes	13	21.7	3	5			
No	47	78.3	57	95			
Total	60	100	60	100	5.255	1.50-18.15	0.007

According to this study there is significant associations between family history of previous baby with NTD and occurance of new cases in subsequent pregnancy. OR reveals that parents with family history of NTDs are 5 times prone to develop NTDs.

3.9 Maternal folic acid intakes

Table 3.9: Maternal history of folic acid intake and occurrence of NTDs.

Folic acid intake	Case		Control		O.R.	95% Conf. Interval	P value
	No.	%	No.	%			
Negative	52	86.7	33	55			
Positive	8	13.3	27	45			
Total	60	100	60	100	5.33	0.078-0.45	0.001

This study shows that mothers who are not taking folic acid before conception and during first trimester more prone to NTDs occurrence than that take folic acid, with significant association P value 0.001.

3.10 Maternal fever in the first trimester of pregnancy

Table 3: 10 Fever in 1st trimester of pregnancy & occurrence of NTDs.

Fever in first trimester 39 C^0	Case		Control		O.R.	95% Conf. Interval	P value
	No.	%	No.	%			
Yes	35	58.3	4	6.7			
No	25	41.7	56	93.3			
Total	60	100	60	100	19.6	6.50-58.37	0.001

^{2}=36.505

This study shows that mothers who had fever more than 39 C^0 in the first trimester are more susceptible to have NTDs infants than others who didn't have fever. the OR19.6 and P value 0.001.

4. DISCUSSIONS

4.1 Gestational age

In the present study, we assessed the influence of selected risk factors in the etiology of NTDs. The study showed that there was a significant association between NTDs and gestational age (less than 37 week) at delivery, low bith weight which was in agreement with other studies which were done in New York in 2005 that reveal the same association between birth weight and gestational age with NTD.[17]

4.2 Gender of neonates

Regarding gender differences, the study showed that there was no significant association between NTDs and gender. This study agree with other study done by Nili F, etal. in Iran in 2006.[23] In contrary to many studies that found that female more prone to NTD Adzick NS, etal in study done in 2003.[6]

4.3 Parity of the mother

Analysis of the effect of parity on the risk of NTDs the study show that the highest percentage of NTD which was 35% was in mother with 1st pregnancy (primigravida) in agreement with a study done by Elwood JM, et al, at England in 1992 concluded that low parity increase the risk of neonates with NTDs.[18]

4.4 Maternal age

1. Number of studies have reported maternal age risk for NTDs to be highest among youngest (<20 years) and oldest women (>35 years), As found by study done by Owen TJ, etal. in Australia in 2000.[19] Also the age was not significant risk factor for NTDs as found by study done by Shaer CM et al ,during 2007.[20]
2. In this study, although most mothers with infants having NTDs were between 20-29 years, the statistical difference between case and control groups was not significant.which is the usual age of fertility.

4.5 Residency

In the present study the majority of parents with affected newborns lived in rural areas, which was in agreement

with other studies done by Slattery ML, Janerich DT in 1991.[21] & by Eichholzer M et al in lancet at 2006.[44] It may be due to factors such as high population growth rates and socioeconomic factors which may cause poor nutrition in our locality.

4.6 Socioeconomic status

Most of affected cases were positioned in low socioeconomic status families which is in agreement with study done by Eichholzer M et al in lancet at 2006.[22] this may be due to lack of nutrition or inability seek the medical care due to low income. Socioeconomic status is an important factor in many studies that found NTDs risk is higher among families of lower socioeconomic status Nili F, Jahangiri M. in Iran in 2006.[23]

4.7 Previous history of NTDs & Family history

This study revealed that if the parents had previously a neonate with NTDs or had positive family history for this congenital anomaly so they are more prone to have a new baby with NTD.

which is in agreement with study done by Mitchell LE at 2005.[13] & in other study done by Nili F, Jahangiri M. in Iran in 2006.[23] That found that the previous history & family history is a risk factors for NTDs.

4.8 Folic acid

Maternal preconception use of folic acid has been found to reduce the risk of both occurrence and recurrence of NTDs. This reduction occurs both in regions of high NTDs rate and in regions of low NTDs rate which is found by Aubry MC, et al in UK in 2003.[24] & Aqrabawi H. at King Hussein Medical Center Jordan.in 2005.[25]

4.9 Maternal hyperthermia

This study shows that if the mother had fever more than 39 C^0 for more than 24 hrs. in the first trimester so she will be prone to have an infant with NTDs, more than others who didn't have high fever which is similar to study done Frel L, Hauser WA. in Epilepsia during 2003.[15]

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