

Retrospective Cohort Study

Perinatal risk factors in newborns with gastrointestinal perforation

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Abstract**AIM**

To investigate correlation of perinatal risk factors in newborns with gastrointestinal perforation (GIP).

METHODS

Single-center retrospective cohort study was conducted between January 1990 and December 2012. Medical records on all newborns with GIP were reviewed ($n = 35$). Surgical records and histopathologic examination of all perforated intestine samples were also reviewed.

RESULTS

The most common cause of GIP was necrotizing enterocolitis (51.4%). The most common site of perforation was large intestine. Mortality rate was 31%. Infants with GIP more frequently had very low birth weight (< 1500 g), especially birth weight below 10th percentile

according to gestational age. Ponderal index was not differing between infants with GIP and control subjects. In infants with GIP anemia was more frequently found than in control group.

CONCLUSION

GIP in newborns is mostly disease of infants with birth weight below 10th percentile according to gestational age. GIP occurs more often in infants with anemia.

Key words: Gastrointestinal perforation; Newborn; Necrotizing enterocolitis; Ponderal index

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Core tip: Gastrointestinal perforation (GIP) in newborns is a severe and life threatening condition associated with high mortality. GIP usually occurs in prematures with necrotizing enterocolitis. GIP in newborns is mostly disease of infants with birth weight below 10th percentile according to gestational age. GIP occurs more often in infants with anemia. The most common site of perforation was large intestine Mortality rate was 31%. Infants with GIP more frequently had very low birth weight (< 1500 g), especially birth weight below 10th percentile according to gestational age.

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INTRODUCTION

Gastrointestinal perforation (GIP) in newborns is a severe and life threatening condition associated with high mortality of 17%-60%^[1-4]. GIP usually occurs in prematures with necrotizing enterocolitis^[1-11]. The major causes of GIP are low gestational age, low birth weight, feeding with adapted formulas instead of breastfeeding, early and fast increase in meal volume, bacterial colonization and intestinal ischemia^[5,6].

Although most frequently observed in prematures, necrotizing enterocolitis also occurs in term newborns. In the latter, it is clearly associated with perinatal factors, *i.e.*, intrauterine drug exposure, in particular cocaine, in mothers drug addicts; intestinal anomalies (aganglionosis or atresia); congenital heart disease; sepsis; polycythemia; asphyxia; respiratory distress syndrome; presence of umbilical catheter; and exsanguinotransfusion. These factors can affect blood flow through the mesenteric blood vessels of the newborn and lead to hypoperfusion and consequential intestinal hypoxia^[7,8]. In prematures, necrotizing enterocolitis mostly develops in the second week of life, whereas in

term newborns it usually occurs earlier, *i.e.*, in the first week of life^[7,9,10].

Spontaneous intestinal perforation is a specific clinical entity that should be differentiated from necrotizing enterocolitis. Spontaneous intestinal perforation is a multifactorial disease of very low birth weight infants (< 1000 g), which is not related to the mode of feeding. Local intestinal ischemia is considered to be the major risk factor for the occurrence of spontaneous intestinal perforation. In addition, the following risk factors have hitherto been associated with spontaneous intestinal perforation: Neonatal hypotension, umbilical arterial catheter, dehydration, indomethacin and steroids^[11,12]. The less frequent causes of perforation include intestinal obstruction, idiopathic gastric perforation and iatrogenic perforation^[12-15].

To the best of our knowledge, ponderal index has not yet been assessed relative to the occurrence of GIP. Studies suggest low ponderal index or lean neonates to have been exposed to hypoxic-ischemic events during gestation, which then results in increased perinatal mortality and morbidity, in particular a higher prevalence of perinatal infection^[16].

The aim of the study was to assess the correlation of ponderal index and other risk factors with GIP; the prevalence of GIP (according to causative disorder and site of perforation); and GIP mortality (according to causative disorder and site of perforation).

MATERIALS AND METHODS

Medical records of infants born at the niversity Hospital of Split from January 1, 1990 till December 31, 2012 were reviewed. There were 103852 live births, 5193 (13%) of them were prematures. Study group included 35 newborns (19 males, 16 females) with confirmed GIP, gestational age 25-40 wk. Control group comprised of all newborns admitted immediately before or immediately after study group subjects, matched by no more than plus or minus one gestational week ($n = 76$), free from neonatal intestinal perforation. Study group was compared to control group matched by gestational age (case-control study).

