



The role of genital tract infection in preterm delivery: a retrospective study

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ABSTRACT

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Preterm delivery is associated with higher mortality and morbidity of neonates, also increases their risk of having growth and development impairment. This study aimed to identify the role of genital tract infection in preterm delivery. A retrospective study was conducted on medical records of mothers who had preterm delivery in a tertiary hospital in Surakarta, Indonesia during 2017. The data collected were mothers' age and their gestational age, the history of current pregnancy, the number of previous abortion(s), mothers' body temperature, the extent of abnormal vaginal discharge, and laboratory findings (white blood cell count, platelet count, red blood cell count, hemoglobin count, hematocrit level, urinalysis and microbiology results). The statistical differences amongst categorical and numerical data were analyzed using the Chi-Square test and the Mann-Whitney test. Based on the patient's history and the examination results, we suspected genital tract infections in 22.52% (25/111) of subjects. All of them had abnormal vaginal discharge despite only one case had been confirmed as streptococcal infection. This study found that the majority of mothers with probable genital tract infection had preterm premature rupture of the membrane whilst preeclampsia was more evident in those without genital tract infection. We conclude that genital tract infection during pregnancy is a significant contributor to the occurrence of premature birth so that microbiological testing is needed to confirm the diagnosis.

ABSTRAK

Kelahiran *preterm* berkaitan dengan meningkatnya mortalitas dan morbiditas neonatus, serta meningkatkan risiko terjadinya kelainan tumbuh kembang. Penelitian ini bertujuan untuk mengidentifikasi peranan infeksi saluran genital terhadap kelahiran *preterm*. Penelitian dilakukan secara retrospektif menggunakan data rekam medis dari ibu-ibu yang melahirkan *preterm* di sebuah rumah sakit tersier di Surakarta, Indonesia pada tahun 2017. Data yang dikumpulkan adalah usia ibu dan usia kehamilan, riwayat kehamilan saat ini, jumlah abortus sebelumnya, suhu tubuh ibu hamil, adanya keputihan yang abnormal, dan hasil pemeriksaan laboratorium (hitung sel darah putih, hitung trombosit, hitung sel darah merah, hitung hemoglobin, kadar hematokrit, urinalisis, dan hasil pemeriksaan mikrobiologi). Perbedaan statistik yang ada pada data kategorikal dan numerik dianalisis menggunakan uji *Chi-Square* dan uji *Mann-Whitney*. Berdasarkan data hasil anamnesis dan pemeriksaan, 25 dari 111 subjek penelitian (22,52%) diduga menderita infeksi saluran genital. Pasien yang terduga infeksi tersebut seluruhnya mengalami keputihan yang abnormal meskipun hanya satu kasus yang terdiagnosis infeksi streptokokus. Pada penelitian ini didapatkan ketuban pecah dini *preterm* pada mayoritas ibu hamil yang dicurigai menderita infeksi saluran genital sedangkan preeklampsia lebih banyak dijumpai pada kelompok ibu hamil yang tidak terinfeksi. Dapat disimpulkan bahwa infeksi saluran genital berperan penting dalam terjadinya kelahiran prematur sehingga pemeriksaan mikrobiologi diperlukan untuk menegakkan diagnosis.

Keywords:
preterm labor
preterm delivery
premature birth
premature rupture of membrane
genital tract infection

INTRODUCTION

Preterm delivery occurs in 5-18% of total delivery worldwide.¹ It was reported that preterm delivery is associated with the increased neonatal mortality and morbidity. Preterm delivery is also considered as a strong risk factor for impaired growth and development in children.^{2,3} The condition of preterm delivery is attributed to many risk factors, either infectious or non-infectious causes.^{4,5} The infectious causes of preterm delivery can be originated from the genital tract itself or systemic infection such as sepsis.^{6,7}

In pregnancy, genital tract infection could induce preterm labor through several mechanisms. The mechanisms include early uterine contraction, early cervical ripening, and preterm premature rupture of membrane.^{7,8} Preterm premature rupture of membrane (pPROM) is a pre-labor rupture of the membrane that happens before the 37 weeks of gestation.⁹ It can be caused by several factors, with genital tract infection accounted for 50-60% of total pPROM cases. The condition itself is responsible for the 35% of the preterm delivery cases.¹⁰

