Title: Clinical Profile and Outcomes of Congenital Gastrointestinal Malformations: A Single Hospital Study

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ABSTRACT

Aims: To determine the prevalence, clinical profile and outcomes of gastrointestinal (GI) malformations in neonates in a tertiary care hospital.

Settings and Design: A prospective observational case-control study was conducted at a tertiary care hospital in New Delhi.

Methods: The study was conducted on live neonates from October 2014 to November 2015. Cases of neonates with GI malformations were compared against healthy babies. Outcome measures assessed were prevalence, associated risk factors, clinical profile, and mortality of GI malformation.

Statistical analysis: Qualitative variables were compared using Chi-Square test/Fisher's exact test. Multivariate logistic regression was used to assess the significant risk factors after adjusting for confounding variables. A P-value <0.05 was considered statistically significant.

Results: Among the 25,116 live births, 41 cases were diagnosed with GI malformations. To compare, 82 controls (healthy babies) were taken. The prevalence of GI malformations was 0.163 or 1.63/1,000 live births with a male to female ratio of 1.1:1. The tracheoesophageal fistula was the most frequent anomaly (39.02%). Multivariate analysis revealed a lack of periconceptional iron and folic acid supplementation and baby birth weight <2.5 kg as independent significant factors related to the occurrence of congenital GI defects (when compared to controls). Among 41 cases, 20 neonates died (48.78% mortality rate). Causes of mortality were prematurity, sepsis, asphyxia, and shock.

Conclusion: In a developing country like ours, the association of GI malformations (0.163%) with lack of periconceptional iron and folic acid supplementation and low birth weight shows that increased counseling and implementation of the supplements during the pregnancy can help decrease the prevalence. Mortality remains high among such children and thus they demand urgent necessary surgery and management.

Keywords: Congenital Anomaly, Gastrointestinal Malformation, Prematurity, Prevalence, Risk Factors

INTRODUCTION

Birth defects or congenital malformations can be defined as structural or functional anomalies, including metabolic which are present at the time of birth.[1] About 7% of all under five deaths globally are caused by congenital anomalies. In developing countries, they contribute to about 5-7% of mortality which is progressively increasing due to improved screening and diagnosis.[2] India has the largest number of infants born with birth defects in the world; and gastrointestinal (GI) malformations are the third most common cause of congenital birth defects with the reported incidence of 38.37 per 10,000 births.[3-5]

GI malformations can be easily diagnosed by simple modalities like abdominal x-ray and contrast studies with very good surgical intervention and outcome. Till now, data pertaining to the congenital GI malformations among various countries show that increasing maternal age, low birth weight and early gestational birth are significantly associated with the occurrence of GI malformations among which absence, stenosis or atresia of the small intestine (Q41) and esophageal malformations(Q39) are relatively common and increasing in the trend.[4,5]

ICD classification for congenital diseases (by WHO) is the most used classification system under which GI malformations are classified under the category Q38-Q45. Most of the studies have followed the ICD classification of diagnosis to maintain the consistency in the reporting of the prevalence of the disease.[4]

The data collection and the association studies show that the knowledge about the geographical prevalence can help determine the causal and associated risk factors for congenital GI malformations. It may thus help in formulating the management plans by the government and thereby reduce the mortality and morbidity. The present study was thus planned to determine the prevalence and associated risk factors of GI malformations in neonates in one of the largest tertiary care hospitals in India.

METHODS

Safdarjung hospital is a tertiary care hospital, with annual delivery rate of approximately twenty five thousands births. Out of these around 20% of the babies are admitted in the nursery annually. A prospective observational case-control study was conducted at the Department of Pediatrics and Department of Obstetrics and Gynecology from October 2014 to November 2015 during which, there were 25,116 live births; out of which 41 cases were diagnosed as GI malformations and were included in the study as Cases. The senior pediatric surgeon diagnosed the congenital anomalies. To match them, every second healthy babies born consecutive to the study case and having no GI malformation were enrolled as controls. A total of 82 control neonates were included in the study. Ethical clearance was taken from the ethical committee of the institution. Informed, written consent was taken from parents/guardians of the neonates. The parents/guardians of the neonates were informed about their right to refuse and regarding the confidentiality access to the database was only with the primary investigators.