The following perinatal risk factors were observed: maternal age and parity; maternal edema, proteinuria, hypertension (EPH) gestosis-preeclampsia; prolonged amniotic sac rupture; fetus presentation; method of delivery termination; neonate sex; Apgar score at 1 min; birth weight (BW); birth length (BL); and ponderal index.

Considering particular population specificities for birth weight determination according to gestational age, sex and maternal parity, percentile curves developed for our population at the Department of Gynecology and Obstetrics, University Hospital of Split in 2005 were used^[17,18]. Ponderal index (PI) was determined for each study subject using the following formula: $PI (g/cm^3) = 100 \times BW (g)/BL (cm^3)$.

The following postnatal risk factors were also ob-

Table 1 Perinatal risk factors n (%)

Perinatal risk factor	GIP n = 35	Control group n = 76
Maternal age (years, min-max)	26 (18-44)	28 (18-41)
Maternal parity		
Primipara	20 (58.8)	35 (46.7)
Secundipara	10 (29.4)	27 (36.0)
Multipara	4 (11.7)	13 (17.4)
EPH gestosis-preeclampsia	5 (15.2)	2 (2.6)
Prolonged membrane rupture	5 (15.2)	13 (17.1)
Breech presentation	5 (15.2)	7 (9.2)
Cesarean section	11 (32.4)	17 (22.4)
Sex (male)	19 (54.3)	38 (50.0)
Apgar score at 1 min		
0-3 (severe hypoxia)	2 (5.9)	1 (1.3)
4-7 (moderate hypoxia)	13 (38.2)	23 (30.3)
8-10 (normal vitality)	19 (55.9)	52 (68.4)
Birth weight (BW)		
< 1500 g (very low BW)	8 (22.9)	7 (9.2) ^a
1500-2499 g (low BW)	4 (11.4)	24 (31.6)
≥ 2500 g (normal BW)	23 (65.7)	45 (59.2)
Birth length (cm)	47 (34-53)	48 (32-55)

^a*P* < 0.05 (χ^2 -test). GIP: Gastrointestinal perforation; EPH gestosis: Edema, proteinuria, hypertension (EPH) gestosis.

served: Respiratory distress syndrome; presence of central venous umbilical catheter; sepsis; polycythemia; and anemia. GIP was demonstrated radiologically by visualizing free air intraperitoneally.

The risk factors for GIP were divided into perinatal and postnatal variables. Ponderal index was analyzed by *t* test; qualitative variables and maternal parity were analyzed by use of χ^2 test; and maternal age was analyzed by Mann-Whitney *U* test. Epidemiological measures of correlation or measures of relations, *i.e.*, odds ratio, was employed on assessing the power of statistical relationship between a particular risk factor and the disease (GIP) and on drawing conclusions on the potential causative relationship. An approximate risk for the occurrence of GIP was obtained by calculating the probability of a particular risk factor exposure in study subjects and control group. Then the 95%CI was calculated. All data were interpreted at the level of significance of *P* < 0.05.

The prevalence of GIP was calculated using the following formulas: (1) number of children with GIP/total number of live births × 1000; (2) number of children with GIP/number of children treated at clinical department × 1000; and (3) number of prematures with GIP/number of prematures × 1000.

Mortality following GIP shows the ratio of newborns with GIP that died during the neonatal period (28 d) and total number of newborns with GIP. Neonatal mortality due to GIP was determined according to the cause and site of GIP.

RESULTS

During the 22-year study period, there were 103852 live births at the University Hospital of Split, and 5193 of

Table 2 Number (%) of newborns according to ponderal index mean value: arithmetic mean ± SD, birth weight and birth length percentiles

Variable	GIP n = 35	Control group n = 76
PI, mean ± SD, g/cm ³	2.53 ± 0.3	2.52 ± 0.3
BW, %		
SGA (< 10 th percentile)	31.4	13.2 ^a
AGA (10 th -90 th percentile)	51.4	77.6
LGA (> 90 th percentile)	17.1	9.2
BL, %		
< 10 th percentile	18.2	9.2
10 th -90 th percentile	66.7	84.2
> 90 th percentile	15.2	6.6

^a*P* < 0.05 (χ^2 -test). SGA: Small for gestational age; AGA: Appropriate for gestational age; LGA: Large for gestational age.

them were preterm infants. During the study period 35 patients with GIP were identified, yielding a 0.34‰ GIP incidence and 3.66‰ incidence of prematures in overall live births. The matched control group consisted of 76 infants. The study and control infants were matched for gestational age.

