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Research paper

The correlation between prelabour rupture of the membranes and neonatal infectious diseases, and the evaluation of guideline implementation in China: a multi-centre prospective cohort study ☆

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ABSTRACT

Background: The aim of this study was to describe the epidemiology of prelabour rupture of membranes (PROM) in China and to assess the association between clinical practice following the guidelines and early neonatal infections.

Methods: We conducted a prospective cohort study of 15926 deliveries in ShenZhen Baoan Women's and Children's Hospital, Xibei Women's and Children's Hospital and Chengdu Women's and Children's Hospital between August 1, 2017, to March 31, 2018. Clinical data were collected for each participant. The epidemiology of PROM was described. The association between PROM with early neonatal infectious outcomes and the influence of the implementation of the guideline on early neonatal infectious outcomes were assessed.

Findings: The incidence of PROM was 18•7%. PROM was showed to be a risk factor for neonatal infectious diseases (adjusted OR 1•92, 95%CI 1•49~2•49, $p<0•0001$), early-onset pneumonia (EOP) (adjusted OR 1•81, 95%CI 1•29~2•53, $p=0•0006$) and early-onset sepsis(EOS) (adjusted OR 14•56, 95%CI 1•90~111•67, $p=0•01$) for term neonates. For term neonates born from mother with PROM, induction of labor according to the guideline was a protective factor for neonatal diseases(adjusted OR 0•50, 95%CI 0•25~1•00, $p=0•00498$) and EOP(adjusted OR 0•32, 95%CI 0•11~0•91, $p=0•03$). For preterm neonates born from mother with PROM, using antibiotics according to the guideline showed to be protective for neonatal infectious diseases (adjusted OR 0•14, 95%CI 0•09~0•23, $p<0•0001$) and EOP (adjusted OR 0•08, 95%CI 0•04~0•14, $p<0•0001$).

Interpretation: Our study showed the risk of PROM for infectious diseases (including EOP and EOS) and the benefit of the usage of antibiotics according to the guideline for infectious diseases and EOP for preterm neonates.

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Research in context

Evidence before the study

☆ Non-declamatory title: PROM in China and assessment of current guideline.

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We searched PubMed for articles with no language restrictions published between January 1, 2015 and August 31, 2017, using the terms “prelabor rupture of membranes” or “premature rupture of membranes”, and “neonate” or “newborn”. 62 articles were found and 15 of them were focus on prelabor rupture of membranes (PROM). One study gave the incidence of PROM (15.27%) in a survey of obstetrical diseases based on 111767 cases but there was no detailed epidemiology of PROM. There were 13 researches on preterm PROM, with the largest sample size being 336 and seldom of them focused on neonatal infections. One study included both term and preterm PROM with the sample size 4629 but the outcome focused on neonatal respiratory distress syndrome and transient tachypnea of the newborn. No study evaluated the influence of treatments of the current guideline on infections of neonates born from mother with PROM.

Added value of this study

This large, multi-centre cohort study represented the details of epidemiology of PROM. In addition, our study revealed the association of PROM and neonatal infections and evaluated the influence of induction of labor, usage of antibiotics and expectant management recommended by the current guideline. The risk of PROM for neonatal infections and the benefit of induction of labor and the usage of antibiotics according to the guideline were demonstrated. Our study also showed that neonates born from mother with PROM and diabetes mellitus arising in pregnancy (GDM) were of higher risk of early-onset pneumonia.

Implications of all the available evidence

Term neonates born from mother with PROM were exposed to a higher risk of neonatal infectious diseases. Preterm neonates born from pregnancies with PROM and GDM should be paid for more attention to the prophylaxis of early-onset pneumonia. Induction of labor and the usage of antibiotics according to the guideline were recommended as the current guideline described. Expectant management should be considered carefully based on the evaluation of gestational age, infection, abruptio placentae, and umbilical cord accident.

1. Introduction

Prelabour rupture of membranes (PROM), previously known as premature rupture of membranes [1], refers to the rupture of membranes before the onset of labor.

At term, prelabour rupture of membranes (PROM) complicates approximately 8% of pregnancies in term [2], while preterm prelabour rupture of membranes is responsible for one third of preterm births[3,4] and represents a major cause of neonatal mortality and morbidity [3,5,6]. The most significant maternal consequence of PROM is intrauterine infection, the risk of which increases with the duration of membrane rupture [7], and for neonates are complications of prematurity [8], short-term neonatal disease(neonatal sepsis, neonatal pneumonia et al.) [9] and long-term disability (cerebral palsy, blindness, and deafness) [10].

The knowledge of PROM is important information for perinatologists. Management hinges on knowledge of gestational age and evaluation of the relative risks of delivery versus the risks of expectant management (eg, infection, abruptio placentae, and umbilical cord accident) [2]. In China, the management of patients with PROM had been according to the routine of the local hospital until the first practice bulletin developed by the society of obstetrics and gynaecology, Chinese medical association in January, 2015[11]. The practice bulletin was formulated referred to the guidelines of American College of Obstetricians and Gynaecologists, Royal College of Obstetricians and Gynaecologists (RCOG) and the latest evidence of evidence-based medicine.

It was reported that in China, the prevalence of PROM is higher than developed countries [4]. However, there were still little knowledge about the epidemiology of PROM in China. Most of the data from epidemiology survey and evidence-based medicine were from the United States, Ireland, Brazil et al. and the guideline was also followed the guidelines from European and American countries for the White, Black and Hispanic people. As a populous country, it is imperious for us to study the epidemiology of PROM.

As the bulletin in China was mainly referred to guidelines of the USA and Europe, it is necessary to find out the effect of the bulletin for Chinese pregnancies. It is also necessary to find out the characteristics of PROM in China. In the present study, we aimed to: 1) find out the characteristics of PROM and describe the epidemiology and outcomes of PROM in China; 2) analyze the relationship of PROM and neonatal infectious diseases; 3) assess the influence of implementation of the practice guideline on neonatal infectious diseases and further provide information to assist clinicians to accurately counsel women about maternal and fetal risks associated with PROM.

2. Methods

2.1. Study design and data sources

This study was a multi-centre prospective cohort study involving data from participants from Shenzhen Baoan Maternity and Children’s Hospital, Xibei Women and Children’s Hospital and Chendu Women and Children’s Hospital between August 1, 2017, to March 31, 2018 (). PROM was considered as the exposure. Participants were recruited from patients admitted the three participating medical centres with a diagnosis of PROM All of the women with PROM were included in the study and participants at an estimated gestational age of $<$24 weeks and $\geq$42 weeks were excluded. Pregnancies without PROM were eligible for the inclusion of unexposed group (non-PROM Group) if they satisfied the following conditions: the same gestational week, admission date$\pm$3 days and age$\pm$5 years compared with recruited PROM pregnancies. Maternal and neonatal data were collected until 7 days (death or hospital discharge if hospitalized for no more than 7 days). Clinical data including demographic, pregnancy history, obstetric and neonatal treatment regiments, laboratory test results and diagnosis were collected. This study was approved by the Ethical Committee of PLA Army General Hospital, China (2017-42) and assigned on the Protocol Registration and Results System of ClinicalTrials.gov (NCT03251898). All participants provided written informed consent to have their information collected and used for this study.

