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CQ 3

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Rees 2010	Peritoneal drainage does not stabilize extremely low birth weight infants with perforated bowel: data from the NET trial
Sola 2010	Peritoneal drainage versus laparotomy for necrotizing enterocolitis and intestinal perforation: a meta-analysis.

Ⅱ資料

1. 疾患概要
2. 研究業績
   （ア）学会発表
   （イ）論文発表
3. 発表論文 PDF
4. ガイドライン外部評価結果
5. 研究者名簿

１．疾患概要

消化器系疾患分野

低出生体重児の消化管機能障害

1. 概要 近年の低出生体重児の出生数は増加傾向にある。周産期医療の進歩により低出生体重児の救命率は 改善傾向にあるが、その一方で種々の臓器の未熟性に起因する合併症が周産期医療における大きな 課題となってきた。なかでも壊死性腸炎、特発性腸穿孔、胎便関連性腸閉塞、胎便性腹膜炎といっ た消化管機能障害は、低出生体重児によくみられる重篤な消化管合併症であり、生命予後だけでな く長期予後を左右する重要な因子となっている。

2. 疫学 日本小児外科学会のアンケート(全国 NICU263 施設を対象、回答率 47%)では、2003-2007 年の5 年間で超低出生体重児 8282 例中消化管穿孔発生症は 444 例/5 年間(発生率 5.36%)という報告が ある。消化管機能障害の多くが超低出生体重児に発生することやアンケートの回答率などを考慮す れば、本邦で年間 200 例前後の発生があると考えられる。

3. 原因 壊死性腸炎、特発性腸穿孔、胎便関連性腸閉塞、胎便性腹膜炎のほとんどは極低出生体重児に発生 することから、腸管の未熟性を背景として、感染やストレスといった種々の周産期因子が関与して 発症すると考えられている。しかし、個々の疾患の危険因子は明らかではなく、病態や病因も不明 である。

4. 症状 ほとんどの場合、生後数日から生後 1-2 週間の新生児期に発症する。腸炎症状で発症する場合、腸 閉塞症状で発症する場合、突然の腸穿孔で発症する場合など様々である。一旦腸穿孔を起こせば腹 膜炎を併発して敗血症性ショックに陥り、全身状態は急速に悪化する。

5. 合併症 周産期管理の進歩とともに、本疾患の迅速な診断・治療により救命率は上昇してきた。しかし長期 フォローに基づく最近の報告では、救命例の半数以上に精神運動発達遅延がみられることが明らか になってきた。そのため個々の疾患の周産期背景因子の解析から、その発症機序を明らかにして予 防法を確立することが、低出生体重児全体の予後改善に不可欠であると考えられる。

6. 治療法 腸炎症状や腸閉塞症状が先行する場合は、絶食、抗生剤投与といった保存的治療が試みられる。保 存的治療が有効でなく全身状態が悪化する場合や腸穿孔を併発した場合は手術適応となる。腸瘻造 設術が一般的だが、全身状態が良ければ穿孔部の縫合閉鎖や腸吻合も行われる。

7. 研究班　　低出生体重児消化管機能障害の疾患概念確立にむけた疫学調査研究
（　H26-難治等（難）-一般-010　）

２．研究業績

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Risk factors for surgical intestinal complications in very low birth weight infants: A multicenter case-control study

Hiroomi Okuyama

9th Annual Conference of Cambodian Society of Pediatric Surgery November 19, 2015 Phnom Penh, Cambodia

低出生体重児消化管機能障害における腸瘻閉鎖時期と術後経過

望月響子、奥山宏臣、早川昌弘、漆原直人、横井暁子、白石淳、藤永英志、大橋研介、永田公二、天江新太郎、古川泰三、矢内俊裕

1)神奈川県立こども医療センター　外科

2)低出生体重児消化管機能障害の疾患概念確立に向けた疫学調査研究班

第51回　日本周産期新生児医学会、福岡　2015.7.12-12 一般演題

極低出生体重児における MRI についての検討　NEC、FIP との差異

江角 元史郎, 永田 公二, 落合 正行, 田口 智章, 早川 昌弘, 漆原 直人, 望月 響子, 横井 暁子, 白石 淳, 藤永 英志, 大橋 研介, 大藤 さとこ, 天江 新太郎, 古川 泰三, 矢内 俊裕, 田附 裕子, 奥山 宏臣