Non-infectious conditions that account for preterm delivery include multiple gestation, polyhydramnios, and preeclampsia.^{11,12} The mechanism contributing to preterm delivery in a non-infectious state is similar to that in an infectious state, i.e. inflammation.¹³ The inflammatory condition in a non-infectious state could also lead to early uterine contraction, early cervical ripening, and preterm premature rupture of membrane, as it happens in the infectious state. In addition, preeclampsia can cause medically indicated preterm delivery due to emergency condition for both the mother and fetus.¹⁴

As there are many factors that can contribute to preterm delivery, an evaluation is needed to determine the role

of genital tract infection so that control measures and better management of pregnancy could be implemented. Such implementation is important in order to reduce the morbidity and mortality associated with preterm delivery in neonates.

Previous studies showed that several factors such as number of previous pregnancy, history of abortion, infection during pregnancy, preeclampsia, and multiple gestations contribute to preterm labor.^{15,16} However, those studies did not compare the contributing factors in the presence or absence of genital tract infection despite the risk that genital tract infection possess in imposing preterm labor. Therefore, this study aimed to identify the role of genital tract infection in preterm deliveries occurred in a tertiary hospital in Indonesia.

MATERIALS AND METHODS

Study design and data collection

In this study, we reviewed the medical records of women with preterm delivery who admitted to Dr. Moewardi General Hospital's obstetric ward in 2017. Dr. Moewardi General Hospital is a tertiary hospital located in Surakarta, Central Java, Indonesia. This hospital is a major referral hospital in Central Java and serves 34,257,865 population in the province.¹⁷ As one of two main referral hospitals in the province, uncomplicated pregnancies and normal deliveries are rarely seen in this hospital because such cases are commonly treated at primary care levels. Thus, the vast majority of obstetric cases in this hospital are that with pathological conditions.

The records were identified from the hospital database by using the search code of ICD-X O60 (international classification of diseases representing preterm delivery). The following data were retrieved from the medical records: mothers' age and gestational

age, the history of current pregnancy, the number of previous abortion(s), the mothers' body temperature, the extent of abnormal vaginal discharge, laboratory findings (white blood cell count, platelet count, red blood cell count, hemoglobin count, hematocrit level, urinalysis and microbiology results). The comorbid conditions such as preeclampsia and multiple gestations were also recorded.

The incidence of neonatal sepsis was recorded as the outcome of the pregnancy and preterm delivery. Neonatal sepsis is defined as a systemic infection in the first 28 days of birth. This condition can be categorized as early onset if the sepsis occurs before 72 hours after birth and it is called as late-onset sepsis if it occurs after 72 h of birth.¹⁸

In this study, genital tract infection is characterized by vaginal and vulvar itch, dyspareunia, dysuria, and abnormal vaginal discharge. These local manifestations can be accompanied by a rise in body temperature, an increased white blood cell count, or purulent premature rupture of membranes. Subjects who complained an increase of vaginal discharge might be categorized into a non-infection group if there were no accompanying symptoms and signs of infection. An increase in thin, white, milky, and mild smelling of vaginal discharge is considered normal during pregnancy. The study protocol has been approved by the Health Research Ethics Committee of Faculty of Medicine, Universitas Sebelas Maret, Surakarta (Ref. 135/UN27.6/KEPK/2018).

Statistical analysis

The Mann-Whitney and Chi-square tests were used to determine the difference of subjects' characteristics and laboratory findings between the two study groups i.e. subjects who had probable genital infections and those who did not. A p value of <0.05 was considered to be statistically significant.

RESULTS

We evaluated the medical records of 127 subjects with preterm delivery. Sixteen subjects (12.6%) were excluded due to intra-uterine fetal death (IUFD) and incomplete data in their medical records. As a result, only 111 medical records were further reviewed. Based on the assessment of the mothers' history, body's temperature, genital examination, white blood count, and the result of human immunodeficiency virus (HIV) test, 86 pregnant mothers were considered to be placed in the non-infectious group and 25 pregnant mothers were presumed to have genital tract infection (FIGURE 1).

