http://jmscr.igmpublication.org/home/
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v7i8.99

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Research Article

Effects of Consangineous Marriages Maternal Teratogenecity and Antenatal Maternal Illness on Neonatal Congenital Aanomalies

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Abstract
Maternal factors greatly influence the neonatal congenital anomalies Infection of the fetus by rubella, cytomegalovirus, varicella and toxoplasma can be teratogenic[13]. Exposure of the fetus to some medication can cause congenital anomalies. Some maternal health conditions have shown increased risks for congenital anomalies including obesity, insulin-dependent diabetes, various forms of folate deficiencies and phenylketonuria[19]. Pregnancy induced hypertension, vaginal bleeding early in pregnancy, twin pregnancy, oligohydramnios, polyhydramnios, breech presentation, period of gestation, antenatal care during pregnancy, history of previous abortions and still births have been observed to be maternal factors associated with congenital anomalies.
Aims and Objective: *To study the proportion of congenital anomalies at tertiary rural health careand to find the corelation in between the antenatal maternal illness maternal teratogenicity, cooking sources of the mother consangineous marriage , liquor status of anc on usg and neonatal congenital anomalies*
Sample Size: *We took a sample size of 150 patients.. All neonates diagnosed with any congenital anomalies born in or coming to nicu of prh.*
Results: *Proportion of congenital anomalies were seen more in consanguineous marriage and in the mothers with antenatal illness .teratogenicity also had a significant rolec.*
Conclusion: *Regular check up of the mother and proper counseling for non addiction and avoidance of consanguineous marriage and simple diagnostic means such as x-ray and ultrasound can help in reducing the number of anomalies.*

Introduction

According to the World Health Organization (WHO) the term congenital anomaly includes any morphological, functional, biochemical or molecular defects that may develop in the embryo and foetus from conception until birth, that is present at birth, whether detected at that time or not[1].

Between 40% to 60% of congenital anomalies have no specific designated cause[2,3,]. Some 15%-25% of congenital anomalies are thought to have their origin from genetic disorders, involving a

single gene defect or the chromosomal abnormalities. 8%-12% are caused by environmental factors; including drugs or chemical exposures and maternal related conditions and 20%-25% are due to multifactorial inheritance.

Congenital anomalies due to genetic causes include Mendelian-inherited and chromosomal disorders. In Mendelian-inherited conditions, a genetic disease or an at-risk gene is inherited from one or both parents[04]

Chromosome abnormalities are due to changes in structure or number of chromosome leading to loss or gain of genetic materials. Down syndrome (DS) or trisomy 21 is the common chromosomal disorder that causes physical and mental problems[05].

In an executive summary in 2001 from March of Dimes Birth Defects Foundation New York five common serious birth defects of genetic or partially genetic origin were identified as Congenital heart disease, neural tube defects, hemoglobin disorders, Down; syndrome and G6PD deficiency. Combined these five conditions account for about 25% of all of birth defects of genetic or partially genetic origin. They also mentioned in 2001 that 7000 different birth defects of genetic origin were identified till then [06].

Maternal age is a risk factor for congenital anomalies. In a study done in Gujarat out of total 4210 babies studied in neonatal period immediately after birth , incidence of congenital malformation was 0.88% but incidence was significantly higher (6.1%) in mothers aged > 30 years as compared to younger age group[07]. In gametogenesis the first meiotic division is completed shortly before ovulation. If the first meiotic division takes a long time, especially up to 45 years, there are high chances for meiotic errors as the primary oocyte would have been in prophase for a long time and therefore susceptible to various teratogens. With maternal age above 35 years there is a high frequency of chromosomal abnormalities in the embryo like Down syndrome and other trisomies. The possibility of new gene mutation also increases with age [08]. Advanced paternal age is associated with genetic changes in the sperm; this could lead to an increased risk for congenital anomalies in offspring. Previous studies have found associations between advanced paternal age and several congenital anomalies, including orofacial clefts, hypospadias, neural tube defects, hydrocephalus and Down syndrome [09]. In another publication from National birth defects prevention study, 1997 – 2004 paternal age has also been suspected a risk factor for some multifactorial defects[10].

Lack of Folic acid supplementation or using foods fortified with Folic acid during periconceptional period is associated with occurrence of congenital anomalies. Folic acid is known to be necessary for growth and function of human cells as it is crucial for biosynthesis and methylation of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). This is important for cell division, differentiation and regulation of gene expression especially when there is rapid cell division like during embryogenesis[11]. Folic acid is crucial for normal brain and spinal cord development during the first 4 weeks of gestation. Peri conceptional use of folic acid has been proved to cause significant reduction of the risk for neural tube defects and other congenital anomalies like orofacial clefts, congenital heart diseases, urinary tract, limb and digestive system anomalies[12].

