Maternal and Fetal Factors that Affect Preterm Birth at the Professor Ngoerah Central General Hospital

Ni Nyoman Budiani[1]✉, Ni Luh Sudarmi[2], Ni Wayan Ariyani[1]
[1]Departement of Midwifery, Poltekkes Kemenkes Denpasar, Denpasar, Indonesia
[2]RSUP Prof Ngoerah, Denpasar, Indonesia
✉Corresponding author: budiani.jkb2@gmail.com

ABSTRACT

Introduction: Preterm birth occurs in 7-10% of all live births, leading to complications such as low birth weight, asphyxia, hypothermia, and hypoglycemia, which increase the risk of neonatal death. This research aims to prove the influence of maternal factors (age, occupation, marital status, gravida, hypertension) and conception results (number of fetuses and ruptured membranes) on preterm birth. **Method**: This correlational research, using a cross-sectional approach, was conducted at Prof. Ngoerah Hospital, Bali, in 2021. The study population included all women who gave birth in 2020, fully recorded in medical records, with a total sample size of 997 women, obtained through total sampling. Data were analyzed using crosstabulation, Chi-square test (X^2), and binary logistic regression with computer assistance, setting significance at α 0.05. **Results**: Preterm birth was significantly influenced by maternal age (p=0.001), occupation (p=0.001), blood pressure (p=0.000), and the condition of the amniotic membranes (p=0.000). These factors collectively contributed to 22.7% of the variance in preterm births. **Conclusion**: Maternal factors such as age, occupation, blood pressure, and amniotic membrane condition significantly influence the incidence of preterm birth. Preventive measures, focusing on education before and during pregnancy, are crucial to reducing the risk of preterm births.

INTRODUCTION

The greater risk of infant morbidity and death is in line with the younger the gestational age of the baby at birth. Preterm birth (preterm birth) occurs before 37 weeks of gestation. Preterm neonates have a greater risk of morbidity and death than term neonates born at 37 weeks to 42 weeks' gestation. The incidence of preterm birth always exists, especially in developing countries, 7%-10% of live births (Hudić, Stray-Pedersen, and Tomić 2015). The incidence of preterm labor at the Prof. Ngoerah Bali Central General Hospital (RSUP) from 2018 to 2020 was 22.49%, 23.05%, and 21.5% respectively (Sudarmi, Budiani, and Novya Dewi 2022). Premature birth is related to unfinished growth and development during the fetal period.

Organ formation begins after the fertilization process. Cell division, the formation of two germ layers, followed by the gastrulation process until the embryo of the organ is determined, is a complex event involving many genes. Overall, organ formation or organogenesis occurs during the first trimester of pregnancy, followed

by organ growth and maturation occurring in the second to third trimesters, which continues postnatally. Organ formation and maturation occurs in a structured and continuous manner (Sarathi 2022; Shahbazi 2020). The maturation of the body's organs occurs during pregnancy. The fetus's body signals the mother to produce the hormone progesterone and cytokines which modulate the mother's adaptation to her pregnancy (Keelan 2018). When a baby is born preterm, it means that some of the time for growth and development has been missed or has not been achieved. Therefore, the baby's body organs have not completed growth and maturation in the womb, so they are not yet able to function properly. This condition triggers problems for neonates and later life (K H Yu and Bower 2014).

The Ministry of Health of the Republic of Indonesia reports that the majority of under-five deaths occur during the neonatal period (0-28 days), namely in 2022 as many as 85.24% of 21,447 under-five deaths; In 2021, 73.1% of 27,566 deaths; and in 2020 as many as 72% of 28,158 under-five deaths (Kemenkes R.I 2021, 2022, 2023). This data shows that the incidence of neonatal deaths continues to increase in the 2020-2022 period. The causes of neonatal death for the period 2020 to 2022 have also not changed. Low birth weight (LBW) is the main cause of neonatal death in 2022 (28.2%), 2021 (34.5%), 2020 (35.2%). Next in line is Asphyxia, in 2022 (25.3%), 2021 (27.8%) and 2020 (27.4%). Other causes of death are congenital abnormalities, infections, including neonatal tetanus (Kemenkes R.I 2021, 2022, 2023).

