A Spectrum of Neural Tube Defects: An Observational Study in the Eastern State of India

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ABSTRACT
Objective: This study aimed to determine the prevalence and types of neural tube defects (NTDs) in eastern India, examine the associated maternal and paternal risk factors, and evaluate the impact of antenatal ultrasonography for early detection and management.
Materials and Methods: A four-year observational study was conducted at the IMS and SUM Hospital, SOA University, Bhubaneswar, India, from July 2020 to June 2024. Pregnant women attending the antenatal clinic were screened for NTDs by using high-resolution ultrasonography. Diagnosed cases were further confirmed by postmortem autopsy, when available. Relevant maternal and paternal demographic data, including age, socioeconomic status, consanguinity, body mass index (BMI), hyperthermia, and paternal occupation, were collected. Statistical analysis was performed using Fisher's exact test to identify significant associations between these factors and NTD occurrence, with significance set at $P < 0.05$.
Results: The incidence of NTDs was 9.12 per 1000 deliveries, with spina bifida (43.4%) being the most prevalent, followed by anencephaly (32.9%), and encephalocele (11.1%). NTDs were significantly associated with maternal age (20-24 years), lower socioeconomic status, consanguinity (12.93% of cases), maternal obesity (BMI $\geq$30 kg/m²), and hyperthermia ($\geq$100 °F). Fathers engaged in labor-intensive occupations had higher rates of offspring with NTDs (56%). This study highlights the effectiveness of antenatal ultrasonography for early detection and management, particularly in high-risk populations.
Conclusion: NTDs continue to pose a significant public health challenge in Eastern India. This study underscores the need for improved prenatal care, genetic counseling, and targeted public health interventions, including folic acid supplementation and lifestyle modifications, to mitigate risk factors. Future research should focus on expanding geographic coverage and integrating genetic analysis to better understand the complex interplay between environmental and genetic factors contributing to NTDs.

1. Introduction

Neural tube defects (NTDs) are significant congenital malformations that occur because of incomplete closure of the neural tube during embryonic development, leading to severe morbidity and mortality among affected neonates. The neural tube forms the early brain and spinal cord, and its incomplete closure can result in anomalies such as anencephaly, spina bifida, and encephalocele, which are among the most common birth defects worldwide [1]. The etiology of NTDs is multifactorial and involves a complex interplay between genetic and environmental factors, including maternal nutritional deficiencies, genetic mutations, and exposure to teratogens [2].

Folic acid, a B-vitamin, plays a crucial role in DNA synthesis and methylation, and is an essential process during cell division and embryonic development. Adequate folic acid intake before conception and during early pregnancy has been shown to significantly reduces the risk of NTDs [3]. Periconceptional folic acid supplementation is widely recommended to reduce the incidence of these anomalies. However, adherence to folic acid supplementation remains inconsistent, especially in low- and middle-income countries (LMICs) where access to healthcare and nutritional guidance is often limited [4]. Various studies have demonstrated the effectiveness of mandatory folic acid fortification in reducing NTDs, particularly in countries where food fortification policies have been implemented [5].

In addition to folic acid deficiency, several other maternal factors have been identified as significant contributors to NTD risk. These include maternal obesity, hyperthermia, diabetes, antiepileptic drug use, and advanced maternal age [6]. Obesity and hyperglycemia are associated with metabolic changes that may affect embryonic development of the neural tube, increasing the risk of defects [7]. Additionally, maternal hyperthermia during the first trimester, often caused by febrile illnesses, has been linked to an increased risk of NTDs [8]. Genetic factors also play a critical role in NTD pathogenesis. For instance, mutations in the methylenetetrahydrofolate reductase (MTHFR) gene, especially the C677T variant, have been associated with an elevated risk of NTDs owing to impaired folate metabolism [9].

Epidemiological studies have highlighted the impact of socioeconomic factors such as low income, education, and access to healthcare on the prevalence of NTDs. Socioeconomic status influences dietary habits, healthcare access, and exposure to environmental risk factors, thereby contributing to the risk of NTDs [10]. In regions with high rates of consanguineous marriages, such as parts of South Asia and the Middle East, the prevalence of NTDs is notably higher, suggesting a genetic predisposition in these populations [11]. Consanguinity increases the likelihood of homozygosity for recessive alleles, which can manifest as congenital anomalies including NTDs [12].

