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Prematurity Combined with Parental Risk Factors Increase the Number of Intestinal Perforations: A Case Control Study

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Abstract: Background: Survival in preterm infants is strongly related to the occurrence of necrotizing enterocolitis (NEC) with intestinal perforation (NECp) compared to preterm with a focal intestinal perforation (FIP). Objective: The aim of this study was to elicit potential parental risk factors through a detailed maternal medical history and a comprehensive family history. Methods: A case-control design was used to compare both maternal medical history, factors such as drug use, individual lifestyle habits and external risk factors using standardized antenatal based questionnaires. The survey is completed by an interview with the participating parents of NEC, NECp, FIP and the control group (CG). Approval was granted by the local ethics committee (no. 13/15). Results: NEC/NECp mothers took more contraceptives (p=0.001), paracetamol (p=0.004), iodide (p=0.05) and calcium (p=0.04) and suffered from placental abruption (p=0.047), while fathers smoked more cigarettes/d (p=0.049). FIP mothers suffered from prolapsing amniotic sac (p=0.028) and alcohol consumption (p=0.034). NECp/ FIP mothers took more antibiotics (p<0.001). NEC/ FIP mothers were more likely to have uterine isthmus insufficiency (p=0.042). Conclusion: The accumulation of external factors such as alcohol consumption and passive nicotine use, the use of antibiotics and oral contraceptives together with pregnancy-associated maternal factors such as placental abruption and uterine isthmus insufficiency leads to higher rates of intestinal perforation in preterm infants.

Keywords: Risk Factor, Necrotizing Enterocolitis, Focal Intestinal Perforation, Preterm, Bowel Perforation

1. Introduction

The postnatal diagnosis of necrotizing enterocolitis without perforation (NEC) or with perforation (NECp) and focal intestinal perforation (FIP) mainly affects preterm new-born in their first weeks of life [1]; presenting parents and practitioners alike with great challenges. In addition to the known risk factors of prematurity, there are assumptions that various factors such as young maternal age [2], obesity [3], cholestasis or blood transfusion [4] may also have a potential impact on the subsequent development of a NEC, NECp or FIP. While Lee et al. have shown maternal neutrophil-to-lymphocyte ratio, multiparity [5] or hypertension [6] as risk for NEC or FIP, there have been no influence of pregnancy risks established [6]. Based on these results, this study hypothesizes, that parental and external risk factors combined with prematurity are responsible for higher NEC, NECp and FIP rates. To address this hypothesis, this research established three objectives: 1) to evaluate potential medical and prenatal risk factors, 2) to investigate risk factors in pregnancy and 3) to establish new recommendations for the prevention and reduction of NEC, NECp and FIP occurrence. In order to achieve these objectives all data were collected in three phases to allow for a complete overview of NEC, NECp or FIP pregnancies: (a) study of maternal prenatal records, (b) use of focused questionnaires and (c) postnatal adapted interview with mothers.

2. Methods

2.1. Design

This study was designed as a retrospective, observational control group-supported examination enrolling mothers of

preterm with NEC, NECp and FIP. Study period was 1st January 2004 to 31st December 2014. The local ethics committee approved this study (No. 13/15). Information was obtained through recorded in-hospital files and specialized surveys conducted using questionnaires.

2.2. Inclusion Criteria

Mothers of preterm <37th pregnancy week with NEC, NECp and FIP during study period were included. CG mothers were recruited from children age matched to NEC and FIP group during study period (age 0-11years) treated for other diseases on the pediatric surgery ward (n=30). All mothers completed the same prenatal questionnaires.

2.2.1. Exclusion Criteria

Mothers of newborn >37th pregnancy week, as well as all mother of premature without any of the 3 above mentioned conditions and with stillbirth were excluded. CG mothers whose children were admitted for abdominal surgeries, short bowel syndrome or abdominal wall defects were excluded.

2.2.2. Patients and Surveyed Subjects

The International Classification of Diseases (ICD-9 and ICD-10) was used to identify all mothers. The diagnostic codes P07.3 (premature babies), P77 (necrotizing enterocolitis) and P78.0 (bowel perforation in neonatal period) were used. During the survey period 26396 deliveries occurred, therefrom 76 mothers represent our cohort of sick preterm.

