



## NEURAL TUBE DEFECTS (NTDS); RISK FACTORS ASSOCIATED WITH CONGENITAL NEURAL TUBE DEFECTS

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**ABSTRACT... Background:** The most common congenital malformations are Neural tube defects (NTDs) occurring in 0.6 per 1,000 live births in the United States, and almost 4000 pregnancies are recorded of babies with neural tube defects, among them anencephaly and Spina bifida are the most common and their annual incidence is 2,500 to 3,000 births in the United States. The etiology of NTDs is still an enigma, however, in the past few decades valuable advances has been made in understanding the causation and measures to prevent NTDs and many risk factors are indentified which are associated with it. **Objectives:** This study was designed to determine the risk factors and their association with neural tube defects. **Study Design:** Case control study. **Place and Duration of Study:** This study was conducted at unit 111 Lady Willingdon Hospital Lahore and duration was one year from 1.1.2016 to 31.12.2016. **Methodology:** A total of 120 mothers were included in the study, of which 30 were having of babies delivered with NTDs, matched with 90 mothers delivered babies without NTDs (Three controls for each NTD case). Informations were collected on special Performa, data was analyzed on SPSS version 20. **Results:** Majority of the patients in both groups were found between 31-40 years of age, 43.33 % (n13) in patients with NTD group and 56.67 % (n51) in controls while only 16.67% (n5) in NTD and 17.78 % (n16) were found between 21-30 years. The mean age was recorded as 33.06+1.21 and 32.12+ 0.89 respectively. Regarding parity, 23.33% (n7) were found between P1-2, 26.67% (n11) were P2-3 while 40% (n12) with Parity >4 in the NTD group, while 21.11% (n19) were p1-2, 37.77% (n 34) with P 3-4 and 41.12% (n37) were P >4 in control group. 86.67% (n 26) were found with poor economic status and 13.33% (n4) were found with rich status in NTDs, while 18.89% (n17) were found with poor and 81.11% (n73) with rich status in control group. Distribution of fetuses according to their gender revealed that 20% (n6) were males, and 80% (n24) were females in NTDs while 47.77 % (n43) were found males and 52.23% (n47) were females in controls. Regarding family history 80% (n24) with positive history of NTDs in patients of NTD group and 20% (n6) with no history while 4.44% (n4) had positive history and 95.56% (n86) had no familial history of NTD in control cases. About previous history of NTDs, 93.33% (n28) were found with positive previous history of NTDs and only 6.67% (n2) with no previous history of NTDs in NTD group, while only 5.56% (n5) were found with positive previous history of NTDs and 94.44%(n85) with no previous history in controls. **Conclusions:** Poor socio economic status, family history and previous history of a baby with Neural tube defects are the major risk factors.

**Key words:** Neural tube defects, risk factors, socio economic status, previous history of NTDs.

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### INTRODUCTION

Neural tube defects (NTDs), resulting from the abnormality due to closure of neural tube around 3rd and 4th weeks of intra uterine life and one of the most common and serious congenital malformation responsible for infant disability, morbidity and mortality.<sup>1</sup> Along with this condition there is an association of other

body organ dysfunctions like skeletal system, skin, genitourinary system and the abnormalities of nervous systems, as a result of this, there is a development of Hydrocephalus in the majority of these cases. In spite of numerous progresses that have been done towards understanding the causation of NTDs, the etiology of the majority of the cases is still unknown. Although substantial