All the subjects in the group of mothers with probable genital infection had an abnormal vaginal discharge (25/25, 100%) and half of them had premature rupture of the membrane (13/25, 52%). For subjects in the non-infection group, the diagnosis of preeclampsia, severe preeclampsia, or impending eclampsia was made in 38.37% (33/86) of the subjects (TABLE 1).

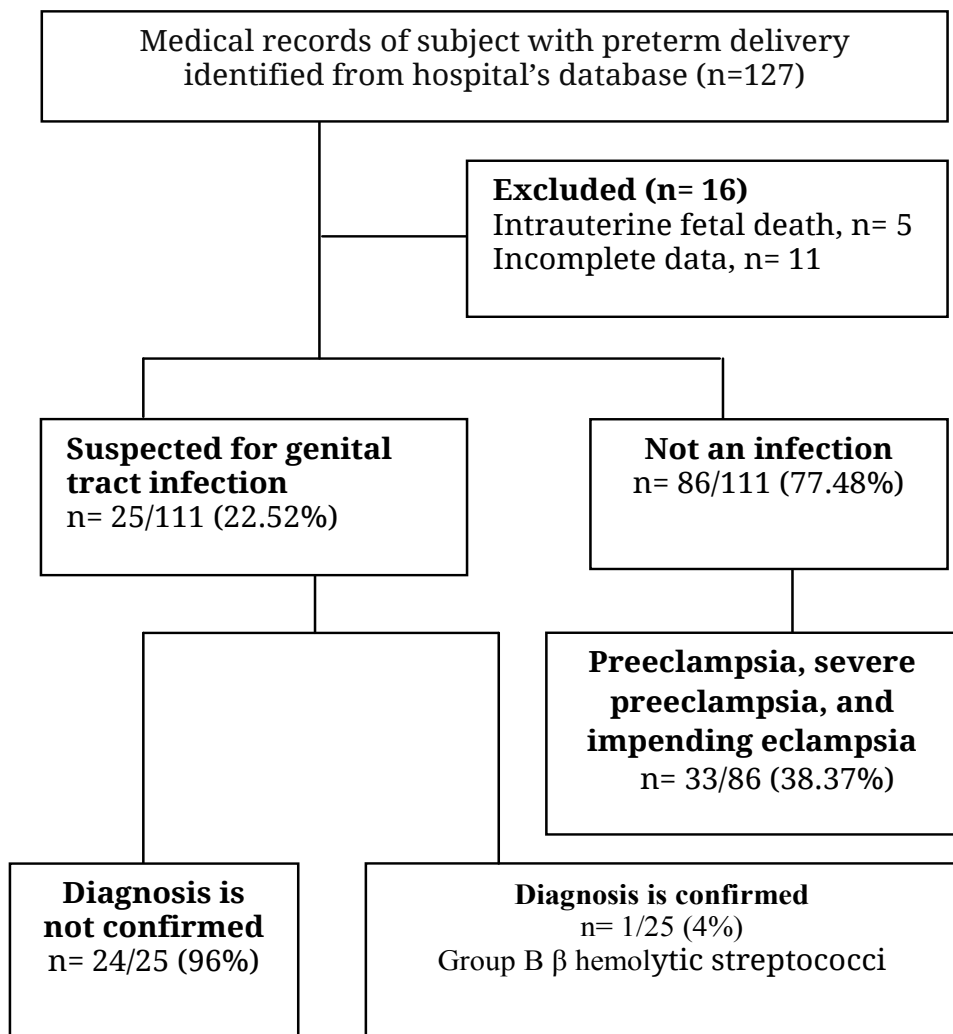


FIGURE 1. Flowchart of the study

TABLE 1. Subjects' characteristics and laboratory findings among two groups. Data are presented as the median (interquartile range) or as the proportion (%)