After enrolling the neonates in the study, they were followed till the baby passed meconium or 48 hours whichever was later. Data was collected related to mother such as demographic profile (age, education, socioeconomic status as per the modified Kuppuswami scale), obstetrical history in terms of birth order, consanguinity, iron and folic acid supplementation, development of gestational diabetes mellitus (GDM), presence of eclampsia, severe anemia (<5 g/dL of hemoglobin), maternal infections, toxoplasmosis, rubella cytomegalovirus, herpes simplex, and HIV (TORCH), birth defects, addictions (tobacco chewing, smoking, alcohol consumption), previous spontaneous abortion, rubella, previous still birth, and febrile illness in first trimester.

The neonate underwent investigations which included abdominal X-ray erect view, ultrasound abdomen and contrast study of GI tract. Other supportive investigations included hemogram, and electrolytes. The related birth findings for the neonate were also noted which included labor progression, cord entanglement, obstruction in the labor, birth trauma, birth weight, gestational age of mother at delivery, gender of the baby, any complications, use of surfactant, intravenous fluids (IV), bag and mask ventilation and antibiotics. Whenever there was one malformation,

other known malformations were ruled out. A skilled pediatric surgeon performed the surgery (>20 surgeries already performed by him).

Follow-up of the babies were done for one month to detect any other birth defect. Outcome measures were prevalence of GI malformations, associated risk factors for GI malformations, clinical profile, and mortality among neonates GI malformation.

Standards and criteria

Gestational diabetes: GDM was diagnosed by Diabetes in Pregnancy Study Group of India (DIPSI) method where all participants were asked to get non fasting oral glucose challenge test with 75g glucose. A diagnosis of GDM was made if 2 h post-glucose blood sugar was >=140 mg/dl.

Pre-Eclampsia: Blood pressures (BP) and urine proteinuria was measured after 20 weeks of pregnancy in the antenatal visits to note the development of pre-eclampsia which was defined as de novo BP elevations (Systolic blood pressure of 140 mm Hg or more or diastolic blood pressure of 90 mm Hg or more on two occasions at least 4 hours apart) after 20 weeks of gestation coupled with proteinuria (300 mg or more per 24 hour urine collection or Protein/creatinine ratio of 0.3 mg/dL or more or Dipstick reading of 2+ or other end-organ dysfunction in the absence of proteinuria.

Congenital anomalies: We adopted the world health organization (WHO) criteria which defined congenital anomalies/ birth defects/ congenital disorders/congenital malformations as “structural or functional anomalies (for example, metabolic disorders) that occur during intrauterine life and can be identified prenatally, at birth, or sometimes may only be detected later in infancy, such as hearing defects”.[5]

GI malformations: We adopted the International Classification of Diseases-10 (ICD10) classification by WHO which defined GI malformations as “congenital structural abnormalities of the digestive system which includes tongue, mouth, pharynx, the esophagus; other congenital malformations of the upper alimentary tract; congenital absence, atresia, and stenosis of the small intestine; congenital absence, atresia, and stenosis of the large intestine; other congenital

malformations of the intestine; congenital malformations of the gallbladder, bile duct, and liver, and other congenital malformations of the digestive system".[6]

Statistical Analysis: Qualitative variables were compared using Chi-Square test/Fisher's exact test. Multivariate logistic regression was used to assess the significant factors associated with the occurrence of GI malformations after adjusting for confounding variables. A p-value <0.05 was considered statistically significant. The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, version 21.0.

RESULTS

During the study period, there were 25,116 live births; out of which 41 cases were diagnosed as GI malformations; giving a prevalence of 0.163 or 1.63/1,000 live births. The sex wise distribution of birth defects was 20 males out of 13,106 male born child, 18 females out of 12,007 female born child; with male to female ratio being 1.1:1 (three cases not included due to ambiguous genitalia).