amount of literature is available about the theories of pathogenesis and lot of teratogenic research has been done, but not a single hypothesis regarding the etiology of NTDs is widely acceptable and thoroughly proven.<sup>2</sup> One of the suggested etiological mechanism is that, there is an interplay between genetic and environmental factors, certain epidemiologic and genetic studies have suggested high risk groups, which include maternal age of less than 20 or more than 35, those who have a past history of having a fetus with NTDs, poor socioeconomic status along with gross nutritional deficiency, two extremes of parity (primipara and grand multipara) and lack of proper antenatal care.<sup>3</sup> Association of genetic factors is also advocated in many cases. The risk of first child having spinal abnormality is around 0.1% to 0.2% but having one affected sibling the risk of a second child is 2% to 5%, and the risk of a third affected child is compounded to 10% to 15%.<sup>4</sup> One historical study which was published in the New England Journal of Medicine, researchers conducted a double-blind, randomized multicenter trial on folic acid to find out its protective role for the occurrence of NTDs in the first pregnancy. Women were divided in to two groups, in group one 2014 women were given 0.8 mg of folic acid with their multivitamins, while the second group consisting of 2052 women were not provided folic acid with their multivitamins. It was observed that folic acid group had no case of NTD. On the other hand, the non-folic acid group had 6 cases of NTDs. These findings proved that use of preconception folic acid remarkably decreased the first occurrence of NTDs.<sup>5</sup> On the basis of this findings, the US Public Health Service issued their strong recommendation to the usage of folic acid supplementation in the preconception and antenatal period. Number of epidemiological and clinical trials have suggested the role of various teratogens in the causation of NTDs which includes, radiations, hyperthermia, heat exposure and hot-tub, hyper vitaminosis A, viral infections, and drugs like anticonvulsants.<sup>2</sup> Mechanism by which teratogens causing NTDs is probably by acting as folic acid antagonists or they can prevent adequate supply of folic acid to developing embryo. Few environmental agents are also linked in the causation of NTDs,

like dietary deficiency of agents like zinc<sup>6</sup>, but association of none of these factors has proven yet. Occupational factors have also been linked with increase risks of NTDs in the offspring such as agriculture (female worker), painting and welding (male).<sup>7</sup> It is recently observed that mildly elevated maternal plasma levels of homocysteine in few pregnancies that resulted in NTDs and other birth defects.<sup>8</sup> Trials have shown in the past 2 decades that mild hyper homocysteinemia linked to an increased risk of early pregnancy loss, occurrence of NTDs, premature atherosclerosis and venous thrombosis.<sup>2</sup> Factors such as maternal age, or parity and season of birth have not been correlated with the incidence of myelomeningocele.<sup>9</sup> Infections and drugs are usually not considered as putative teratogens. One exception is an antiepileptic drug Valproic acid which has been associated with NTDs in the babies of some women using this drug for the prevention and control of seizures.<sup>10</sup> In our study, we investigated few important risk factors associated with NTDs at Lady Willingdon Hospital Lahore.

## MATERIAL AND METHODS

This case controlled study was carried out at department of Obstetrics and Gynaecology unit 111 Lady Willingdon Hospital Lahore and duration was one year from 1.1.2016 to 31.12.2016. 120 women were included in the study, of whom 30 of fetuses delivering with NTDs, matched with 90 mothers delivering fetuses without NTDs (Three controls for each NTD case). They were recruited for the study by Non-probability purposive sampling technique.

### Inclusion Criteria

- All pregnant women with neural tube defects in fetus diagnosed on routine ultrasound at 12 or 18 weeks of gestation
- All pregnant women presented through emergency in labour having no anomaly scan delivered baby showing neural tube defects

### Exclusion Criteria

- Pregnant women before 12 weeks of gestation
- Pregnant women with fetal malformation other than NTD
- Cases complicated by birth trauma

The cases fulfilling the inclusion criteria were registered through Outpatient department, emergency and prenatal ward of Lady willingdon Hospital. An informed consent was obtained from the patients after briefing the detail of the study. Two groups i.e. cases of NTD and their matched controls were identified. The matching was done with regard to age, parity and outcome of previous pregnancies. The demographic information like name, age, address was obtained. Previous obstetrical history, Outcome and current status if delivered were recorded. The history regarding the known risk factors for NTD were explored from both cases and control. Their signs and outcome of routine and special investigations like ultrasonography were recorded. There was no risk involved as no intervention was intended nor avoided from routine.

