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Parity, exposure to cigarette smoke and the presence of bacteria *Stenotrophomonas maltophilia* are related to preterm labor incidence☆

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Abstract
Objective: This study aimed to determine the relationship of parity, exposure to cigarette smoke, and the presence of bacteria *Stenotrophomonas maltophilia* with the incidence of preterm labor.
Method: It was a cross-sectional study the sampling was carried out using a purposive sampling technique for maternity women at the Siti Fatimah Makassar Mother and Child Hospital, Siti Khadija I Makassar Mother and Child Hospital, and Makassar City Regional General Hospital in June until August 2019. The study sample consisted of 50 post-partum mothers and their placenta, consisting of 25 preterm mothers and 25 term mothers. Criteria for respondents in this study were maternal pregnancies at gestational age > 22–36 weeks for the case group, and ≥37 weeks for the control group while the exclusion criteria were mothers with hypertension, preeclampsia, placenta previa, placental abruption, and HIV. Respondent characteristics were collected using a checklist sheet. Bacteria on the placenta were detected using 16S rRNA Polymerase Chain Reaction (PCR).
Results: Characteristics of age, Body Mass Index (BMI), premature rupture of membrane History, abortion history, and preterm birth history did not have significant relationship with the incidence of preterm labor, while parity (OR = 3.03, 95% CI: 1.2–12.0), cigarette smoke exposure (OR = 4.03, 95% CI: 1.2–13.5), *Stenotrophomonas maltophilia* bacteria (OR = 5.90, 95% CI: 1.11–31.20) significantly increases the risk of preterm labor.

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Conclusion: Parity, exposure to cigarette smoke, and the bacteria *Stenotrophomonas maltophilia* are considered as predisposing factors that are closely related to the incidence of preterm labor.

Introduction

Preterm labor is defined as labor before 37 weeks' gestation, which is a major cause of neonatal mortality and morbidity worldwide.[1–3] World Health Organization (WHO), in 2013, each year, around 15 million babies are born prematurely, and more than 1 million babies died from complications of preterm labor. WHO (2013) also mentions that Indonesia ranks fifth with the highest preterm labor in the world.[4,5]

Preterm births in Indonesia as the biggest contributor to neonatal mortality and disability, including low birth weight babies (LBW) followed by asphyxia and infection, as well as the second leading cause of death in infants after pneumonia.[6,7] Preterm labor gives a bad impact on growth and development.[3,4]

Childbirth is related to the contribution of various risk factors. Pregnant women with primiparous and young multiparous parity have a higher risk of preterm labor events.[8] Previous studies also involved pregnant women with active smokers as well as passive smokers during pregnancy had more to improve preterm labor.[9,10]

Stenotrophomonas maltophilia is one of the gram-negative bacilli bacteria that can colonize various body sites and is likely to cause infection.[11] These bacteria are thought to enter the placenta via the respiratory tract, mouth, vagina, and intestine,[12–14] so that products from These bacteria stimulate toll-like maternal immune receptors to release inflammatory cytokines (IL-1, IL-6, TNF), which stimulate the production of prostaglandins and Matrix Metalloproteinases so that preterm labor.[15,16] This study was conducted to find the highest risk factor preterm labor, thus providing effective interventions for pregnant women to prevent premature labor.

Methods

The study design was a cross-sectional study design. Sampling was purposive sampling technique in maternity at the Siti Fatimah Mother and Child Hospital of Makassar, Mother and Child Hospital Siti Khadija I Makassar, and Regional General Hospital of Makassar in June to August 2019 according to the study inclusion criteria. There were 50 samples consisting of 25 preterm and 25 aterm, but 48 nucleotides BLAS successfully analyzed were 48 samples because two samples were not confirmed from PCR products. The inclusion criteria of this study were mothers giving birth at >22–36 weeks for the case group, and ≥37 weeks for the control group while the exclusion criteria were mothers with hypertension, preeclampsia, eclampsia, amused, placenta previa, placental abruption, HIV, and syphilis. The independent variable in this study, namely placental microbiota, while the dependent variable, namely preterm labor. The control variables in this study were age, parity, IMT, history of abortion, KPD, and previous preterm.

