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## ORIGINAL ARTICLE

# FACTORS ASSOCIATED WITH CONGENITAL ANOMALIES AMONG YOUNG INFANTS AT TIKUR ANBESSA HOSPITAL, ADDIS ABABA, ETHIOPIA

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## ABSTRACT

***Introduction****: Congenital anomalies require multitude of surgical procedures at a very early life and impose a large impact on the lives of patients and parents and yet causes are still largely unknown, but assumed to be multifactorial. A few studies focused on environmental risk factors, but evidence is still scarce.*

***Methods:*** *This is a case control study of infants less than three months of age with congenital anomalies evaluated or admitted to the hospital between December 1, 2017 and May 31, 2018. Face-to-face interviews with parents of young infants were carried out to collect socio-demographic and clinical information.*

***Results:*** *Analysis of the data showed that among 200 young infants with congenital anomalies enrolled in the study, gastrointestinal system is most commonly affected organ system. Maternal factors that were significantly associated with congenital anomalies included the lack of peri-conceptional use of folic acid (OR = 3.6; 95% CI = 1.6-7.7; p = 0.005), an inadequate attendance to antenatal clinic (OR = 2.3; 95% CI = 1.5-3.6; p < 0.001), family history of congenital anomalies in 3 %of cases (OR 2.4:95% CI =1.5-3.6; P< 0.001). Infant factors that were significantly associated with congenital anomalies were male sex, and birth weight of 2.5 kg or less.*

***Conclusions****: In this study, the proportion of women taking folic acid supplements during pregnancy was very low and mothers of infants with congenital anomalies have less antenatal follow up. Efforts should be made to ensure that more women use folic acid during the peri-conceptional period, as the use of folic acid supplement could reduce the occurrence of some congenital anomalies.*

***Key words:*** *congenital anomalies , risk factors , young infants*

## INTRODUCTION

Congenital anomalies (CAs) are structural or functional anomalies which are present at the time of birth. A congenital anomaly is defined as a defect in the structure of an organ which resulted from a specific primary abnormality of organogenesis. Over the years, the proportion of infant mortality due to CAs has increased significantly from 15.1% in the 1970s to 22.1% in the late 1990s. An estimated 6% of global infant deaths are attributable to CAs, which makes it the leading cause of infant mortality, and more than 70% die in the first month of life and the majority of whom survived are mentally and physically disabled for life (2).

Every year an estimated eight million children, 6% of the total births worldwide are born with a serious birth defect of genetic or partially origin. Additionally, hundred thousands are born with serious birth defects of post conception origin due to maternal exposure to environmental agents. CAs could lead to long term disability, which may have significant impacts on individuals, families, societies and health care systems (4).

CAs require a multitude of surgical procedures at a very early age and have large impact on the lives of patients and their parents. The impact of CAs is severe in middle and low-income countries. As a matter of fact, it is estimated that approximately 95% of the children who die from birth defects are from those countries. An indirect determinant of this higher risk relates to a possible lack of access to sufficient nutritious food by pregnant mothers, an increased exposure to agents or factors such as infection or alcohol, poorer access to health care facilities (3). In Africa, results from different studies vary on the frequency of CAs . The rate of CAs was found to be 20/1000 among children aged 0-18 years by a study done in Egypt (9). Studies from East Africa reported incidences of above 20/1000 live births, while the incidence of major anomalies was found to be 15/1000 births (4,8). In Asia, the magnitudes of CAs vary also with reported incidence of 2.5% of infants at birth in India (8). The frequency of these anomalies in Pakistan have been described as either related to total birth or to still birth, with the former accounting for 11.4/1000 and 16% for the latter.

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In the United States (U.S) and Canada where CAs are diagnosed intra uterine and aborted, the incidence was 2-5% of all live births (6). Although 50% of all CAs cannot be linked to a specific cause there are some known genetic and environmental risk factors. There is multifactorial cause for 20-25% of anomalies whereby there is a complex interaction of genetic with environmental risk factors. Another 10-13% of anomalies have a purely environmental cause (e.g. infections, illness, or illicit drug in the mother (8). Only 12-25% of anomalies have a purely genetic cause. Of those caused by genetic factors, the majority are chromosomal anomalies.