Incomplete growth and development of body organs in preterm neonates can cause problems with low birth weight (LBW) because there is little muscle mass, little brown fat or fat under the skin, and the organs are not yet fully formed. Organ systems also experience problems, such as asphyxia, hypothermia, hyperthermia, hyperbilirubin, hypoglycemia, blood clotting disorders, easy infection. Problems will continue during infancy and toddlerhood (Sarathi 2022; Suman V. 2022). Various risk factors can cause preterm birth, such as maternal factors and products of conception. Maternal factors, including: mother's age, place of residence. Age < 20 years; 20-34 years old; 35 years or more and mothers living in urban and rural areas were associated with preterm birth (Galinova 2021). Other risk factors are maternal occupation, education, history of preterm birth, comorbidities, and anemia (Dahman H 2020).

Sudarmi, et.al (2022) found that the total number of preterm births at Prof. year, 74.9% of preterm births occurred at secondary education level, 90.1% occurred in married mothers. Based on pregnancy complications, 30.5% were due to preeclampsia, 23.3% due to PROM, 1.3% due to anemia, 0.9% due to hydramion, 6.3% due to APB, 3.6% due to chronic disease, 9.0% due to multifetal pregnancy and 25.1% due to idiopathic/unknown factors.

The description of risk factors in data that has been reported by Sudarmi, et.al (2022), is not necessarily the cause or influence on the incidence of preterm birth. To prove the influence of these risk factors on the incidence of preterm birth, a correlational analysis was carried out. The difference between this study and the previous one is the review from the child's side (preterm birth), the type of correlational analytical research, not including data on babies born preterm whose mothers had no risk factors, but were diagnosed as ideopathic, as well as the multivariate analysis. The results of this research can help policy holders and resolve and prevent the same problem from recurring.

Factors causing neonatal deaths, based on reports from the Ministry of Health, are related to preterm birth with various conditions or problems. This is an interesting

topic to discuss because the social and cultural differences that exist in society can color the perspective of a husband and wife regarding preparation for pregnancy, labor and the birth of their baby, including how to deal with pregnancy complications. This is the basis/reinforcement for the need for this topic to be researched further. The aim of this research is to prove the influence of maternal factors (age, occupation, marital status, gravida, hypertension) and conception results (number of fetuses and ruptured membranes) on preterm birth.

METHODS

This type of research is correlation, with a cross sectional approach. The research was carried out at Prof. Sampling technique: total sampling (all objects that meet the inclusion and exclusion criteria). How to collect data with documentation. Data collection method: after obtaining ethical clearance from Ethic Committee of Poltekkes Kemenkes Denpasar number 1200/UN 23.2.2.VII.14/LT/2021 and research permission from Prof. Ngoerah Hospital (license number: L.B.02.01/XIV.2.2.1/16474/2021). Researchers quoted data from medical records starting with mother's data including age, occupation, marital status, gravida, hypertension. Fetal factors, including the number of fetuses, amniotic membranes. Collection begins by determining the population, removing data that meets the exclusion criteria. The data collection instrument is in the form of a recording guide (dummy master table), according to the variables studied. The master dummy table is available in the Excel program, so the data is directly input. Data processing carried out includes editing, coding, data entry. Data analysis: descriptive (frequency and crosstabulation), Chi Square test, binary logistic regression test after fulfilling the model fit requirements. In this study, the model tested met the requirements, namely the Omnibus test of model coefficient, obtained p 0.00, which means there is at least one maternal or fetal factor that influences the incidence of preterm birth. Hosmer and Lameshow test obtained p 0.303, which means there is no difference between observed data and predicted data. In this way, data testing can be continued. Data analysis with computer assistance, with a confidence level of 95% (α 0.05).