Perinatal risk factors of 35 infants with GIP compared with control subjects are shown in Table 1. There were trends toward a higher incidence of male infants in the study group compared with control subjects. There were no differences between groups in prolonged rupture of membranes, method of delivery, presentation at delivery and Apgar score. Mothers were young in both groups (mean age 26 and 28 years in study group and control group, respectively) and tended to be primiparae. Mothers of infants suffering from GIP showed a trend toward increased pregnancy-induced hypertension, but the number of mothers with pregnancy-induced hypertension was too small for statistical analysis.

The mean values of ponderal index, and number and percentage of newborns according to birth weight and birth length percentiles *per* gestational age are shown in Table 2.

Infants suffering from GIP were significantly more likely to have birth weight less than 1500 g (22.9% vs 9.2%, *P* < 0.05) and birth weight below 10th percentile according to gestational age (31.4% vs 13.2%, *P* < 0.05). There was no statistically significant difference between groups in the mean value of ponderal index.

Table 3 shows postnatal risk factors in the both groups. More infants in the study group had anemia (25.7% vs 3.9%), yielding a statistically significant difference (*P* < 0.05).

Additional statistical tests of logistic regression and multiple logistic regressions were employed to confirm birth weight less than 10th percentile and anemia as risk factors for GIP. The results obtained by logistic regression are shown in Table 4.

The likelihood of GIP development was threefold greater in the group of hypotrophic for gestational age infants as compared with the group of eutrophic and

Table 3 Postnatal risk factors *n* (%)

Variable	GIP (<i>n</i> = 35)	Control group (<i>n</i> = 76)
RDS	13 (38.2)	29 (38.1)
RDS + mechanical ventilation	12 (35.3)	14 (18.4)
CVUC	5 (14.7)	9 (11.8)
Positive blood culture	4 (11.8)	11 (14.5)
Polycythemia ¹	5 (14.3)	6 (7.9)
Anemia ²	9 (25.7)	3 (3.9) ^a

¹Polycythemia was defined as hematocrit > 0.60; ²Anemia was defined as hemoglobin level < 140 g/L in venous blood; ^a*P* < 0.05 (χ^2 -test). RDS: Respiratory distress syndrome; CVUC: Central venous umbilical catheter.

hypertrophic for gestational age infants, with 95%CI. The probability of GIP was 8.4-fold greater in infants suffering from anemia as compared to those without anemia, with 95%CI. Multiple logistic regression confirmed both risk factors, *i.e.*, birth weight below 10th percentile for gestational age (hypotrophy) and anemia to be statistically significant for GIP development (Table 5).

The infants suffering from GIP were diagnosed mostly during the first 7 d (60%), and the age at diagnosis ranged from 1 to 25 d of life. Enteral feeding was started in 57.1% of case patients and in all matched control subjects.

All case patients underwent exploratory laparotomy, except one patient who underwent thoracotomy because of esophageal perforation. Stoma was established in 80% of patients. Direct suture was performed in five infants. The most common location of perforation was large intestine (45.7%), followed by ileum (20.0%), jejunum (11.4%), multiple perforation of both small and large intestine (11.4%), duodenum (5.7%) and esophagus in one patient (2.9%).

The causes of perforation were divided into four categories according to pathological and intraoperative reports. Necrotizing enterocolitis was the predominant cause of perforation (*n* = 18; 51.4%), followed by intestinal obstruction (22.9%), meconium plug (14.3%), spontaneous perforation (8.6%) and iatrogenic perforation of the esophagus (2.8%).

The overall mortality rate was 31.4% (during the neonatal period of 28 d). In the early study period (1990–2000), seven of 17 (41.2%) infants with GIP died, but later a considerably lower mortality rate was recorded, *i.e.*, four of 18 (22.2%) infants with GIP died in the 2001–2011 period. Most of these deaths were due to perforated necrotizing enterocolitis (63.6%), and the most common site among the expired was small bowel (36.4%).