Variable	Suspected for genital tract infection group (n=25)	Non-infection group (n=86)	p
Subject's age (year)	30 (19-39)	30 (15-45)	0.096
Week of gestation	34 (21-36)	34 (24-36)	0.116
Number of current pregnancy	2 (1-5)	2 (1-6)	0.278
Number of previous abortion	0 (0-1)	0 (0-3)	0.055
Body temperature (°C)	36.6 (36-39)	36.5 (34-40)	0.245
Abnormal vaginal discharge	100% (25/25)	5.8% (5/86)	0.000*
White blood cells count (x 10 ⁹ /L)	12.7 (5.5-26.2)	11.5 (5-31.8)	0.381
Platelet count (x 10 ⁹ /L)	245 (31-589)	211 (17-498)	0.445
Red blood cells count (x 10 ⁹ /L)	4.030 (2.120-5.700)	3.900 (2.120-5.170)	0.498
Hemoglobin level (g/dL)	10.8 (8.2-18.3)	10.8 (6.2-17.5)	0.439
Hematocrit (%)	33 (23-58)	33 (18-54)	0.387

Preterm premature rupture of membrane	52.0%(13/25)	25.6% (22/86)	0.005*
Bacteria and yeast urine examination	12.0% (3/25)	10.5% (9/86)	0.828
Preeclampsia and impending eclampsia	8.0% (2/25)	38.4% (33/86)	0.004*
Multiple gestations(twin and triplet)	12.0% (3/25)	8.1% (7/86)	0.553

*The difference among two groups is considered statistically significant if $p < 0.05$

The majority of subjects with preterm delivery had a normal body temperature (107/111, 96.4%) and a normal white blood count (85/111, 76.58%). More than half (59/111, 53.15%) of subjects were anemic (had a low hemoglobin count) whereas just above one-third (40/111,

36%) of patients had a low hematocrit level. Among patients who underwent a urinalysis for bacteria and yeast examination, most of them (9/12, 75%) had positive bacteriuria and a quarter of them (3/12, 25%) had a result of positive yeast in the urine (FIGURE 2).