The characteristics of respondents were collected using a checklist sheet. Placental sampling was performed by hospital analysts immediately after delivery, as much as 1 × 1 cm using a sterile instrument; the sample was confirmed to be free of contamination. The placenta sample is inserted into a sample tube and then placed at −80 °C until DNA extraction. DNA extraction uses the Genaid method, after which the sample is PCR with 16S rRNA primers. The results of the PCR were then electrophorized and visualized by DNA genes at the Hasanuddin University Medical Research Center (HUM-RC) Laboratory in Makassar. The results of the DNA gene visualization were then sequenced in the 1st Base Malaysia laboratory, and then the sequencing results were analyzed by the nucleotide BLAST. This study was approved by the Hasanuddin University research ethics commission, number: 458/UN4.6.4.5.31/PP36/2019 and received written approval from all respondents.

Data were analyzed by Chi-Square, Kruskal–Wallis, Mann–Whitney, and Fisher's Exact tests and were considered statistically significant if p-value < 0.05.

Results

Characteristics of age, Body Mass Index (BMI), premature rupture of membrane History, abortion history, and preterm birth history did not have significant relationship with the incidence of preterm labor, while parity (OR = 3.03, 95% CI: 1.2–12.0), cigarette smoke exposure (OR = 4.03, 95% CI: 1.2–13.5), *Stenotrophomonas maltophilia* bacteria (OR = 5.90, 95% CI: 1.11–31.20) significantly increases the risk of preterm labor (Table 1).

Discussion

Based on statistical tests in Table 1, shows the characteristics of age, Body Mass Index (BMI), history of premature rupture of membranes, history of abortion, and history of preterm birth did not differ significantly in the preterm group either preterm (p > 0.05), whereas parity, exposure to cigarette, and the presence of *Stenotrophomonas maltophilia* bacteria showed a significant difference in the relationship of preterm labor with a p-value < 0.05.

The parity of preterm mothers in this study was the majority of primipara (68.2%), while the majority of mothers at aterm were multipara (61.5). Parity significantly increased the risk of preterm labor by (OR = 3.03, 95%

Table 1 Preterm and aterm incidence.

Variable	Preterm (*N* = 25)	Aterm (*N* = 25)	*p-Value*	*OR (CI 95%)*
Age n (%)				
High risk (<20 and >35)	11 (52.4)	10 (47.6)	0.082[a]	1.17 (0.27–2.61)
Low risk (20–35 years old)	14 (48.3)	15 (51.7)		
Parity n (%)				
Primipara	15 (68.2)	7 (31.8)		
Multipara (2–4 times)	10 (36.5)	16 (61.5)	0.015[b]	3.93 (1.28–12.01)
Grande multipara (>4 times)	0.0 (0.0)	2 (100.0)		
Body mass index (BMI) n (%)				
Underweight (<18.5 kg/m^2)	4 (66.7)	2 (33.3)		
Normal (18.5–24.9 kg/m^2)	16 (48.5)	17 (51.5)	0.479[b]	1.44 (0.54–3.85)
Overweight (≥25.0 kg/m^2)	5 (45.5)	6 (54.5)		
Premature rupture membrane history n (%)				
Yes	6 66.7)	3 (33.3)	0.274[c]	2.31 (0.50–10.54)
No	19 (46.3)	22 (53.7)		
Abortion history n (%)				
Yes	3 (60.0)	2 (40.0)	0.641[c]	1.56 (0.23–10.30)
No	22 (48.9)	23 (51.1)		
Preterm birth history n (%)				
Yes	3 (100.0)	0 (0.0)	0.077[c]	–
No	22 (46.8)	25 (53.2)		
Exposure to cigarette smoke n (%)				
Yes	14 (70.0)	6 (30.0)	0.042[d]	4.03 (1.20–13.52)
No	11 (36.7)	19 (63.3)		
Stenotrophomonas maltophilia n (%)				
Yes	9 (81.8)	2 (18.2)	0.039[d]	5.90 (1.11–31.20)
No	16 (43.2)	21 (56.8)		