RESULTS

The number of births at Prof Ngoerah Hospital in 2020 was 1037 people, consisting of preterm 223 people (21.5%) and term 814 people (78.5%). The research analyzed 997 birth data, consisting of 212 preterm births, and 785 term births. The following describes data on age, occupation, marital status, frequency of pregnancy (gravida), hypertension in pregnancy, number of fetuses, and rupture of amniotic membranes.

Table 1. Relationship between Maternal and Fetal Factors with Preterm Birth

Variables	Preterm birth		Non-preterm birth		p-value
	f	%	f	%	
Mother's age					0.00
unhealthy reproduction	59	33.0	120	67.0	
healthy reproduction	153	18.7	665	81.3	
Occupation					0.02
outside the house	96	18.4	426	81.6	
inside the house	116	24.4	359	75.6	

Variables	Preterm birth		Non-preterm birth		p-value
	f	%	f	%	
Marital Status					0.049
unmarried	22	31.0	49	69.0	
Married	190	20.5	736	79.5	
Gravida					0.06
Multigravida	123	23.6	397	76.4	
Primigravida	89	18.7	388	81.3	
Blood Pressure					0.00
Hypertension	67	36.4	117	63.6	
normotension	145	17.8	668	82.2	
Amniotic membranes					0.00
Rupture	45	34.6	85	65.4	
Intact	167	19.3	700	80.7	
Number of fetuses					0.00
Gemelli	18	66.7	9	33.3	
Single	194	20.0	776	80.0	

Table 1 provides information that maternal age, maternal occupation, maternal marital status, frequency of pregnancy (gravida), hypertension, rupture of amniotic membranes, and gemelli fetus are associated with preterm labor ($p<0.05$). The incidence of preterm labor is more common in unhealthy reproductive ages, working at home, unmarried, multigravida, hypertension in pregnancy, ruptured membranes, and gemelli fetuses.

The Influence of Maternal and Fetal Factors on Preterm Birth

The Nagelkerke R Square test results obtained were 0.227. These results show that the contribution of all maternal and fetal factors to preterm birth together in this study was 22.7%. The remaining 77.3% is influenced by other factors. The influence of each variable and the Odds ratio were tested using Wald, presented in table 2 below.

Table 2. The Influence of Maternal and Fetal Factors on Preterm Birth

Variables	Sig	Exp (B)	95% CI (Exp B)	
			Lower	Upper
Mother's age	0.001	1.958	1.316	2.913
Occupation	0.000	0.454	0.320	0.645
Marital status	0.172	1.495	0.839	2.662
Gravida	0.337	1.174	0.846	1.630
Blood Pressure	0.000	0.294	0.197	0.440
Amniotic membrane	0.000	2.312	1.506	3.549
Number of fetuses	0.000	8.629	3.621	20.565

The influence of the independent variables is explained using the Wald test. Table 2 provides information that marital status and frequency of pregnancy (gravida) have no effect on preterm birth ($p>0.05$), while the variables age, occupation, hypertension in pregnancy, and ruptured membranes show an influence on preterm birth ($p < 0, 01$).

DISCUSSION

One of the hormones that plays a role in pregnancy and childbirth is progesterone. This hormone can change cytokine responses, prevent the formation of prostaglandins and nitric oxide, and reduce the formation of corticotropin releasing hormone (CRH). The progesterone hormone also prevents the degradation of cervical stroma, induces the formation of cervical stromal matrix proteins, and induces lymphocytes to release progesterone-induced blocking factor (PIBF), which mediates immunomodulatory and antiabortive effects. This causes upregulation of progesterone receptors on activated lymphocytes between placental cells and CD8+ cells. The PIBF concentration continues to increase from the 7th to the 37th week of pregnancy. Sufficient progesterone levels are able to trigger cells in the reproductive tract tissue, myometrium, decidua, uterine cervix and fetal membranes to synthesize PIBF (Hudić et al., 2015). Pregnant women who experience preterm birth show an increased rate of cervical stromal degradation, decreased neutrophil recruitment, increased proinflammatory cytokines, low or no PIBF during pregnancy, and decreased IL-10 expression on lymphocytes (Hudić et al., 2015). The results of this study showed that there was an influence on the variables of age, occupation, hypertension in pregnancy, ruptured membranes showed that there was an influence on preterm birth (p < 0.01).