This study aimed to explore the prevalence and types of NTDs in the eastern state of India using antenatal ultrasonography, and to compare these findings with autopsy results to provide a comprehensive understanding of the epidemiology and potential risk factors associated with these defects. Given the high burden of NTDs in India and various contributing factors, there is a critical need to enhance public health strategies, including folic acid supplementation, targeted genetic counseling, and community education to reduce the prevalence of NTDs and improve neonatal outcomes [13,14].

2. Materials and Methods

Study Design and Setting

This observational study was conducted at the IMS and SUM Hospital, SOA University, Bhubaneswar, India, over a period of four years, from July 2020 to June 2024. This study aimed to detect craniospinal anomalies through antenatal ultrasonography and compare these findings with autopsy results in cases of pregnancy termination or stillbirth to establish a comprehensive understanding of NTDs in the study population.

Study Population

The study population consisted of pregnant women attending the antenatal clinic at IMS and SUM hospitals during the study period. Participants were included in the study based on routine referrals for ultrasonography due to clinical indications or a history of fetal anomalies. High-risk patients were identified and referred for emergency services or medical termination of pregnancy (MTP) as appropriate. The inclusion criteria were as follows.

- Pregnant women aged 18-45 years.
- Singleton pregnancies.
- Clinically suspected or at-risk cases for carrying a fetus with NTDs based on prior obstetric history or physical examination.

Exclusion criteria were:

- Women with multifetal pregnancies.
- Pregnancies with chromosomal abnormalities unrelated to NTDs.
- Incomplete medical records or refusal to provide informed consent.

Ethical Considerations

Ethical clearance was obtained from the Institutional Ethics Committee of SOA University. Informed consent was obtained from all participants prior to their inclusion in the study, ensuring adherence to ethical standards regarding confidentiality, the right to withdraw, and data protection.

Data Collection

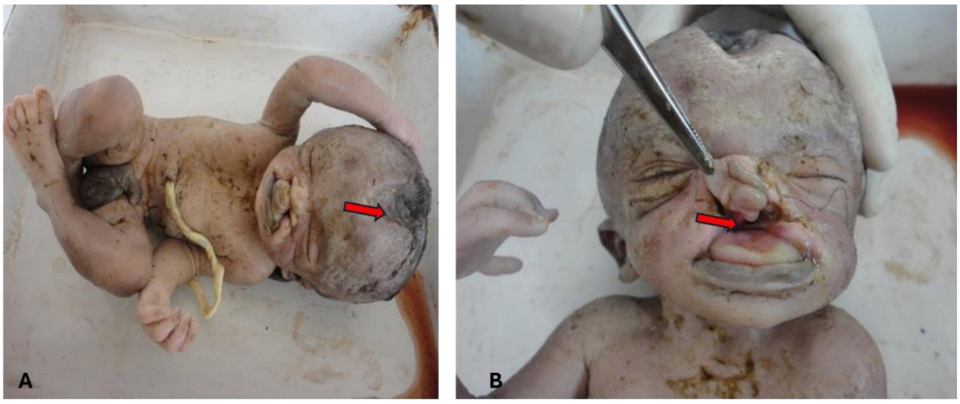
Data were collected using both antenatal ultrasonography and postmortem autopsy in cases in which pregnancy was terminated or stillbirth was observed. Ultrasonography was performed by experienced radiologists using high-resolution equipment (Voluson E8; GE Healthcare, Chicago, IL, USA) to detect craniospinal anomalies. Anomalies assessed included anencephaly, spina bifida, encephalocele, holoprosencephaly, and iniencephaly. The following criteria were used for the ultrasound diagnosis of each anomaly:

- Anencephaly: Absence of cranial vault and brain tissue above the orbits as shown in Fig 1.
- Spina Bifida: Failure of vertebral arches to fuse, with or without herniation of the spinal contents as shown in Fig 2.
- Encephalocele: Herniation of brain tissue and/or meninges through a skull defect.
- Holoprosencephaly: Failure of the prosencephalon to divide into hemispheres.
- Iniencephaly: Occipital bone defect with cervical dysraphism and retroflexion of the head.

Autopsy findings were recorded by a certified pathologist to confirm the ultrasound findings and further classify anomalies when possible.

Photographs Included:

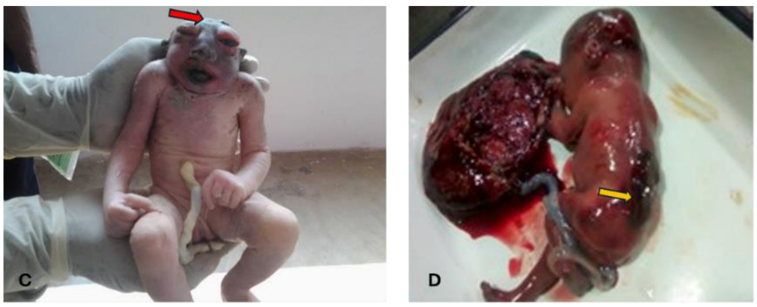
- Photos A, B & C: Anencephaly with cleft lip and cleft palate — These photographs illustrate the most severe type of cranial defect identified during the study. They serve as visual documentation of the types of NTDs encountered.