2.2.3. Data Collection

All families were initially contacted by phone (this was possible in 48.7%; n=37), 59.9% (n=22) of them consent to participate. First a modified questionnaire of Malformation Monitoring, Otto-von-Guericke-University (Magdeburg, Germany) was sent to fill in, mothers were invited to a structured interview to evaluate the previous medical and social history and for some questions and maternal prenatal records had to be evaluated. Data on medical history, complications during pregnancy, hormonal treatment, any changing of life habits (nutrition, diet, medication), body weight, drug consumption (alcohol, smoking, illicit drugs) were composed, as well as exposure to nuclear waste or poisonous substance exposition.

2.2.4. Statistics

The recorded data were initially analyzed with descriptive methods and clearly outlined. The mean, standard deviation, median and range were reported in the case of quantitative parameters, absolute and relative frequencies for the qualitative parameters. Exploratory tests between interesting subsets were selected based on the underlying parameters. When analyzing frequencies, the Chi-Square Test and Fisher's Exact Test were used. The t-test and the Kruskal-Wallis test were used in the study of continuous variables. Given the size of the subsets, t-test and non-parametric tests such as Mann-Whitney test, Wilcoxon and Kruskal-Wallis were performed in addition to ANOVA, including post-hoc testing. Significance was established as $p \leqslant 0.05$. All statistical tests were analyzed using the IBM SPSS software, version 26 (IBM. Illinois. USA).

3. Results

3.1. Number of Pregnancies and Live Births, Mothers' Weight and Age

No significant differences between CG mothers and NEC, NECp or FIP preterm mothers were found compared to maternal age, weight prior pregnancy and life birth. (Table 1)

Table 1. *Risk factors of NEC, NECp and FIP compared to CG mothers.*

Risk Factors	NEC (n; %) (Mean, SD, Range)	FIP (n; %) (Mean, SD, Range)	NECp (n; %) (Mean, SD, Range)	CG (n; %) (Mean, SD, Range)	x^2-value	p-value
BMI prior pregnancy	5 (18.5%), (25.6; SD 3.78; 22-32)	6 (50%), (25.7; SD 6.12; 21-37)	6 (16.2%), (23.7; SD 3.5; 20-28)	29 (96.7%), (24.7; SD 14.1; 19.15-41.8)		0.89
Body weight (kg) prior pregnancy	7 (26%), (68.7; SD 11.73; 45-83)	6 (59%), (71; SD 13.82; 59-97)	6 (16.2%) (65.1; SD 9.39; 55-80)	29 (96.7%), (68; SD 14.1; 54-118)		0.89
Age of mother (y)	9 (33.3%), (28.3; SD 6.34; 21-37)	12 (100%), (31.7; SD 4.08; 25-37)	20 (54%), (31,5; SD 7.2; 19-43)	30.8 (100%), 30.8; SD 6.2; 20-40)		0.58
Sterility treatment	4 (50%)	1 (16.7%)	5 (62.5%)	No data		0.86
Invasive prenatal diagnostics	3 (37.5%)	1 (16.7%)	3 (37.5%)	No data		
Medication prior pregnancy						
Oral Contraceptives	4 (50%)	3 (50%)	2 (25%)	0 (0%)	17.065	0.001
Paracetamol	3 (37.5%)	0 (0%)	2 (25%)	0 (0%)	13.166	0.004
Ibuprofen	1 (12.5%)	0 (0%)	0 (0%)	0 (0%)	5.608	0.132
Anti- epileptics	0 (0%)	0 (0%)	1 (12.5%)	0 (0%)	5.608	0.132
Iodide	0 (0%)	1 (16.7%)	0 (0%)	0 (0%)	7.817	0.05
Vitamin D + Calcium	0 (0%)	1 (16.7%)	1 (12.5%)	0 (0%)	5.807	0.121
Medication during pregnancy						
Antibiotics	2 (25%)	4 (66.7%)	5 (62.5%)	0 (0%)	23.771	<0.001
Iodide	2 (25%)	0 (0%)	0 (0%)	0 (0%)	11.440	0.010
Vitamin D + Calcium	2 (25%)	0 (0%)	1 (12.5%)	0 (0%)	8.313	0.040
Iron	2 (25%)	0 (0%)	0 (0%)	5 (16.7%)	3.357	0.340
ASS	0 (0%)	0 (0%)	0 (0%)	1 (3.3%)	0.748	0.862
Eating habits						