Various environmental factors have been identified to be risk factors for CAs . Among the risk factors are advanced maternal and paternal ages, parental consanguinity, maternal *toxoplasma*, rubella, cytomegalovirus, and herpes simplex virus (TORCH) infectious and nutritional deficiencies (10). The association between maternal smoking and the risk of malformation is especially important for mothers who do not take folic acid periconceptional (14). Maternal health conditions that contribute to increased risks for CAs include obesity, chronic hypertension and insulin-dependent diabetes mellitus. Periconceptional alcohol exposure has long been known to confer an increased risk for neurodevelopmental deficits in offspring, but its impact on the development of structural anomalies is less clear (26). Many CAs occur more frequently in one sex than the other, the cause of deviated sex ratio remains unclear (11).

## PATIENTS AND METHODS

***Study design***

A case–control study design was employed at Tikur Anbessa Specialized hospital in Addis Ababa.

***Patients and controls***

A sample of 692 infants (200 cases, 472 controls) was used for this study; cases were infants less than three months of age with external major anomalies. Daily admission records of infants less than three months of age at pediatric surgical wards, causality, pediatric intensive care unit (ICU) and pediatric surgical referral clinics between December 1 2017 to May 30 2018 were identified, evaluated and included in the study regardless of whether they underwent a surgical procedure or died in hospital. Infants with isolated central nervous system, cardiac, or facial and limb abnormalities were not included in the study since almost all such cases were handled in other centers.

Controls were randomly chosen in a 2:1 ratio relative to cases from among all infants without a diagnosis of CAs born during the same time frame and visited the hospital vaccination clinics and those admitted to wards for reasons other than CAs.

***Covariates***

Exposures of interest were maternal characteristics including maternal smoking during pregnancy (yes/no), maternal alcohol use during pregnancy (yes/no), maternal drug use and maternal diagnoses of chronic hypertension (diagnosed prior to pregnancy, not pregnancy-induced) and pregestational diabetes mellitus (yes/no).

Potential confounders that were identified before data collection included clinical factors previously known to be associated with CAs or presumed to be potential confounders of the association of interest. These factors were gender of the infant, maternal age (<20 years, 20–34 years, and 35+years), preterm delivery (<37 weeks); birth weight (< or >2500 grams); use of folic acid, maternal parity, and maternal body mass index (BMI) in kg/m2 (<19, 19–25, 25–30, >30), family history of birth defects, defined as two or more first- or second-degree relatives with a birth defect.

***Statistical analysis***

Chi-square test was used to assess for statistical significance between the frequencies of the background variables among cases and controls. Crude odds ratios (CORs) with 95% confidence intervals (CIs) were calculated to assess the strength of association between the potential maternal and paternal risk factors using logistic regression analyses. The variables considered as potential confounders included all potential determinants that are known or suspected risk factors from the literature. To prevent having too many covariates in the initial multivariable models, we first checked whether a factor changed the risk of CAs by at least 10% in bivariable analyses.

However, those that shared the causal pathway between the risk factor of interest and the outcome were excluded. All relevant variables were included in multivariable logistic regression models for each potential maternal and paternal risk factor to calculate adjusted ORs with 95% CIs. Only risk factors with two or more exposed cases were used in the analyses. Factors with a P value of less than 0.1 on univariate analysis were subjected to multivariate logistic regression analysis.

## RESULTS

We identified 200 infants with CAs during the study period and 492 controls. About 55.4% of case infants presented in the first week of life with the age range at presentation of 1-80 days. About four (2%) and 46 (9.4 %) of mothers whose children had and did not have CAs, respectively, were in the15-19 years of age group. Besides, 99 (91.5%) and 368 (74.8%) of mothers whose children were exposed and not exposed to CAs, respectively, were 20-34 years of age 30–34 years of age group. Likewise, 17 (8.5 %) and 78 (15.9%) of the mothers who had affected and non-affected children, respectively, were 35years and above.