The definition of PROM is rupture of membranes before the onset of labor. Membrane rupture before labor and before 37 weeks of gestation is referred to as preterm PROM(PPROM) [11]. In our study, PROM at gestational age after 24^{+0} weeks in hospital were available in the dataset. The time between RPOM to delivery was measured.

Clinical chorioamnionitis is characterized by maternal fever, leukocytosis, maternal and/or foetal tachycardia and uterine tenderness. Deliveries with fever and one of above symptoms (leukocytosis, maternal and/or foetal tachycardia and uterine tenderness) were considered as suspected chorioamnionitis [11]. Subclinical/histologic chorioamnionitis is asymptomatic and defined by inflammation of the chorion, amnion, and placenta, which is more common than clinical chorioamnionitis. We defined degree I, II and III meconium-stained amniotic fluid as “amniotic fluid pollution” [12,13]. Gestational hypertensive (GH) is defined as a systolic blood pressure of 140 mm Hg or more or a diastolic blood pressure of 90 mm Hg or more, or both, on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure [14]; The definition of diabetes mellitus arising in

pregnancy (DMP) and essential hypertension (EH) were according to the international classification of Diseases (ICD), 11th Revision (https://icd.who.int/browse11/l-m/en).

The GBS (Group B Streptococci) examination was by culture from vaginal or rectum swabs. For antibiotic usage according to the guideline [11], term pregnancies with clinical chorioamnionitis or a GBS positive result (no matter before or after admitted to the hospital) should receive antibiotics. If there was no GBS result or the GBS result is negative, those who had a fever of ≥38•0 °C or whose interval from PROM to delivery were ≥18 hours should receive antibiotics. For preterm pregnancies, a 7-day course of therapy with broad-spectrum antibiotics were recommended. We defined the treatment follow the above procedure to be "using antibiotics according to the guideline" (Antibiotic).

According to the guideline, induction of labor within 2~12 hours after PROM is suggested for term pregnancies. During induction of labor with oxytocin, a sufficient period of adequate contractions (at least 12–18 h) should be allowed for the latent phase of labor to progress before diagnosing failed induction and moving to caesarean delivery. We defined the treatment follow the above procedure to be "induction of labor according to the guideline" (IL). For preterm pregnancies before 34^{+0} weeks of gestation, expectant management were recommended if no maternal or fetal contraindications exist.

The definition of fetal distress, large newborn for gestational age and small for gestational age were according to the ICD 11th Revision. Foetal death (FD) included antepartum foetal death, intrapartum foetal death and Unspecified time of foetal death, cause not specified.

Diagnosis including Neonatal pneumonia, neonatal sepsis, omphalitis of newborn, neonatal urinary tract infection, congenital syphilis, neonatal conjunctivitis or dacryocystitis, necrotising enterocolitis of newborn, pyogenic abscess of the skin, neonatal peritonitis, congenital cytomegalovirus infection, bacterial meningitis, fungal infection of foetus or newborn, gastroenteritis due to Rotavirus of the neonates born from participated pregnancies were defined as "Neonatal infectious diseases" in our study.l. The definition of each above disease was according to the ICD 11th Revision. The perinatal period was referred to the period between 28^{+0} weeks gestation to 7 days after birth.

The primary outcome were neonatal infectious diseases, neonatal early-onset sepsis (EOS, neonatal sepsis at <72 hours of age) and early-onset pneumonia (EOP, neonatal pneumonia at <72 hours of age). Besides, the maternal outcome including chorioamnionitis and placental abruption, fetal outcome including fetal distress, and for neonates were the transition to department of neonatology, and the duration of hospitalization were also calculated.

2.2. Statistical Analysis

We performed a calculation of sample size using PASS 11. The lowest incidence of neonatal infectious disease of neonate born from mother with PROM reported was 1•46% (P1) [15]. There is no data of the incidence of neonatal infectious disease of neonate born from mother without PROM(P2). The relative risk was supposed to be 2(P1/P2). With the 98% power using two-sided 5% significance tests, the sample size of the exposure group was estimated as 6828 (For un-exposure group, 6828).

Data were analysed by SAS (version 9•4). We determined the prevalence of PROM per 10000 pregnancies. We provided descriptive statistics of obstetric and neonatal information. Continuous variables were summarized as mean (SD) or median (Q1~Q3), and categorical variables were summarized as frequencies and proportions. Mother with or without PROM were compared with respect to maternal and neonatal baseline characteristics and outcome measures. Fisher's exact probability test and χ^2 were used when appropriate for categorical variables. The student *t* test, ANOVA and non-parametric test was used to compare differences for continuous variables. Regression models were adjusted to assess the association between risk factors and outcomes adjusting for important covariates available that were selected a priori.

We conducted multiple logistic models including the non-PROM Group to assess the association of PROM with neonatal infectious diseases, EOP and EOS. Totally 6 models were conducted. For models of term neonates including the non-PROM Group (3 models with the outcome neonatal infectious diseases, EOP and EOS, respectively), key covariate in the models were PROM. We add the following potential confounding variables: the city where the hospital locates (sorted by latitude from low to high, CITY), mode of delivery(caesarean section or vaginal delivery, CS), clinical chorioamnionitis (CC) or subclinical chorioamnionitis (SC), large or small for gestational age(LGA, SGA), amniotic fluid pollution (AP), gestational hypertensive (GH), essential hypertension (EH), diabetes mellitus arising in pregnancy (DMP), multiparity(MP) and multiple birth(MB). We added the following potential confounding variables: For models of preterm neonates including the non-PROM Group (3 models with the outcome neonatal infectious diseases, EOP and EOS, respectively), expectant management (EM) and gestational age (GA, every one week from 24^{+0} to 36^{+6}) were added as variables besides the variables enrolled in the models of term neonates. increased weekly.

We also conducted multiple logistic models that only include the participants from PROM Group with respect to the assess the influence of using antibiotics and induction of labor according to the guideline on the neonatal infectious diseases, EOP and EOS. Totally 6 models were conducted. For models of term neonates born from mother with PROM (3 models with the outcome neonatal infectious diseases, EOP and EOS, respectively), key covariates in the modes were induction of labor according to the guideline and antibiotic usage according to the guideline. The confounding variables were: the city where the hospital locates (sorted by latitude from low to high, CITY), mode of delivery, clinical chorioamnionitis, subclinical chorioamnionitis, large or small for gestational age, amniotic fluid pollution, the period from PROM to delivery (every 6 hours, Time), GH, EH, DMP, multiparity and multiple birth. For models of preterm neonates born from mother with PROM (3 models with the outcome neonatal infectious diseases, EOP and EOS, respectively), expectant management and gestational age (every one week from 24^{+0} to 36^{+6}) were added as variables, induction of labor according to the guideline was deleted because the management wouldn't be handled on the preterm pregnancies with PROM according to the guideline.

