A cohort study of intrapartum group B streptococcus prophylaxis on atopic dermatitis in 2-year-old children

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Abstract

Objective

To understand the occurrence of atopic dermatitis (AD) in children aged 2 years on exposure to maternal group B streptococcus (GBS) antibiotic prophylaxis (IAP).

Design

Retrospective cohort study of 2909 mother-child pairs.

Setting

Taixing People's Hospital in Eastern China.

Participants

Term infants born 2018–2019, followed longitudinally from birth to 2 years.

Exposures

The GBS-IAP was defined as therapy with intravenous penicillin G or ampicillin or cefazolin ≥ 4 hours from delivery. Reference infants were defined as born with intrapartum antibiotic exposure via cesarean sections.

Outcomes

The logistic regression models were employed to analyze the effect of intrapartum GBS prophylaxis on AD in 2-year-old children during delivery. Analysis was a priori stratified according to the mode of delivery and adjusted for relevant covariates.

Results

Univariate and multivariate logistic regression models before and after covariate-adjusted treatment simultaneously showed that preventive GBS-IAP was associated with increased incidence of AD in children delivered vaginally (OR: 6.719,95% CI: 4.730–9.544,P < 0.001;aOR: 6.562,95% CI: 4.302–10.008, P < 0.001), whereas cesarean delivery in 2-year-old children (OR: 0.555,95% CI: 0.276–1.117, P = 0.099;aOR: 0.560,95% CI: 0.271–1.155, P = 0.116) was not related to AD.

Conclusion

Prophylactic treatment of intrapartum GBS may raise the risk of AD in vaginally delivered children. Children delivered through cesarean section, on the other hand, did not have an elevated risk of AD. These findings

highlight the need to better understand the risk between childhood AD and current GBS-IAP intervention strategies.

Highlights

► Maternal group B streptococcus antibiotic prophylaxis (GBS-IAP) was associated with the occurrence of atopic dermatitis in 2-year-old children with vaginal delivery.

► The findings were significant in vaginal delivery before and after adjusting for multiple covariates.

Introduction

Research over the past decades has revealed the emergence of group B Streptococcus (GBS) is the leading cause of neonatal infections in China [1]. Intrapartum antibiotic prophylaxis (IAP) was initially introduced in the 1980s to lower the prevalence of perinatal GBS disease and offered to women with particular obstetric risk factors during parturition [2, 3]. The treatment of IAP has significantly diminished the incidence of neonatal GBS early-onset disease (GBS-EOD) in newborns [1, 4]. However, new research has shown that using maternal antibiotics during pregnancy increases the incidence of atopic dermatitis in offspring [5].

Atopic dermatitis (AD), a chronic and recurrent inflammatory skin disease that commonly occurs in infancy, is clinically characterized by intense itching and eczematous lesions, and its incidence has increased sharply over the past decade in response to lifestyle changes [6]. A multicentric study conducted between January and December 2014 showed that the overall point prevalence of AD in infants reached 30.48% in China [7]. Notably, previous studies evidenced the associations between the occurrence of allergic diseases and gut microbiota after cesarean section in children[8]. Recent reports also evidenced the shifts of neonatal gut microbiota when intrapartum antibiotics are administered[9, 10]. However, whether such antibiotic-mediated effects are related to childhood AD is unknown.

To better understand the association between GBS-IAP and AD in children, a retrospective cohort study was administrated in the present project by analyzing 2909 full-term newborns approximately 2 years old to establish a theoretical basis for formulating GBS intervention strategies in China.

Methods

Design and setting

The subjects selected pregnant women and full-term newborns delivered in the present hospital from June 2018 to December 2019. A total of 3500 pregnant women were enrolled in the study. Among them, 320 were excluded from miscarriage and induced labor, 271 for incomplete information on mother-child pairs, and incomplete disease records. Finally, 2909 pairs of mother-child that met the criteria were included and divided into two cohorts, *i.e* vaginal delivery, and cesarean section according to the mode of delivery.