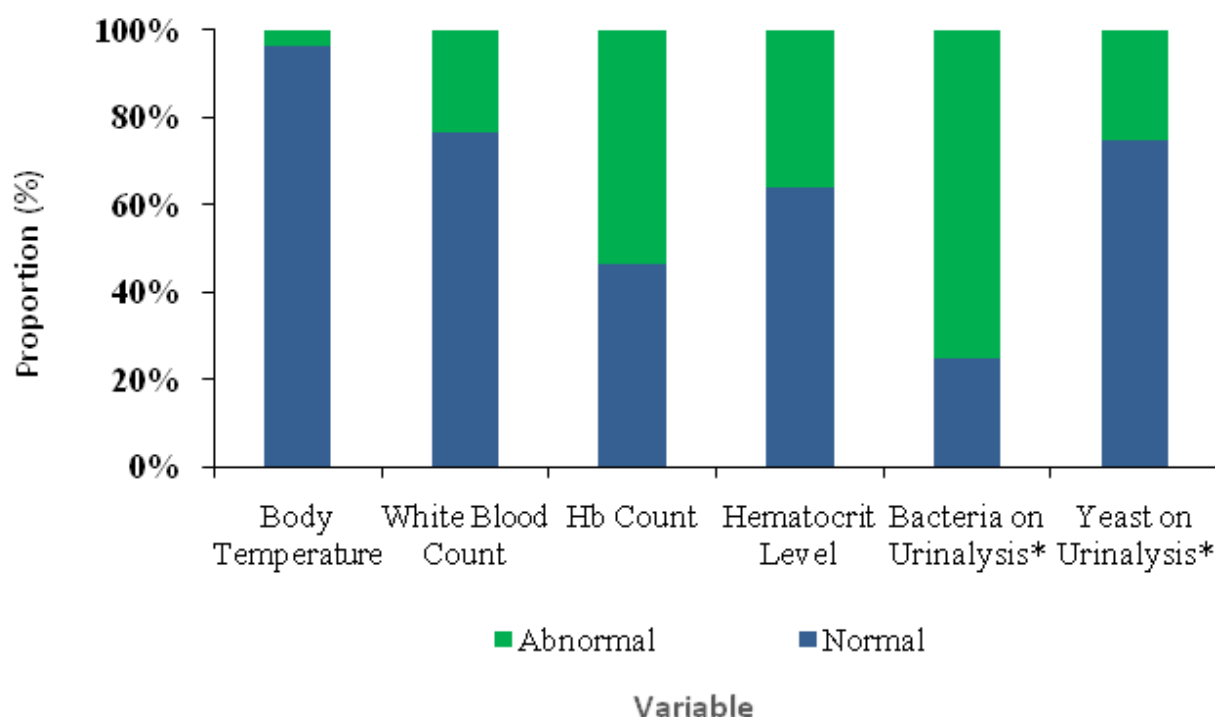


FIGURE 2. The results of tests performed on the subjects.*Only 12 out of 111 subjects with preterm delivery were tested for urinalysis

One subject was suffered from sepsis and underwent an emergency cesarean section. However, no further tests were performed to confirm the diagnosis of this maternal sepsis. Our study recorded five cases of early-onset neonatal sepsis in the group of subjects without genital tract infection. A blood culture was done for all of these five cases and the etiological agents of neonatal sepsis were detected in two cases i.e. *Candida haemulonii* and *Staphylococcus epidermidis*. There were no growth from the blood cultures taken from the other three cases.

Two HIV-positive cases were found. One of them had a genital tract infection by group B staphylococci confirmed by culture. This patient had a low CD4⁺ count and percentage; thus, met the criteria for having acquired immunodeficiency syndrome (AIDS). The patient's CD4⁺ count was 17 cells/ μ L with the cut off value for defining AIDS was CD4⁺ count of less than 200/ μ L. This patient had a CD4⁺ percentage of 5.67% of the total leukocytes with the cut off value for defining AIDS was CD4⁺ percentage of less than 14%.

DISCUSSION

Genital tract infection in pregnancy is significantly associated with preterm delivery.^{10,19,20} The condition can be caused by sexually transmitted pathogens such as *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and *Trichomonas vaginalis* and by the imbalance of vaginal normal flora. The imbalance of normal flora in the vagina often leads to a condition called bacterial vaginosis that affects 4.5-50% of the women population worldwide and 134 million women have vulvovaginal candidiasis.^{21,22} Meanwhile in 2012, *C. trachomatis*, *N. gonorrhoeae*, and *T. vaginalis* infected 357 million of people and about 790 million people were infected by *Human papillomavirus* (HPV) and *Herpes simplex virus* (HSV).^{23,24}

In this study, 25 of the 111 patients

(22.5%) were suspected for having genital tract infection. The condition was presumed based on the data of the patient's history, the body temperature, the findings of genital examination, and the white blood count. We did not perform a confirmatory diagnosis to establish the definitive diagnosis of the genital tract infection due to the retrospective design used in this study. While conducting this study, we discovered that a screening test or confirmatory examination for genital tract infection had not been routinely conducted in Dr. Moewardi General Hospital, Surakarta. We found that only 4% (1/25) of subjects who were presumed to have genital tract infection had actually undergone a microbiology test to confirm the diagnosis. The microbiology test performed was a culture of the vaginal discharge that grew group B β hemolytic Streptococci (GBS) as the causative agent. It had been reported previously that the bacteria is part of vaginal normal flora of the 10-30% of adult women and can also cause genital tract infection and chorioamnionitis.^{25,26}

The statistical analysis in this current study showed a significant difference ($p= 0.000$) in the presence of abnormal vaginal discharge among the two groups of subjects i.e. mothers with probable genital tract infection and those without genital tract infection. Vaginal discharge is a symptom that commonly occurs in women and its incidence is higher during pregnancy. This condition resulted from the secretion of Bartholin's and cervical glands, accompanied with desquamation of the vaginal epithelial cells. An increased vaginal discharge is either a physiological change during pregnancy or can be caused by genital tract infection where it presents with a change in color, consistency, and odor. The pathological discharge is often accompanied by other symptoms such as pruritus, dysuria and dyspareunia.²⁷ In this study, we found that a small proportion of women in non-infectious

group reported an increased vaginal discharge. We considered this as “normal or non-infectious” due to the absence of other symptoms.