2.3. Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

3. Results

3.1. Overall prevalence of PROM

From August 1, 2017, to March 31, 2018, there were a total of 43543 deliveries (24≤GA≤42 weeks), among which there were 8151 cases of PROM(24≤GA≤42 weeks) at the three centres, giving an incidence of 18•72% (Fig. 1). All of the 8151 pregnancies with PROM were included in the PROM Group and 7775 pregnancies without PROM who met the criteria were included in the

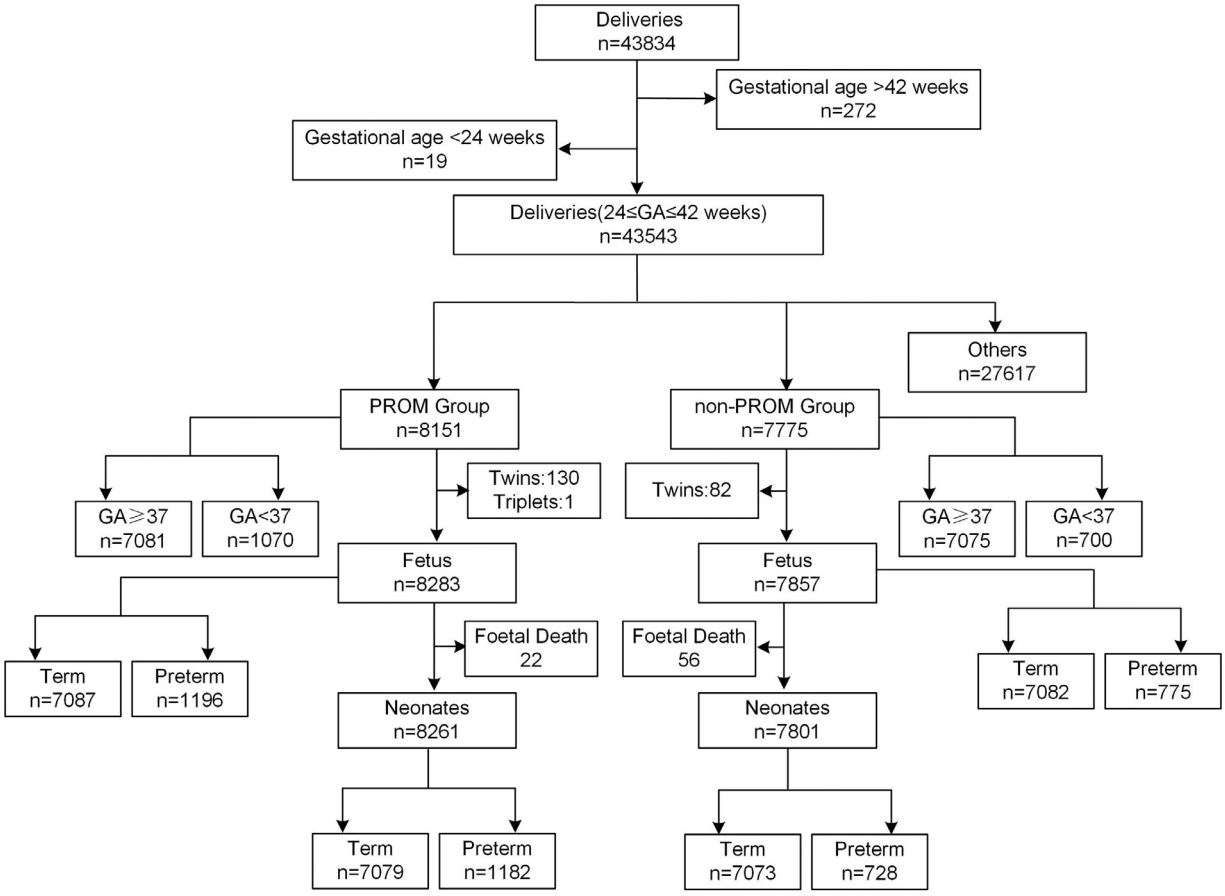

Fig. 1. Flow cart of the participants in the study. The flow chart summarizes how the sample size of the analysis was reached.

non-PROM Group. In particular, the prevalence of PROM (GA≥37^{+0} weeks) was 16•26% (7081/43543) and PPROM was 2•5 cases per 100 birth (1070/43543). For different gestation weeks, the rate of PROM varies. Among the 234 deliveries at 24–27 weeks gestation, there were 16(6•84%) cases of PROM. For 28–31 weeks gestation, there were 19•47% (133/683) of the deliveries with PROM. Among the 4156 deliveries at 32-36 weeks gestation, 921(22•16%) cases were with PROM. For the 37–41 gestation, 7081(18•41%) cases of the total 38470 deliveries were with PROM. The incidence of PROM was different between the four gestation periods (p<0•0001).

3.2. Characteristics of PROM subjects and controls

8151 women with PROM and 7775 without PROM who met the inclusion criteria were enrolled in the study. The demographic characteristics of the population are shown in Table 1. Of the 1070 preterm delivery with PROM, 25 (2•34%) were with gestational hypertension which is lower than that without PROM (45/700, 6•43%, p<0•0001). There was no significant difference of GDM in term and preterm pregnancies between PROM Group and non-PROM Group (977/7081,13•80% vs. 1035/7075, 14•63%, p = 0•15; 206/1070, 19•25% vs. 125/700 17•86%, p = 0•46). However, there were more thyroid disease during pregnancy in term deliveries with term PROM than those without PROM (547/7081, 7•72% vs. 463/7075, 6•54%, p = 0•006). The mean duration between PROM to delivery in term PROM pregnancies (median, 26•38 hours; Q1~Q3, 10•15–40•87 h) was significantly less as compared to preterm PROM pregnancies (median, 34•82 hours, Q1~Q3, 10•42-76•58 hours) (p<0•0001). As there were 131 pregnancies with more than one foetus (130 had twins and 1 had triplets) in the PROM Group and 82 (all had twins) in the non-PROM Group, there were totally 8283 and 7857 birth foetuses in the PROM Group and the non-PROM Group, respectively. Totally 8261 and 7801 neonates were survived after delivery in the PROM Group and the non-PROM Group. The baseline characteristics of the neonates were similar.

Table 1
Maternal Characteristics among pregnancies with and without PROM[a].

	n (%) PROM	Controls	p Value
Sample Size	8151	7775	
Age, mean (SD), y	30•19 (±4•08)	30•23 (±3•99)	0•11
PROM			
GA<37^{+0} weeks	1070 (13•13)		
GA≥37^{+0} weeks	7081 (86•87)		
Parity			0•0001[b]
Primiparous	5621 (68•96)	4255 (54•73)	
Multiparous	2530 (31•04)	3520 (45•27)	
Multiple birth	131(1•61)	82(1•05)	0•002[b]

Abbreviations: GA, gestational age; Q1, quartile 1; Q3, quartile 3.
[a] Percentages were tested with a χ^2 test. Medians were tested with a wilcoxon rank sum test.
[b] P value is significant at α = 0.05 level of significance.

3.3. Prevalence of GBS in pregnancies with PROM and their neonates

Of the 8151 pregnancies with PROM, 2486 took swabs of vagina or rectum for GBS examination and 271(10•91%) were found to be

colonized with GBS. Of the 132 cervix swabs, 42 were positive according to bacterial culture results. GBS was the third most frequent bacteria detected (5/42, 11•90%), while the first was *Candida albicans* (13/42, 30•95%) and the second most was *Escherichia coli* (10/42, 23•81%). Of the 102 placenta swabs from pregnant women undergoing caesarean section, only 2(1•96%) of them were GBS positive and 15 were positive for other bacteria (6 of them were *E. coli*). No invasive GBS infection was found in the 2528 neonates (83 of them were multiple birth) born from them. What's more, no invasive GBS infection was found from the 16062 neonates (427 of them were multiple birth).