Risk Factors	NEC (n; %) (Mean, SD, Range)	FIP (n; %) (Mean, SD, Range)	NECp (n; %) (Mean, SD, Range)	CG (n; %) (Mean, SD, Range)	x^2- value	p-value
Multivitamin juice during pregnancy daily	0 (0%)	1 (16.7%)	2 (25%)	2 (6.6%)	5.000	0.082
	0 (0%)	1 (16.7%)	4 (50%)	5 (16.7%)	6.933	0.074
Whole-meal products prior pregnancy	2 (25%)	0 (0%)	0 (0%)	16 (53.3%)	12.383	0.006
Drug consumption						
Smoking						
Mother prior pregnancy	5 (62.5%)	1 (16.7%)	2 (25%)	12 (40%)	3.800	0.284
Mother during pregnancy	3 (42.9%)	0 (0%)	2 (25%)	5 (16.7%)	4.176	0.243
Partner during pregnancy	4 (50%)	1 (16.7%)	5 (62.5%)	12 (40%)	3.212	0.360
Alcohol						
Mother prior pregnancy	5 (62.5%)	6 (100%)	2 (25%)	20 (66.7%)	8.694	0.034
• daily alcohol	1 (20%)	0 (0%)	0 (0%)	1 (3.3%)	3.164	0.367
Mother during pregnancy	0 (0%)	0 (0%)	1 (12.5%)	8 (26.7%)	4.895	0.180
• occasionally alcohol	0 (0%)	0 (0%)	1 (12.5%)	4 (13.3%)	2.103	0.551
Illicit drugs						
Mother prior pregnancy	0 (0%)	0 (0%)	0 (0%)	1 (3.3%)	0.748	0.862

3.2. Smoking, Illegal Drug Use and Alcohol Consumption

Smoking and illegal drugs showed no significant influence in our cohort. Mothers of NECp smoked more often but without significance, however fathers of NEC and NECp smoked significantly more cigarettes/d than FIP fathers (p=0.049). Prior pregnancy alcohol intake was significant higher in FIP mothers (p=0.034; 100%) compared to NECp (25%), NEC (62.5%) and CG mothers (66.7%). Eight CG (n=8) and one NECp mother (n=1) continued drinking alcohol during pregnancy (p=0.180), this corresponds to 17.3% of all mothers who participated in the full survey (n=52). (Table 1)

3.3. Pre-Existing Conditions, Medicine Intake Before and During Pregnancy

NEC, NECp and FIP mothers used significantly more oral contraceptives (p=0.001) and antibiotics (p<0.0001) compared to CG. NEC and NECp mothers took significantly more frequent paracetamol (p=0.004). FIP and NECp mothers suffered significantly more often of hypertension (p=0.048) compared to NEC and CG mothers. Iodide intake of FIP mothers was significantly higher (p=0.05) and they used more antibiotics during pregnancy compared to all others (0.0001). NEC mothers had higher iodide (p=0.010), vitamin D and calcium intake (p=0.040) compared to CG mothers. (Tables 1 and 2).