Our analysis also detected a significant difference ($p= 0.005$) in the occurrence of preterm premature rupture of membrane amongst the two groups. A previous study showed that genital tract infection is the cause of 50-60% of preterm premature rupture of membrane.²⁸ One of the mechanisms involved in genital tract infection-related preterm premature rupture of the membrane is the release of inflammatory cytokines that cause structural changes of the membrane and result in the membrane rupture.^{18,29}

Genital tract infection could be transferred vertically to the fetus by endogenous bacteria colonizing the genital tract. The bacteria, which frequently are the part of genital tract normal flora, could also be transmitted to the neonate during vaginal delivery. The neonate could get infected even if the mother does not show any symptoms or sign of infection.³⁰ There was no vertical transmission observed in our study. Instead, we found five cases of early-onset neonatal sepsis in the group of mothers who did not have genital tract infection so that other sources of infection should be considered.

In preterm neonates, the immaturity of the immune system, including low transplacental transfer of maternal IgG makes them prone to acquired infections. Thus, preterm neonates are at a higher risk to develop sepsis compared to full term neonates.³¹ The risk of acquiring neonatal sepsis is also increased when there is a maternal genital tract infection whether the infection is clinically apparent (symptomatic) or inapparent (asymptomatic infection or maternal genital tract colonization, in which the conditions pose the risk for preterm labor.^{18,29,30,32} The most common agents causing early-onset sepsis are GBS and

Escherichia coli, while the most common causes of late-onset sepsis are coagulase-negative Staphylococci and *Candida spp.*³³ In our present study, however, we found two cases of early-onset neonatal sepsis caused by *Staphylococcus epidermidis* and *C.haemulonii*. This might reflect a high circulation of *S.epidermidis* and *C.haemulonii* in Dr Moewardi General Hospital, particularly in obstetric and neonatal wards.

We found a significant difference ($p= 0.004$) in the number of subjects with preeclampsia between the infection and non-infection groups. Preeclampsia is a pregnancy disorder with a distinctive sign of high blood pressure (systolic ≥ 140 mmHg or diastolic ≥ 90 mmHg) and frequently accompanied with proteinuria which occurs after 20 weeks of gestation.³⁴ Preeclampsia could contribute to preterm delivery through inflammation due to maternal responses against decidual hemorrhage and cell-free fetal DNA. Cell-free fetal DNA is a hypomethylated DNA that could evoke inflammatory responses via toll-like receptor 9 pathway.^{13,35} On top of that, preeclampsia is highly associated with the medically indicated preterm birth. Medically indicated preterm birth occurs in 27-40% of preterm birth in which preeclampsia accounted for 17-38% of the cases.¹⁵

There are several weaknesses in this study. Firstly, since the study was done retrospectively and the data were obtained during the pregnancy period of the subjects, at present we could not perform the confirmatory examination to establish a definitive diagnosis of genital tract infection. Secondly, we were forced to exclude several subjects as their medical records had incomplete data, especially the results of history taking and genital examination.

Despite its weaknesses, this study provides important information with regards to factors associated with preterm delivery in infectious and non-

infectious mothers as well as the lack of microbiological testing to investigate the infectious causes of preterm delivery. In addition, the results of this study can be used for education materials in primary care levels so that the expectant mothers can be better-prepared in welcoming premature birth. Pregnant women should be aware of abnormal vaginal discharge and can distinguish it with the normally increased discharge during pregnancy. In addition, should be cautious if they have premature rupture of the membranes and preeclampsia as these conditions might serve as “warning signs” for preterm labor.

We recommend that further study should be directed to elaborate the causes of preterm delivery in a larger scale and involve women with full-term pregnancy to determine more accurate causal relationships. Based on this present study, we urge that microbiological testing should be performed on pregnant mothers with apparent clinical symptoms and signs of genital tract infection so that the prevalence of preterm delivery could be reduced.

CONCLUSION

Genital tract infection during pregnancy is an important cause of premature birth. Microbiological testing is needed for diagnosis appraisal so that the infected mothers can be treated appropriately to prevent the occurrence of premature delivery and its associated outcomes in neonates and children.

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