Infection of the fetus by rubella, cytomegalovirus, varicella and toxoplasma can be teratogenic[13]. Exposure of the fetus to some medication can cause congenital anomalies. These medication includes vitamin A derivatives, androgens, coumarin derivatives, iodine (overdose), cocaine, polychlorinated biphenyls, thalidomide, cytostatic agents and antiepileptic drugs. Exposure to anti epileptic drugs during the first trimester of pregnancy is well known to increase the risk for congenital anomalies[14]. The use of monotherapy for treatment of epilepsy during first trimester causes 2 to 3 fold increases of major congenital anomalies in off springs. The risk is estimated to

be even higher for offsprings exposed to polytherapy. Valproic acid has been found to be associated with greater incidence of major congenital anomalies than any other anti epileptic drug [15]. The use of antiretroviral therapy (ARVs) during pregnancy as treatment of HIV infection and/or prevention of mother to child transmission of HIV raises concerns about teratogenic effects of these drugs. Efavirenz is an antiretroviral drug which was found to have more teratogenic effects than other antiretroviral drugs. The use of cotrimoxazole for the prophylaxis or treatment of pneumocystis carinii pneumonia also raises concerns about possible teratogenicity[16]. Alcohol is a known teratogenic agent, and a wide spectrum of alcohol effects on the fetus has been demonstrated. There has been a positive association between maternal cigarette smoking and oral facial clefts from a number of studies[17]. It has also been found that Ionizing radiation has toxic effects to the embryo. There has been a growing concern about environmental contamination caused by chemical agents produced by industrial, mining and agricultural activities, and their possible relationship to the increase in the prevalence of congenital anomalies [18]. In a report of WHO of 2016 over congenital anomalies maternal exposure to certain pesticides and other chemicals was also related to increased risk of fetus with congenital anomalies . The teratogenic risks associated with most maternal environmental exposures are not well-established. Effects of paternal environmental exposures are poorly understood. Often environmental exposures involve multiple agents and other confounding elements, creating difficulty in identifying the underlying cause. Some maternal health conditions have shown increased risks for congenital anomalies including obesity, insulin-dependent diabetes, various forms of folate deficiencies and phenylketonuria[19]. Pregnancy induced hypertension, vaginal bleeding early in pregnancy, twin pregnancy, oligohydramnios, polyhydramnios, breech presentation, period of gestation, antenatal care during pregnancy, history of previous abortions and still births have been observed to be maternal factors associated with congenital anomalies. In a study, 224 cases of Oligohydramnios and congenital malformations were found out of a series of 225,669 consecutive births[20]. To diagnose different congenital anomalies it is important to consider family background, genetic examination and advice, clinical examination and investigations. Advances in ultrasound technology and fetal echocardiography have led to improved prenatal diagnosis. The ability to detect microscopic and submicroscopic chromosome abnormalities as well as single gene disorders, has brought great improvements in detection of such congenital anomalies. Invasive prenatal diagnosis is still the gold standard for pregnancies at increased risk for chromosomal anomaly or other genetic disease, chorionic villus sampling is the preferred method for the first trimester, mid-trimester amniocentesis is most common form of invasive procedure for prenatal diagnosis. In the low-risk population prenatal diagnosis is done by ultrasound and maternal serum biochemistry as invasive techniques are time consuming, expensive and are associated with risks for abortion. These techniques are only available in developed countries whereas, the diagnosis of congenital anomalies in developing countries, is normally done after birth and mainly based on clinical findings and simple diagnostic means such as x-ray and ultrasound[21,22]

Aims and Objective

To study the proportion of congenital anomalies at tertiary rural health care

To find the correlation in between the ANTENATAL MATERNAL ILLNESS and neonatal congenital anomalies

To find the correlation in between the MATERNAL TERATOGENICITY and neonatal congenital anomalies

To find the correlation in between the COOKINC SOURCES OF THE MTHER and neonatal congenital anomalies

To find the correlation in between CONSENGENEOUS MARRAIGE and neonatal congenital anomalies
To find the correlation in between LIQUOR STATUS OF ANC ON USG and neonatal congenital anomalies

Materials and Methods
Observational longitudinal hospital based study.
Sample Size: We took a sample size of 150 patients.
Source of Data: Tertiary care Rural Hospital.
Selection of Cases: All neonates diagnosed with any congenital anomalies born in or coming to NICU of PRH.
Duration of Study: 2 Years (1/7/2016 TO 31/8/2018).
Inclusion Criteria

- All neonates delivered in or referred to NICU of PRH with congenital malformation
- All neonates diagnosed with congenital malformation whose parents or guardian are ready to give written informed consent for the study

Exclusion Criteria

- Still born.