3.4. Prevalence of chorioamnionitis among RPOM subject and controls and risk factor analysis

Among the 8151 pregnancies with PROM, 74(0•91%) were with clinical chorioamnionitis and 903(11•08%) were histological chorioamnionitis, while of the 35392 pregnancies without PROM, the incidence was 0•35% (123/35392, $p<0$•0001) and 2•18% (773/35392, $p<0$•0001), respectively. For pregnancies who got clinical chorioamnionitis after being admitted in hospital, the incidence of clinical chorioamnionitis was significantly higher in PROM group than that in non-PROM Group (For term pregnancies, 47/7081, 0•66% vs. 17/7075, 0•24%, $p = 0$•0003; for preterm pregnancies, 27/1070, 2•52% vs. 3/700, 0•43%, $p = 0$•0009).

3.5. Antibiotic usage

For term PROM pregnancies, there were 47 women with clinical chorioamnionitis and 18 with suspected chorioamnionitis. 25 of the women with clinical chorioamnionitis and 11 of the women with suspected chorioamnionitis used antibiotics. For the 27 preterm PROM pregnancies with clinical chorioamnionitis and the 4 preterm PROM pregnancies with suspected chorioamnionitis, 8(29•63%) and 1(25•00%) use antibiotics.

Pregnancies should receive GBS testing during 35~37 weeks of pregnancy according to the guideline for prenatal care [16]. According to the guideline for PROM [11], women with PROM should receive intrapartum GBS prophylaxis to prevent vertical transmission regardless of earlier treatments. For 7081 PROM pregnancies with GA$\geq 37^{+0}$ weeks, 2117 women had GBS culture results. 249 were positive and all of them were treated with antibiotics (within 2 h). Among the 1865 pregnancies (6 of their neonates were twins) with GBS negative result, 1131(60•64%) of them were treated with antibiotics. However, the rate of neonatal infectious diseases, EOP and EOS showed no statistically difference between the negative GBS term pregnancies no matter use antibiotics or not (10/1131, 0•88% vs. 7/737, 0•95%, $p = 0$•88; 8/1131, 0•71% vs. 2/737, 0•27%, $p = 0$•21; 1/1131, 0•09% vs. 3/737, 0•41%, $p = 0$•15). Among the 2201 pregnancies who did not take GBS examination and went into delivery within 18 hours, 15 pregnancies were with a temperature $\geq$38 °C and 10 were treated with antibiotics. 2710 pregnancies went into labor after 18 hours since PROM and 1783 were treated with antibiotics. For 1070 preterm pregnancies, 346 of them had GBS culture results and 22 women (6•36%) had positive GBS culture results before or after being admitted to the hospital. All of the 22 GBS-positive pregnancies were treated with antibiotics.

3.6. Termination of pregnancy after PROM

All (74/74) of the PROM pregnancies with clinical received the management of termination of pregnancy as the guideline ordered. Of the 7081 term PROM pregnancies, 4097 should receive induction of labor and only 716 of them did. Totally 2626(2626/8151, 32•22%) of the PROM pregnancies underwent caesarean section. In detail, the rate of caesarean section for term PROM pregnancies was 29•52% (2090/7081) and for preterm PROM pregnancies was 50•28% (538/1070). 476 PROM pregnancies were with a gestational age <34 weeks, and 334 of them received expectant management.

3.7. Maternal and fetal outcome

As there were 131 pregnancies with more than one foetus (130 had twins and 1 had triplets) in the PROM Group and 82 (all had twins) in the non-PROM Group, there were totally 8283 and 7857 foetuses in the PROM Group and the non-PROM Group, respectively. For term-pregnancies, abruptio placentae happened in a significantly higher proportion in PROM Group than in non-PROM Group (33/7087, 0•47% vs. 17/7082, 0•24%, $p = 0$•02). For preterm pregnancies, the proportion of abruptio placentae was 1•76% (21/1196) in PROM Group and 2•45% (19/775) in non-PROM Group, however, the difference was not significant($p = 0$•28). Of the 7087 births at term, more births (273/7087, 3•85%) were combined with foetal distress in PROM Group than in non-PROM Group (165/7082, 2•33%) ($p<0.0001$), while in preterm births, there was no significant difference between the PROM Group (59/1196, 4•93%) and the non-PROM Group (46/775, 5•94%) ($p = 0$•33) (Fig. 2). In the PROM group, there were totally 8283 birth (8020 singleton and 263 multiple-birth). For singletons, 0.27% (22/8020) births died in utero or intrapartum in PROM Group (52/7693, 0•68% in non-PROM Group, $p = 0$•0002). For multiple-birth, no birth died in utero or intrapartum in PROM Group and 4 (4/164, 2•44%) in non-PROM Group ($p = 0$•02). The perinatal mortality (between 28^{+0} weeks gestation to about 7 days after birth) was 0•07% (6/8266) in the PROM group and 0•46% (36/7845) in the non-PROM Group (The difference was statistically significant, $p<0$•0001). Specially, the death mainly happened in preterm foetus or neonates (0•51% (6/1179) for PROM group and 4•59% (35/763) in the non-PROM Group, and the difference was statistically significant, $p<0$•0001).

3.8. Neonatal outcome

Totally 8261 and 7801 neonates were born in the PROM Group and the non-PROM Group. The birthweight was 3169•3±552•5g in the PROM Group the non-PROM Group and 3221•7±503•3g in the non-PROM Group ($p<0.0001$). There was no statistical difference between sex (the proportion of male:4337/8261, 52•50% vs. 4178/7801, 53•56%, $p = 0$•18). Apgar score$\leq$3 at 1 minute (5 minutes, 10 minutes) occurred in 0•15% (0•02%, 0•02%) of neonates born from mother with PROM and of neonates from the non-PROM Group were 0•15% (0•01%, 0•04%), and the difference was not statistically significant ($p = 0$•89, $p = 1$•00, $p = 0$•68).. For preterm birth, 63•62% (752/1182) neonates in PROM Group were transferred to department of neonatology (58•52% in non-PROM Group, $p<0$•0001). For multiple birth, (204/263) (77•57%) neonates in PROM Group were transferred to department of neonatology (70•12%, 115/164 in non-PROM Group, $p = 0$•09). For preterm neonates transferred to department of neonatology, the duration of hospital stays(days) were shorter in PROM Group than in non-PROM Group (17•78±14•78 vs. 21•59±30•45, $p = 0$•004). For term neonates who were transferred to department of neonatology, there was no significant difference between the two groups (days, 6•.69±4.13, 6•89±3•77, $p = 0$•09). 462 of the 8261 (5•59%) neonates born to mothers with PROM and 3•59% (280/7801) neonates in non-PROM Group ($p<0$•0001) got infectious diseases. In particular, of the neonates born to mothers exposed to RPOM, 3•52% (291/8261) neonates got early-onset pneumonia and 0•38% (188/7801) got early-onset sepsis in PROM group. In comparison, the incidence of early-onset pneumonia and early-onset sepsis was lower in non-PROM Group (2•41%, $p<0$•0001 and 0•10%, $p = 0$•0004) (Fig. 2).