Anencephaly with cleft lip & cleft palate: A congenital condition involving brain underdevelopment and an incomplete skull.

Fig 1 Anencephaly with Midline Facial Clefts in a Newborn: Frontal and Lateral Views

- Photo D: Lumbar Meningomyelocele — This photograph demonstrates the posterior spinal defect where the spinal cord and meninges protrude, typical of severe forms of spina bifida.



Anencephaly: A congenital condition involving brain underdevelopment and an incomplete skull. (Red Arrow)
Lumbar Meningomyelocele: A type of spina bifida involving spinal cord herniation. (Yellow Arrow)

Fig 2 Anencephaly with Exophthalmos (C) and Meningomyelocele (D) in a Newborn

These photographs were documented using a SAMSUNG GT-C3630C model camera under standardized conditions to ensure consistency and clarity in imaging.

Statistical Analysis

Statistical analysis was performed using GraphPad Prism Version 8.0 (GraphPad Software, San Diego, CA, USA). Descriptive statistics were used to summarize the demographic and clinical characteristics. The incidence rate of NTDs was calculated as the number of cases per 1000 live births. Fisher's exact test was used to evaluate the associations between potential risk factors (e.g., maternal age, socioeconomic status, consanguinity, maternal obesity, and hyperthermia) and the occurrence of NTDs. Statistical significance was set at $P < 0.05$. Confidence intervals (CIs) were calculated to provide an additional context for the findings.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request and in accordance with the policies of SOA University and ethical considerations involved in patient confidentiality.

3. Results

Incidence of NTDs

Over the four-year study period from July 2020 to June 2024, a total of 152 cases of NTDs were identified among 16,666 deliveries at IMS and SUM Hospital, resulting in an overall incidence of 9.12 per 1000 deliveries. The annual distribution of NTDs is presented in Table 1. The highest incidence of NTDs was recorded from July 2021 to June 2022 (50 cases; 11.2 per 1000 deliveries), while the lowest was recorded from July 2023 to June 2024 (31 cases; 7.4 per 1000 deliveries).

Table 1: Year-wise Distribution of NTDs (July 2020 - June 2024)

Period	Anencephaly	Spina Bifida	Encephalocele	Holoprosencephaly	Iniencephaly	Total
July 2020 – June 2021	8	19	4	3	2	36
July 2021 – June 2022	16	22	5	4	3	50
July 2022 – June 2023	15	13	3	2	2	35
July 2023 – June 2024	11	12	5	1	2	31
Total	50	66	17	10	9	152

Among the various types of NTDs, spina bifida was the most prevalent, accounting for 43.4% (66 cases), followed by anencephaly (32.9%, 50 cases), encephalocele (11.1%, 17 cases), holoprosencephaly (6.6%, 10 cases), and iniencephaly (5.9%, 9 cases).

Demographic Distribution of NTDs

The distribution of NTDs according to maternal age is summarized in Table 2. The highest incidence of NTDs was observed among mothers aged 20-24 years, comprising 29.6% (n = 45) of all cases. Anencephaly was more common in mothers aged > 30 years (32.85%, 17 out of 50 cases), whereas spina bifida was most prevalent in mothers aged 20-24 years (31.8%, 21 out of 66 cases).

Table 2: Maternal Age Distribution of NTDs

Age Group (Years)	Anencephaly (n=50)	Spina Bifida (n=66)	Encephalocele (n=17)	Holoprosencephaly (n=10)	Iniencephaly (n=9)	Total
<20	10	13	4	1	0	28
20-24	12	21	4	4	4	45
25-29	8	7	1	1	0	17
30-34	17	15	5	3	3	43
≥35	3	10	3	1	2	19
Total	50	66	17	10	9	152

Paternal Occupation and Neural Tube Defects

The relationship between paternal occupation and NTD occurrence is shown in Table 3. Labor-intensive occupations (Class IV employees, such as laborers, cooks, gardeners, and sweepers) were significantly associated with higher rates of NTDs. Anencephaly and spina bifida were most frequently observed among fathers in these occupations, accounting for 56% and 56.06% of cases, respectively.