DISCUSSION

According to available data, the prevalence of GIP is low. There are few studies addressing and assessing all causes of GIP and their interplay leading to this severe disorder. Asabe *et al.*^[3] found 34 cases of GIP during a

Table 4 Logistic regression results *n* (%)

Risk factor	GIP <i>n</i> = 35	Control group <i>n</i> = 76	OR (95%CI)
Hypotrophy	11 (31.4)	10 (13.2)	3 (1.14–8) ^a
Eutrophy and hypertrophy	24 (68.5)	66 (86.8)	
With anemia	9 (25.7)	3 (3.9)	8.4 (2.1–33) ^a
Without anemia	26 (74.3)	73 (96.1)	

^a*P* < 0.05.

Table 5 Multiple logistic regression results

Risk factor	OR	95%CI
Birth weight < 10 th percentile for gestational age (hypotrophy)	4.01 ^a	1.45–11.2
Anemia	10.9 ^a	2.6–45

^a*P* < 0.05.

30-year period^[3]. Khan *et al.*^[19] report on 89 cases of GIP that accounted for 16.5% of all newborns admitted to the Department of Pediatric Surgery. In their multi-center study, Calisti *et al.*^[4] recorded 85 cases of neonatal GIP in the region of Lazio, Italy, during a ten-year period. The authors estimate the prevalence of GIP in newborns treated at neonatal intensive care units to range between 1% and 3%.

In our study, necrotizing enterocolitis was the most common causative entity leading to GIP (51.4%), followed by intestinal obstruction (22.9%). This is consistent with literature data, where necrotizing enterocolitis is also reported as the most common cause of GIP^[1–4,19,20]. A low prevalence of necrotizing enterocolitis (0.2%) has only rarely been reported^[21]. According to the literature, spontaneous or idiopathic intestinal perforation has been postulated as the second leading cause of GIP, and less frequently meconium peritonitis^[2–4,14]. Gastrointestinal obstruction as the cause of GIP is more common in term newborns. In our study, the rate of intestinal obstruction was high, as expected considering the high proportion of term newborns.

In our study, the most common site of GIP was large intestine (45.7%), whereas small intestine perforation was recorded in 37.1% of cases. In the literature, the most common site of GIP is small intestine, in particular distal ileum^[22–24]. Colon perforation is considered a rare event; however, in a recent study, Sakellaris *et al.*^[25] found colon perforation in 18.5% of newborns. According to literature reports, colon perforation is more common in high birth weight newborns (> 2500 g), which predominated in our study sample (65.7%)^[26].

Considering maternal characteristics, we found no statistically significant between-group difference in maternal age and parity. However, there are literature reports on the newborns with GIP to be born to young mothers (22 to 28 years on average) with a lower number of previous deliveries. In our study, mothers in both case and control groups were young (26 and 28 years on average, respectively) and most of mothers in

both groups were primiparae^[22,27].

In all previous studies, GIP was more common among male newborns, with a rate ranging from 59% to 89% of cases^[5,6,19,22,24,27]. In our study, the rate of male newborns with GIP was 54.3%.

The group of newborns with GIP included a significantly higher proportion (22.9%) of very low birth weight (< 1500 g) infants. Literature reports reveal GIP to occur more frequently in very low birth weight newborns^[4-6,10,20,22-24]. In our study, the group of newborns with GIP also included a high proportion of hypotrophic infants (31.4%). Thus, the likelihood of GIP was threefold greater in the group of hypotrophic infants as compared to other study subjects.

According to literature reports, intrauterine growth retardation (IUGR) leads to hypotrophy but has been rarely tackled specifically as a risk factor for GIP. Some studies dealing with IUGR failed to confirm its association with necrotizing enterocolitis or spontaneous intestinal perforation, whereas others compared case and control groups matched by gestational age and found IUGR to be a potential clinical risk factor for necrotizing enterocolitis as the most common cause of GIP^[22,27,28]. Recently, however, there are ever more studies observing IUGR by fetal and neonatal blood flow Doppler monitoring. These studies recorded a higher prevalence of necrotizing enterocolitis in infants with impaired umbilical artery or superior mesenteric artery blood flow^[29].