All the information was recorded through a specially designed Performa. The collected information was entered in SPSS version 20 and analyzed through it. The variable analyzed were including demographic (age, socioeconomic status), history. These were presented as descriptive statistics including frequency, proportion and percentage for socio-economic status and exposure to known risk factors. Mean+ SD was calculated for all quantitative variables including (age, duration of pregnancy)The association of outcome variables (risk factors) if found different were tested for significance by applying chi square test as a p value of 0.05 or less as the outcome were qualitative in nature.

## RESULTS

A total of 120 cases fulfilling inclusion/exclusion criteria were studied to determine the risk factors and their association with neural tube defects. Majority of the patients in both groups were found between 31-40 years of age, 43.33%(n13)

in patients with NTD group and 56.67%(n51) in controls, 40%(n12) were found under the age of 20 years in NTD group, 25.55%(n23)in controls while only 16.67% (n 5) in NTD and 17/78%(n16) were found between 21-30 years. The mean age was recorded as 33.06+1.21 and 32.12+0.89, can be seen in Table-I.

Regarding parity, 23.33% (n 7) were found P1-2 in NTDs, 26.67%(n11) were P 3-4 and 40%(n12) were having parity >4 in this group, while 21.11% (n19) were P1-2, 37.77% (n34) were P 3-4 and 41.12% (n 37) with parity >4 in control group Value <0.05.results can be seen in Table-II.

Table-III describes socio economic status of the patients, in this table 86.67% (n 26) were found with poor economic status and 13.33% (n04) were found with rich status in NTDs, while 18.89%(n17) were found with poor and 81.11%(n73) with rich status in control group. P Value <0.05.

Distribution of fetuses according to their gender revealed that 20% (n06) were found male, and 80% (n24) were found female in NTDs whereas, 47.77 % ( n 43) were found male and 52.23% (n 47) were females in controls. (Table-IV)

Family history of NTDs was found in 80%(n 24) in NTDs group , and 20%(n 6) had no history while 4.44% (n 4) in control group had NTD positive family history and 95.56% (n 86) had no familial history of NTD in control cases. (Table-V)

Regarding previous history of NTDs, 93.33%(n28) were found with positive previous history of NTDs and only 6.67% (n2)with no previous history of NTDs in NTD group, while only 5.56% (n5) were found with previous history of NTDs and 94.44%(n85) with no previous history in controls. (Table-VI).

Age (in years)	NTDs	(n=30)	Controls	(n=90)
	No. of Patients	%	No. of Patients	%
<20	12	40	23	25.55
21-30	05	16.67	16	17.78
31-40	13	43.33	51	56.67
Total	30	100	90	100
Mean and S.D.	33.06	+1.21	32.12	+0.89

Table-I. Age incidence of the patients

Para	NTDs		Controls	
	No. of Patients	(n=30) %	No. of Patients	(n=90) % age
1-2	07	23.33	19	21.11
3-4	11	36.67	34	37.77
>4	12	40	37	41.12
Total	30	100	90	100

Table-II. Parity of the patients

Socio economic status	NTDs		Controls	
	No. of Patients	(n=30) %	No. of Patients	(n=90) % age
Poor	26	86.67	17	18.89
Rich	04	13.33	73	81.11
Total	30	100	90	100

Table-III. Socio-economic status of the patients

Gender	NTDs		Controls	
	No. of Patients	(n=30) %	No. of Patients	(n=90) %
Male	06	20	43	47.77
Female	24	80	47	52.23
Total	30	100	90	100

Table-IV. Gender distribution of fetuses

NTDs in family	NTDs		Controls	
	No. of Patients	(n=30) %	No. of Patients	(n=90) % age
Yes	24	80	04	4.44
No	06	20	86	95.56
Total	30	100	90	100

