ORIGINAL RESEARCH

Profile of Congenital Defects in Fetuses: Incidence and Risk Factors—A Prospective Observational Study

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Received on: 11 May 2021; *Accepted on:* 16 June 2023; *Published on:* XX XXXX XX

Abstract

Background: Perinatal outcome is one of the major indicators of evaluating the health care system of a country. Congenital defects form important components of this parameter. This prospective observational study aims to determine the risk factors associated with congenital malformations in fetuses.

Methods: All antenatal mothers whose fetuses were detected to have congenital defects on ultrasonography irrespective of the period of gestation were enrolled for the study.

Results: Eighty-six pregnant women with prenatally diagnosed fetal anomalies were enrolled for the study, out of which, 87.2% (n = 75) belonged to the 20–30-years age group. The majority of the subjects were educated till secondary school. Compared to primigravidae, the incidence of malformations was significantly higher in the multigravida group (69.8% vs 30.2%). Thirty-eight (44.2%) mothers with malformed fetuses missed folic acid intake during early pregnancy. Only 40% mothers had prior history of abortions. Smoking was seen in 9% of subjects with malformations. Seven (8.3%) mothers had previous history of malformations and 5 (5.8%) reported a family history of malformations. Consanguineous marriage was observed in 4.7% of couples. Oligohydramnios or anhydramnios was associated with 11.6% fetuses, while polyhydramnios was seen in 53.5%. Central nervous system (CNS) malformations were seen in 57% of fetus, followed by genitourinary system malformations (9.2%).

Conclusion and Clinical significance: Tertiary-level hospitals need to be upgraded with a dedicated multidisciplinary team of fetal medicine to cater to the medical, clinical, surgical, preventive and therapeutic needs of malformed fetuses.

Keywords: Birth defects, Congenital malformations, Counseling, Risk factors.

Journal of South Asian Federation of Obstetrics and Gynaecology (2023): 10.5005/jp-journals-10006-2349

Introduction

Advancements in healthcare and improved standards of living have caused a shift in the prevalence of diseases. A decline in infectious diseases and a surge in inherited disorders is visualized of which congenital malformations constitute a major section. Congenital anomalies account for 15% of perinatal and neonatal deaths in India.[1] The incidence of congenital malformations varies widely between developed and developing countries. Major congenital malformations occur in approximately 3–4% of live births, although minor anomalies are more frequent.[2]

According to the March of Dimes and WHO report, 70% of birth defects are preventable provided genetic services could be introduced at the community level.[3] However, these services have not received due attention in India because of various reasons including cultural, religious, and social; apart from inadequate resources and trained manpower. Small interventions such as the introduction of periconceptional care and better control of medical diseases in this crucial period can reduce the incidence of birth defects and stillbirths.[4]

Single gene and chromosomal disorders, environmental pathogens and micronutrient depletion can cause various birth defects.[5] Syphilis and rubella infection in pregnancy, pregestational diabetes mellitus, iodine and folic acid deficiency, radiation exposure, teratogenic drugs cause significant birth defects. The common risk factors for developing birth defects in India are advanced maternal age at delivery, fetal growth restriction, low birth weight, consanguineous marriage, poor socioeconomic status and multifetal gestation.[4]

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How to cite this article: Jaiswal P, Sehgal A, Kaur A, *et al*. Profile of Congenital Defects in Fetuses: Incidence and Risk Factors—A Prospective Observational Study. J South Asian Feder Obst Gynae 2023;x(x):xx–xx.

Source of support: Nil

Conflict of interest: None

Among the structural birth defects, inborn errors of metabolism constitute a major role. These range from congenital malformations to fetal cardiomyopathy, hydrops fetalis or isolated ascites and fetal death.[6] Hydrops fetalis may be a presentation of glycogen storage disorder IV and lysosomal storage disorders. On the contrary, metabolic errors which lead to decreased fetal energy production such as mitochondrial oxidation defects may present with cardiomyopathy, oedema, ascites, and fetal demise.[6]

In developing countries, dedicated efforts to evaluate the etiological factors specifically incorporating cytogenetic studies,

syndromes, minor congenital malformations or heart lesions are lacking because of lack of consistent approach and follow-up.

While studying the incidence of anencephaly in our own institute, it was felt that detailed information on unexpected fetal loss and perinatal counseling for prevention of recurrences is required. However, the study was limited to fetuses presenting with anencephaly.[7] The prerequisite for better neonatal outcomes is still lacking in medical care managements except in select institutes. Hence, the present study is being planned to study the profile of congenital defects in fetuses presenting in a tertiary level hospital based on their clinical presentation. The planned study can help us identify possible risk factors in the population leading to congenital defects.