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SGA 児の長期予後改善にむけた周産期管理

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奥山宏臣＊

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＊大阪大学大学院医学系研究科外科学講座小児成育外科学

第51回　日本周産期新生児医学会、福岡　2015.7.12-12 シンポジウム

消化管機能障害を有する低出生体重児の短腸症候群に対する戦略

横井暁子

低出生体重児消化管機能障害の疾患概念確立にむけた疫学調査研究班
兵庫県立こども病院　外科
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小児外科におけるナショナルスタディと診断治療ガイドラインの構築
極低出生体重児の消化管機能障害に関する周産期背景因子ならびに予後の検討
奥山 宏臣, 大藤 さとこ, 早川 昌弘, 漆原 直人, 横井 暁子, 白石 淳, 望月 響子, 藤永 英志, 大橋 研介, 永田 公二, 天江 新太郎, 古川 泰三, 矢内 俊裕, 田附 裕子, 皆川 京子
低出生体重児消化管機能障害の疾患概念確立に向けた疫学調査研究班
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第51回日本周産期新生児医学会学術集会シンポジウム2次抄録
SGA 児の長期予後改善にむけた周産期管理
SGA 児の消化管機能障害ー胎便関連性腸閉塞ー
奥山宏臣＊
低出生体重児消化管機能障害の疾患概念確立にむけた疫学調査研究班
＊大阪大学大学院医学系研究科外科学講座小児成育外科学
（日本周産期新生児学会雑誌　in press）

「改訂第2版　症例から学ぶ周産期診療ワークブック」
Ⅲ新生児編　10. 消化器　1）新生児壊死性腸炎
和田和子＊、奥山宏臣＊＊
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（メジカルビュー社　in press）

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Original Article

Risk factors for surgical intestinal disorders in VLBW infants: Case–control study

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Abstract ***Background:*** Very low-birthweight (VLBW) infants (VLBWI) are at increased risk for surgical intestinal disorders including necrotizing enterocolitis (NEC), focal intestinal perforation (FIP) and meconium-related ileus (MRI). The aim of this study was to identify disease-specific risk factors for surgical intestinal disorders in VLBWI.

Methods: A retrospective multicenter case–control study was conducted at 11 institutes. We reviewed VLBWI who underwent laparotomy for intestinal disorders including perforation and intractable bowel obstruction. The surgical disorders were classified into four categories (NEC, FIP, MRI, others) based on the macroscopic findings at operation. In order to identify risk factors, two matched controls for each subject were chosen based on gestational age and birthweight. OR and 95%CI were calculated using a conditional logistic regression model and a multivariate model.

Results: A total of 150 cases (NEC, n = 44; FIP, n = 47; MRI, n = 42; others, n = 17) and 293 controls were identified. The cases and controls were similar in terms of gestational age and birthweight (cases/controls, 26.7 ± 2.5/26.5 ± 2.6 weeks; 790 ± 256/795 ± 257 g). On multivariate modeling, disease-specific risk factors were as follows: female (OR, 0.23; 95% CI: 0.06–0.89), respiratory distress syndrome (OR, 35.7; 95%CI: 2.48–514) and patent ductus arteriosus (OR, 10.9; 95% CI: 1.51–79.3) for NEC; outborn delivery (OR, 5.47; 95%CI: 1.48–20.2) for FIP; and twin pregnancy (OR, 4.25; 95%CI: 1.06–17.1), PROM (OR, 6.85; 95%CI: 1.33–35.4) and maternal steroid (OR, 0.23; 95%CI: 0.07–0.79) for MRI.