Population

Healthy infants with a gestational age of > 37 weeks and a birth weight of > 2500 g were included in the study. The following criteria that may impact the exposure or outcome were excluded for the subjects (Fig. 1).

Exposure

The intrapartum antibiotic prophylaxis (IAP) was defined as the exposure factors that intravenous penicillin G or ampicillin, or cefazolin were being administered ≥ 4 hours before delivery [11, 12]. Notably, the IAP was given at the onset of labor or membrane rupture for those pregnant women with positive GBS screening. However, no antibiotics were prescribed when a cesarean section is selected before labor or membrane rupture. The diagnostic of AD in infants was confirmed by > 3 criteria according to Williams standards in Supply Table 1 (10).

Table 1
Basic characteristics of the two groups of cohorts.

Basic situation	Vaginal birth(n = 1510)				Cesarean section(n = 1399)			
	No IAP	GBS-IAP	*t/χ 2*	*P*	No IAP	GBS-IAP	*t/χ 2*	*P*
	(n = 1346)	(n = 164)			(n = 1279)	(n = 120)		
Mother's age (years)	27.3 ± 3.9	27.5 ± 4.1	-0.379	0.414	29.0 ± 4.4	29.2 ± 4.5	-0.382	0.702
Mother's BMI(x ± s)	20.8 ± 1.6	21.0 ± 1.5	-1.094	0.274	21.0 ± 1.8	21.0 ± 1.9	-0.272	0.786
Parity (n, %)			5.733	0.017			2.521	0.112
One child	724(53.8)	72(43.9)			596(46.5)	65(54.1)		
Second child or more	622(46.2)	92(56.0)			683(53.4)	55(45.8)		
GBS Screening(n, %)			1206.195	< 0.001			730.014	< 0.001
Positive	33(2.5)	162(98.7)			65(5.1)	108(90.0)		
Negative	1313(97.5)	2(1.3)			1214(94.9)	12(10.0)		
Mother's allergy history(n, %)	128(9.5)	12(7.3)	0.835	0.361	110(8.6)	14(11.7)	1.277	0.258
Whether received higher education(n, %)	1081(80.3)	132(80.5)	0.003	0.957	922(72.1)	91(75.8)	0.770	0.380
Gender (man, n, %)	702(52.1)	103(62.8)	6.662	0.010	711(55.6)	58(48.3)	2.334	0.127
Gestational age(weeks x ± s)	39.5 ± 1.0	39.2 ± 1.1	1.645	0.100	39.3 ± 1.0	39.4 ± 1.0	-1.210	0.227
Weight of birth (g x ± s)	3362 ± 396	3416 ± 415	-1.644	0.100	3462 ± 447	3542 ± 473	-1.850	0.065
Feeding method(n, %)			10.846	0.004			1.336	0.113
Breast feeding	1060(78.7)	138(84.1)			963(75.2)	96(80.0)		
Artificial feeding	12(8.9)	5(3.0)			24(1.8)	2(1.7)		

BMI, body mass index; GBS, group B Streptococcus; IAP, intrapartum antibiotic prophylaxis.

Basic situation	Vaginal birth(n = 1510)				Cesarean section(n = 1399)			
	No IAP	GBS-IAP	*t/χ 2*	*P*	No IAP	GBS-IAP	*t/χ 2*	*P*
	(n = 1346)	(n = 164)			(n = 1279)	(n = 120)		
Mixed feeding	274(20.4)	21(12.8)			292(22.8)	22(18.3)		
Whether used antibiotics in infant(n, %)	92(6.8)	68(41.4)	185.044	< 0.001	99(7.7)	46(38.3)	110.521	< 0.001
Incidence of atopic dermatitis in 2 years children(n, %)	150(11.1)	75(45.0)	140.204	< 0.001	163(12.7)	9(7.5)	3.370	0.185

BMI, body mass index; GBS, group B Streptococcus; IAP, intrapartum antibiotic prophylaxis.