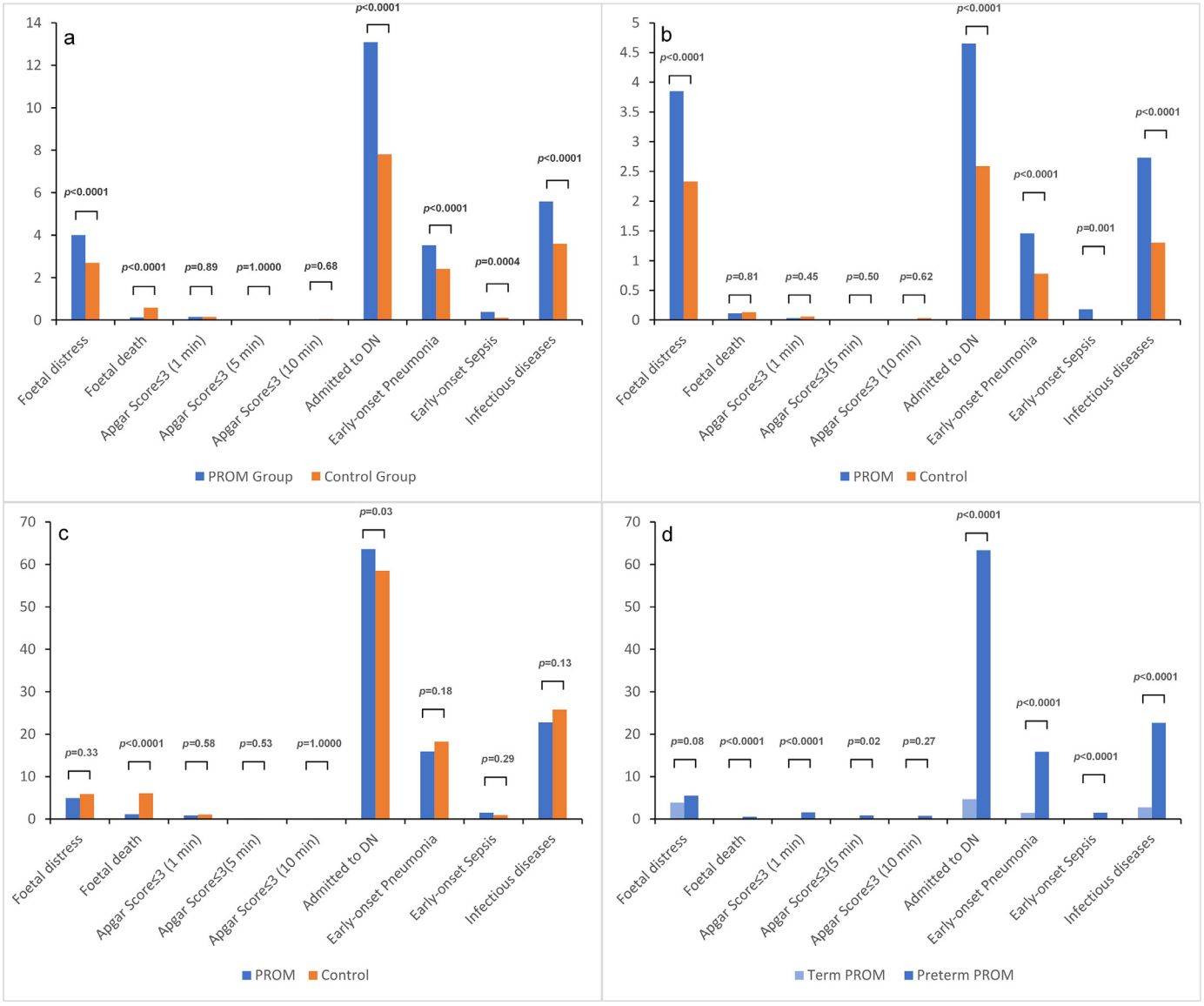

Fig. 2. The foetal and neonatal outcomes. A. The Fig. showed the differences of outcomes between foetus or neonates in the PROM Group (8283 foetus and 8261 neonates) and the non-PROM Group (7857 foetuses and 7801 neonates in the non-PROM Group). DN means department of neonatology. B. The Fig. showed the differences of outcomes between term foetus or neonates in PROM Group (7087 foetus and 7079 neonates) and non-PROM Group (7082 foetuses and 7073 neonates in the non-PROM Group). DN means department of neonatology. C. The Fig. showed the differences of outcomes between preterm foetus or neonates in the PROM Group (1196 foetus and 1182 neonates) and the non-PROM Group (775 foetuses and 728 neonates in the non-PROM Group). DN means department of neonatology. D. The Fig. showed the differences of outcomes between term (7087 foetus and 7079 neonates) and preterm (1196 foetuses and 1182 neonates in the non-PROM Group)foetus or neonates in PROM Group. DN means department of neonatology.

3.9. Multivariate analysis of the association between PROM and neonatal infectious diseases, early-onset pneumonia and early-onset sepsis

For term neonates, PROM was a risk factor for neonatal infectious diseases (adjusted OR 1•92, 95%CI 1•49~2•49, $p<0•0001$), EOP (adjusted OR 1•81, 95%CI 1•29~2•53, $p = 0•0006$) and EOS(adjusted OR 14•56, 95%CI 1•90~111•67, $p = 0•01$)(Figs. 3a, b, c). Clinical chorioamnionitis was a risk factor for both neonatal infectious diseases (adjusted OR 2•91, 95%CI 1•15~7•36, $p = 0•02$) and EOS (adjusted OR 8•70, 95%CI 1•08~70•16, $p = 0•04$) (Fig. 3a, 3c). Amniotic fluid pollution was a risk factor for neonatal infectious diseases (adjusted OR 1•61, 95%CI 1•22~2•13, $p = 0•0007$) and EOP (adjusted OR 1•61, 95%CI 1•22~2•13, $p = 0•01$) (Fig. 3a, 3b). Specially, caesarean section was a risk factor of EOP (adjusted OR 1•45, 95%CI 1•05~2•02, $p = 0•0006$) (Fig. 3b) and LGA was a risk factor for neonatal infectious diseases (adjusted OR 1•38, 95%CI 1•04~1•84, $p = 0•03$) (Fig. 3a). The higher latitude of city where the hospital locates was a protective factor for EOP (adjusted OR 0•78, 95%CI 0•64~0•94, $p = 0•008$) and EOS (adjusted OR 0•50, 95%CI 0•27~0•93, $p = 0•03$) (Fig. 3b and 3c). In addition, multiparity was a protective factor for neonatal infectious diseases (adjusted OR 0•62, 95%CI 0•47~0•82, $p = 0•0009$) (Fig. 3a).