Table 2. *Pre-existing illnesses or conditions of NEC, NECp and FIP compared to CG mothers.*

Pre-existing illnesses or conditions	NEC (n; %)	FIP (n; %)	NECp (n; %)	CG (n; %)	x^2- value	p-value
Hypertension	0 (0%)	1 (16.7%)	1 (14.3%)	0 (0%)	6.133	0.048
Epilepsy	0 (0%)	0 (0%)	1 (14.3%)	0 (0%)	6.411	0.093
Lung maturation induction corticosteroids	23 (85.2%)	12 (100%)	26 (70.3%)	0 (0%)	5.696	0.058
Hypothyroidism	2 (25%)	1 (16.7%)	1 (14.3%)	0 (0%)	3.988	0.263
Birth mode						
Caesarean section	20 (74.1%)	7 (58.3%)	8 (21.6%)	no data	1.881	0.390
Vaginal delivery	7 (25.9%)	5 (41.7%)	8 (21.6%)	no data		

3.4. Sexual Anamnesis, Methods of Contraception and Mothers' Dietary Habits

Differences between mothers of sick preterm compared to CG were not significant in terms like number of sexual partners, duration of cohabitation time, methods of contraception and week of pregnancy notification. (Data not shown) NEC and FIP mothers had significantly less consumed whole grains before pregnancy than CG (p=0.006); dietary habits with intake of fruits, vegetables, dairy products or meats were not significantly different as well as diet changes during pregnancy. (Table 1)

3.5. External Risk Factors and Socioeconomic Status of Parents

Parents of children with NEC, NECp or FIP were significantly more often exposed to intensive agriculture, monocultures, garbage, bio-waste, hazardous waste landfill, nuclear power plant, nuclear repository or chemical industry before or during pregnancy compared to CG parents (p=0.033). Exposure to chemical or physical toxins as well as agricultural profession with increased contact to animals showed no significance (data not shown). NECp fathers worked more often in job training (p=0.099) or significantly without any job training compared to NEC, FIP or CG fathers (p=0.014). (Table 3)

Table 3. *External risk factors and socioeconomic status of NEC, NECp and FIP compared to CG parents.*

Socioeconomic status and external factors	NEC (n=8; %)	FIP (n=6; %)	NECp (n=8; %)	CG (n=30; %)	x^2- value	p-value
Housewife	2 (25%)	1 (16.7%)	3 (37.5%)	3 (10%)	3.371	0.292
Mother in job training	1 (12.5%)	0 (0%)	1 (12.5%)	1 (3.3%)	2.028	0.567

Socioeconomic status and external factors	NEC (n=8; %)	FIP (n=6; %)	NECp (n=8; %)	CG (n=30; %)	x^2- value	p-value
Mother without any job training	0 (0%)	0 (0%)	1 (12.5%)	1 (3.3%)	2.201	0.532
Mother with profession	2 (25%)	2 (33.3%)	0 (0%)	13 (43.3%)	5.646	0.130
Mother in higher rank or leading position	3 (37.5%)	3 (50%)	3 (37.5%)	12 (40%)	0.288	0.962
Father in job training	1 (14.3%)	0 (0%)	0 (0%)	0 (0%)	6.268	0.099
Father without any job training	1 (14.3%)	0 (0%)	3 (42.9%)	1 (3.3%)	10.688	0.014
Father with profession	1 (14.3%)	3 (50%)	2 (28.6%)	18 (60%)	5.987	0.112
Father in higher rank or leading position	4 (57.1%)	3 (50%)	2 (28.6%)	11 (36.7%)	1.627	0.653
Home base <25km to landfill / waste disposal site	6 (75%)	6 (100%)	7 (87.5%)	17 (56.7%)	5.255	0.033
Partner smoking/ cigarettes per day	4 (57.1%)	1 (16.7%)	5 (62.5%)	12 (40%)	3.212	0.049

3.6. Invasive Prenatal Diagnostics, Sterility Treatment and Abnormalities in Pregnancy

Invasive prenatal diagnostics or use of sterility treatment (hormones, in vitro fertilization or intracytoplasmic sperm injection) does not show any significant influence (data not shown). In >80%, mothers of affected preterm, showed abnormalities during pregnancy: NEC mothers showed significant higher premature placental detachment (p=0.047) and uterine isthmus insufficiency rate (p=0.042), that remained significant when perforation vs. no perforation was tested (p=0.021). FIP mothers suffered significantly more often of prolapsed amniotic sac (p=0.028). (Table 4)