In this study, out of 41 cases of GI malformations, 16 cases were picked up on antenatal ultrasonography while 25 cases were diagnosed after birth among which 18 cases presented within 24 hours of birth and rest seven after 24 hours of birth. Amongst gastrointestinal (GIT) birth defects, the tracheoesophageal fistula was the most frequent (16 cases, 39.02%), followed by anal atresia (10 cases, 24.39%), esophageal atresia (4 cases, 9.76%), mesenteric cyst (3 cases, 7.32%), ileal atresia (2 cases, 4.88%), omphalocele (2 cases, 4.88%), and single case each of duodenal atresia, Hirschsprung's disease, intestinal atresia and meconium cyst as depicted in Figure 1. The representative images of some of the cases are shown in Figure 2-5.

As compared to the control group, the study group had significantly lesser number of women < 30 years of age (63.41% vs. 80.49%, P=0.04), and comparable father's age (P=0.42). The number of illiterate women in the study group was comparable to the control group (48.78% vs. 32.93%, P=0.229). Most of the fathers were also illiterate in both study and control groups

(P=0.263). In comparison with the control group, the study group had significantly more number of women with the lower socioeconomic class (58.54% vs. 30.49%, $p<0.05$).

No significant association was observed between the birth order and the occurrence of birth defects among cases and controls (P = 0.571). A significantly higher proportion of women among the cases had a history of consanguineous marriage (P = 0.042). A significantly higher proportion of women among the cases did not receive periconceptional iron and folate supplementation (P = 0.0016) and a significantly higher proportion of women among the cases had a history of febrile illness in the first trimester as compared to the control group (P = 0.016)

Among the cases and controls, no significant difference was observed between maternal comorbid conditions [gestational diabetes mellitus (GDM), pre-eclampsia, severe anemia, and TORCH group infection], intrapartum complications (nonprogress of labor, cord complication, obstructed labor, prolonged second stage labor, oxytocin = for induction, birth trauma) and gestational age of delivery (Table 1).

Among the neonate factors, babies with GI malformations had significantly less birth weight (<2.5 kg), $p<0.05$. (Table 2)

On multivariate analysis, lack of periconceptional iron and folic acid supplementation and baby birth weight <2.5 kg was observed to have an independent, significant association with the occurrence of GI birth defects (Table 3).

In this study, out of 41 cases of GI malformations, 36 (87.80%) were transferred for pediatric surgery intervention. Five who were not transferred died (four from asphyxia and one from prematurity). Out of 36 GI birth defects, [two were not operated due to prematurity and one left against medical advice (LAMA)]. Total 33 were operated, out of which, 13 died intraoperatively and postoperatively. So, overall there were 20 deaths among babies of GI malformations with eight deaths among the 16 cases of tracheoesophageal fistula and five deaths among the 10 cases of the anal atresia. Rest of the neonates were discharged and kept under follow-up for one month. (Table 4) In the study group, the average time to onset of first feed was 7 days (range 3–14 days) and average time of hospital stay was 14 days (range 5–21 days).

DISCUSSION

The prevalence of GI birth defects was 1.63 per 1,000 (0.16%) in the present study. In comparison to our study, Jafar et al reported a prevalence rate of 1 per 1,000 live births;[3] where this lower value may be due to differences in genetic and environmental factors. In another study by Kumar A et al, a slightly lower prevalence of 0.721/10,00 live births was recorded.[4] The Indian studies by Gupta et al and Taksande et al showed a slightly higher prevalence of 2.3 per 1,000 and 1.75 per 1,000 respectively.[7,8]

The variation in observations show that developing countries as ours have a high prevalence of malformations. The regional variations also stems from the different data collection, that is, wither from the limited hospital-based settings or from the community-based settings. Other factors accounting for the variation in the prevalence include differences in geographical locale, environmental factors, genetic factors, racial background, nutrition and socioeconomic differences and timing of discharge.[9]

The present study observed a higher proportion of affected male neonates with GI birth defects, but the difference was statistically not significant. Similar results were obtained in the study by Kumar A et al.[4] who also reported male preponderance. On the other hand, Jafar et al. found that risk for GI malformation in females was 1.3 times more than males.[3] However, none of the previous study or our study found a significant association of gender with GI malformations. The case control comparison in our study was also able to show that the equivalent chance of the birth of male or female child with birth defects follows the same chance ratio as of the occurrence of normal male or female child.