For preterm neonate, there was no significance of the influence of PROM on neonatal infectious diseases, EOP and EOS after being adjusted for confounder factors. However, the increase of gestation age showed to be protective in neonatal infectious diseases (adjusted OR 0•74, 95%CI 0•70~0•78, $p<0•0001$), EOP(adjusted OR 0•79, 95%CI 0•75~0•83, $p<0•0001$) and EOS(adjusted OR 0•73, 95%CI 0•62~0•85, $p<0•0001$) (Fig. 3d, 3e, 3f), that is to say, the smaller the GA was, the high the risk for infectious diseases, EOP and EOS was. Small for gestational age was a

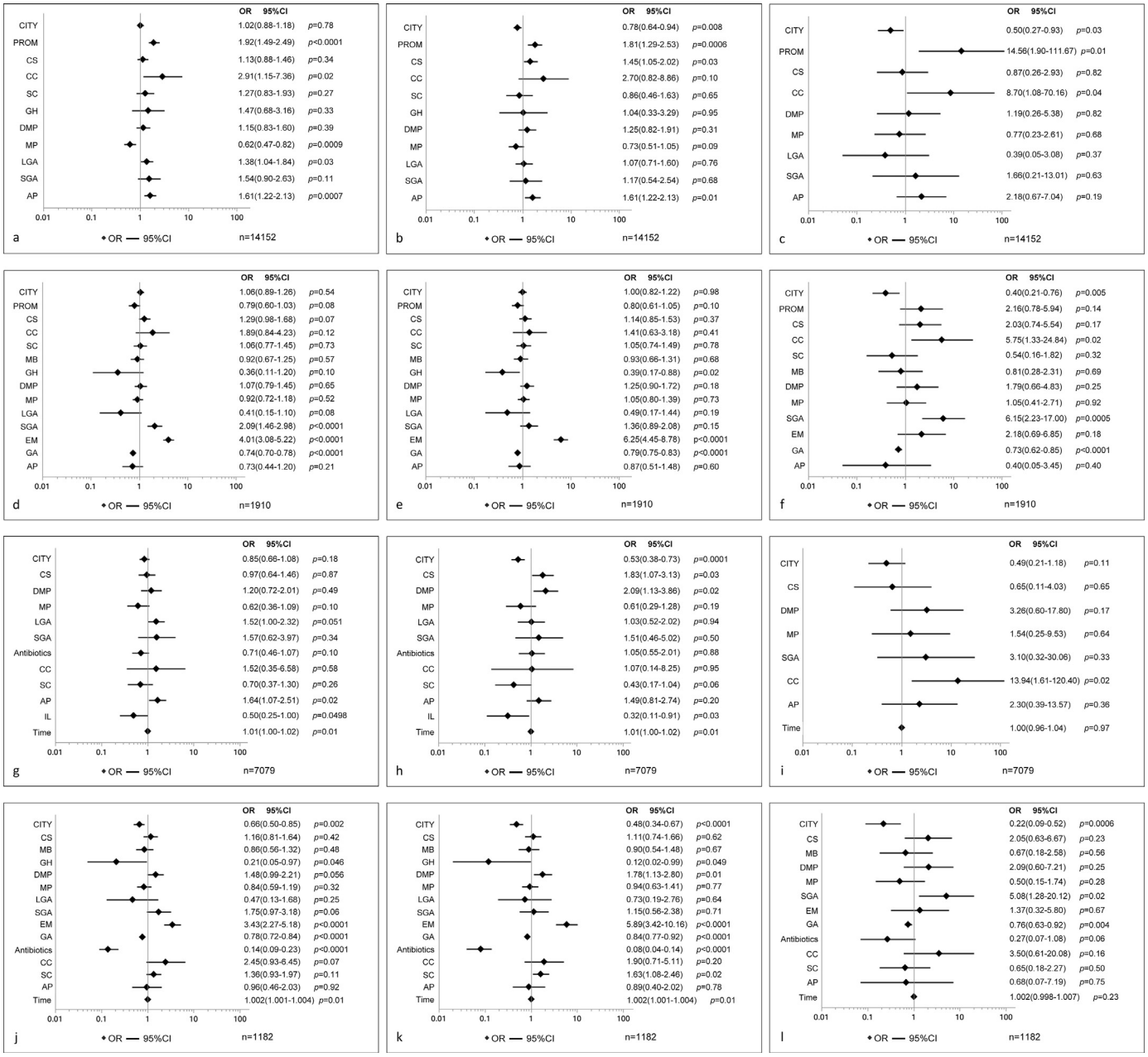

Fig. 3. Factors related with neonatal infectious diseases, EOP and EOS. (a). Factors related with neonatal infectious diseases for term neonates; (b). Factors related with EOP for term neonates; (c). Factors related with EOS for term neonates; (d). Factors related with neonatal infectious diseases for preterm neonates; (e). Factors related with EOP for preterm neonates; (f). Factors related with EOS for preterm neonates; (g). Factors related with neonatal infectious diseases for term neonates born from mother with PROM; (h). Factors related with EOP for term neonates born from mother with PROM; (i). Factors related with EOS for term neonates born from mother with PROM; (j). Factors related with neonatal infectious diseases for preterm neonates born from mother with PROM. (k). Factors related with EOP for preterm neonates born from mother with PROM; (l). Factors related with EOS for preterm neonates born from mother with PROM; The black points are the adjusted ORs for death and the black error bars are the 95% CIs. ORs and 95% CIs were calculated with logistic model for infectious diseases, EOP and EOS. Stepwise selection was used for logistic regression: a significance level of 0.3 is required to allow a variable into the model (SLENTRY=0.3), and a significance level of 0.25 is required for a variable to stay in the model (SLSTAY=0.25). n means the number of neonates in the model. Not all of the factors were showed in the Fig.s, only valuable factors were showed in the Fig.s. CITY, the city where the hospital locates (sorted by latitude from low to high); PROM, prelabour rupture of membranes; CS, caesarean section; CC, clinical chorioamnionitis; SC, subclinical chorioamnionitis; MB, multiple birth; GH, Gestational hypertensive; EH, essential hypertension; DMP, diabetes mellitus arising in pregnancy; MP, multiparity; LGA, large for gestational age; SGA, small for gestational age; AP, amniotic fluid pollution; EM, expectant management; GA, gestational age (every one week from 24^{+0} to 36^{+6}); "Antibiotics" means use antibiotics according to the guideline; IL, induction of labor according to the guideline; "Time" means the length of time from RPOM to delivery (every 6 h).

risk factor for neonatal infectious diseases (adjusted OR 2•09, 95%CI 1•46~2•98, p<0•0001) and EOS (adjusted OR 6•15, 95%CI 2•23~17•00, $p = 0•0005$) (Figs. 3d and f). Expectant management was a risk factor for neonatal infectious diseases (adjusted OR 4•01, 95%CI 3•08~5•22, p<0•0001) and EOP (adjusted OR 6•15, 95%CI 2•23~17•00, $p = 0•0005$) (Figs. 3d and e). Clinical chorioamnionitis was a risk factor for EOS (adjusted OR 5•75, 95%CI 1•33~24•84, $p = 0•02$) (Fig. 3f). Specially, gestational hypertension was a protective factor for EOP (adjusted OR 0•39, 95%CI 0•17~0•88, $p = 0•02$) (Fig. 3e), and the higher latitude of city where the hospital locates was a protective factor for EOS (adjusted OR 0•40, 95%CI 0•21~0•76, $p = 0•005$) (Fig. 3f).