As far as the birth order of children was concerned, 37, 31.7, and 31.3 were first, second, third and above (3+) children to their families, respectively. Among the controls, about 32.9, 19.8, and 47.3% were first, second, third and above (3+) children, respectively, to their parents. In on our study, 62.5% of the cases and 29% of controls are from outside Addis Ababa. Compared to controls, a greater proportion of cases were male.

Most of the cases were gastrointestinal anomalies 135 (67.5%) followed by genitourinary anomalies 37 (18.5%) and abdominal wall 20 (10%). Chest, lung, and vascular malformations constitute the rest 8 (4%). The most common gastrointestinal anomaly identified was Hirshsprung disease comprising (29.6% cases), followed by anorectal malformations (27.4% of cases), tracheoesophageal atresia (23.7%), the rest are intestinal atresia (8.8 %), malrotation and duplication cysts (3.3%). Most common genitourinary anomaly was hypospadias (29.7%) followed by Posterior urethral valve (24.9%), bladder extrophy (18.9%), pelviurethral junction obstruction (10. 8%), disorders of sexual differentiation (2.7%) and others (13.5 %). The most common abdominal wall defect was omphalocele (65%) followed by gastroshsis (25%) and others (10%).

About 66.5% of mothers whose children had CAs and 10% of the mothers who had children without CAs, had no antenatal care (ANC) visits) or three or less antenatal clinic (ANC) visits (OR = 2.3; 95% CI = 1.5-3.6; $p < 0.001$). (Table 1)

**Table 1:** Parental characteristics and risk factors in cases and controls, Tikur Anbessa Specialized hospital, Addis Ababa, December 1, 2017 and May 31, 2018.

| | **Cases n=200** | **Controls n=492** | **P value** |
|---|---|---|---|
| Maternal age (years) | | | |
| <20 | 4 (2) | 46 (9.4) | |
| 20-34 | 99 (91.5) | 368 (74.8 | 0.23 |
| 34+ | 17 (8.5) | 78 (15.9) | |
| Maternal parity | | | |
| Primiparous | 75 (34.9) | 144 (27) | 0.12 |
| Multiparous | 125 (65.1 | 348 (73 | |
| Maternal BMI | | | |
| <19 | 6 (3) | 11 (4) | |
| 19-25 | 109 (54.5) | 128 (46.9) | 0.08 |
| 25-30 | 20 (20) | 65 (23.8) | |
| >30 | 15(15) | 69 (25.3) | |
| Unknown | 50 | 219 | |
| Antenatal visit | | | |
| Yes | 133(66.5) | 440(89.4) | 0.02 |
| No | 67(33.5) | 52(10) | |
| Number of ANC Visit | | | |
| <4 | 79 (39.7) | 117(23.8) | 0.001 |
| >4 | 121(56.3) | 375(76.2) | |
| History of birth defect | | | |
| Yes | 3(1.5) | 3(.6) | |
| No | 197(98.5) | 489(99.4) | 0.001 |
| Passive smoking | | | |
| Yes | 6(3) | 16(3) | 0.820 |
| No | 194(97) | 476(97) | |
| Drug intake | | | |
| Yes | 8(4) | 28(5.6) | 0.92 |
| No | 192(96) | 464 (94.3) | |
| Folic acid | | | |
| Yes | 50(25) | 400(81.3) | 0.005 |
| No | 150(75) | 92(18.7) | |

About 75% of mothers whose children had CAs and 18.7% of the mothers who had children without CAs, had no use of folic acid preconception or during pregnancy. Non-use of folic acid during pregnancy (OR = 3.6; 95% CI = 1.6 - 7.7; p = 0.005).

Maternal and paternal age at childbirth was not different between the groups but fathers of infants with CAs were lower educated than controls and family income for cases were low than controls. More infants with CAs were first-borns, were born preterm, or had a low birth weight compared to control children (Table 2).