Methods

A prospective cross-sectional observational study was carried out for a period of 18 months from January 2016 to July 2017 in the Department of Obstetrics and Gynecology in collaboration with department of Anatomy, and Radiology at a tertiary care hospital.

Inclusion Criterion

All antenatal mothers whose fetuses were detected to have congenital defects on ultrasonography irrespective of period of gestation were enrolled for the study. Enrollment was started after approval by the institutional ethics committee. In these cases, after taking informed consent, detailed information on preconceptional counseling, intake of micronutrient, past and present history of medical disorders of pregnancy and details of treatment, any past history of previously affected pregnancy, congenital malformations and any defects in sibling or family member were collected. Online Mendelian Inheritance in Man (OMIM) database was used in evaluation of fetuses with multiple malformations. Study was ethically conducted in accordance with Declaration of Helsinki.

Exclusion Criterion

Couples undergoing sterilization or not planning further pregnancy, or not willing to participate in the study.

Statistical Analysis

Data was analyzed using Student's *t*-test for comparing quantitative parameters in different subgroups. Normal test of proportion was used for comparison of proportion in different subgroups. Chi-square test was used for testing significance of association between different attributes. Logistic regression analysis was done for investigating risk factors of multiple genetic defects/abnormalities. A *p*-value below 0.05 was considered significant.

Results

Out of 9,155 pregnancies which were screened, 115 pregnancies were diagnosed fetal anomalies, citing incidence of 1.3% of congenital malformations. Eighty-six women who fulfilled the inclusion criteria were enrolled in the study. Of 86 malformed fetuses, 39 (45.3%) were in the age group 20–25 years and 33 (38.4%) between 25 and 30 years (Table 1 shows the sociodemographic details of the subjects). Since a large number of referrals are made to our institute from rural areas of surrounding states, only 8 (9.3%) mothers of the study group resided in urban state of Chandigarh, India. Forty-four (51.2%) fetuses with malformations were born to resident couples from rural Punjab, 22 (25.6%) from Haryana, and 12 (14%) from Himachal. These cohort of women were referred for further counseling to our tertiary institute. As per Kuppuswamy categorization, 2 (2.3%) belonged to class II, 22 (25.6%) to class III, 24 (27.9%) to class IV, and 38 (44.2%) to class V. Out of 86 mothers, 19 (22.1%) were illiterate, and 61 (70.9%) had received education till secondary standard. Out of the 86 malformed fetuses, 26 (30.2%) fetuses were born to primigravida mothers and 60 (69.8%) to multigravida.

Table 1: Sociodemographic features of the subjects (*N* = 86)

Characteristics	*Categories*	*Frequency*	*Percentage*
Age (years)	<20 years	2	2.3
	20–25 years	39	45.3
	25–30 years	33	38.4
	>30 years	12	14.0
Socioeconomic status (SES)	Upper middle	2	2.3
	Lower middle	22	25.6
	Upper lower	24	27.9
	Lower	38	44.2
State	Punjab	44	51.2
	Haryana	22	25.6
	Himachal	12	14.0
	Chandigarh	8	9.3
Education status of mother	Illiterate	19	22.1
	Up to XII	61	70.9
	Graduation	3	3.5
	Postgraduation	3	3.5
Gravida	Primigravida	26	30.2
	Multigravida	60	69.8

Majority of malformations, 70 (81.4%) were detected by second trimester and 16 (18.6%) detected in late pregnancy after 28 weeks of gestation (Table 2 shows the clinical features of the subjects). In our study population, majority of mothers reported for antenatal check-up in late first trimester, 38 (44.2%) mothers with malformed fetuses missed folic acid intake during early pregnancy and this was statistically significant ($p = 0.03$). Of those who did not take folic acid, 26 (68.4%) had central nervous system (CNS) involvement. Seven (8.3%) mothers had previous history of malformations and 5 (5.8%) reported a family history of malformations. Both co-relations were significant statistically. Of 86, only 4 (4.7%) fetuses were born out of consanguineous marriage.

Five mothers with congenital malformed babies had history of taking potentially teratogenic antiepileptic drugs and it was not statistically significant. Among multigravida mothers with malformed fetuses, 24 (40%) had prior history of abortions. Among medical disorders in the study group, 6 (7%) mothers had hypothyroidism (7%), 2 (2.3%) each with diabetes mellitus and hypertension. Out of 86 malformations, oligohydramnios or anhydramnios was associated with 10 (11.6%) fetuses out of which, 8 fetus had genitourinary malformations. Polyhydramnios was seen in 46 (53.5%) mothers with malformed fetuses out of which 36 (78.2%) had neural tube defects and 8 (17.4%) had gastrointestinal malformations.