3.10. Multivariate analysis of the influence of managements according to the guideline in PROM pregnancies

The main management for term PROM pregnancies were induction of labor and antibiotic usage, and for preterm PROM were antibiotic usage and expectant management.

For term neonates born from mother with PROM, induction of labor according to the guideline was a protective factor for neonatal diseases(adjusted OR 0•50, 95%CI 0•25~1•00, $p = 0•00498$) and EOP(adjusted OR 0•32, 95%CI 0•11~0•91, $p = 0•03$)(Fig. 3g, h). The higher latitude of city where the hospital locates was a protective factor for EOP (adjusted OR 0•53, 95%CI 0•38~0•73, $p = 0•0001$) (Fig. 3h).The risk of neonatal infectious diseases and EOP increased by 1% (adjusted OR 1•01, 95%CI 1•00~1•02, $p = 0•025$) for every 6 hours from PROM to delivery. Amniotic fluid pollution was a risk factor (adjusted OR 1•64, 95%CI 1•07~2•51, $p = 0•02$) for neonatal infectious diseases (Fig. 3g) and clinical chorioamnionitis was the only risk factor (adjusted OR 13•94, 95%CI 1•61~120•40, $p = 0•02$) for EOS (Fig. 3i). Caesarean section was also a risk factor (adjusted OR 1•83, 95%CI 0•38~0•73, $p = 0•0001$) of EOP of term neonates born from mother with PROM (Fig. 3h). Specially, diabetes mellitus arising in pregnancy could raise the risk of EOP (adjusted OR 2•09, 95%CI 1•13~3•86, $p = 0•02$) of term neonates born from mother with PROM (Fig. 3h).

For preterm neonates born from mother with PROM, the increase of gestation age and the higher latitude of city where the hospital locates showed to be protective in neonatal infectious diseases(adjusted OR 0•78, 95%CI 0•72~0•84, $p<0•0001$; adjusted OR 0•66, 95%CI 0•50~0•85, $p = 0•002$), EOP(adjusted OR 0•84, 95%CI 0•77~0•92, $p<0•0001$; adjusted OR 0•48, 95%CI 0•34~0•67, $p<0•0001$) and EOS(adjusted OR 0•76, 95%CI 0•63~0•92, $p = 0•004$; adjusted OR 0•22, 95%CI 0•09~0•52, $p = 0•0006$)(Figs. 3j, 3k, 3l). Using antibiotics according to the guideline showed to be protective for neonatal infectious diseases (adjusted OR 0•14, 95%CI 0•09~0•23, $p<0•0001$) and EOP (adjusted OR 0•08, 95%CI 0•04~0•14, $p<0•0001$) (Figs. 3j, 3k). Surprisingly, gestational hypertension was also protective for neonatal diseases(adjusted OR 0•21, 95%CI 0•05~0•97, $p = 0•046$) and EOP (adjusted OR 0•12, 95%CI 0•02~0•99, $p = 0•049$) of preterm neonates born from mother with PROM(Fig. 3j, 3k). The risk increased weakly (0•2%) every 6 hours from PROM to delivery for neonatal infectious diseases (adjusted OR 1•002, 95%CI 1•001~1•004, $p = 0•01$) and EOP (adjusted OR 1•002, 95%CI 1•001~1•004, $p = 0•01$) (Figs. 3j, 3k). Expectant management was a risk factor for both neonatal infectious diseases (adjusted OR 3•43, 95%CI 2•27~5•18, $p<0•0001$) and EOP (adjusted OR 5•89, 95%CI 3•42~10•16, $p<0•0001$) (Fig. 3j, 3k). Diabetes mellitus arising in pregnancy was also a risk factor for EOP (adjusted OR 1•78, 95%CI 1•13~2•80, $p = 0•01$) (Fig. 3k). Small for gestational age was a risk factor for EOS(adjusted OR 5•08, 95%CI 1•28~20•12, $p = 0•02$).

4. Discussion

Our study gave a detailed description of the epidemiology of PROM in China. Until recently, there hasn't any accurate population-based epidemiological data on PROM is yet available in China. Seldom studies described the epidemiology of PROM in China systematically. In addition, studies nowadays focused on the previable PROM (GA <23 weeks) or the interventions including induction of labor, antibiotics, tocolysis and expectant management. However, seldom studies evaluate the effect of practices of the current guidelines. Our study described the epidemiology and outcomes of PROM, analysed the relationship between PROM and neonatal infectious diseases and assessed the influence of implementation of the practice guideline on neonatal infectious diseases.

In our study, the incidence of term PROM in the three centres in China was 16•26%, which was higher than the incidence (8%) reported in the USA [2]. The prevalence of preterm premature rupture of the membranes is similar between developed countries and developing countries: Pakistan (3•27%) [17], Nigeria(2•5%) [18], USA(3%~4•5%) [2,19] and in our study it was 2•5%.

The rate of GBS colonization in PROM pregnancies of our cohort was 10•91%, which is similar with that of East Asia reported in a systematic review (11% [95% CI, 10%–12%]) [20]. The Caribbean had the highest prevalence of GBS colonization in virgin and/or rectum (34% [95% CI, 29%–38%]) [20]. In other regions, the rate is quite similar with some variations ranging from 6.5 up to 36% in Europe, 10 to 30% in United states, 9•1 to 25•3% in the Middle East and 11•9 to 31•6% in Africa [21–23]. A recent comprehensive review and meta-analyses represent a pooled incidence of invasive GBS disease in infants which was highest in Africa(1•12‰), 0•46‰ in developed countries and lowest in Asia(0•3‰) [24]. Differences in prevalence of GBS colonization and serotype distribution among mothers in different regions may help to explain apparent differences in incidence of newborn invasive GBS disease. The neonatal GBS infection could be well controlled by intrapartum antibiotic prophylaxis. It reported that the incidence of early-onset neonatal group B streptococcal disease (EOGBSD) declined by a strikingly 65% from 1993 to 1998 in the USA [25]. A previously study in China investigated the EOGBSD in neonates before and after GBS prophylaxis and found the rate of EOGBSD decreased from 0•3‰(11/31773) to 0 [26].

Of the 3 hospital our study enrolled, only one hospital carried out comprehensive screening of GBS in pregnancies as the guideline recommended. One hospital partly screened and the other did not carry out GBS screening item. As the infant invasive GBS disease case fatality rate is high, yet the incidence is likely considerably underestimated in settings with limited access to care and diagnostics as <10% of neonates with suspected serious infection have a positive blood culture [27,28], the intrapartum antibiotic prophylaxis should be paid more attention.

For the pregnancies with PROM, 62•16% (46/74) of the clinical chorioamnionitis developed after PROM. A significantly higher rate of pregnancies developed clinical chorioamnionitis after PROM than the rate of those without PROM (0•65% vs. 0•24%, $p = 0•003$). Similarly, more histological chorioamnionitis were found in PROM group than in the non-PROM Group (11•08% vs. 2•48%, $p<0•0001$). These results suggest that pregnancies with PROM may face a higher risk of infection. However, the rate of perinatal mortality was higher in the non-PROM Group. The reason of the higher rate of perinatal mortality in the non-PROM Group may due to that the pregnancies who admitted to hospital not due to spontaneous labor at term were more likely because of complications during pregnancy, and this may also explain the higher apgar score and the longer duration of hospitalization of neonates born from mother in the non-PROM Group. There were more cases of foetal distress in PROM Group. As expected, there were more neonates who born from mother with PROM were suffered from infectious diseases suggested that they were exposed to a higher risk of infection than those born from mother without PROM.