Covariates

In addition to the exposure factors and mode of delivery, potential confounding factors that may affect outcomes were screened including genetic and environmental issues[1, 11–14]. A questionnaire was used to collect the covariates information of pregnant women and newborns including age, weight, height, parity, mode of delivery, previous GBS colonization, allergies, smoking history, pet ownership, resident place, education level, antibiotic usage, and feeding patterns. The data sources and definitions of model covariates were list in Supply Table 1.

Statistical analysis

Initially, chi-square tests and one-way ANOVA were employed for comparison between groups of two cohorts. Then a univariate logistic regression model was performed to analyze the exposure and preselected risk factors for atopic dermatitis in children. To better evaluate the the association between maternal IAP and AD in children, a multivariate logistic regression model was enrolled to adjust the confounding factors such as maternal age, maternal allergy history, parity, gestational age, neonatal birth weight, etc. The Data were imported into Epidata 3.0 database. SPSS 22.0 software was used for statistical analysis. The forest plots were drawn with R 4.1.3. Two-sided tests were employed with an inspection level set at $\alpha = 0.05$.

Results

Overview of the cohorts

A total of 2909 mother-child pairs were included in the cohort study (Table 1). Of these, 1510 cases (52%) were delivered through the vagina and 1399 cases (48%) were by cesarean section. Furthermore, 368 pregnant mothers were screened positive for GBS with a colonization rate of 12.6%, with 284 (9.8%) receiving GBS-IAP, comprising 164 cases from the vaginal group and 120 cases from the cesarean section group.

Characteristics of the cohorts

Multiple characteristics of mother-child pairs were compared between the IAP and non-IAP groups in the two cohorts. As shown in Table 1, characteristics were detected across the vaginal birth cohorts in terms of breastfeeding rates, and antibiotics usage within 72 hours after birth (Table 1). In the cohort of vaginal delivery, the IAP group had a higher rate of multipara compared with the control group. Moreover, the prenatal IAP group also had higher GBS-positive rate, frequent maternal breastfeeding, and higher antibiotic use within 72 hours of birth in the vaginal delivery cohort (Table 1). In the cohort of cesarean section, significances were observed in the IAP group on primipara, GBS-positive rate, maternal breastfeeding and children were more likely to receive antibiotics use with 72 hours after birth in this cohort (Table 1).

Outcome of the cohorts

Atopic dermatitis affected 397 (13.6%) of the children in the present cohorts, of which 225 (56.7%) were delivered vaginally and 172 (43.3%) were delivered by cesarean section (Table 1). To be specific, the GBS-IAP group had a higher incidence of atopic dermatitis (45% vs 11.1%) compared with the control group in the vaginal delivery cohort ($p < 0.01$). However, in cesarean delivery, the presence of AD was not associated with intrapartum GBS-IAP exposure (7.5% vs. 12.7%, $p > 0.05$).

Analysis of risk factors for atopic dermatitis

A univariate logistic regression model was initially performed to analyze the exposure and preselected risk factors for atopic dermatitis in children. Results showed that children exposed to GBS-IAP had an increased incidence of atopic dermatitis in the vaginal delivery cohort compared to those without GBS-IAP exposure (OR: 6.719, 95% CI: 4.730–9.544, Table 2). Particularly, the vaginal delivery cohort also revealed an association between childhood AD and other factors such as maternal allergy history (OR: 2.357, 95% CI: 1.575–3.527), mixed feeding rate (OR: 1.479, 95% CI: 1.061–2.061), parity (OR: 1.509, 95% CI: 1.134–2.007), and antibiotic usage (OR: 2.544, 95% CI: 1.793–3.609, Table 2). In the cohort of cesarean section, however, only maternal allergy history (OR: 1.721,95% CI: 1.061–2.792) was evidenced to be associated with the incidence of atopic dermatitis while no significance was observed between the GBS-IAP group and control group in 2 years children (OR: 0.555,95% CI: 0.276–1.117, Table 2).

Table 2
Univariate logistic regression analysis of variables in the cohorts.