Conclusions: Different risk factors were identified for NEC, FIP and MRI, suggesting that each disease has a different etiology, and that different strategies are required to prevent these diseases.

Key words case–control study, focal intestinal perforation, meconium-related ileus, necrotizing enterocolitis, very low-birthweight.

Despite recent advancements in neonatal care, surgical intestinal disorders remain the most devastating gastrointestinal diseases in very low-birthweight (VLBW) infants. In addition to being associated with high mortality rate, survivors are left with significant long-term morbidity.[1,2] Therefore, prevention of the intestinal complications is required to improve the overall outcome of VLBW infants. There are several diseases that cause surgical intestinal disorders without mechanical obstruction in VLBW infants, including necrotizing enterocolitis (NEC), focal intestinal perforation (FIP) and meconium-related ileus (MRI).

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Necrotizing enterocolitis is one of the most common and serious intestinal disorders involving systemic inflammatory responses in VLBW infants. Although previous numerous studies showed multiple risk factors for NEC including immaturity of the intestine, formula feeding and microbial colonization, the case fatality rate with surgical intervention remains as high as 50%, and is highest for the smallest infants.[3,4] Therefore, risk factors for surgical NEC in VLBW infants should be analyzed separately from medical and term NEC.

Focal intestinal perforation, characterized by the presence of focal intestinal perforation with no or minimal adjacent bowel inflammation, has become an increasingly common intestinal disorder in VLBW infants. While the pathogenesis of FIP is poorly understood, recent research has confirmed FIP to be a separate disease entity from NEC based on pathological findings[5] and genome expression profiles.[6]

To date, several types of meconium obstruction in the absence of cystic fibrosis in VLBW infants have been described. In 1999, Kubota *et al.* proposed the term "meconium-related ileus" as a single pathophysiologic entity with a wide spectrum of symptoms

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caused by meconium obstruction in the absence of cystic fibrosis.[7] Although MRI responds to conservative management in most cases, delayed identification leads to increased risk of intestinal perforation. Thus, it is important to identify risk factors for the severe type of MRI requiring surgery.

Prematurity and low birthweight are the consistently recorded risk factors for the development of these diseases, but risk factors for surgical intestinal disorders in VLBW infants have not been well described. Because macroscopic findings of affected intestines are important indicators in the definitive diagnosis of NEC, FIP and MRI, the diseases should be categorized based on the operative findings in order to analyze the etiology of each disease. Therefore, the aim of this study was to identify disease-specific risk factors associated with surgical intestinal disorders in VLBW infants based on definitive diagnosis at surgery.

Methods

A retrospective multicenter case–control study was conducted at 11 institutes in Japan. We reviewed VLBW infants who underwent laparotomy for intestinal disorders including perforation and intractable ileus between January 2003 and December 2012. In order to detect risk factors other than prematurity and low birthweight, two matched controls for every subject were chosen based on gestational age (±1 week) and birthweight (±50 g). The prenatal and preoperative data for each infant and their mothers were collected from the medical records. The data included disease category, gestational age, birthweight, maternal factors (i.e. outborn delivery, mode of delivery, multiple pregnancies, placental abruption, diabetes, pregnancy hypertension, maternal smoking, chorioamnionitis, premature rupture of membranes [PROM], maternal steroid treatment) and patient factors (i.e. sex, Apgar score, small for gestational age/appropriate for gestational age, umbilical artery catheter use, respiratory distress syndrome [RDS], surfactant treatment, steroid treatment, symptomatic patent ductus arteriosus [PDA], transfusions, breast/formula feeding, and probiotics treatment).

Definition of surgical intestinal disorders

The surgical intestinal disorders observed in the VLBW infants were classified into the following four categories based on the operative findings.