The present study observed that tracheoesophageal fistula and anal atresia were the commonest GI malformations Our study was in line with Saiyed SS et al[10] and Asandi et al,[11] where imperforate anus was the most common malformation followed by tracheoesophageal fistula. Other GI malformations found in our study were Esophageal Atresia, Mesenteric cyst, omphalocele, Ileal atresia, Meconium cyst, Intestinal Atresia, Duodenal atresia and Hirschsprung's disease.

The present study observed that a significantly higher proportion of pregnant women in the study group were in the age group >30 years (P < 0.040). These observations are in accordance with those of Taksande et al and Sugnabi et al who also reported that higher risk of producing malformed babies was noted in mothers above 30 years and 35 years, respectively. [6,12] This notion has also been seen to be associated with other genetic disorders such as Down syndrome and Klinefelter syndrome where the maternal age (>35 years) becomes a significant risk factor. The reason was the fragility of the chromosome after a certain age which leads to increased chances of chromosomal breaking at the junctional centromeres.

The present study observed that the increase in the birth order was not significantly associated with the occurrence of GI birth defects. Contrary results were shown by Mohanty et al., Taksande et al., and Taboo et al., who reported that increasing birth order (para ≥4) was associated with an increased incidence of congenital anomalies.[6,13,14]

We observed that more women in the study group were from the lower socioeconomic status as compared to the control group. As such, low socioeconomic status is a significant risk factor for the occurrence of birth defect. Raza et al. also observed a lower socioeconomic status to be associated with GI birth defect.[15] Lower socioeconomic status is generally associated with poor literacy; a combination of the two factors generally leads to lack of antenatal supervision and ignorance regarding the teratogenic potential of various drugs. This may predispose to an increase in GI birth defects.

This study did not observe any significant association between the parent's education and the occurrence of birth defects. This may be due to the limited sample size, and because our study was a purely hospital-based study, so women with poor literacy and lower social strata may have been under-represented.

The present study observed that significantly more women in the study group did not receive periconceptional iron and folic acid supplementation (P<0.016). On multivariate analysis, the significance persisted even after the adjustment for confounding factors (P=0.024). These observations are in concordance with those of Raza et al., who reported that the majority of women who delivered neonates with birth defects, did not take iron and folic acid supplementation periconceptionally.[15] These observations emphasize the significance of periconceptional maternal counseling regarding the significance of folic acid supplementation in early pregnancy.

The present study observed more women in the study group with a history of consanguineous marriage. Similar observations have been reported by Ali et al. and Naoom et al. who observed consanguinity to be a statistically significant risk factor associated with a rise in birth defects.[16,17]

The present study found a history of birth defects in previous pregnancy in 9.76% women in the study group and 3.66% in the control group; however the difference was not statistically significant (p 0.220). None of the women in either of the groups gave a history of birth defects in the family. Taboo et al. reported a history of previously affected children or other family members in 1.85% cases.[14] There is lack of awareness in the general population, regarding the significance of the history of birth defects in family/ previous births, Women with one or more affected family members may be at risk of having a child with a major GI birth defect.

On comparing the study and control group, the present study observed a significant association between history of febrile illness and the occurrence of GI birth defects (P = 0.016). Most of the studies have not commented on this association; only Taboo et al. have reported that viral infections were not independent risk factors for birth anomalies.[14] It can be recommended that future studies assess the cause of the febrile illness to determine the exact nature of the disease that is having a cause-effect relationship with the GI malformations.

