

Maternal Illness and Congenital Defects: A Review

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ABSTRACT: In recent decades a majority of neonatal deaths, chronic medical conditions and disabilities are found to be associated with the congenital defects. Congenital defects are the structural and functional malformations in babies present at the birth. These defects can cause reduced survival rates of affected individuals and considerable percentage of neonatal death worldwide. In this study an extensive review of existing/published data from multiple sources relating the effects of maternal illnesses during pregnancy on the fetal outcomes is done. The study suggests the maternal exposure to chronic illnesses like obesity, diabetes, influenza induced hyperthermia, gastro-intestinal disturbances, medications, stress, auto-immunity etc. during the pregnancy (first trimester in most of the cases) as stronger risk factors for neonatal morbidity and mortality. Such studies representing association between sickness status of expecting mothers and congenital defects can help in early diagnosis of associated medical conditions and implementation of better strategies and appropriate management.

INTRODUCTION

World Health Organization (WHO) has defined the term “Congenital Defect” as the structural and the functional malformation including metabolic disorders in infants present at the time of the birth. An estimated 2, 70,000 infants’ deaths per year during the first 28 days of life due to congenital defects have been reported by WHO. Congenital defects leads to the malformation in body parts and affects the working of the body systems. This type of defect increases the risk of childhood deaths, chronic illness, many system dysfunctions, reduces the life expectancy and hence causing the long term complications in individuals. Etiology of Congenital Defects is still unknown but it is accepted that along with genetic-environmental interactions, maternal nutritional status and health conditions also plays an important role.

Usually the first trimester of pregnancy is considered to be the crucial phase of development as

most of the organogenesis occurs during initial trimester. This type of malformation occurs soon after conception in first trimester and often before the mother realizes that she is pregnant. Maternal pre-gestational diabetes and pre-pregnancy obesity (Andreason *et al.*, 2004; Watkins *et al.*, 2003; Waller *et al.*, 2007), febrile illness (Botto *et al.*, 2001), influenza induced hypothermia (Luteijn *et al.*, 2013), folate deficiency diarrhea (Felkner *et al.*, 2003; McGarel *et al.*, 2015), maternal stress during peri-conceptional and pregnancy (Carmichael *et al.* 2000; Carmichael *et al.*, 2007) may lead to increased incidences of congenital defects in infants. Absence of conditions necessitated for the sound psychological and physical health not only affects the mother’s well-being but also affects the pregnancy outcomes causing negative consequences.

Maternal health conditions and its impact on pregnancy outcome is matter of concern as the congenital defects are turning out to be causative factor for infant mortality in neonatal life. Although

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the advancements in science and technology have increased the survival rates of the affected individuals but still in few cases affected socio-psychological adjustments and disturbed self-esteem among the individuals and within the families (Vermaes *et al.*, 2005; Despars *et al.*, 2011; Montiroso *et al.*, 2011; Rumsey *et al.*, 2003) have been observed. This article is an attempt to find an association between sickness status of the pregnant mothers and possible risk of congenital defects in infants by the secondary (published) data. An understanding of the above given association might provide help in individual and public health strategies in promoting healthy pregnancies, reduction of global health burden and betterment of lives of affected individuals. Through this review the author has tried to find the association between the exposure of pregnant mother to various kinds of illnesses and the common congenital defects like neural tube defects, congenital heart defects and orofacial clefts.

MATERNAL ILLNESS AND NEURAL TUBE DEFECTS

Neural Tube Defects (NTDs) are the birth defects that occur due to the incomplete formation or malformation of the spinal cord, brain and related structure during early development of the fetus (National Institute of Child Health and Human Development, 2012). Approximately 400,000 infants with spina bifida are born worldwide each year (Pulikunnel *et al.*, 2005). The various types of neural tube defects may include spina bifida, anencephaly, encephalocele, iniencephaly, meningocele etc. These defects cause a greater risk of infant mortality and lifelong complications for the infants who survive at the time of birth causing various levels of disability and reduced life expectancy. Though the exact cause for the occurrence of NTDs is not known but a complex interaction between the genetic and environmental factors are thought to be probable reason.