Necrotizing enterocolitis is a condition of diffuse or segmental necrotic injury to the mucosal and submucosal layers of the bowel with systemic inflammatory responses. FIP is defined as an isolated perforation of the bowel with no obvious inflammation in the adjacent site or the rest of the bowel.[6] MRI is characterized by functional ileus due to impaired meconium excretion not associated with cystic fibrosis and is usually diagnosed when laparotomy for intractable ileus indicates a microcolon or small-sized colon extending to the distal ileum with a dilated proximal ileum filled with sticky meconium.[7] The classification "others" was assigned to conditions not belonging to any of the aforedescribed three categories.

Statistical analysis

Comparison of subject characteristics between the cases and controls was done using chi-squared tests for categorical variables and Wilcoxon rank–sum test for continuous variables. Summarized data for continuous variables are presented as mean ± SD. A conditional logistic regression model was used to calculate OR and 95% CI for surgical intestinal disorders. The trend of association was assessed by assigning ordinal scores to each level within the category. The following explanatory variables were used to construct the multivariate models: (i) crude OR on univariate analysis; (ii) an initial multivariate model involving variables with statistically significant crude OR for both surgical intestinal disorders and at least one disease; and (iii) a final multivariate model excluding variables with no association with the diseases in the initial model.

In order to examine disease-specific risk factors, a stratified analysis was conducted according to each disease (e.g. NEC, FIP and MRI).

All tests were two-sided, and $P < 0.05$ was regarded as statistically significant. All analyses were performed using the SAS version 9.1.3 (SAS Institute, Cary, NC, USA).

Ethics

This study was performed after being approved by the ethics committee of Hyogo College of Medicine (approval number: 1483) and the independent ethics committees of 10 other participating institutions: National Center for Child Health and Development, Kyushu University, Nagoya University Hospital, Japanese Red Cross Nagoya Daiichi Hospital, Anjyo-kousei Hospital, Osaka Medical Center and Research Institute for Maternal and Child Health, Hyogo Children's Hospital, Shizuoka Children's Hospital, Kanagawa Children's Hospital and Nihon University School of Medicine.

Results

A basic description of the study sample is provided in Table 1. A total of 150 cases (NEC, n = 44; FIP, n = 47; MRI, n = 42; others,

Table 1 Disease categories in VLBW infants

Category	Cases			Controls		
	n	Gestational age (weeks) Mean ± SD	Birthweight (g) Mean ± SD	n	Gestational age (weeks) Mean ± SD	Birthweight (g) Mean ± SD
NEC	44	25.6 ± 1.9	750 ± 207	86	25.4 ± 1.9	745 ± 206
FIP	47	26.7 ± 2.3	811 ± 246	92	26.5 ± 2.3	818 ± 252
MRI	42	27.3 ± 2.9	756 ± 281	81	27.5 ± 3.0	771 ± 277
Others	17	27.1 ± 2.7	903 ± 297	34	27.8 ± 2.5	946 ± 275
Total	150	26.7 ± 2.5	790 ± 256	293	26.5 ± 2.6	795 ± 257

FIP, focal intestinal perforation; MRI, meconium-related ileus; NEC, necrotizing enterocolitis; VLBW very low-birthweight.

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n = 17) and 293 controls were identified. "Others" consisted of nine cases of meconium peritonitis, three cases of torsion, one case of invagination, one case of adhesion ileus, one case of internal hernia and two cases of unclassified entities. The cases were similar to the controls in terms of both gestational age and birthweight (cases/controls gestational age, 26.7 ± 2.5/26.5 ± 2.6 weeks; birthweight, 790 ± 256/795 ± 257 g).

Disease-specific risk factors

The investigated maternal and patient risk factors for surgical NEC are listed in Table 2. The conditional logistic regression models indicated that twin pregnancy (OR, 5.21; 95%CI: 1.68–16.2), RDS (OR, 16.3; 95%CI: 2.09–128), surfactant treatment (OR, 11.6; 95%CI: 1.46–92.0) and PDA (OR, 2.33; 95%CI: 1.00–5.41) were significantly associated with the development of surgical NEC. In addition, female sex (OR, 0.40; 95%CI: 0.18–0.89) was a protective factor. On multivariate modeling, female sex, RDS and PDA remained significant risk factors associated with surgical NEC.