Table 4. *Pregnancy associated abnormalities of NEC, NECp and FIP.*

Pregnancy associated particularities	NEC (n)	FIP (n)	NECp (n)	NEC vs. FIP vs. NECp (x^2- value)	p-value	Perforation vs. no perforation (x^2- value)	p-value	NEC/ NECp vs. FIP (x^2- value)	p-value
Abnormalities during pregnancy	24	10	30	0.724	0.696	0.689	0.521	0.008	1.000
Infection	18	6	20	1.383	0.501	1.322	0.333	0.364	0.751
Vaginal bleeding	8	3	5	2.573	0.276	1.854	0.240	0.134	0.708
Isthmus cervix insufficiency	6	0	2	6.364	0.042	6.082	0.021	1.676	0.342
Multiple births	6	1	10	1.824	0.402	0.001	1.000	1.616	0.279
Premature rupture of membranes	10	5	13	0.167	0.920	0.001	1.000	0.143	0.751
Premature placental detachment	3	0	6	2.304	0.316	0.021	1.000	1.914	0.339
Gestational diabetes	1	0	1	0.446	0.800	0.188	1.000	0.385	1.000
Hypertension	4	1	3	0.818	0.664	0.818	0.444	0.073	1.000
Proteinuria	0	0	3	3.292	0.193	1.721	0.548	0.586	1.000
Placenta insufficiency	3	0	3	1.415	0.493	0.596	0.660	1.221	0.581
Complications during childbirth									
Prolapsed amniotic sac	0	3	3	7.145	0.028	3.590	0.064	5.734	0.047
Pre-eclampsia	4	0	4	1.942	0.379	0.818	0.444	1.676	0.342
Growth-retardation	4	1	5	0.313	0.855	0.101	0.737	0.290	1.000
Anhydramnios	0	1	2	1.926	0.382	1.721	0.548	0.723	0.407
Oligohydramnios	5	0	5	2.501	0.286	1.053	0.314	2.159	0.348
Polyhydramnios	1	0	0	1.839	0.399	1.839	0.355	0.190	1.000

3.7. Linear Regression for Intestinal Perforation (Yes/No) and Relative Risk for Intestinal Perforation 95% CI

Regression analysis included factors which occur in case of preterm which suffered of an intestinal perforation such as cervix insufficiency and a prolapsed amnion sac. The probabilities of variables for an intestinal perforation are listed in Table 5. The relative risk for an intestinal perforation is just for preterm with mothers who took oral contraceptives 1.561-fold higher, other factors like lung maturation induction corticosteroids, a prolapses amnion sac or an isthmus insufficiency showed no impact. (Table 5)

Table 5. *Linear regression analysis (Yes/ No) and Relative Risk for perforation (95%CI).*

Linear regression analysis				
Factor	**OR**	**Significance**	**Lower estimate**	**Higher estimate**
Cervix insufficiency	0.149	0.021	0.280	0.800
Prolapsed amnion sac	0.878	0.064	0.790	0.970

Relative Risk for perforation				
Factor	**Relative Risk**	**Significance**	**Lower estimate**	**Higher estimate**
Lung maturation induction corticosteroids	0.601	0.552	0.171	2.110
Prolapse amnion sac	0.878	0.083	0.790	0.974
Isthmus insufficiency	0.149	0.021	0.028	0.800
Oral contraceptives	1.561	0.003	0.565	2.558

4. Conclusion

Number of pregnancies and live births, mothers' weight and age

The assumption that young maternal age prejudiced development of NEC and NECp [2], or mothers overweight [3] influenced their incidence could not be confirmed in this study. This research found no higher scores for NEC, NECp or FIP in mothers with fewer live births as well as in multiparity mothers contrarily to Lee et al. [5].

Smoking, illegal drug use and alcohol consumption

Ding et al. showed a significant correlation between maternal smoking during pregnancy and the development of NEC and FIP [7], this study could support this and add that fathers of NEC and NECp smoked significantly more cigarettes per day than FIP fathers (p=0.049), maybe passive nicotine consumption is also an additional risk factor for NEC and NECp, this was first described in our study. This research could not acknowledge findings of Gebhart et al., who identified cocaine as a risk factor for NEC, NECp and FIP [8]. Without significance, but not without dismay, this study showed that occasionally nearly 30% of all CG mothers are consuming alcohol during pregnancy; this was close to results of Alshaarawy et al. [9].