Out of 55 fetuses with CNS malformations, 25 (45.4%) had anencephaly, 5 (9%) each of meningomyelocele and hydrocephalus (Table 3 shows the systemic distribution of congenital malformations). Musculoskeletal system was involved in 5 fetuses. Four (80%) had skeletal dysplasia and one had distal arthrogryposis. Out of 10 fetuses with malformations of gastrointestinal tract (GIT), 5 (50%) had omphalocele. Nine fetuses had genitourinary malformations, with

Table 2: Clinical features of the subjects (*N* = 86)

Characteristics	*Categories*	*Frequency*	*Percentage*
Period of gestation (weeks)	<13	2	2.3
	13–28	68	83.7
	28–34	6	7.0
	>34	10	7.0
History of intake of folic acid	Yes	48	55.8
	No	38	44.2
History of drug intake in pregnancy	Present	12	13.9
	Absent	74	86.1
History of abortion (*N* = 60)	Present	24	40
	Absent	36	60
History of malformations (*N* = 60)	Present	5	8.3
	Absent	55	91.6
Family history of malformations	Present	5	5.8
	Absent	81	94.2
History of smoking in mother	Present	8	9.3
	Absent	78	90.7
History of alcohol in mother	Present	04	4.6
	Absent	82	95.3
History of consanguineous marriage	Present	4	4.7
	Absent	82	94.2
Amniotic fluid	Oligohydramnios	10	11.6
	Polyhydramnios	46	53.5
	Normal	29	33.7
Medical disorders in pregnancy	Absent	74	86.0
	DM	2	2.3
	Hypothyroidism	6	7.0
	Hypertension	2	2.3
	Epilepsy	1	1.2
	Cholestasis	1	1.2

Table 3: Congenital malformations and its systemic distribution

Characteristics	*Categories*	*Frequency*	*Percentage*
Number of systems involved (*N* = 86)	Single	77	89.5
	Multiple	9	10.5
CNS malformations (*N* = 55)	Meningomyelocele	5	9.0
	Anencephaly	25	45.4
	Spina bifida	4	7.3
	Encephalocele	4	7.3
	Hydrocephalus	5	9.1
	Arnold Chiari	4	7.3
	Dandy Walker	3	5.4
	Aqueductal stenosis	1	1.8
	Hypoplastic cerebellar hemispheres	2	3.6
	Holoprosencephaly	1	1.8
Genitourinary malformations (*N* = 9)	Vesicourethral reflux	2	22.2
	Hydronephrosis	1	11.1
	Multicystic kidneys	4	44.4
	Bladder outlet obstruction	1	11.1
	Bladder exstrophy	1	11.1
Gastrointestinal malformations (*N* = 10)	Omphalocele	5	50
	Gastroschisis	2	20
	Bowel atresia	2	20
	Imperforate anus	1	10
Musculoskeletal malformations (*N* = 5)	Distal arthrogryposis	1	20
	Skeletal dysplasia	4	80
Cardiovascular malformations (*N* = 4)	Hypoplastic left heart	3	75
	Transposition of great vessels	1	25
Other malformations (*N* = 9)	Hydrops fetalis	5	55.5
	Cystic hygroma	4	44.4

4 (44%) cases of multicystic kidneys. Cardiovascular malformations were found in 4 fetuses, out of which 3 (75%) had hypoplastic left heart. Five cases of hydrops fetalis and 4 cases of cystic hygroma were found. Out of 86 malformed fetuses, 77 (89.5%) had a single malformation and 9 (10.5%) fetuses had multiple malformations.

Discussion

Congenital malformations are a major cause of perinatal morbidity and mortality. Ideally to bridge the gap of understanding the natural course of congenital anomaly, a multidisciplinary team of fetal medicine specialist, geneticist and pediatric surgeon is needed for counseling.