The investigated maternal and patient risk factors for FIP are given in Table 3. Condition logistic regression modeling indicated that outborn delivery (OR, 5.47; 95%CI: 1.48–20.2) was the only significant risk factor associated with FIP.

The investigated maternal and patient risk factors for surgical MRI are listed in Table 4. On conditional logistic regression modeling, PROM (OR, 3.10; 95%CI: 1.05–9.13) and surfactant treatment (OR, 4.83; 95%CI: 1.01–23.1) were significant risk factors associated with surgical MRI. In contrast, maternal steroid treatment (OR, 0.38; 95%CI: 0.15–0.96) was identified to be protective. Multivariate modeling showed that twin pregnancy, PROM, and maternal steroid treatment remained significant factors associated with MRI.

The disease-specific risk factors identified on multivariate modeling are listed in Table 5. The significant risk factors for each disease were as follows: male sex, RDS and PDA for NEC; outborn delivery for FIP; and twin pregnancy, PROM, and lack of maternal steroid treatment for MRI, showing that the risk factors of each disease were different.

Discussion

Although the macroscopic findings of NEC, FIP and MRI are clearly different from each other, it is often difficult to make a definitive diagnosis without laparotomy. For example, NEC without pneumatosis or portal vein gas may be diagnosed as a form of MRI with mild inflammation. Inaccurate diagnosis could nullify

Table 2 Maternal and patient risk factors for surgical NEC

Conditional logistic regression models						
		Cases	Controls	*P*	OR (95%CI)	*P*
		n = 44 (%)	n = 86 (%)			
Twin pregnancy	Single	30 (68)	77 (90)		1.00	
	Twin	14 (32)	8 (9)		**5.21** (1.68–16.2)	0.004
Sex	Male	32 (73)	44 (51)	0.018	1.00	
	Female	12 (27)	42 (49)		**0.40** (0.18–0.89)	0.026
RDS	No	2 (5)	22 (26)	0.003	1.00	
	Yes	42 (95)	63 (74)		**16.3** (2.09–128)	0.008
Surfactant	No	1 (2)	16 (19)	0.008	1.00	
	Yes	43 (98)	69 (81)		**11.6** (1.46–92.0)	0.021
PDA	No	19 (43)	51 (59)	0.081	1.00	
	Yes	25 (57)	35 (41)		**2.33** (1.00–5.41)	0.050

Multivariate models	OR	95%CI	*P*
Twin pregnancy	2.33	0.41–13.1	0.340
Maternal steroid	0.40	0.09–1.71	0.215
Sex (female)	**0.23**	0.06–0.89	0.033
RDS	**35.7**	2.48–514	0.009
PDA	**10.9**	1.51–79.3	0.018

Bold, $P < 0.05$. NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; RDS, respiratory distress syndrome.

Table 3 Maternal and patient risk factors for FIP

Conditional logistic regression models						
		Cases	Controls	*P*	OR (95%CI)	*P*
		n = 47 (%)	n = 92 (%)			
Outborn delivery	No	33 (70)	79 (86)	0.027	1.00	
	Yes	14 (30)	13 (14)		**5.47** (1.48–20.2)	0.011

Bold, $P < 0.05$. FIP, focal intestinal perforation.

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Table 4 *Maternal and patient risk factors for MRI*

Conditional logistic regression models						
		Cases	Controls	*P*	OR (95%CI)	*P*
		n = 42(%)	n = 81(%)			
PROM	No	24 (60)	59 (74)	0.124	1.00	
	Yes	16 (40)	21 (26)		**3.10** (1.05–9.13)	0.040
Maternal steroid	No	25 (66)	38 (48)	0.063	1.00	
	Yes	13 (27)	42 (49)		**0.38** (0.15–0.96)	0.042
Surfactant	No	6 (14)	21 (26)	0.139	1.00	
	Yes	36 (86)	60 (74)		**4.83** (1.01–23.1)	0.049

Multivariate models	OR	95%CI	*P*
Twin pregnancy	**4.25**	1.06–17.1	0.042
PROM	**6.85**	1.33–35.4	0.022
Maternal steroid	**0.23**	0.07–0.79	0.019
Surfactant	17.7	0.94–333	0.055

Bold, $P < 0.05$. MRI, meconium-related ileus; PROM, premature rupture of membrane.