The OR for the age variable in this study was 1.96, 95% CI (1.316-1.913). This means that pregnant women who are not of healthy reproductive age are at risk of preterm birth 1.96 times greater than those of healthy reproductive age (20-35 years). Women aged less than 20 years (teenagers) are not ready to get pregnant physically and emotionally. At that age the reproductive organs are immature (not ready to accept pregnancy). The endometrial layer is inadequate to receive nidation and place the development of the products of conception (fetus or placenta). Teenagers have unstable emotions and are more easily stressed. Married during school with an unplanned, perhaps even unexpected, pregnancy. These pregnant women receive less support from their husbands or family. This triggers psychosocial problems (Sykes & Bennett, 2018). All the psychosocial problems and physical unpreparedness of pregnant teenagers can induce preterm birth due to inhibition of the secretion of the hormone progesterone so that levels are less than required. An imbalance in the ratio of progesterone to estrogen can cause preterm labor (Prairie et al., 2021). Age over 35 years, uterine muscles are not elastic, degenerative diseases tend to appear, such as hypertension, diabetes mellitus, kidney disease, heart disease. The risk of preterm birth increases with increasing maternal age (Fuchs et al., 2018). This research is in line with research conducted at Arifin Achmad Hospital Pekanbaru in 2010-2012 which found that age OR 2.7 CI 95% (1.84-3.97) (Maita, 2012).

Occupation was found to have an effect on preterm birth in this study (p < 0.05) with OR 0.454, 95% CI (0.320 - 0.645). Working inside the home carries a 0.45 times greater risk of preterm birth than working outside the home. Work in the house includes cooking, cleaning the house, washing and ironing, looking after children and/or the elderly, sometimes accompanied by raising pigs/cows/chickens/goats. This work carries the risk of causing accidents such as falls, fatigue and lack of rest. Fatigue inhibits the secretion of prostaglandins and proinflammatory cytokines (Keelan, 2018). This condition is likely to reduce the immune system thereby inducing the secretion of pro-inflammatory cytokines, such as IL6 and degradation of the cervical stroma. IL 6 can modulate the activity of cells from maternal and fetal body tissues, resulting in preterm birth (Prairie et al., 2021).

The results of this study found that there was a relationship between marital status and preterm birth (p < 0.05), but the effect was very small. OR 1.495, CI 95% (0.839-2.662). This means that unmarried women are at 1,495 greater risk of preterm birth than married women. Marriage provides a bond between husband and wife. Husbands can provide support and affection to their wives, so that they can provide a sense of comfort and security for their wives. On the other hand, unmarried women receive less support, such as fulfilling the nutrition needed by pregnant women and their fetuses (Liu and Gao 2022); do not receive information regarding antenatal care so they do not maintain their pregnancy adequately (Do Carmo Leal et al. 2016). Marriage provides a special status in social life in Indonesia. Without marriage, women will become the subject of gossip, have lower value, and even be ostracized. This is a risk of psychological problems that trigger preterm labor. Sudarmi, et.al. found that 9.9% of preterm births had unmarried status (Sudarmi et al. 2022). Research by Granese, et al. (2019) also found a relationship between preterm birth and unmarried (p=0.003) (Granese et al. 2019).

The results of data analysis from this study found that there was a relationship between gravida and the incidence of preterm birth, but the effect was small. The OR of the gravida variable is 1.174, which means that multigravida pregnancies have a risk of preterm birth 1.174 times greater than primigravidas. Multigravid pregnancies are related to multifetal pregnancies which cause uterine overdistension, thereby stimulating the posterior pituitary to secrete the hormone oxytocin early, resulting in preterm birth. Overdistention also risks causing the membranes to rupture prematurely, thereby causing preterm birth. Legawati and Riyanti (2018) found that the risk of PROM was 1.5 times greater in multigravida pregnancies, while Octavia and Fairuza (2019) found that the risk of premature rupture of membranes was 5,519 times greater in multipara-grandemultipara compared to primipara (Octavia R & Fairuza F, 2019; Riyanti, 2018). Research at the Tembuku I Community Health Center UPT, Bangli-Bali District found that risky pregnancies had a risk of preterm birth 1.56 times greater than non-risky pregnancies (Ni Luh De Dwijasistawati et al., 2023).