Table-V. Family history of NTDs

Previous history	NTDs		Controls	
	No. of Patients	(n=30) %	No. of Patients	(n=90) % age
Yes	28	93.33	05	5.56
No	02	6.67	85	94.44
<b>Total</b>	<b>30</b>	<b>100</b>	<b>90</b>	<b>100</b>

Table-VI. Previous history of NTDs

## DISCUSSION

The actual meaning of the term “neural tube defects” is the collection of biologically interrelated set of malformations of the central nervous system and their overlying tissues. It is considered that brain and/or spinal cord have defective morphology, associated with varying degrees of absence or malformation of the meninges, skin, bones and muscles. Along with morphologic similarities, these lesions are probably related epidemiologically and genetically.<sup>11</sup> Many risk factors are identified of having an association with NTDs, however etiology of the problem is still not fully identified.<sup>12</sup>

Many studies have suggested that risk of NTDs

is more among babies of the mothers with poor socioeconomic status<sup>13</sup>, however, other studies have disapproved this etiological finding.<sup>6</sup> Mothers of lower socioeconomic status and teenage mothers with poor dietary habits can lead to higher NTD rates, but they were not diagnosed in the antenatal period, probably due to lack of antenatal care and probably resulting in fewer induced terminations of NTD affected pregnancies among women in these groups.<sup>14</sup> In this study, the socioeconomic status between the two groups was compared. Most of the mothers having babies with NTDs were from poor socioeconomic families as compare to the control group. That proved the association of the lower socioeconomic factor in the causation of NTDs.

Few studies have shown the association of maternal age with the risk of NTDs and proved that it was highest among younger and old aged women<sup>15</sup>, however, few recent studies have found the risk was decrease with advancing maternal age or the reverse.<sup>16</sup> Although in our study, most of the mothers having babies with NTDs were above 18 years of age, i.e., majority of them were between 31-40 years of age, showing the significant statistical difference between case and control group. This noticeable difference may be due to poor socioeconomic status of mothers in the studied cases. Dietary deficiencies because of poor socioeconomic status and poverty related issues could predispose these women to NTDs. A local study which was conducted by Iqbal et al showed that there was an increase incidence of NTDs in a woman aged more than 30 years and having dietary deficiencies especially of folic acid.<sup>17</sup>

Association of Parity has also been observed with NTDs risk, with risk is increased with increasing parity and higher risk was seen in at both extremes, i.e., in primigravida and grand multipara. Proved in our study that in the NTDs group 23.33% (n 7) were found P1-2. While 40% (n12) were having parity >4 whereas, 21.11% (n19) were P1-2 and 41.12% (n 37) with parity >4 in control group. P Value <0.05 which was significant.

It has been proved by the research that a mother with a previous history of NTDs birth has 10 times increased risk for another NTDs baby.<sup>18</sup> In our study we also had higher rate of previous history of NTDs in NTD group and it was observed that 93.3% of the women were having a baby with NTDs in this group whereas in the controlled group 94.4% were having previous normal babies. which favored the hypothesis that prevention of the first occurrence of NTDs is of real public health importance.<sup>19</sup>

Balanced nutritious diet containing plenty of fruits and vegetables along with other nutritional contents can prevent the occurrence of NTDs. It has been observed that in majority of the geographic areas during periods of famine, drought and war the rate of NTDs remarkably

elevated, and during an era of prosperity it declines.<sup>20</sup>

It is therefore recommended that practical Programs should be planned to educate obstetricians, other health care personals and the women on mass level about the importance of folic acid in prevention of NTDs. It should also be made aware that not all NTDs could be prevented by Folic acid supplementation. All the pregnant women should be given the option of prenatal screening or diagnostic testing to diagnose NTDs as early as possible for timely intervention.

## CONCLUSION

NTDs remain a frequent problem. Known risk factors are lack of awareness and socio economic status of the pregnant women with previous family and Neural tube defects history.

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*“The art of being wise is knowing what to overlook.”*

**William James**

**AUTHORSHIP AND CONTRIBUTION DECLARATION**

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