Table 5 Multivariate risk factors for NEC, MRI and FIP

	NEC	FIP	MRI
Outborn delivery		↑*	
Maternal steroid			↓*
PROM			↑*
Twin pregnancy			↑*
Sex (female)	↓*		
RDS	↑*		
PDA	↑*		

*$P < 0.05$. FIP, focal intestinal perforation; MRI, meconium-related ileus; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; PROM, premature rupture of membranes; RDS, respiratory distress syndrome.

precise analysis of the etiology of each disease. In the present study, in order to avoid making an unclear or suspected diagnosis, we categorized the diseases based on the operative findings. Therefore, infants who did not undergo laparotomy were excluded. Consequently, the present incidence of surgical MRI was similar to that of surgical NEC and FIP. This suggests that MRI should be recognized as a major entity causing surgical intestinal disorder in VLBW infants, as well as NEC and FIP.

In the present study male sex, RDS and PDA were associated with the development of NEC. These results are consistent with those of a recent large cohort study showing that RDS and PDA are related to the onset of NEC.[8] An epidemiologic study in the USA has shown that the incidence of NEC increased after surfactant use became a standard of care in the 1990s.[9] This suggests that RDS requiring surfactant replacement therapy is associated with the development of NEC. In 2013, Wariki *et al.* showed that PDA was the most significant risk factor for NEC based on an international collaborative database of four Asian countries.[10] Furthermore, the Israel Neonatal Network reported that PDA is a significant risk factor associated with the development of NEC in VLBW infants.[11] The present results and these previous findings suggest that the reduced mesenteric blood perfusion due to PDA may subsequently result in the development of NEC. In contrast, we did not identify any relationships between the development of NEC and previously reported risk factors, such as the use of red blood cell transfusions,[12,13] maternal cigarette smoking,[14] placental abruption[15] and pre-eclampsia.[16] The fact that the present study was limited to surgical NEC among VLBW infants may account for the differences between the present results and the findings of former reports. Given that preterm neonates who required surgery were smaller and sicker compared with those managed medically, surgical NEC should be evaluated as distinct from non-surgical NEC.[17] Regarding preventive factors of NEC, many previous studies have shown that the use of antenatal glucocorticoids decreases the incidence of NEC,[18,19] In contrast, Guthrie *et al.* reported that exposure to antenatal glucocorticoids was associated with an increased risk for NEC using a national database of the USA.[17] The effect of antenatal glucocorticoids on the development of NEC remains controversial. The present study did not show any associations between antenatal glucocorticoids use and NEC development. In order to determine whether antenatal glucocorticoids have a preventive effect on NEC, a prospective study based on a unified treatment protocol of antenatal glucocorticoids is necessary.

In contrast to that observed for NEC, we identified only one risk factor, "outborn delivery", for FIP. The transfer of patients to participating hospitals after the development of intestinal perforation may account for this result. Although some studies have shown that the use of indomethacin for PDA closure is a significant independent risk factor for FIP,[20,21] other studies have identified postnatal use of dexamethasone, but not indomethacin, as a significant risk factor for FIP.[22] In the present study we found no associations of dexamethasone or indomethacin with FIP. Differing protocols for the dexamethasone and indomethacin therapy may account for the different results. Recently, there have been several reports indicating that congenital or acquired defects in the muscular layer of the intestine may be involved in the pathogenesis of FIP.[6,23] This suggests that FIP is due not only to acquired but also to congenital factors.

Regarding MRI, several risk factors including cesarean section, maternal $MgSO_4$ therapy and maternal diabetes have been identified, based on small cohorts.[24,25] Most of these studies, however, included both surgically and medically treated MRI, and both

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