We observed a significantly higher proportion of low birth weight <2.5 kg in the study group, as compared to the control group. Our observations are similar to those of Mohanty et al. and Taksande et al.[8,13] On the contrary, Naoom et al. found no significant association of birth weight with the occurrence of GI birth defects.[17] We found no significant difference in the proportion of preterm birth in control group and study group. Our observations are different from those of Ali et al., who reported that prematurity was associated with a significant rise in birth defect and Naoom et al. also observed that congenital anomalies are common in preterm neonates than their term counterparts.[16,17] The difference in observation maybe because of the small size of the present study and probably because of maternal and low birth weight.

The overall case fatality rate in the index study was 20(48.78%) which was quite higher than other comparable studies such as 15.2% by Kumar A et al[4] and 12% by Asindi AA et al.[11] The causes of death included prematurity, sepsis, asphyxia and shock. It is accounted for by the lesser

developed immunity in such patients with acid base dysbalance and preterm births. Though surgery was immediately performed in all the babies with GI malformations, it can be seen that the mortality causes are diverse owing to the disturbed physiology of the neonates which leads to metabolic complications rather surgery related deaths. The accountability and regular monitoring of the associated factors and mortality is warranted to decrease the case fatality for such children. In addition, we also recommend that pregnant women more than 30 years of age should be counseled regarding the increased risk of birth defects, the significance of early screening for birth defects, and periconceptional folic acid supplementation. A coordinated multidisciplinary approach for prevention, management and rehabilitation of affected babies is required; which should include a team of neonatologists, radiologists, obstetricians, and pediatric surgeon.

Strengths and limitations of the study

The findings of the present study would be helpful in establishing the basis for database of prevalence rate of gastrointestinal malformations in the study area. Our study can act as a stepping zone for further larger studies to find out the prevalence and associated risk factors of GI malformations among neonates. This study has the potential to give valuable information to health system policymakers to use this information for the better management of such neonates in the advent of associated factors in the delivery like iron and folic acid supplementation and low birth weight child.

Our study had limitations as our study was a single hospital-based study. Secondly, autopsies were not performed in the study which may have subsumed the extra information. We recommend multi-centric studies to elaborate the data on the prevalence and associated risk factors for congenital GI malformations among the neonates.

CONCLUSION

The overall prevalence of GI birth defects was 16.3/10,000 births. Tracheoesophageal fistula was the commonest anomaly. Lack of periconceptional iron and folic acid supplementation, and baby

birth weight <2.5 kg were observed to have an independent, significant association with the occurrence of GI birth defects. The mortality rate among such children were high (48.78%). Thus, for a developing country as ours, it becomes essential to counsel the women for periconceptional iron and folic acid supplementation and manage low birth weight babies to better the fetal outcomes in such children.

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Table 1: Demographic and clinical profile of study patients with respect to controls

	Cases(n=41)	Control (n=82)	P-value
Mother age (years)			
<30	26 (63.41%)	66 (80.49%)	0.04
>30	15 (36.59%)	16 (19.51%)	
Father age (years)			
<30	25 (60.98%)	56 (68.29%)	0.42
>30	16 (39.02%)	26 (31.71%)	
Mother education			
Graduate	6 (14.63%)	17 (20.73%)	0.229
Prime- intermediate	15 (36.59%)	38 (46.34%)	
Illiterate	20 (48.78%)	27 (32.93%)	
Father education			
Graduate	7 (17.07%)	13 (15.85%)	0.263
Prime- intermediate	11 (26.83%)	34 (41.46%)	
Illiterate	23 (56.10%)	35 (42.68%)	
Socioeconomic status			
Upper	5 (12.20%)	14 (17.07%)	0.011

(LM+UM)	12 (29.27%)	43 (52.44%)	
Lower	24 (58.54%)	25 (30.49%)	
Birth order			
1 & 2	15 (36.59%)	38 (46.34%)	0.571
3 & 4	17 (41.46%)	30 (36.59%)	
5 & more	9 (21.95%)	14 (17.07%)	
consanguinity	4 (9.76%)	1 (1.22%)	0.042
Iron and folic acid supplementation	21 (51.22%)	60 (73.17%)	0.016
Gestational diabetes mellitus	8 (19.51%)	11(13.41%)	0.378
Pre-Eclampsia	3(7.32%)	4(4.88%)	0.685
Severe anemia (<5 g/dL)	8(19.55%)	10(12.20%)	0.279
TORCH	0(0.00%)	0(0.00%)	-
Tobacco	6(14.63%)	7(8.54%)	0.3
Smoking	7(17.07%)	8(9.76%)	0.242
Alcohol	2(4.88%)	1(1.22%)	0.257
Previous spontaneous abortion	9(21.95%)	10(12.20%)	0.158
Rubella	0(0.00%)	0(0.00%)	-
Previous still births	4(9.76%)	3(3.66%)	0.22