Most of the studies focus on preterm PROM because the preterm neonate is a special population due to their immature gastrointestinal, respiratory, neurological and immunological systems of the preterm neonates. Our study compared the maternal, fetal and neonatal outcomes of preterm and term neonates. Generally, preterm neonates born from mother with PROM were worse than those term neonates. More preterm neonates born from mother with PROM had suffered from placental abruption. Not surprisingly, among the neonates born from mother with PROM, there were much more preterm neonates admitted to department of neonatology than term neonates and the duration of hospitalization were

longer for the preterm neonates. More preterm neonates suffered from infectious diseases than term neonate.

Our study, which used large amounts of data collected prospectively, offers a credible estimate of the influence of PROM on neonatal infectious diseases, early-onset pneumonia and neonatal early-onset sepsis. Our study gave the evidence that for term neonates, PROM was a risk factor for neonatal infectious diseases, EOP and EOS. It was reported that chorioamnionitis was associated with a higher risk of EOS [29]. Our study showed that clinical chorioamnionitis was associated with a higher risk of neonatal infectious diseases and EOS. For EOP, caesarean section was a risk factor. The reason may due to the rapid clearance of foetal lung fluid during the process of vaginal birth, however, the neonates born from caesarean section lack of the process and so that there would be residual fluid in their pneumonia [30]. Multiparity was a protective factor of infectious diseases may be because of the shorter time of the duration of labor. It is known that the cervical dilation rates and foetal descent process of multiparous women is faster than that of nulliparous women [31,32], and we concluded that the shorter labor process may be the reason of lower risk of infection.

For preterm neonates, the influence of PROM was adjusted and the most important risk factor were smaller gestational age and expectant management. Specially, small for gestational age presented to be high risk for EOS of preterm neonates. The result also indicated that preterm neonates who were with the immature of the gastrointestinal, respiratory, neurological and immunological systems were at a higher risk of infectious diseases. What's more, the fact that preterm neonates are more likely to be put on artificial respiration and fed artificially or parenterally make them exposed to a higher risk of infection.

For neonates born from mother with PROM, the main interventions for PROM are induction of labor, the use of antibiotics and expectant management. The influence of induction, use of antibiotics and expectant management were assessed. It is showed that the influence of induction of labor according to the guideline were protective for neonatal infectious diseases and EOP of term neonates while the influence of antibiotic usage according to the guideline were not significant. For preterm neonates, expectant management was still a risk factor for neonatal infectious diseases and EOP even though adjusted with gestational age. Use antibiotics according to the guideline was showed to be for infectious diseases and EOP of preterm neonates.

Our results showed that neonates born from mother with PROM and GDM were of higher risk of early-onset pneumonia and it could be explained by the adverse effects on foetal pulmonary maturity associated with exposure to diabetes in utero which have been documented in epidemiological and experimental studies [33]. Surprisingly, gestational hypertension showed protective for EOP in preterm neonates. It is with broad agreement that prenatal corticosteroids for foetal lung maturation should be given between 24^{+0}~34^{+0} weeks gestation and may be given up until 38^{+0} weeks [34]. Therefore, the decreased risk of EOP may due to the therapy for feotal lung maturation.

Interestingly, we found the higher latitude where the hospital locates was a protective factor in most of the models. China locates in the Northern Hemisphere (north of 3°N). From August 1, 2017, to March 31, 2018, the humidity and temperature decreases gradually with the rise of latitude and this might be the reason of the lower the risk of the neonatal infectious diseases.

It is worth mentioning that PROM was associated with neonatal infectious disease in term neonates and expectant management was associated with infectious disease among preterm neonates. To avoid collinearity issue of the multiple regression model, we did the correlation analysis between the two variables. The contingency coefficient value between PROM and expectant management was 0•05 (among the deliveries with GA<34 weeks), so that we concluded that the two variables were independent of each other and the models were stable. When study associations between PROM and infectious disease in preterm births, PROM and expectant management were included in the model simultaneously.

Scaling up evidence-based interventions addressing maternal risk factors and underlying causes could reduce neonatal infections by 84% [35]. Our study showed the risk of PROM for infectious diseases (including EOP and EOS) term neonates. The results also showed that the preterm neonates born from mother with PROM were also exposed to risk of infections (including EOP and EOS). Thus, the prevention of infection should be paid more attention for neonates born from mother with PROM. In addition, our study suggested the benefit of the usage of antibiotics according to the guideline for infectious diseases and EOP for preterm neonates and emphasized the importance of the use of prophylactic antibiotics.

One of the limitations of our study was that it would be better to have all the 43,543 deliveries enrolled in the cohort. However, due to the limitation of the practical constraints (time, number of investigators and cost of funding), it was impossible for us to collect all of the data of 43543 deliveries. We had only the rates of PROM and chorioamnionitis based on the 43,543 deliveries. We set restrictions for the un-exposure group to keep balance of some basic characteristics with exposure group. Those deliveries without PROM who met the restrictions were enrolled in the cohort. However, as there were not enough preterm pregnancies without PROM matched with preterm PROM cases, we failed to match the exposure group 1:1 even though we've tired our best.

The other drawback was that the number of EOS cases were not sufficient to assess the influence of maternal usage of antibiotics. In our study, clinical chorioamnionitis was adjusted except for infectious diseases of preterm neonates. However, there was a previously study including 2390 infants(GA≤27 weeks) born from mother with chorioamnionitis indicated that chorioamnionitis was a risk factor of neonatal EOS [36].

In 2015, infection accounted for 15% of the 2•7 million neonatal deaths globally or some 400 000 deaths [37]. The vast majority of these neonatal deaths occur in low/middle-income countries [38,39]. In China, the incidence of EOS among inborn infants was up to 9•7 cases per 1000 live births <34 weeks' gestation and neonatal GBS invasive infection was rather rare [40]. However, the guideline in western countries were mainly focus on the prevention of GBS. As there were still lack of high-quality data of the colonization spectrum of microbes in pregnancies of China, more study should be conducted to find out the colonization and transmission characteristics of the pathogens.

Contributors

F-ZC, XL, S-DH and LZ designed the study. LZ, Z-KL, Y-FZ and RJ wrote the manuscript. Z-KL, Y-FZ, RJ, C-ZY, Y-PZ, LL, TL, YY, WZ, JC, X-YC, J-YP recruited and followed up the participants and collected the data. LZ, X-YC, J-YP did the statistical analyses. All authors contributed to review and revision, and have seen and approved the final version of the manuscript.

Data sharing statement

After publication, the data will be made available to others on reasonable requests to the corresponding author. A proposal with detailed description of study objectives and statistical analysis plan will be needed for evaluation of the reasonability of requests. Additional materials might also be required during the process of evaluation. Deidentified participant data will be provided after approval from the corresponding author and Seventh Medical Centre, PLA general hospital.

Declaration of Competing Interest

We declare no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lanwpc.2020.100029.

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