Variables	Vaginal delivery			Cesarean section		
	OR	95%CI	*P*	OR	95%CI	*P*
No IAP	Reference			Reference		
GBS-IAP	6.719	4.730–9.544	< 0.001	0.555	0.276–1.117	0.099
Mothers age	1.018	0.982–1.056	0.322	0.997	0.962–1.034	0.873
Mothers without allergic history	Reference			Reference		
Mothers with allergic history	2.357	1.575–3.527	< 0.001	1.721	1.061–2.792	0.028
One child	Reference			Reference		
Second child and more	1.509	1.134–2.007	0.005	0.906	0.658–1.246	0.543
Gestational age	0.696	0.607–0.798	< 0.001	1.135	0.965–1.335	0.127
BMI	0.976	0.894–1.065	0.584	0.964	0.881–1.054	0.421
Weight of birth	1.238	0.87–1.762	0.236	1.159	0.816–1.646	0.411
Breast feeding	Reference			Reference		
Artificial feeding	0.386	0.051–2.929	0.357	2.283	0.899–5.795	0.082
Mixed feeding	1.479	1.061–2.061	0.021	1.207	0.832–1.753	0.321
No antibiotics used within 72h				Reference		
antibiotics used within 72h	2.544	1.793–3.609	< 0.01	0.741	0.417–1.318	0.308
No smoking	Reference			Reference		
Smoking	1.420	0.933–2.161	0.102	1.012	0.593–1.728	0.966
No keeping pets	Reference			Reference		
keeping pets	1.140	0.849–1.532	0.384	1.329	0.950–1.859	0.097
P value is for the comparison of the GBS IAP groups among vaginal and caesarean cohorts.						
OR, odds ratio; BMI, body mass index; GBS, group B Streptococcus; IAP, intrapartum antibiotic prophylaxis.						

Association between the risk factors and atopic dermatitis after adjustment

Multivariate logistic regression model was enrolled to explore the association between the cohorts and atopic dermatitis after covariates adjustment. The adjusted results revealed that the vaginal delivery cohort still had a higher occurrence of atopic dermatitis in children with GBS-IAP exposure (adjusted OR: 6. 562, 95% CI: 4.302–10.008, Table 3, Fig. 2). On the contrary, no significant risk factors were identified for atopic dermatitis in children without GBS-IAP exposure delivered by cesarean section (adjusted OR: 0.560, 95% CI: 0.271–1.155, Table 3, Fig. 2). In addition, the vaginal delivery cohort also witnessed the association between childhood AD and other

factors in the multivariate logistic regression model including maternal allergy history (adjusted OR: 2.642, 95% CI: 1.699–4.109), mixed feeding rate (adjusted OR: 1.844, 95% CI: 1.281–2.655), and gestational age (adjusted OR: 0.758, 95% CI: 1.003–2.701) that relate to childhood AD. However, only maternal allergy history was evidenced to be associated with the occurrence of childhood AD in the cesarean section cohort (adjusted OR: 1.646, 95% CI: 1.003–2.701, Table 3, Fig. 2).

Table 3
Multivariate logistic regression analysis of variables in the cohorts.

Variables	Vaginal delivery			Cesarean section		
	aOR	95%CI	*P*	aOR	95%CI	*P*
No IAP	Reference			Reference		
GBS-IAP	6.562	4.302–10.008	< 0.001	0.562	0.271–1.155	0.116
Mothers age	0.994	0.953–1.036	0.769	1.011	0.969–1.055	0.614
Mothers without allergic history	Reference			Reference		
Mothers with allergic history	2.642	1.699–4.109	0.000	1.645	1.003–2.701	0.049
One child	Reference			Reference		
Second child and more	1.495	1.074–2.081	0.017	0.986	0.664–1.472	0.954
Gestational age	0.758	0.653–0.879	0.000	1.172	0.977-1.4	0.087
No smoking	Reference			Reference		
Smoking	1.282	0.782–2.101	0.324	1.169	0.675–2.057	0.564
BMI	0.966	0.879–1.061	0.470	0.961	0.877–1.053	0.397
Breast feeding	Reference			Reference		
Artificial feeding	0.203	0.025–1.628	0.133	2.245	0.865–5.78	0.097
Mixed feeding	1.844	1.281–2.655	0.001	1.187	0.809–1.734	0.384
No antibiotics used within 72h	Reference			Reference		
antibiotics used within 72h	1.234	0.795–1.915	0.348	0.851	0.472–1.564	0.619
No keeping pets	Reference			Reference		
Keeping pets	1.276	0.92–1.77	0.144	1.282	0.905–1.831	0.161

aOR, adjusted odds ratio; BMI, body mass index; GBS, group B Streptococcus; IAP, intrapartum antibiotic prophylaxis.