Febrile illness in first trimester	5(12.20%)	1(1.22%)	0.016

Table 2: Neonatal clinical profile of cases with respect to controls

	Study (n=41)	Control (n=82)	P-value
Non progress of labor	4(9.76%)	5(6.10%)	0.479
Cord complication	4(9.76%)	5(6.10%)	0.479
Obstructed labor	5(12.20%)	5(6.10%)	0.196
Use of Oxytocin for labor induction	20(48.78%)	40(48.78%)	1
Birth trauma	1(2.44%)	1(1.22%)	1
Gestational age of delivery (weeks)	15(36.59%)	22(26.83%)	0.266
Birth weight (kg)	14(34.15%)	9(10.98%)	0.002
Gender (3 children with ambiguous genitalia among cases excluded)			
Male	20 (48.78%)	51(62.20%)	0.09
Female	18(43.90%)	31(37.80%)	
Birth asphyxia	9(21.95%)	12(14.63%)	0.309
Hypoglycemia	3(7.32%)	3(3.66%)	0.399
Hypothermia	3(7.32%)	3(3.66%)	0.399
Respiratory distress	12(29.27%)	15(18.29%)	0.166
Sepsis	7(17.07%)	10(12.20%)	0.46
Hyperbilirubinemia	2(4.88%)	2(2.44%)	0.6
Surfactant use	7(8.54%)	2(4.88%)	0.716

Table 3: Multivariate analysis for the risk assessment of congenital GI malformations

	P-value	Odds ratio	95% C.I. for odds ratio	
			Lower	Upper
Mother age	0.454	1.799	0.387	8.363
Socioeconomic status				
0	0.057	1		
1	0.112	0.175	0.02	1.505
2	0.986	0.982	0.136	7.088
Consanguinity	0.561	22.249	0.001	775969
Iron and folic acid	0.024	5.465	1.251	23.885
Febrile illness	0.225	61.081	0.079	47176.1
Birth weight	0.027	6.688	1.247	35.877

Table 4: Outcome and cause of death among neonates with gastrointestinal birth defects.

Type of defects	**Death (n=20, 48.78%)**
Tracheoesophageal Fistula	8(40%)
Anal Atresia	5(25%)
Esophageal Atresia	2(10%)
Mesenteric cyst	2(10%)
omphalocele	1(5%)
Meconium cyst	1(5%)
Intestinal Atresia	1(5%)
Causes of death	
PREMATURITY	9 (45%)
SEPSIS	4 (20%)
ASPHYXIA	6 (30%)
SHOCK	1 (5%)