This study found that there was an influence of hypertension in pregnancy with preterm birth (p, 0.05). OR 0.294 CI 95% (0.197-0.440), meaning that women who suffer from hypertension during pregnancy are at 0.294 times greater risk of giving birth preterm. The endothelial function of the blood vessels of pregnant women who experience hypertension decreases and the thickness of the intima media layer increases, which causes blood flow from the mother to the fetus to decrease (hypoperfusion), so that the fetus lacks oxygen and nutrients. Inflammatory processes, oxidative stress, and endocrine disorders also occur in pregnant women with hypertension. This can induce preterm labor (Bertagnolli et al., 2016). In line with the findings in this study, An,et.al (2021) found that hypertension in pregnancy has a strong relationship with preterm birth, especially early-onset hypertension. RR 2.13, 95% CI (1.71 - 2.65 (An et al. 2022).

Ruptured amniotic membranes cause preterm birth, with an OR of 2.312 CI 95% (1.506 – 3.549). Pregnant women whose amniotic membranes rupture are at risk of preterm birth 2.312 times greater than those with intact amniotic membranes. Amniotic fluid functions as a cushion for the fetus. When the amniotic membrane ruptures, the lowest part of the fetus can press on the cervix, causing degradation of the cervical stroma. In this event, an inflammatory process also occurs, thereby inducing preterm labor. The results of this study strengthen the findings of Sari, et.al (2020), premature rupture of membranes is associated with preterm birth OR 2.97 CI

95% (1.92 - 4.59) (Sari et al., 2020). Preterm birth is associated with premature rupture of membranes, with risk factors: maternal age less than 20 years, history of abortion, vaginal pH, and heavy growth of microorganisms (Hosny et al., 2020).

Preterm birth from mothers with multiple pregnancies was 66.7% in this study. Pregnancy with more than one fetus has an 8.629 greater risk of preterm birth (CI 95% 3.621-20.565). More than one fetus causes the uterus and abdomen to experience overdistension. Stretching of the uterus, including the cervix, causes an inflammatory process, triggering the cervical stroma to release pro-inflammatory cytokines such as IL6 and prostaglandins. This event causes cervical ripening which is followed by uterine contractions and cervical opening. which can trigger preterm birth (Suman V. 2022). Overdistention is a risk factor for premature rupture of membranes, thereby triggering preterm birth. Basiri, et.al (2019) found a relationship between the number of fetuses (multiple pregnancies) and preterm birth (Basiri et al. 2019).

CONCLUSION AND RECOMMENDATION

Maternal factors that influence the incidence of preterm birth are age (p=0.00), occupation (p=0.00), and hypertension in pregnancy (p=0.00). Fetal factors that influence the incidence of preterm birth are the number of fetuses (p=0.00) and amniotic membranes (p=0.00). Together, all risk factors contributed 22.7% to the incidence of preterm birth. The smallest influence is the gravida factor (p=0.17) and marital status (p=0.33). Health workers should carry out early detection of risk factors for preterm birth. Early recognition of risk factors for preterm birth to prospective pregnant women and their partners, so that it can prevent its occurrence. The results of this research can be used as an educational reference for midwives and other health workers in preventing or reducing the risk of preterm birth.

ACKNOWLEDGEMENTS

DISCLAIMER

Researchers declare there is no conflict of interest.