Table 3: Incidence of Neural Tube Defects by Paternal Occupation

Occupation	Anencephaly (n=50)	Spina Bifida (n=66)	Encephalocele (n=17)	Holoprosencephaly (n=10)	Total
Professional (I)	0 (0%)	2 (3.03%)	0 (0%)	0 (0%)	2 (1.32%)
Businessman/Technicians/Managers (II)	6 (12%)	8 (12.12%)	3 (17.64%)	0 (0%)	17 (11.18%)
Farmers/Forestry (III)	16 (32%)	19 (28.78%)	4 (23.52%)	2 (20%)	41 (26.97%)
Laborers/Cooks/Gardeners (IV)	28 (56%)	37 (56.06%)	10 (58.82%)	8 (80%)	83 (54.60%)

Consanguinity and Neural Tube Defects

The relationship between consanguinity and NTDs is presented in Table 4. Consanguineous marriages were noted in 12.93% (15 out of 116) of the NTD cases, with spina bifida cases having a slightly higher prevalence of consanguinity (15.15%, 10 out of 66 cases) than anencephaly (10%, 5 out of 50 cases).

Table 4: Neural Tube Defects and Consanguineous Marriages

Consanguinity	Anencephaly (n=50)	Spina Bifida (n=66)	Total
Yes	5 (10%)	10 (15.15%)	15 (12.93%)
No	45 (90%)	56 (84.84%)	101 (87.06%)

Obstetric Parameters and Neural Tube Defects

Table 5 provides data on the gestational age at diagnosis and gravida status of mothers carrying fetuses with NTDs. Most NTDs were diagnosed during the second and third trimesters via ultrasonography, with 56% of anencephaly cases and 61.84% of spina bifida cases diagnosed between 29-40 weeks of gestation. Additionally, 40% of anencephalic cases and 42.42% of spina bifida cases occurred during the first pregnancy (gravida 1).

Table 5: Gestational Age and Gravida in Neural Tube Defects

NTD Type	Gestational Age (Wks) 20-28	Gestational Age (Wks) 29-40	Gravida 1	Gravida ≥2
Anencephaly	19 (38%)	28 (56%)	20 (40%)	30 (60%)
Spina Bifida	28 (42.42%)	37 (56.06%)	28 (42.42%)	38 (57.58%)
Encephalocele	6 (35.29%)	11 (64.71%)	6 (35.29%)	11 (64.71%)

Maternal BMI and Hyperthermia

Table 6 shows the relationship between maternal BMI, hyperthermia, and NTD occurrence. Of the mothers of NTD-affected infants, 63.79% had a normal BMI (≤25 kg/m²), whereas 13.79% were obese (BMI ≥30 kg/m²). Maternal hyperthermia (≥100 °F) was associated with 30.17% of NTD cases.

Table 6: Maternal BMI and Hyperthermia in Neural Tube Defects

Parameter	Anencephaly (n=50)	Spina Bifida (n=66)	Total
BMI (kg/m²)			
≤25	34 (68%)	40 (60.06%)	74 (63.79%)
26-29	11 (22%)	15 (22.72%)	26 (22.41%)
≥30	5 (10%)	11 (16.66%)	16 (13.79%)
Hyperthermia			
<100°F	34 (68%)	47 (71.21%)	81 (69.82%)
≥100°F	16 (32%)	19 (28.78%)	35 (30.17%)

4. Discussion

Prevalence and Incidence Trends

The overall incidence of NTDs observed in this study was 9.12 per 1000 deliveries, which is higher than that reported in several other regions of India and globally. Previous studies have documented varying incidence rates, ranging from 0.5 to 8 per 1000 births, depending on geographic location, genetic predispositions, and maternal factors [15,16]. The high incidence observed in this study could be attributed to regional differences in maternal health, socioeconomic factors, and access to prenatal care. Our findings are consistent with studies from other low- and middle-income countries, where NTDs remain a significant public health concern owing to inadequate access to healthcare and nutritional deficiencies [17,18].

Risk Factors for Neural Tube Defects

Our study identified several significant risk factors associated with NTDs, including maternal age, socioeconomic status, consanguinity, maternal obesity, and hyperthermia. The highest incidence of NTDs was found in mothers aged 20-24 years, accounting for 29.6% of all cases. This finding is consistent with other studies that have indicated an increased risk of congenital anomalies among younger mothers owing to potential nutritional deficiencies and limited access to prenatal care [19,20]. However, anencephaly was notably more common in mothers aged >30 years, suggesting that advanced maternal age might also play a role in increasing the risk of certain types of NTDs owing to age-related metabolic changes and comorbidities [21].