FIGURES

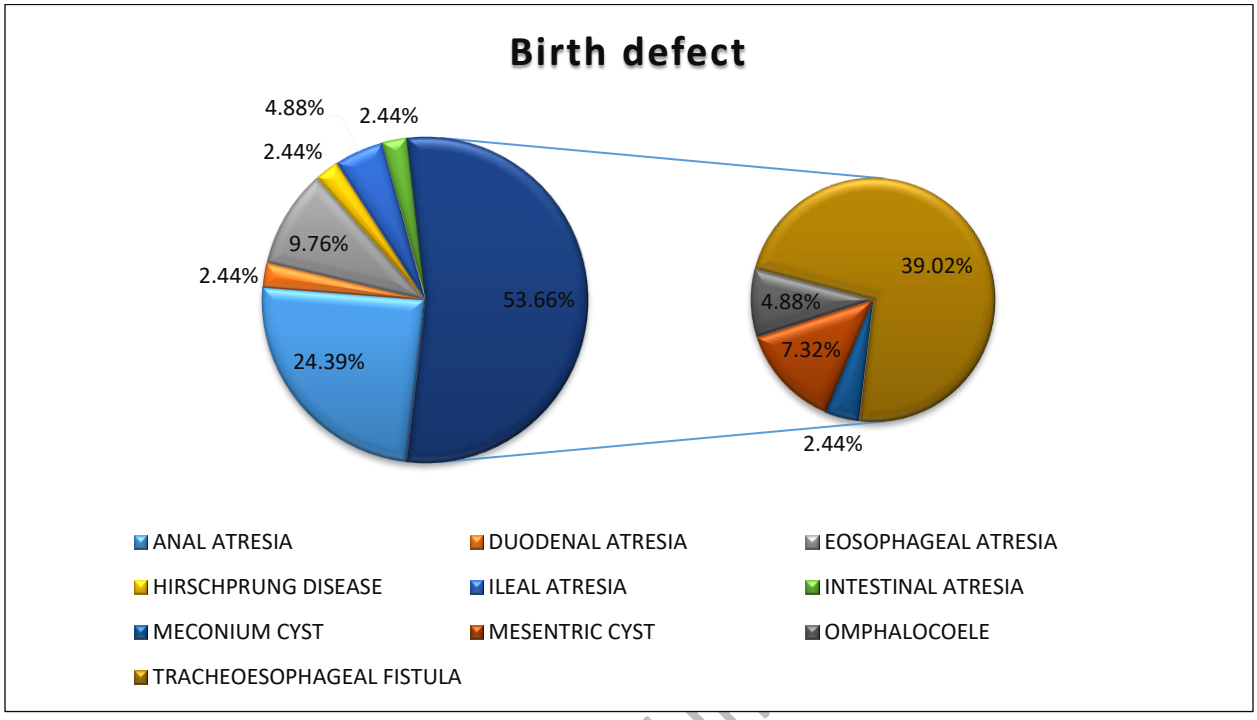

Figure 1: Spectrum of congenital gastrointestinal birth defects.

Figure legends

Figure 2: Neonates with absent anal opening.

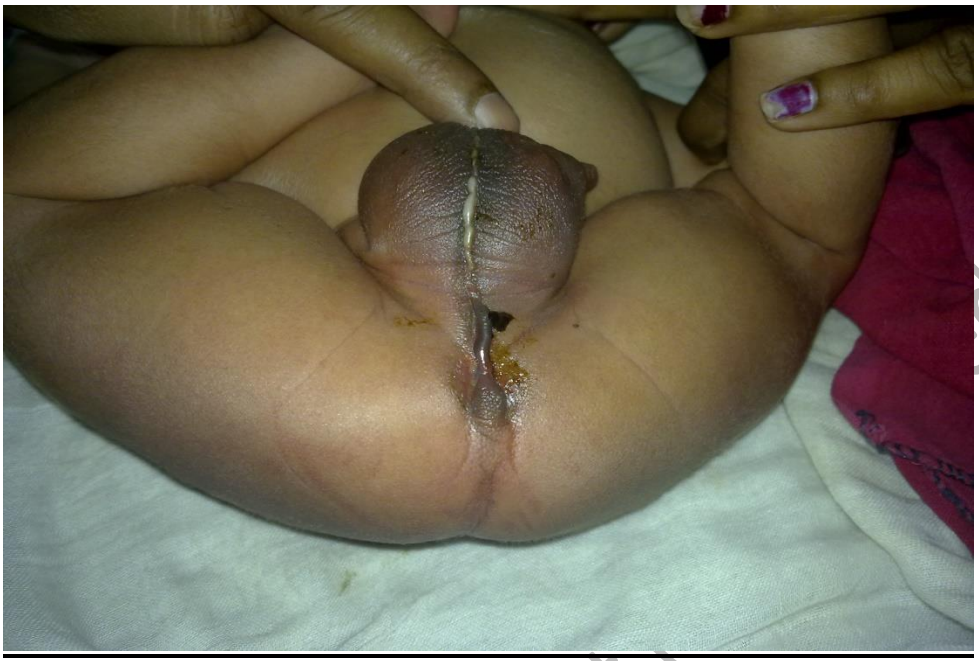

Figure 3: Intraoperative picture of neonate with ileal atresia.