Pre-existing conditions, medicine use of the mother before and during pregnancy

Maternal hypertension was often correlated to development of NEC and FIP [10] this study confirms this observation for both groups with bowel perforation. This could possibly be caused by disturbances of placental blood supply, which promotes intestinal ischemia and in particular may increase the risk of bowel perforation. Wadhawan et al. found different relation of lower rate of hypertension in FIP mothers compared to mothers of surgical treated NEC [11], this cohort is too small to make any statements. There are several drugs suspected after using during pregnancy to promote the development of NEC, NECp [12] or FIP [13], one of them are contraceptives [14], this research support this finding. Wadhawan et al. could show that FIP mothers used significantly more antibiotics than NEC, NECp and CG mothers [11], this study support their conclusion. The research result, that prior pregnancy use of paracetamol is associated with NEC and NECp was never described before and needed further studies to verify. In this cohort 88.5% of preterm mothers received prenatal corticosteroids, a clear benefit was known to affect mortality in preterm [15], but it is still unclear whether this represents a risk factor for a NEC, NECp or FIP and a benefit risk consideration should always be given prior to administration. This study found significant influence on NECp and FIP for mothers' vitamin D and calcium intake, which was also never described before. For FIP and NECp preterm this study founds a significant higher maternal iodide intake contrarily to Cetinkaya et al., who observed a maternal vitamin D deficiency as risk for this preterm disease [16].

Mothers dietary habits

Influence of maternal nutrition before and during pregnancy on the development of NEC, NECp or FIP is not yet described. This research found a relationship between less consume of whole-wheat products prior pregnancy and affected preterm mothers, which implicated a protective effect for health by special parts of nutrition. This was described well for other diseases and the immune system [17].

Abnormalities in pregnancy

A variety of possible birth complications exist, which are considered to be risk factors for development of NEC, NECp or FIP. Ahle et al. could show that there is a link between onset of NEC, maternal genitourinary tract infection and premature rupture of the membranes frequently caused by chorionic amnionitis [18]. This study also found this association, but without significance. Duci et al. found an association between chorionic inflammation and placental insufficiency with subsequent significant increased risk for NEC [19], this research confirms this finding and support theses, in which cervical insufficiency facilitates the ascension of germs and thereby increases the risk of infection. Other complications like early placental abrupt [12], umbilical cord prolapse [8] result in deficiency across the placenta and promote ischemia of the intestine, additionally this study found a significant accumulation for prolapse of the amniotic sac in NECp and FIP mothers compared to NEC mothers, this was first described. Tiwari et al. described an increase of FIP after premature rupture of the membranes [20]. Contrarily this research found only NEC and NECp mothers to be affected, but none FIP mother, maybe further studies and a larger cohort could verify this finding.

External risk factors and socioeconomic status of parents

Effect of socioeconomic status on congenital malformations was well known for abdominal wall defects [21] or disorder of sex development [22], but not yet clearly described for NEC or FIP. This study found that NEC and NECp fathers were less well educated than FIP and CG group fathers this correlation was first described.

Linear regression analysis and Relative Risk for perforation

This research has observed that the occurrence for bowel perforation was influenced by cervix insufficiency and a prolapsed amnion sac. These results were also detected and confirmed by multiple regression analysis. The relative risk for bowel perforation is 1.5-fold higher for mothers who used oral contraceptives. A result with 0.8-fold higher for mothers with a prolapsed amnion sac, 0.6-fold after lung maturation induction corticosteroids and 0.1-fold after isthmus insufficiency showed that these factors are without influence. (Table 5)

This research concludes that a combination of paternal risk factors additionally those of the prematurity itself influence the development of NEC, NECp and FIP. The surprising negative result of alcohol consume in nearly 30% of CG mothers during pregnancy was a warning sign. It showed, that actual education about the dangerous effects of alcohol to the unborn child does not seem to be sufficient and that the scaling up of efforts in terms of raising awareness of these dangers is far from over.

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