**Table 2:** Univariate and multivariate analysis of congenital anomalies and explanatory factors, Tikur Anbessa Specialized hospital, December 1, 2017 and May 31, 2018.

| | Cass n=200 | Controls n=492 | Unadjusted OR [95%CI] | P-value | Adjusted OR [95%CI] | P-value |
|---|---|---|---|---|---|---|
| **Sex** | | | | | | |
| **Female** | 87(43.2) | 142(28.9) | 1 | | 1 | |
| **Male** | 112(56.3) | 350(71.1) | 1.3[0.9-2.0] | 0.156 | 1.8[1.1-2.8] | 0.013 |
| **Birth order** | | | | | | |
| ≤4 | 183 (23.7) | 280(57) | 1 | 0.47 | | |
| | | | 1.5 | | | |
| >4 | 17(57.3) | 212(43) | 1.5[0.5-4.7 | | | |
| **GA at birth** | | | | | | |
| >37 | 153(76.5) | 400(81.3) | 1 | | 1 | |
| <37 | 47(23.5) | 92(18) | 5.3[1.9-15.1] | 0.002 | 3.5[1.2-10.9] | 0.027 |
| **Birth weight** | | | | | | |
| >2.5 | 141(70.5) | 400(81.3) | 1 | | 1 | |
| <2.5 | 59(29.5) | 92(18.6) | 3.0[1.9-4.9] | <0.001 | 2.3[1.4-3.9] | 0.002 |

Obesity is seen in 15 % of case mothers and 20 % of control mothers. Pregestational hypertension was diagnosed in 1.5 % of cases and 3% of controls .More case parents reported a family history of congenital malformations in 1.5% of cases but only in 0.6% of controls. Infant factors that were significantly associated with CAs were: male sex (OR = 1.3; 95% CI = 0.9-2.8; p = 0.013), a birth weight of 2.5 kg or less (OR = 3; 95% CI = 1.9-4.9; p =0.000).

About 3% of cases have history of passive smoking in mothers even if it not significantly associated. 3% of cases and 5.8% of controls have history of drug use, aspirin and unspecified medications though the timing of exposure could not be recalled by parents. There is no significant association between maternal pregestational diabetes and hypertension and CAs .

## DISCUSSION

The incidence of CAs in our study was higher in male than in female. A study by Molla et al. from Ethiopia reported the incidence of anomalies to be 58.5% male, 41.5% female.

Another study by Mashuda et al., from Tanzania reported that 54.6% of the male and 44.9% of the female children were observed with CAs. A study by Bakare et al., in Nigeria and Zhang et al., in China pointed out that the proportions of CAs were 51.3% and 48.7%, and 54,9% and 38.7% for male and female, in that order. Although, some rare studies have shown a difference with a higher prevalence of congenital malformations among female than male.

In our study statistically significant association was found between CAs and low birth weight. Similar results also found in other study done in northern Ethiopia. Low birth weight was associated with increased risk of CAs. This highlights the fact that the presence of congenital anomaly itself hampers the growth of a developing fetus. In our study statistically significant association was found between congenital malformation and prematurity. This is particularly a cause of concern as prematurity and stillbirths are a major cause of perinatal mortality.

In our study advanced maternal age was not associated with an increased risk of CAs. In Turkey, studies show that 5.2% of the mothers are older mothers (35 years of age or older) (26) and 8.7% of anomalous births were from older mothers, although this was not statistically significant. In a large prospective cohort study, Hollier et al demonstrated an additional 1% age-related risk of non-chromosomal abnormalities in women age 35 or older. Conversely, Baird et al found no association between the incidence of congenital malformations and advancing maternal age. More recent studies suggest that young maternal age actually may be a stronger risk factor for certain CAs compared with advanced age.

Our study also showed a significantly higher risk of overall CAs in infants of preterm births. This could be explained by the fact that preterm newborns spend more time in the intensive care unit and are subjected to more diagnostic tests, compared to term newborns. This increases the odds of diagnosing subtle CAs in preterm newborns than in term newborns. Another possible explanation for our finding may be that CAs and prematurity may share some underlying maternal risk factors such as smoking, obesity, hypertension, and diabetes mellitus.