Recently a number of researches have indicated that the maternal health conditions during pregnancy have a major role to play in the occurrence of NTDs among the infants as the mother provides the very first environment during the fetal development. Health conditions like Obesity, diabetes, increased body temperature due to fever, nausea, vomiting, diarrhea,

etc. can cause negative effect on the fetal development. The two well documented risk factors for NTDs reported in various studies are maternal pre-gestational diabetes and obesity during pregnancy and pre-pregnancy period (Andreason *et al.*, 2004; Stothard *et al.*, 2009; Watkins *et al.*, 2003; Waller *et al.*, 2007). Although mechanisms underlying these risks are not certain, there are studies showing that the babies born to obese and/or diabetic mothers may get the similar pathogenic exposures, including modification in glucose homeostasis and hyperglycemia (Cabera *et al.*, 2004; Carmichael *et al.*, 2010). Increased risk of congenital defects has been reported in the cases of mothers with co-existence of diabetes and obesity as compared to either of two (Andreason *et al.*, 2005; Moore *et al.*, 2000). During the process of organogenesis, developing embryo does not have pancreatic function and it is reliant on maternal anaerobic glycolysis for fulfilling the energy demand before the development of chorioallantoic placenta. Thus, at the time of neural tube closure (approximately the fourth week of gestation period), mothers with imbalance in glucose levels are likely to have the altered conditions in the uterus, which is difficult to be managed by the developing embryo, resulting in disturbed organogenesis (Lupo *et al.*, 2012). Furthermore maternal diabetes may affect gene expression in the developing fetus, in particular set of genes causing NTD and may cause teratogenic effects. It is reasonable to assume that deregulation of genes are the most likely to contribute to the molecular etiology for maternal diabetes-induced birth defect (Salbaum *et al.*, 2010).

Also obesity which is defined as the state of chronic oxidative stress (Vincent *et al.*, 2007) and oxidative stress caused by maternal diabetes reduces the expression of Pax3, a gene required for neural tube development and closure and thus, is related with significantly increased risks of NTDs (Loeken 2005; Lupo *et al.*, 2012). In few cases the non-diabetic but obese mothers that have high sugar level intake with significant risk of NTD affected birth were also reported (Watkins *et al.*, 2003).

Occurrence of disorders such as diabetes, obesity, and the metabolic disorder that may adversely affect cholesterol levels among the expecting mothers during

the pregnancy and pre-pregnancy period. Other diabetes related conditions like hyperglycemia and hyper-insulinemia also have greater influence on increased risk of NTDs (Parker *et al.*, 2012). Studies have shown associations between high dietary glycaemic index and neural tube defects among non-diabetic women (Shaw *et al.*, 2003; Yazdy *et al.*, 2010), while a study of dietary glycaemic load found no association with neural tube defects (Shaw *et al.*, 2008). Hyper-insulinemia, or insulin resistance, is known to increase with obesity and has been associated with the development of neural tube defects (Hendrick *et al.*, 2001).

A North Indian population based study confirmed the diseased condition like infection with fever in mothers during pregnancy with births of infants with NTDs (Kalla *et al.*, 2001). Study conducted on the effect of maternal influenza on fetal outcome has also pointed out the risk associated with first trimester maternal influenza exposure with increased incidence of non chromosomal congenital defects including neural tube defects, hydrocephaly, cleft lip etc. (Luteijn *et al.*, 2013). Evaluation of maternal flu or fever and the use of antipyretics in the first trimester and NTDs in infant have proved an increased risk of NTDs births (Medveczky *et al.*, 2004; Wang *et al.*, 2013).

The cases of severe megaloblastic anemia or folate deficiency diarrhoea in early pregnancy lead to defective development and congenital defects like NTDs (McGarel *et al.*, 2015). Even the low folate status and impaired folate metabolism may introduce a medical condition known as hyperhomocysteinemia which has been related with an increased risk of NTDs (De Marco *et al.*, 2010).