Study Conduct: All the neonates satisfying the above mentioned inclusion and exclusion criteria will be studied for the following:
Maternal Parameters
Full term / Pre term.
History of any chronic illness.
Addiction .
Drug History .
Consanguinity.

Clinical examination
Anthropometry
Any malformation
Type of Malformation
Health Status of Neonate

Study Conduct: Printed proforma will be used for recording thorough clinical examination of new born
Head to toe examination
Systemic Examination
Investigational Profile: List of investigations as mentioned in study
Outcome Parameters:
Type of intervention done:
Surgical / Non surgical
Untreated
Status at discharge
Statistical analysis will be done with descriptive statistics

Performa
Maternal History
Mother's name_____
Age_____
Education_____
Occupation-_____
Income
Father's name
Age -____
Education
Occupation -____
Income-_____
Religion Caste
Antenatal history
Registered delivery Yes No

Menstrual History
Age at menarche
cycle
LMP EDD
Maternal risk factors
Age
Pre pregnancy weight
Height
Previous abortion/ still birth
Previous neonatal death
Previous low birth weight
History of Toxaemia
Diabetes
TORCH

UTI
Fever with rash
Addiction smoking tobacco chewing alcohol
Drugs history anticonvulsant,
Antipshychotic
Any other drug during pregnancy
Radiation
pollutants (a) mining (b)other industrial (c) pesticides

Personal History
Water supply
Housing
Income –education
Waste disposal
Family history
H/O Consanguinity 1st /2nd /3rd
Any history of cong. defects in
Siblings
Relative
Neighbor hood
History of repeated abortions

Dietary History
Vegan/non vegetarian

Clinical examination of mother
Anthropometry /any malformation
Maternal investigation
Blood group
Haemoglobin %
Routine urine examination
VDRL
HIV Blood sugar USG Fetal Scan

Clinical Examination of Neonate
Term
Age
Sex
Single twin
Mode of delivery
Vaginal ceasarian
Apgar
Vit.k
Duration of labour
Anthrometry-
HC- ____
Wt- ____
Lt- ____
Cc- ____

Head to Toe Examination of Newborn
Skull
Eyes
Ears
Face
Nose
Oral cavity
Neck
Chest
Upper extremity
Finger
Position
Abd.
Lower extremity
Toes
Foot
Spinal examination
Continuation
Neural tube defect

Systemic Examination
Cardiovascular system
heart rate
murmur
Respiratory system
Respiratory rate
Type of respiration
Abdominal examination
Tenderness
organomegaly

Central nervous system examination
Power
Cry
Muscle tone
Activity

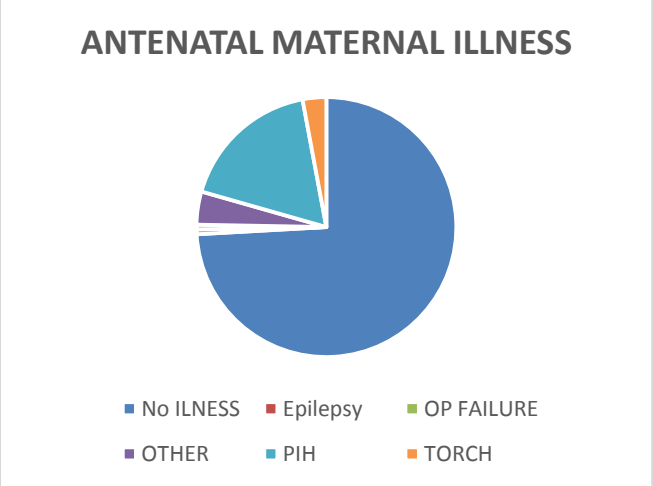
Investigation
Complete blood count
Blood group
Blood sugar

S. calcium
CRP
In specific condition
VDRL
TORCH titre
Karyotyping
Neurologicalinv.
Eeg
CT
MRI
Neurosonography
Infantogram
Invertogram
xray
all the investigations will be done as per need