Chi-Square, Kruskal–Wallis, Mann–Whitney, and *Fisher's Exact*

CI: 1.2–12.0). These results are in line with previous research which showed that nulliparity was associated with an increase in birth weight Low Birth Weight (LBW) by (OR = 1.41, 95% CI: 1.26–1.58), small for gestational age (SGA) (OR = 1.89, 95% CI: 1.82–1.96) and preterm labor (OR = 1.13, 95% CI: 0.96–1.34) while multiparity and grand multiparity are not associated with risk outcomes labor. From 14 prospective cohort studies also comparing nulliparous mothers with age <18 years with mothers parity 1–2 and ages 18 to <35 years had a preterm maternal risk of OR = 1.2.[17,18]

As shown in Table 1, pregnant women who are directly exposed to cigarette smoke from their husband and family ± 30 min/week at home have a significant relationship to preterm labor and can increase the risk of preterm labor by (OR = 4.03, 95% CI: 1.2–13.5). The results of this study are in line with previous studies which showed an increased risk of preterm labor in mothers who had passive smoking overall (OR = 1.12, 95% CI: 0.95–1.32) and an increase in risk of 98% in very preterm (<32 weeks) (OR = 1.98, 95% CI: 1.41–2.76), research by Windham et al. Also suggests that pregnant women exposed to secondhand smoke have a 2-fold risk of experiencing preterm labor.[9]

The presence of the bacterium *Stenotrophomonas maltophilia* in the placenta from preterm labor. Both the case group (preterm labor) and the control group (term delivery) were significantly different ($p = 0.039$, $p < 0.05$) and *Stenotrophomonas maltophilia* had the highest risk of preterm labor (OR = 5.90, 95% CI: 1.11–31.2). The *Stenotrophomonas maltophilia* bacterium is a gram-negative; it is a water organism that able to survive for a long time in liquids.[19,20] This bacterial infection is susceptible to expand and increase the number that causes urinary tract infections, pneumonia, decreased antibodies. *Stenotrophomonas maltophilia* bacteria has port of entry; the vaginal, respiratory tract, and intestines which then enter the placenta and cause intrauterine infections,[20] thereby stimulating toll-like maternal immune receptors to release inflammatory cytokines (IL-1, IL-6, and TNF) which stimulate prostaglandin and Matrix Metalloproteinase (MMP) production. Prostaglandins stimulate uterine contractions while the degradation of the extracellular matrix in the fetal membrane causes Preterm Premature Rupture of the Membrane (PPROM), so preterm labor occurs.[3,12]

The results of this study are in line with previous studies that the microbial Enterobacter, Enterococcus, Lactobacillus, and Tannerella correlate with preterm labor and these bacteria are proven to be able to stimulate the inflammatory response.[2] Lactobacillus, and Streptococcus bacteria are the most number of non-complicated placenta

but different from those detected in maternal placenta with complications such as: Preeclampsia, preterm labor, bacteria that are detected more are pathogenic bacteria such as Burkholderiales, Acinetobacter, Fusobacterium and Ureaplasma.[13]

Conclusion

Parity, exposure to cigarette smoke, and *Stenotrophomonas maltophilia* are considered as predisposing factors that are closely related to the incidence of preterm labor so that preventive efforts are needed to prevent preterm labor, which is very detrimental to the baby. However, further research is needed in the prevention of preterm labor. This study did not identify the origin of exposure to bacteria found in the placenta whereas this is important for prevention.

Conflict of interest

The authors declare no conflict of interest.

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