MATERNAL ILLNESS AND CONGENITAL HEART DEFECTS

Congenital heart defects are the problems with the heart structure that are present at the birth. These defects may involve the defects of the interior walls of the heart, the arteries and the veins the valves of the heart. Congenital heart defects are among the most common reasons for infant mortality. According to Department of Health and Human Services, U.S. (2001) an estimated prevalence rate of congenital heart defects is 8 per 1,000 newborn (Department of

Health and Human Services. National Heart, Lung and Blood Institute, U.S., 2011) Many remarkable associations have been found in infants born with congenital defects and illness status of their pregnant mother. Chronic illness like pre-gestational diabetes particularly type 1 diabetes mellitus is observed to be a strong risk factor for congenital heart defects compared to gestational diabetes. Studies have indicated the cardiovascular malformations due to diabetes mellitus before the seventh week of gestation due to a link between glycaemic control during organogenesis and fetal malformations (Mikhali *et al.*, 2002; Lisowski *et al.*, 2010; Liu *et al.*, 2013). Offspring of pregnant mothers suffering from congenital heart disease and/or diabetes mellitus were found to be more prone to heterotaxy (Hunter *et al.*, 2015), conotruncal defects, atrio-ventricular septal defects obstruction of right and left ventricles, septal and multiple defects (Liu *et al.*, 2013). Obesity, which has become a global health concern, also contributes to the development of other chronic illnesses like arterial hypertension or high blood pressure, gestational diabetes etc thereby affecting the pregnancy outcomes. Babies born to obese mothers have been identified at a greater risk of suffering from diseases, such as non-insulin dependent diabetes or diabetes type 2, insulin resistance and overweight, fatness ,obesity ,heart defects (Sieaga-Riz AM *et al.*, 2006; Gilboa *et al.*, 2010; Stothard *et al.*, 2009). Maternal over-weight is also found to be documented with an increased risk for cardiovascular defects (Mc Mohan *et al.*, 2015).

The relationship between febrile illness during pregnancy before one month of the pregnancy through the third month of the pregnancy and cardiac defects in the offspring in a population-based case-control study in metropolitan Atlanta provided a positive association. In the study the risks were found to be increased for cyanotic heart defects like tricuspid atresia , left obstructive defect, transposition of great arteries, ventricular septal defects VSD (Botto *et al.*, 2001). Exposure of developing fetus to maternal fever proved to be a higher risk factor of specific group of congenital heart defects like VSD and right obstructive defects (Shi *et al.*, 2014). A meta-analysis on relationship between first trimester influenza in pregnant mothers and congenital birth defects in infants indicated that influenza can not only effects

the fetus via viral infection or by inducing hyperthermia and toxic metabolites with fever but also anti-pyretic and anti-viral use (Luteijn *et al.*, 2013). Epileptic Offspring born to the woman with epilepsy are more likely to be affected by congenital malformations including congenital heart defects. Many therapy-associated factors could provide explanation for this increased risk, including direct interference in development of fetus as the effects of anticonvulsant drug therapy or arrhythmogenic effect and an indirect effect of the drugs by causing interference in folate metabolism (Barret *et al.*, 2003). A positive association between untreated phenylketonuria in pregnant mothers and affected babies represented a 6-fold-increased risk of heart defects among infants (Levy HL *et al.*, 2001; Matalon *et al.*, 2003).

Studying the role played by autoimmunity against maternal Cardiac Myosin and congenital heart defects in fetal rat model brought a novel concept to lime light. Autoimmune response against Cardiac myosin (CM) in mother's body can also cause Hypo-plastic heart syndrome (HLHS) like lesions in fetus. In observational studies an elevated auto-antibodies against CM, including heart-specific binding of CM-immunized maternal and affected serum, IgG accumulation in rat embryo and HLHS phenotype have been reported (Cole *et al.*, 2014).