Observations and Results

Antenatal Maternal Illness

NO ILLNESS	126
EPILEPSY	1
OP FAILURE	1
OTHER	7
PIH	30
TORCH	05
TOTAL	170

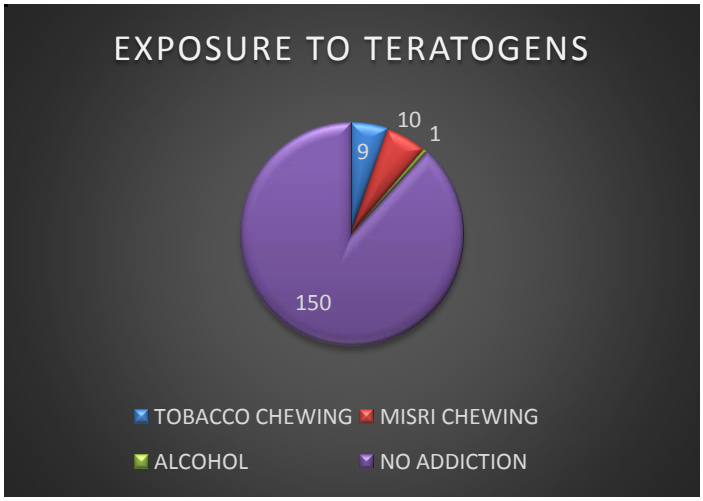


There was no history of antenatal maternal illness in 126 cases. However, history of PIH and TORCH was seen in 30 and 5 mothers, and others were 7 respectively and one case was due to op failure

Teratogenicity

TOBACCO CHEWING	09
MISRI CHEWING	10
ALCOHOL	01
NO ADDICTION	150
TOTAL	170

9 of the mothers were tobacco chewers ten were MISRI chewers 1 had a history of alcohol addiction and 150 were not having any addiction

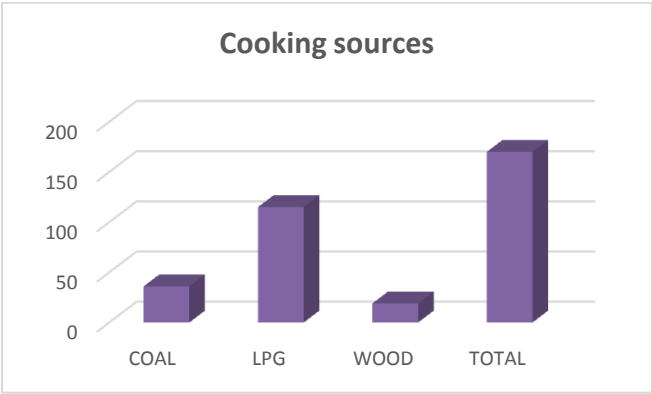


Majority of mothers had no history of exposure to addiction. Seven mothers each had history of tobacco chewing and MISRI, while one mother had history of alcohol consumption.

Cooking Sources

Count

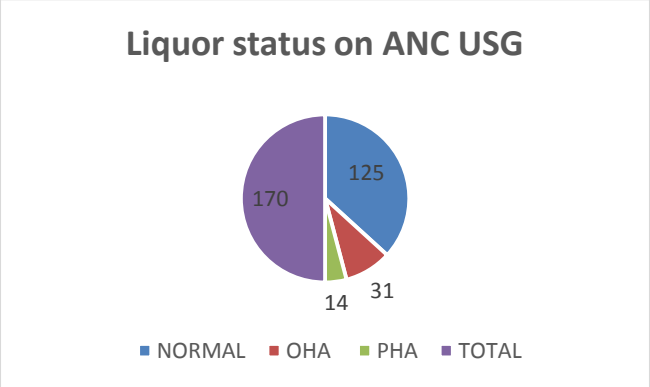
COAL	36
LPG	115
WOOD	19
TOTAL	170



36 Mother cooked on coal 19 cooked on wood others used LPG

Liquor Status on ANC USG

NORMAL	125
OHA	31
PHA	14
TOTAL	170

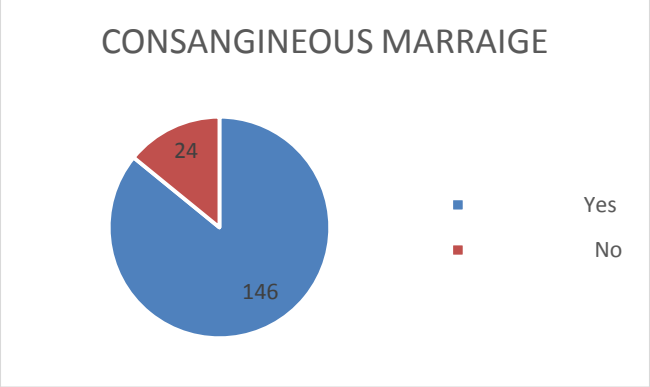


31 Mothers were of OHA 14 mothers were with PHA

Consanguineous Marriages

Count

Yes	146
No	24
TOTAL	170



24 Cases Had a History of Consanguineous Marraige

Results and Discussion

Correlation between Antenatal Maternal Illness and Congenital Malformations

In the present study 102 of new born had an association with various maternal antenatal risk factors like PIH, TORCH infection, Anemia ,diabetes mellitus, maternal, vericella and epileptic mother. Distribution of anomalies according disease status of mother (P= 0.86, Chi squared test for independence).was found to be non significant