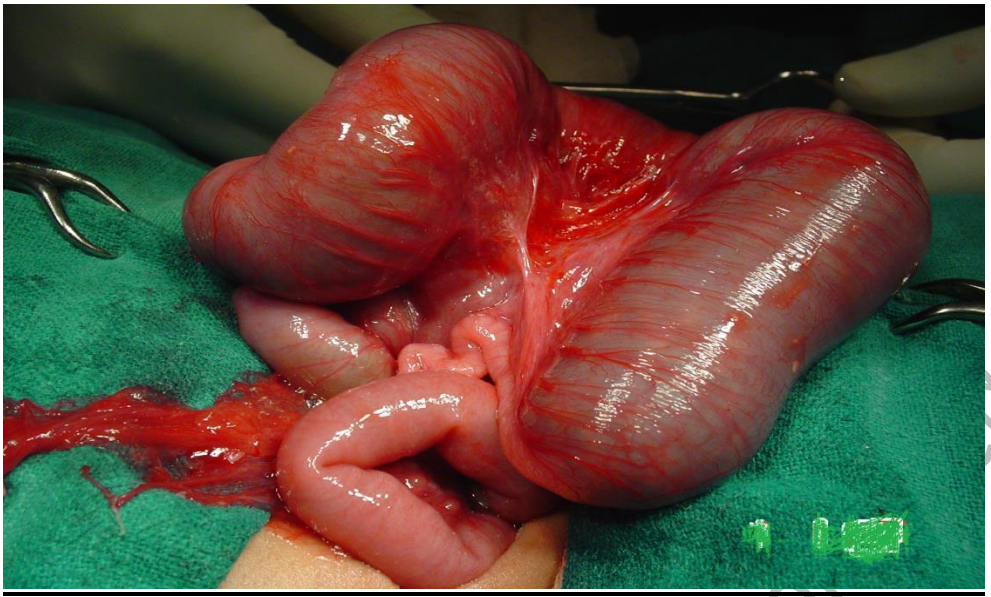

Figure 4: Intraoperative picture of neonate with Hirschsprung's disease.

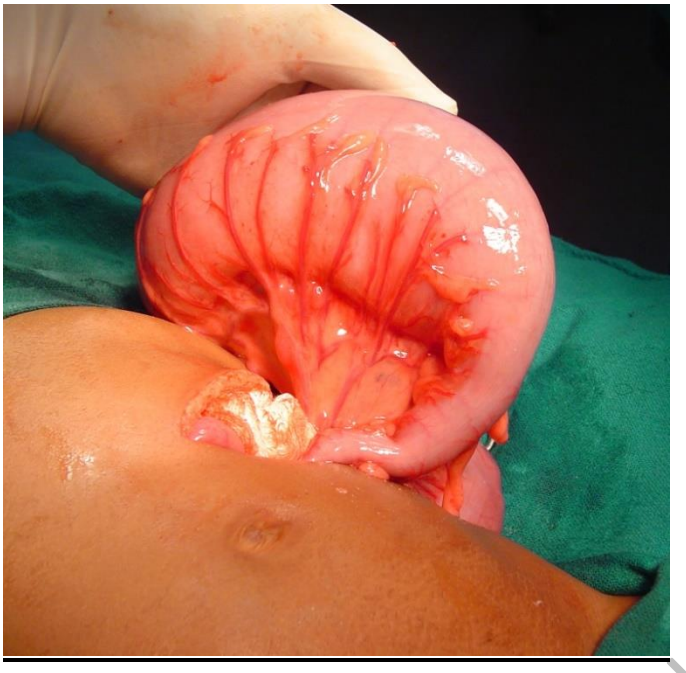

Figure 5: Neonate with omphalocele.