MATERNAL ILLNESS AND ORO-FACIAL CLEFTS/PALATES

aOro-facial Clefts/Palates are the births defects related to the improper formation of lips and mouth in infants during embryonic development. These defects include Cleft lip, in which the lip doesn't join completely and results in an opening of the upper lip and Cleft palate. An individual can have a cleft lip, a cleft palate or both a cleft lip and cleft palate (Centre for Disease Control and Prevention, 2014). Since the organogenesis occurs during the fetal stage, so the impact of adverse maternal health conditions is inevitable. An incidence rate of oro-facial cleft in infants is estimated to be 10.5 per 10,000 for cleft lip with or without cleft palate and 6.4 per 10,000 for cleft palate alone (Stott-Miller *et al.*, 2010) Researches are being conducted to find the association between pregnant mothers suffering from illnesses like

obesity, fever, diabetes etc. and birth of babies with oro-facial clefts in infants. Obesity has become very common disorder in present scenario and can have major impact on the fetal outcome. Obese mother are found to be at increased risk of giving birth to the offspring with congenital anomalies including neural tube defects, spina bifida, cardiovascular disorder, and clefts (Canfield *et al.*, 1999-2001; Stothard *et al.*, 2009). A positive relationship between disorder associated with obesity like glucose intolerance or insulin resistance in mothers and infants with Cleft lip/palate is also observed. Another reason for occurrence of orofacial clefts in infant of obese mother could be adiposity related to obesity causing direct or indirect influence on biological metabolism. Hypoxic stress to the fetus due to hyperglycemia or hyper-insulinemia or advanced glycation production resulting in DNA damage could be the mechanism involved. Studies have also reported pre-gestational diabetic women to more likely to have increased risk of giving birth to infants with oro-facial cleft (Stott-Miller *et al.*, 2010).

Greater chances of suffering from cleft palate/lip are observed in offspring born to mother exposed to maternal illness and bad mood during the first trimester of the pregnancy (Qi *et al.*, 2015). Cases of febrile illness in pregnant mother without the use of antipyretic during the first two months of pregnancy were reported to have more number of cleft palate/lip affected births in comparison to the cases of non-illness (Hashmi S. *et al.*, 2010). Though some association between the occurrence of Maternal Angina Pectoris mothers and Oral cleft in infants have been found but the exact mechanism for the association is not known. A plausible cause could be association of origin of both MAP and oro-facial clefts with hyper-homocysteinemia (Cziesel *et al.*, 2015). Stress-related gene polymorphisms also causing a higher risk of oro-facial clefts affected births were also reported in the study (Mostowska *et al.*, 2011).

CONCLUSION

Impact of maternal illness during prepregnancy and pregnancy period on the pregnancy outcomes can't be ignored. This study evaluated an impact of sickness status of pregnant mother on the fetal outcomes with special reference to common

congenital anomalies like neural tube defects, congenital heart defects and oro-facial clefts. In addition, this review attempted to provide a summary of studies reporting various maternal adverse health conditions during pregnancy (first trimester in most of the cases) with the increased risks of negative pregnancy outcomes in the form of birth defects. Stronger association between the illnesses like obesity, diabetes, influenza, hyperthermia or fever, folate deficiency diarrhoea and an increased risk of congenital defects in infants are observed. Various studies have reported obesity and diabetes as two well-established factors for embryopathy related to congenital malformation causing metabolic alteration in mechanisms like abrupt glycemic, hyperinsulinemia, glucose homeostasis, disturbed cholesterol, oxidative stress etc. and thus disturbed organogenesis. Significant role of autoimmune response mother against cardiac myosin and HLHS phenotype in babies, studied in mouse model provides insight into a new concept of immune-mediated pathogenicity. Also the first trimester influenza can have teratogenic effect via several pathways including induced hypothermia toxic metabolites, viral, use of anti-pyretic and anti-viral medications. The relation between illnesses in mothers and defects in infants could be uncertain where risk factors like independent effect of the disease, its treatment of autoimmune response of the body on fetus is not clear as in the case of therapy associated factors causing arrhythmogenic and anticonvulsant effects. Though in a recent study maternal obesity is found to be negatively associated with neural tube defects. The negative association could be real or may reflect effect of people belonging to different groups exhibiting different inherent susceptibility and inhabiting different environmental conditions. The information presented here can provide summarized literature work addressing the need to improve the understanding of given association. It can also help in imparting knowledge to minimize the chances of having an affected baby for prospective parents and in introducing effective treatments to reduce the occurrence of these anomalies. The dissemination of appropriate information can also help concerned professionals, specialists in providing pre-conceptional and peri-conceptional care like dietary

management, nutrition, multivitamin intake, physical activities, vaccinations, medications etc. in order to improve the pregnancy outcomes.

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