In our study, anemia was the major risk factor for GIP. The likelihood of GIP was 8.4-fold greater in neonates with anemia as compared with those without anemia. In the literature, anemia is sporadically associated with individual cases of GIP. Pelizzo *et al.*^[30] describe intrauterine anemia with consequential fetal hydrops and signs of meconium peritonitis caused by distal ileum perforation. On the other hand, others report on anemia detected by laboratory testing, along with thrombocytopenia and elevated C-reactive protein, in infants with GIP caused by necrotizing enterocolitis^[31,32].

Recent studies confirm the association of deplasmated red blood cell transfusion for anemia and necrotizing enterocolitis^[33-35]. Other studies assessing the effect of administering erythropoietin and iron agents for anemia found a lower incidence of necrotizing enterocolitis^[33]. In our study, anemia was an important risk factor for GIP; the more so, it also proved important for the prognosis after GIP. In more than half of the study subjects (54.5%) that died from GIP, anemia had been diagnosed even before the clinical signs of the diseases that caused GIP. In their recent study, Bracho-Blanchet *et al.*^[35] also identified anemia as a prognostic factor associated with mortality in newborns with necrotizing enterocolitis.

In our study, 57.1% of infants were fed per oral, as a rule with adapted formulas, until GIP onset. In necrotizing enterocolitis, perforation generally occurs upon switching to oral feeding^[6]. It is considered that

there is no causative relationship between oral feeding and spontaneous intestinal perforation. Ragouilliaux *et al.*^[22] report on enteral nutrition to have been introduced before the onset of GIP in 69% of newborns. As necrotizing enterocolitis was the most common cause of GIP in our study, the proportion of newborns on oral feeding before GIP occurrence was high, as expected.

Our study results showed that 31.4% of the newborns died from GIP. However, in the last 11 study years, the mortality was nearly half that recorded in the first 11 study years (22% vs 41%). Search of the literature yielded a mortality following GIP to range from 17% to 60%^[2,4,19]. A 31.6% mortality rate has been reported for newborns with GIP in Japan in 2003. However, the same authors report on 50% mortality among 34 newborns during a 30-year period^[3]. These figures correspond to the trend observed in our study on the mortality decline in the past decades. Advances in operative techniques, anesthesiology procedures and intensive care measures probably have contributed to the GIP mortality decline.

In our study, necrotizing enterocolitis was the most common cause of GIP in deceased infants (63.6%). Other studies also report on the highest mortality following GIP to be associated with necrotizing enterocolitis^[2,19,25]. Although colon was the most frequent site of perforation, small intestine perforation was found in the majority of deceased neonates (36.4%). According to literature reports, the small intestine perforation mortality is also higher than colon perforation mortality^[26]. Exploratory laparotomy is considered as the surgical method of choice in newborns with intestinal perforation, in particular the one caused by necrotizing enterocolitis. Most studies report on laparotomy with intestinal segment resection to be performed in all or nearly all infants with GIP^[4,25]. Primary management with peritoneal drainage instead of laparotomy is less frequently described^[19]. However, definite recommendations in favor of either laparotomy or peritoneal drainage are still lacking. In our study, percutaneous stoma after intestinal segment resection was established in 80% of newborns with GIP. According to literature data, stoma formation following resection is associated with better survival than primary anastomosis after resection^[4,35].

In conclusion, Based on our study results, newborns with anemia and hypotrophic newborns, along with all very low birth weight newborns should be considered at high risk of GIP. The pattern of fetal growth (neonatal proportions, *i.e.*, birth weight to birth length ratio) as determined by ponderal index is not a risk factor for GIP development.

COMMENTS

Background

Gastrointestinal perforation (GIP) in newborns is mostly associated with necrotizing enterocolitis. Congenital anomalies with obstruction can also be the cause of GIP. There are little informations in literature about perinatal risk factors,

and ponderal index in infants with GIP has not been reported.

Research frontiers

A single institutional retrospective study of patients undergoing surgery because of GIP from 1990 to 2012 was performed.

Innovations and breakthroughs

GIP in newborns is mostly disease of infants with birth weight below 10th percentile according to gestational age. GIP occurs more often in infants with anemia.

Applications

Newborns with very low birth weight and anemia should be monitored carefully for GIP.

Terminology

Ponderal Index is a measure of leanness of a person calculated as a relationship between mass and height.

Peer-review

The manuscript is well written and important in its field.

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