REFERENCES

Basiri, B., Sabzehei, M. K., Shokouhi, M., & Sabahi, M. M. (2019). Incidence and short outcome in multiple pregnancies: A single center cross-sectional study in Iran 2016-2017. *Medical Journal of Indonesia*, *28*(1), 28–34. https://doi.org/10.13181/mji.v28i1.2827

Bertagnolli, M., Luu, T. M., Lewandowski, A. J., Leeson, P., & Nuyt, A. M. (2016). Preterm Birth and Hypertension: Is There a Link? *BMJ Open*, *12*(9), 1–7. https://doi.org/10.1136/bmjopen-2021-058068

Dahman H. (2020). Risk factors associated with preterm birth : a retrospective study in Mukalla Maternity and Childhood Hospital , Hadhramout Coast / Yemen. *Sudanese Journal of Paediatrics*, *20*(2), 99–110. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7423304/pdf/sjp-20-99.pdf

Do Carmo Leal, M., Esteves-Pereira, A. P., Nakamura-Pereira, M., Torres, J. A., Theme-Filha, M., Domingues, R. M. S. M., Dias, M. A. B., Moreira, M. E., & Gama, S. G. (2016). Prevalence and risk factors related to preterm birth in Brazil. *Reproductive Health*, *13*(Suppl 3). https://doi.org/10.1186/s12978-016-0230-0

Fuchs, F., Monet, B., Ducruet, T., Chaillet, N., & Audibert, F. (2018). Effect of maternal age on the risk of preterm birth: A large cohort study. *Obstetrical and Gynecological Survey*, *73*(6), 340–342. https://pubmed.ncbi.nlm.nih.gov/29385154/

Galinova, I. V. (2021). Risk Factors for Premature Birth. Is Everything Unambigu-Ous? *NAUKA MOLODYKH (Eruditio Juvenium)*, *9*(1), 77–90. https://doi.org/10.23888/hmj20219177-90

Granese, R., Gitto, E., D'Angelo, G., Falsaperla, R., Corsello, G., Amadore, D., Calagna, G., Fazzolari, I., Grasso, R., & Triolo, O. (2019). Preterm birth: Seven-year retrospective study in a single centre population. *Italian Journal of Pediatrics*, *45*(1), 1–6. https://doi.org/10.1186/s13052-019-0643-9

Hosny, A. E. D. M. S., Fakhry, M. N., El-Khayat, W., & Kashef, M. T. (2020). Risk factors associated with preterm labor, with special emphasis on preterm premature rupture of membranes and severe preterm labor. *Journal of the Chinese Medical Association*, *83*(3), 280–287. https://doi.org/10.1097/JCMA.0000000000000243

Hudić, I., Stray-Pedersen, B., & Tomić, V. (2015). Preterm Birth: Pathophysiology, Prevention, Diagnosis, and Treatment. *BioMed Research International*, *2015*. https://doi.org/10.1155/2015/417965

K H Yu, C., & Bower, S. (2014). Fetal Growth. In *Twining's Textbook of Fetal Abnormalities, Third Edition* (Third Edit). Elsevier Ltd. https://doi.org/10.1016/B978-0-7020-4591-2.00010-3

Keelan, J. A. (2018). Intrauterine inflammatory activation, functional progesterone withdrawal, and the timing of term and preterm birth. *Journal of Reproductive Immunology*, *125*(December 2017), 89–99. https://doi.org/10.1016/j.jri.2017.12.004,

Kemenkes RI. (2021). Profil Kesehatan Indonesia 2020. In *Kemenkes RI* (Vol. 48, Issue 1). Retreived from at: https://kemkes.go.id/id/category-download/profil-kesehatan

Kemenkes RI. (2022). Profil Kesehatan Indonesia 2021. In *Pusdatin.Kemenkes.Go.Id*, downloaded at: https://kemkes.go.id/app_asset/file_content_download/170295833666658115008345c5.53299420.pdf

Kemenkes RI. (2023). Profil Kesehatan Indonesia 2022. In *Pusdatin.Kemenkes.Go.Id*. https://www.kemkes.go.id/downloads/resources/download/pusdatin/profil-kesehatan-indonesia/Profil-Kesehatan-2021.pdf