Discussion

Previous studies have shown an association between postnatal antibiotic exposure and allergic disease in children, while fewer cases of atopic dermatitis were of concern in the context of presumed prenatal antibiotic use. A European cohort report conducted in 2019 revealed a positive association between antenatal antibiotic use and the appearance of AD in the first year of rural-born children [15]. Simultaneously, a prospective birth cohort in China also demonstrated that maternal antibiotic exposure was significantly associated with AD in postnatal childhood [5]. However, a recent meta-analysis claimed that no significant evidence that maternal antibiotic exposure in late pregnancy increases the risk of AD in infants [16].

To better explore the relationship between antibiotic exposure during pregnancy and the risk of atopic dermatitis in children, a retrospective cohort analysis was administrated in this study that identified that vaginal delivery significantly increased the AD risk in children exposed to GBS-IAP. Previous research reported that delivery mode had a greater impact on the establishment of neonatal gut microbiota after birth [13, 17]. Microbiota development was affected in infants born vaginally exposed to IAP for up to 6 months [18]. Specifically, exposure to IAP may change the microenvironment of colonized gut microbiota, leading to a reduction in commensal bacteria but the persistence of pathogenic microorganisms[19]. In the present study, we assumed that the GBS-IAP exposure might result in the disruption of gut microbiota and further influence the course of allergic diseases such as atopic dermatitis processes in childhood. GBS-IAP interventions are usually administered 4 hours before delivery, which overlaps with the establishment of gut microbes in the first colonized neonate [20]. Such overlaps may affect the dysregulation of the gut microbiota throughout the neonatal period, and into infancy [21, 22].

Contrary to the cohort of vaginal delivery, no significant incidence of AD was detected in infants with IAP exposure at the time of cesarean delivery. Similar results were observed in an American study in which cesarean section was not associated with atopic dermatitis in 4-year-old children and was neither affected by intrapartum antibiotics nor other indications [23]. Another study showed that delivery by cesarean section may cause food allergy in children, but not atopic dermatitis [24], which explained why the colonization of infant gut microbiome was less affected by cesarean section than vaginally born children.

The antimicrobials administered in this study were narrow-spectrum antibiotics, which may lead to changes in the composition and diversity of gut microbiota during the perinatal period. After therapy with the narrow spectrum penicillin, Nogacka and Aloisio found a decrease in symbiotic bacteria but an increase in pathogen abundance in infants [25, 26]. Taipianen revealed that the effect size of IAP was comparable to that caused by postnatal antibiotics in newborn infants [27]. When narrow-spectrum antibiotics were given to pregnant women, the effects on the newborn gut microbiota were comparable to when broad-spectrum antibiotics were given directly to neonates. Moreover, Cox reported that postnatal administration of low-dose penicillin induces metabolic changes and affects the ileal expression of immune-related genes [28]

Other genetic and environmental factors, such as the history of family allergic disease, climate change, passive smoking, pet ownership, and other confounding factors, were believed to be connected with the incidence of atopic dermatitis [29]. To better adjust the logistic regression model, these indicators, initially screened by univariate logistic regression, were selected for multivariate regression analysis, and the adjusted results showed that maternal history of allergic disease, in addition to IAP exposure, was an independent risk factor. Parental allergic disease may affect skin barrier function and immune homeostasis, leading to a variety of immunological

abnormalities [30]. Other studies have reported that pet ownership and smoking may be linked with the development of atopic dermatitis in children, however, this was not found in our study [31–33].