In the present study history of PIH was present in 25 inborn and 6 outborn mothers who gave birth to malformed children. in our study there was a strong correlation in between the congenital anomalies and PIH similarly anemia in 29 inborn and 24 out born cases torch in 4 inborn and 1 out born case whereas vericella in 1 inborn cases was present

Various studies like Anand et al (1998) [23]5% of malformed babies (2 of 40) were bom to mother with PIH and Verma et al (1991)[24] 7.8% of affected newborn (2 of 359) were bom with PIH have correlated increased incidence of congenital malformations and maternal PIH. The findings in the present study were more when compared with other studies. .In 5 newborns with congenital anomalies there was torch infection the major anomalies encountered were inguinal hernia undescended testis and choanal atresia. here our study corelates with Verma et al (1991)

Correlation between Antenatal Exposure to Teratogens and Congenital Malformations

In the present study history of exposure to known teratogens was asked and it revealed that 09 of the 170 mothers who delivered newborns with anomalies had exposure to tobacco 10 mothers were Misri chewers in its raw form or burnt form, in this we encountered the anomalies related with CVS ,CNS and GIT major of the anomalies were meningomyelocele ASD, VSD and cleft palate along with traecheoesophageal fistula one mother had exposure to alcohol she delivered a girl child with Microcephaly.

Smoking has been suggested to be one of the strongest recognized exogenous sources of human malformations and a dose related teratogenic effect has been found. Tobacco use and alcohol consumption during pregnancy have been associated with unfavorable pregnancy outcomes. Some studies have shown an elevated risk of oral clefts with tobacco smoking during pregnancy,

whereas other studies have not.[5,16] in our study we did not had specific anamoly

Cooking Sources

36 mother cooked on coal 19 cooked on wood others used 115 cooked on LPG in mothers who cooked on coal and wood the major anomalies were hydrocephalus ASD ,VSD, Microcephaly and craniosynostosis followed by cleft lip and cleft palate

Liquor Status on ANC USG

In the present study 67 of which 42were having poly hydroamnios and 25 were having oligohydroamnios .on applying the chi squared test there was no significant diffrence in between the distribution of anomalies and liquor status. newborns had an association with hydramnios in pregnancy cases of tracheoesophageal fistula Meningomyelocele, spina bifida, microcephaly, ASD, complex cynoyic heart decease, CHPS Jejunoileal atresia, imperforate anus, Hirshprung decease, inguinal hernia, duodenal atresia hypospodias, hydronephrosis .polydactylyl and vater were strongly associated with poly hydramnios whereas cleftlip cleft palate, PDA, ASD, VSD, DEXTOCARDIA, CTEV, single kidney and calceneovalgus were strongly associated with oligohydroamnios various studies like Mathur et al (1975)[25] 66. Anand et al (1988)[23] Saifulla et al (1967)[26] have reported increased incidence of malformations in pregnancies associated with hydramnios: this studies strongly coincide our study.

Consanguineous Marriages

On comparing the consanguinity status , 92 had history of consanguineous marriage. of which 33 were female and 59 were males **(P= 0.646, Fisher's Exact Test)** between the gender of the newborn and the consanguinity.

In the present study, history of consanguineous marriages was present in 92 of 170 cases. A marked increase in CNS malformations was reported in babies bom of consanguineous marriages. major of them were meningomyelocele, microcephaly, emphalocele, other major anamolies were pierre Robin, micropthalmos and emphalocele Bhat & Babu etal(1998) [27] reported increased incidence of malformations in children of parents bom to consanguineous marriage . same was the poinion of Agrawal SS et al (1991)[28]

Conclusion

Increase incidence of anonalies were reported in maternal illness, exposure to teratogens, liquor status of the mother and consanguineous marraige regular check up of the mother and prorer councelling for non addiction and avoidance of consanguineous marraige and simple diagnostic means such as x-ray and ultrasound can help in reducing the number of anomalies although Invasive prenatal diagnosis is still the gold standard

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