Liu, Y., & Gao, L. (2022). Preterm Labor, a Syndrome Attributed to the Combination of External and Internal Factors. *Maternal-Fetal Medicine*, *4*(1), 61–71. https://doi.org/10.1097/FM9.0000000000000136

Maita, L. (2012). Faktor Ibu yang Mempengaruhi Persalinan Prematur di RSUD Arifin Achmad Pekanbar. *Jurnal Kesehatan Komunitas*, *2*(1), 31–34. https://doi.org/10.25311/keskom.vol2.iss1.39, downloaded at: https://www.researchgate.net/publication/318195726_Faktor_Ibu_yang_Mempengaruhi_Persalinan_Prematur_di_RSUD_Arifin_Achmad_Pekanbar

Ni Luh De Dwijasistawati, Ni Wayan Ariyani, & Sulaksana, R. T. (2023). Faktor-Faktor Yang Berhubungan dengan Kejadian Persalinan Preterm di UPT. Puskesmas Tembuku I. *Jurnal Ilmiah Kebidanan (The Journal of Midwifery)*, *11*(1), 71–81. https://doi.org/10.33992/jik.v11i1.2539

Octavia R, & Fairuza F. (2019). Faktor-faktor yang berhubungan dengan kejadian ketuban pecah dini di Rumah Sakit Budi Asih Serang Periode Oktober tahun 2018. *Jurnal Ilmiah Kesehatan Delima*, *2*(1), 53–63, retreived from http://www.ejournal-aipkema.or.id/index.php/jrki/article/view/182

Prairie, E., Côté, F., Tsakpinoglou, M., Mina, M., Quiniou, C., Leimert, K., Olson, D., & Chemtob, S. (2021). The determinant role of IL-6 in the establishment of inflammation leading to spontaneous preterm birth. *Cytokine and Growth Factor Reviews*, *59*(January), 118–130. https://doi.org/10.1016/j.cytogfr.2020.12.004

Riyanti, L. and. (2018). Determinan Kejadian Ketuban Pecah Dini (KPD) di Ruang Cempaka RSUD Dr. Doris Sylvanus Palangkaraya. *Jurnal Surya Medika*, *3*(2), 95–105, retrevide from: https://journal.umpr.ac.id/index.php/jsm/article/view/106

Sadler, T. W. (2012). Langmans Medical Embryology. In *Williams & Wilkins Lippincott* (Vol. 12, Issue 1). https://doi.org/10.4091/iken.33-37

Sarathi, S. (2022). Embronic and Fetal Development. *International Journal of Mechanical Engineering, 7*(1), 1467–1473. https://doi.org/10.1007/978-1-4613-4544-2_6,

Sari, I. M., Adisasmita, A. C., Prasetyo, S., Amelia, D., & Purnamasari, R. (2020). Effect of premature rupture of membranes on preterm labor: a case-control study in Cilegon, Indonesia. *Epidemiology and Health*, *42*, 1–6. https://doi.org/10.4178/epih.e2020025,

Shahbazi, M. N. (2020). Mechanisms of human embryo development: From cell fate to tissue shape and back. *Development (Cambridge)*, *147*(14), 1–32. https://doi.org/10.1242/dev.190629

Sudarmi, N. L., Budiani, N. N., & Novya Dewi, I. G. A. A. (2022). Gambaran Persalinan Preterm di RSUP Sanglah Denpasar Tahun 2020. *Jurnal Ilmiah Kebidanan (The Journal Of Midwifery)*, *10*(1), 86–93. https://ejournal.poltekkes-denpasar.ac.id/index.php/JIK/article/view/1561/752

Suman V., L. E. . (2022). Preterm Labor Pathophysiology. *StatPearls*, 1–5, downloaded at: https://pubmed.ncbi.nlm.nih.gov/30725624/

Sykes, L., & Bennett, P. R. (2018). Efficacy of progesterone for prevention of preterm birth. *Best Practice and Research: Clinical Obstetrics and Gynaecology*, *52*, 126–136. https://doi.org/10.1016/j.bpobgyn.2018.08.006