There are some limitations to this study. First, this study was a retrospective analysis but relied on parental feedback on a diagnosis of atopic dermatitis. Second, the lack of detailed information on parents was noticed, including a family history of allergies, and smoking history. Therefore, a prospective large-sample study will be established to collect the feces of newborns after IAP intervention and send for metagenome sequence. A longitudinal study will be conducted to investigate the impact of IAP on children to better understand the risks and benefits of the current GBS-IAP intervention strategies.

Conclusion

GBS-IAP intervention for pregnant mothers significantly increased the incidence of AD in children aged 2 years in vaginal delivery, whereas no significance was observed in cesarean sections.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committees of Taixing People's Hospital (Reference txry2018-003) in Jiangsu Province, China. Written informed consents were obtained from the parents of all the enrolled infants before data collection. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable

Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Competing interests

The authors declare no conflicts of interest.

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Authors' contributions

ZH and RJ designed and organized the performance of the study; DX and YX guided and instructed the data analysis. ZH and RJ performed the study, collected and analyzed the data; LH, XK, ZC, WY and ZB participated in the table and figure analysis. ZH and RJ wrote the manuscript. DX and YX revised the manuscript.

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Figures

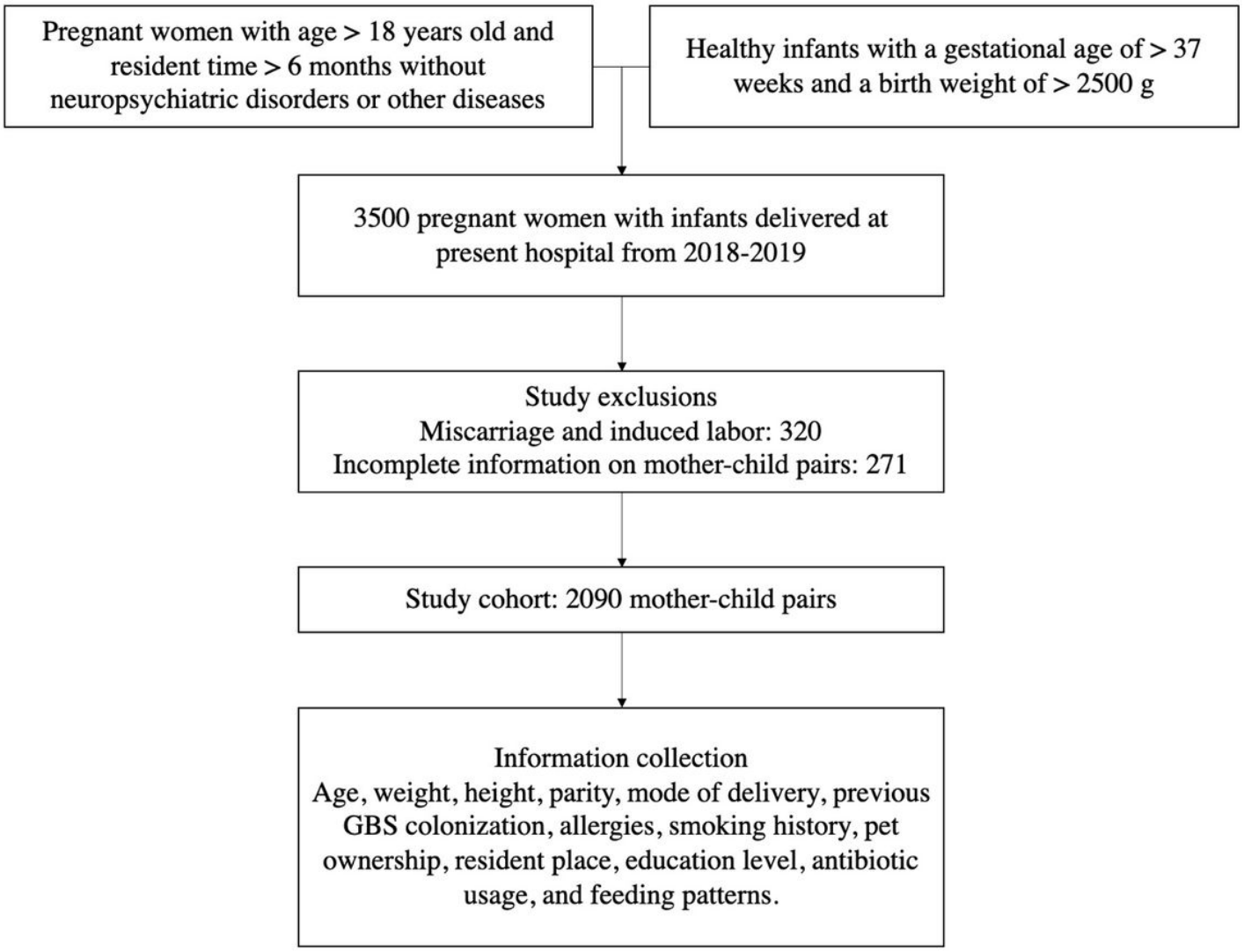

Figure 1

Design of study cohorts. Figure describes the process of inclusion and exclusion criteria for the selected pregnant women and infants.

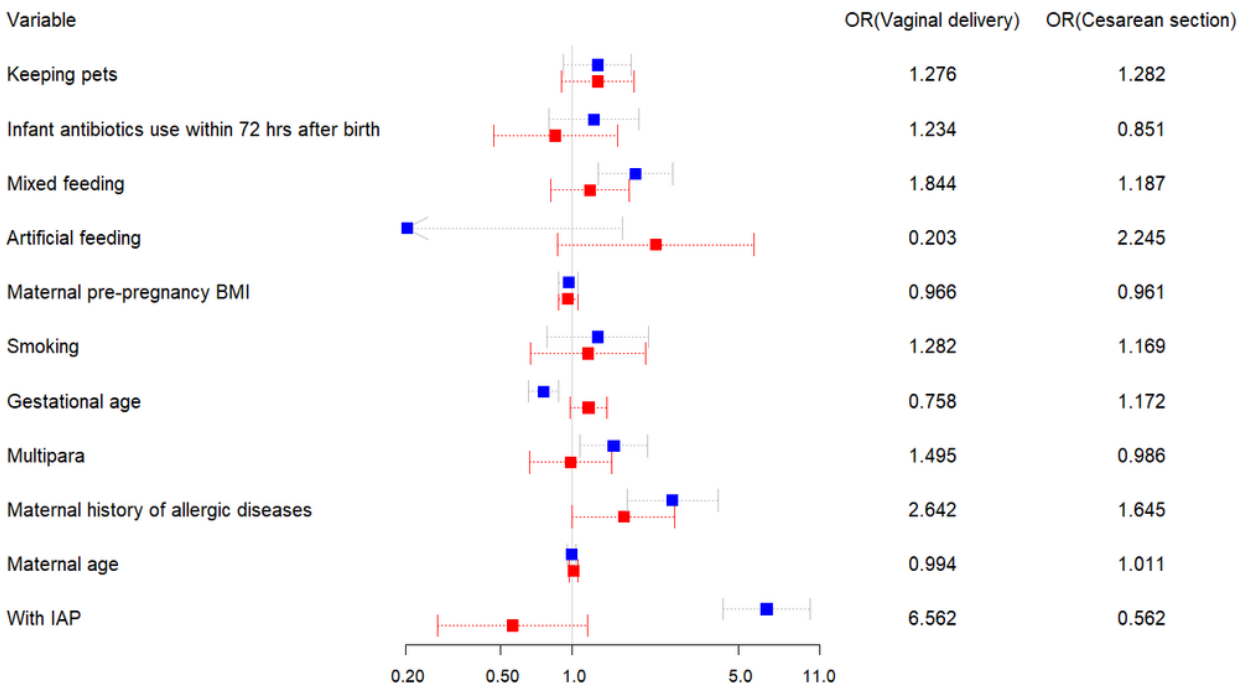

Figure 2

Forest plot for multivariate logistic regression analysis of outcomes. Blue square represents vaginal delivery and red symbol represents cesarean section.

Supplementary Files

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