In this study there is a significant association between lack and irregular ANC follow up with CAs . Folic acid is known to be necessary for the growth and smooth function of human cells, as it is crucial for the biosynthesis and methylation of deoxyribonucleic acid (DNA) and ribonucleic acid. This is important for cell division, differentiation and regulation of gene expression, especially at a time of rapid cell division.

Multiple vitamin supplements containing folic acid are also distributed during the clinic sessions [29]. The antenatal visits therefore aim at ensuring a normal pregnancy with the delivery of a healthy baby from a healthy mother. Few (≤4) or no prenatal clinic visits have previously been associated with the occurrence of CAs (26).

The Chinese cohort study demonstrated that the risk of anal atresia was reduced by half after the periconceptional supplementation of 0.4 mg of folic acid daily. The Hungarian case-control study showed a similar impact on the occurrence of rectal/anal atresia or stenosis if women used high dose of folic acid (3 to 9 mg daily, mainly 6 mg) in the second month of gestationIn this study, passive smoking was not significantly associated with CAs although several researchers reported that smoking/passive smoking was associated with a specific type of CA.

Our results show that only 25% of the mothers of young infants had used folic acid during the first trimester of pregnancy and that nonuse of folic acid was significantly associated with CAs .

In our study, the highest proportion of anomaly was gastrointestinal (34.2%) followed by genitourinary (30.8%) while the least frequent anomalies were vascular and respiratory (6%). Among the gastrointestinal anomalies, Hirsh sprung disease was the most frequently observed defect. A study by Muga et al, Kenya, found 33.9% prevalence rate of the musculoskeletal system defects, followed by 28.1% of the central al nervous system defects which is different from our findings. The differences in incidence may be due to genetic factors or the existence of multifactorial effects in the countries the studies were carried out and exclusion criteria of our study.

In contrast to our findings, other studies conducted in Romania found higher prevalence of congenital heart defects (33.06%), followed by respiratory tract defects (31). A recent study in Arctic Russia found a higher prevalence (8.7%), of congenital malformations and deformations of the musculoskeletal system, followed by (4.3%) congenital malformations of the urinary system [6]. Similar studies elsewhere have reported that the musculoskeletal and gastrointestinal systems are the body systems most commonly affected (9,18).

There is a significant association between family histories of CAs with cases. This study has several important limitations. First, these are observational data and thus associations cannot be assumed to be causal. Similarly, the administrative source of the data is subject to coding errors and misclassification and not all relevant potential confounders are included in the data. All risk factors studied were self-reported, so random misclassification of exposure and recall bias cannot be excluded, especially since parents were asked to recall events that had occurred some time ago. With regard to disease exposures (pre-gestational diabetes, pre-gestational hypertension), we are not able to extract information on disease severity. The relatively small sample size of cases made it difficult to provide reliable findings for less frequently occurring risk factors.

***Conclusion***

In this study, the proportion of women taking folic acid supplements during early pregnancy was very low. Even though, due to its design, our study could not establish a causal relationship between non-use of folic acid and the occurrence of CAs, efforts should be made to ensure that more women use folic acid during the periconceptional period since there is ample documentation about its association with CAs.

Family history of CAs was found to be associated with the risk of recurrent CAs in their second pregnancies. We recommend that:

- Iron folate supplementation is required to reproductive age groups, particularly around conception and during early pregnancy;
- Although the causes of CAs are unknown and not studied in Ethiopia, screening nutritional deficiencies, chronic diseases, such as anemia, diabetics, infections/diseases and establishing preventive measures, for example, health education to the public, specifically to reproductive age women are very important pre-conceptional care including genetic testing and counseling should be available for families at risk; and
- Large scale multi-center and register based studies are needed to clarify the role of key risk factors for the development of CAs.

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***Competing Interest***

The authors declare that this manuscript was approved by all authors in its current form and that no competing interest exists.

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