In the present study, congenital malformations were common in the age groups 20–25 (45.3%) and 25–30 years (38.4%). This was comparable to Taksande A et al.[1] and Sarkar S et al.[8] Majority of the malformations of the CNS (73.4%) were encountered in the reproductive age group. Lower socioeconomic class may show indirect association with congenital anomalies as in our study which may be corelated to risk factors for malformations like deficiency of micronutrients, exposure to infection, or poor access to healthcare.[9] The present study showed that most of the subjects 68 (83%) presented between 13 and 28 weeks of gestational age. In a multicenter European study involving 3686 malformed fetuses, the overall detection rate was 56%, but 44% of the cases were diagnosed before 24 weeks.[10] However, termination was possible till term. This is of bigger challenge for us in India as termination of pregnancy was allowed only up to 20 weeks due to the Medical Termination of Pregnancy (MTP) Act, therefore cases had no option but to continue the pregnancy after 20 weeks. However, in light of late detection of congenital malformation in India, the MTP (Amendment) Act, 2021 has been modified to allow termination of pregnancy till 24 weeks in special circumstances.[11] In the present study, 44.2% of mothers with malformed fetuses did not take folic acid. It was higher than that observed by Singh A and Sinha S from India (19.29%).[12] Periconceptional folic acid supplementation provides a major opportunity to prevent birth defects especially neural tube defects.[13] The incidence of periconceptional folic acid deficiency is higher as concept of preconceptional counseling is largely missing in developing countries. Unfortunately, separate data on this was not attempted in our study. The present study observed that 5.8% had previous history of abortions which was lower than that observed in other studies, namely, Perveen F and Tyyab S (26.3%),[14] Shawky RM and Sadik DI (32.3%),[15] and Singh A and Sinha S (70.5%).[12] Predominance of CNS involvement was found

in the fetuses of mothers who had a previous history of abortions but this was not found to be statistically significant ($p = 0.246$). However, cytogenetic analysis of parents for chromosomal anomalies with recurrent abortions should preferably be a part of investigation for affording couples reporting for preconception counseling.[16] In the present study, it was observed that 8.3% subjects with malformed fetuses had already previous history of malformed fetuses. There was significant difference between subjects with prior malformed fetuses and those without such history ($p = 0.001$). The high recurrence rate of chromosomal abnormalities warrants fetal chromosomal investigation in subsequent pregnancies.[17]

Presence of family history of congenital anomalies was observed in 5.8% of subjects similar to the study by Perveen F and Tyyab S[14] (5.26%). The study highlights that it may be pertinent to undertake pedigree analysis of fetal syndromes with familial inheritance to guide couples through preconception counseling by a geneticist for future.[18] Most of the malformations in patients with similar family history were of the CNS ($p = 0.041$). Consanguineous marriage constitutes 20–50% of all marriages in North Africa and South India.[19] In this study, only 4 cases (4.7%) of consanguineous marriage were observed. There is an urgent need to address this group separately. This apparently appears to correspond to the highest rate of consanguineous marriages in this part of the country. There appears to be associated with cardiovascular and nervous system malformations, which was statistically significant ($p = 0.023$).

Polyhydramnios was present in 54.8% of malformed fetuses which was higher than that observed in the study conducted by Perveen F and Tyyab S[14] (22.9%) and Shawky RM and Sadik DI[15] (10.7%). Our study revealed statistically significant association between polyhydramnios and the malformations of CNS and gastrointestinal system ($p < 0.001$). On the contrary, oligohydramnios was seen in 11.8% of malformed fetuses which was comparable to the study by Shawky RM and Sadik DI[15] (9.8%) and lower than that observed in the study by Stoll C et al.[20] (32.6%). Among those with fetal abnormalities, most cases of oligohydramnios beginning early in gestation are secondary to genitourinary anomalies. Hence, study supports a critical and detailed anomaly scan of all cases of oligohydramnios or polyhydramnios. In the present study, 2.3% mothers with malformed fetuses had pregestational diabetes. This number was lower when compared to Perveen F and Tyyab S[14] (5.26%) and Shawky RM and Sadik DI[15] (7.28%). Although medical disorders, specifically diabetes mellitus, significantly increases the risk of congenital malformations, for correct interpretations the total number of mothers with medical disorders presenting during the study period would be relevant. The study does suggest preconception counseling for women with medical disorders diabetes mellitus and metabolic control as preventive measures to reduce birth defects and maternal morbidity.[21] Various studies as shown above have found different systems to be the commonest system involved in their studies. The most common system involved in the present study was CNS which is comparable to the study conducted by Shawky RM and Sadik DI.[15] In the study by Ronya et al.,[22] GIT was the most common system involved in the malformations (20.4%), and genitourinary in a study by Singh A and Sinha S[12] (29%). Cardiovascular system was the most frequently system to be involved in anomalies in the studies by Taksande A et al.[1] (23.17%), but only 4.1% in our study. In our hospital, fetal echocardiography is not being done routinely which may be responsible for lower proportion of cardiovascular anomalies detected in the present study. Among all subjects, the mothers with congenital cardiac malformations in fetuses were above 30 years of age and this association with elderly age was found to be statistically significant ($p = 0.002$).