Lower socioeconomic status, particularly among Class IV workers (laborers, cooks, and gardeners), was significantly associated with a higher prevalence of NTDs. This finding aligns with previous research indicating that socioeconomic factors such as income level, education, and occupation can significantly impact pregnancy outcomes owing to varying levels of access to healthcare, nutrition, and exposure to environmental risks [22,23]. Paternal occupation also appeared to influence the risk, with labor-intensive jobs associated with a higher incidence of anencephaly and spina bifida, possibly due to increased exposure to environmental toxins or lifestyle factors that could affect fetal development [24].

Genetic Factors and Consanguinity

Consanguineous marriages were noted in 12.93% of the NTD cases, with a slightly higher prevalence in spina bifida cases (15.15%). Consanguinity is a well-documented risk factor for autosomal recessive disorders, including NTDs, due to the increased likelihood of inheriting deleterious alleles from common ancestors [25]. Similar findings have been reported in studies conducted in South Asia and the Middle East, where consanguineous marriages are more common and have been linked to a higher prevalence of NTDs and other congenital anomalies [26,27]. This emphasizes the need for targeted genetic counseling in regions with high rates of consanguineous marriages to reduce the risk of NTDs and other congenital disorders.

Maternal Obesity, Hyperthermia, and Neural Tube Defects

Maternal obesity (BMI $\geq$30 kg/m^2) was found to be significantly associated with an increased risk of NTDs in this study, which corroborates findings from other studies indicating that obesity is a risk factor for NTDs owing to altered glucose metabolism and increased insulin resistance [28]. Watkins et al. [29] also showed a strong correlation between maternal obesity and increased risk of congenital anomalies, including NTDs. Additionally, maternal hyperthermia ($\geq$100 °F) was associated with 30.17% of NTD cases. Elevated maternal body temperature during early pregnancy has been linked to disruptions in neural tube closure, supporting the findings of both experimental and epidemiological studies [30,31]. These findings suggest that interventions to control maternal obesity and prevent hyperthermia during pregnancy can significantly reduce the risk of NTDs.

Strengths and Limitations

One of the strengths of this study is the use of both antenatal ultrasonography and postmortem autopsy for the diagnosis of NTDs, which provided robust and confirmatory data on the incidence and types of NTDs. The large sample size and comprehensive data collection on potential risk factors also enhanced the reliability and generalizability of the findings.

However, this study has several limitations. First, as an observational study was conducted in a single tertiary care center, the findings may not be fully generalizable to other regions of India or other countries. The study also relied on hospital-based data, which may not capture cases managed outside this setting or in home deliveries, potentially underestimating the true incidence of NTDs. Additionally, while consanguinity was identified as a risk factor, a detailed genetic analysis of affected families was not performed, which could have provided deeper insights into the genetic contributions to NTDs in this population.

Public Health Implications and Future Research

The high incidence of NTDs observed in this study underscores the urgent need for enhanced public health strategies including widespread folic acid supplementation programs, targeted interventions for high-risk populations, and increased awareness of preconception care. Special attention should be paid to young mothers, low-income families, and regions with high rates of consanguineous marriages. Genetic counseling and community education programs should be prioritized to reduce the risk of congenital anomalies.

Future research should focus on longitudinal studies with more extensive geographical coverage and the inclusion of genetic analyses to better understand the interplay between environmental and genetic factors in the etiology of NTDs. Additionally, studies exploring the effectiveness of interventions aimed at reducing maternal obesity and preventing hyperthermia during pregnancy could provide valuable insights into reducing the burden of NTDs.

5. Conclusion

This study highlights the significant burden of NTDs in eastern India and underscores the need for continued public health efforts to reduce the incidence of these serious congenital anomalies. Enhanced prenatal care, genetic counseling, and targeted public health interventions are crucial to reduce these defects further. Future research should focus on identifying specific genetic markers and environmental exposures that increase the risk of NTDs in the Indian population.

Conflicts of Interest Statement

The authors have declared that no competing interests exist.

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Data Access Statement

Research data supporting this publication are available from the SOA University repository.

Author Contributions

All authors contributed equally to this manuscript. B Shanta Kumari and Lopamudra Nayak contributed to the design and implementation of this study. Pratima Baisakh & Vinayak Ganesh Bhat contributed to the analysis of results and manuscript writing. Dhiren Kumar Panda performed the revised analysis and was responsible for writing and formatting the documents.

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