In the present study 9 out 86 fetuses were detected to have multiple malformations, that is, involvement of two or more organ systems (Table 4 shows various probable associated syndromes using OMIM database with multisystem malformations). The possibilities are a *de novo* chromosomal (microscopic/submicroscopic) syndrome or single gene multiple malformation syndrome should be born in mind. Fetal chromosomal analysis was offered to all couples with affected pregnancies less than 20 weeks. Additionally, for fetus 1 with ultrasonography or sonography (USG) suggestive of aqueductal stenosis with lissencephaly with distal arthrogryposis, possibility of Baraitser–Winter syndrome or Miller–Dieker lissencephaly syndrome can be kept. For confirmation of these syndromes actin beta (ACTB)

Table 4: Syndromic approach to congenital malformations

Congenital malformations	*Probable syndromes*
1. Aqueductal stenosis with lissencephaly with distal arthrogryposis	• Baraitser Winter syndrome 1 • Miller–Dieker lissencephaly syndrome
2. Parietal meningocele with cystic hygroma	• Pteryguim syndrome multiple lethal type • Currarino syndrome • Knobloch syndrome • Arima syndrome • Joubert syndrome
3. Hydrocephalus and pleural effusion	• Mucopolysaccharidosis type 7 • Costello syndrome
4. Bowel atresia and hypoplastic left ventricle	• Verterbral anomalies (VACTERL) • Alveolar capillary dysplasia with misalignment of pulmonary veins (ACDMPV) • FORKHEAD BOX F1
5. Anencephaly with meningomyelocele with omphalocele	OEIS
6. Anencephaly and omphalocele	• Thoracoabdominal syndrome • Brachial amelia, cleft lip, and holoprosencephaly (ACLH) • Fetal akinesia syndrome • Hydrolethalus syndrome • Short rib thoracic dysplasia 12 • Meckel syndrome 1

(Contd...)

Table 4: *(Contd...)*

Congenital malformations	*Probable syndromes*
7. Sacral agenesis with omphalocele	• OEIS complex • Monosomy 1p36 syndrome • Zinc finger protein of cerebellum 3
8. Hydrocephalus and hydrops fetalis	• Cole carpenter syndrome 1 • Klippel–Trenaunay–Weber syndrome • Myotonic dystrophy 1 • Yunis–Varon syndrome • Mucopolysaccharidosis 7

gene sequencing and chromosomal microarray/fluorescence *in situ* hybridization (FISH) for 17p13.3 deletion can be offered. In a study by Chen CP and Chien,[23] it was concluded that in fetuses with Miller–Dieker lissencephaly syndrome, the main abnormal ultrasound feature is CNS anomalies. They confirmed this syndrome by single nucleotide polymorphism analysis in two fetuses. Cystic hygroma with meningocele in fetus 2 would indicate Pterygium syndrome, Knobloch syndrome and joubert syndrome.[24] Bowel atresia was found in conjunction with hypoplastic left heart in fetus 4 and such combination points towards verterbral anomalies (VACTERL) association.[25] Coloboma, heart defects, atresia choanae, growth retardation, genital abnormalities, and ear abnormalities (CHARGE) syndrome can be a differential although study by Sanlaville et al. shows that the more constant features are external ear anomalies, arhinencephaly and semi-circular canal agenesis.[26] Clinical exome sequencing with chromodomain helicase DNA binding protein 7 (CHD7) gene analysis can be offered in such cases. Omphalocele was seen in association with sacral agenesis, anencephaly and meningomyelocele in fetuses 5, 6, and 7. Omphalocele- exstrophy-imperforate anus-spinal defects (OEIS) complex could be suspected in such cases.[27] Omphalocele with anencephaly indicate towards Thoracoabdominal syndrome.[28] An omphalocele is usually associated with other major anomalies and aneuploidy and thus mandates a complete fetal evaluation including karyotype.[29] Possibility of a lethal lysosomal storage disorder as a cause of non-immune hydrops fetalis (NIHF) as seen in fetus 8 can be kept and a cordocentesis for enzyme analysis can be offered for such cases.[30]

Conclusion

With introduction of biochemical markers and improved sensitivity of ultrasonography, the detection rates of congenital anomalies have increased considerably. Tertiary level hospitals need to be upgraded with a dedicated multidisciplinary team of fetal medicine to cater to medical, clinical, surgical preventive and therapeutic needs of fetus. Counseling of the couple for preconceptional care needs more devotion and attention.

Ethical Approval

Approved by the ethical committee of the Government Medical College & Hospital, Chandigarh, India

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