The Analysis of Premature Rupture of Membrane Outcomes: Comparison Between 34-36 Weeks and Term Gestation

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Abstract
Introduction: This study analysed the maternal and neonatal outcomes in premature rupture of membrane at 34-36 weeks of gestation compared to term gestation to provide an overview of the current protocol's efficacy which is currently widely varied.
Method: This was a cross-sectional study using a simple random sampling technique. The subject of this study consisted of a total of 450 pregnant women diagnosed with PPROM at 34-36 weeks and term gestation during the period January 2019-December 2021. P<0.05 was considered statistically significant.
Results: That women with premature rupture of membrane (PROM) at term gestation had a higher risk of 1.13 times (OR= 1.13, CI 95%) for neonatal asphyxia, 1.34 times for early neonatal death (OR= 1.34, CI 95%), and 4.03 times for developing clinical chorioamnionitis (OR= 4.03, CI 95%) compared to the 34-36 weeks of gestation group. There was no statistically significant difference between gestational age and the incidence of early neonatal death (P= 0.70). There were no maternal deaths in this study.
Conclusion: the management protocol applied for both groups had the same efficacy. The incidence of clinical chorioamnionitis was higher in the term gestation group, which may be associated with risk factors such as COVID-19 and hepatitis B.

Keyword: PROM, Asphyxia, Neonatal Death.

Analisis Hasil Ketuban Pecah Dini: Perbandingan Antara Usia Kehamilan 34-36 Minggu dan Masa Kehamilan Cukup Bulan

Abstrak
Pendahuluan: Penelitian ini menganalisis hasil maternal dan neonatal pada ketuban pecah dini pada usia kehamilan 34 - 36 minggu dibandingkan dengan kehamilan jangka panjang untuk memberikan gambaran tentang kemanjuran protokol saat ini yang sangat bervariasi.
Metode: Penelitian ini adalah studi cross-sectional menggunakan teknik simple random sampling. Subjek penelitian ini terdiri atas total 450 wanita hamil yang didiagnosis dengan PROM pada 34 - 36 minggu dan kehamilan jangka panjang selama periode Januari 2019 - Desember 2021. P<0,05 dianggap signifikan secara statistik.
Hasil: hasil analisis menunjukan bahwa wanita dengan ketuban pecah dini pada usia kehamilan memiliki risiko lebih tinggi 1,13 kali (OR=1,13, CI 95%) untuk asfiksia neonatal, 1,34 kali untuk kematian neonatal dini (OR=1,34, CI 95%), dan 4,03 kali untuk mengembangkan chorioamnionitis klinis (OR=4,03, CI 95%) dibandingkan dengan kelompok kehamilan 34 - 36 minggu. Tidak ada perbedaan yang signifikan secara statistik antara usia kehamilan dan kejadian kematian neonatal dini (P=0,70). Tidak ada kematian ibu dalam penelitian ini.
Kesimpulan: Protokol manajemen yang diterapkan untuk kedua kelompok memiliki kemanjuran yang sama. Insiden chorioamnionitis klinis lebih tinggi pada kelompok kehamilan, yang mungkin terkait dengan faktor risiko seperti COVID-19 dan hepatitis B.

Kata kunci: Ketuban pecah dini, asfiksia, kematian neonatal

Introduction

Premature rupture of membranes (PROM) is defined as rupture of the amniotic sac before delivery. Premature rupture of membranes that occurs at or after 37 weeks of gestation (term pregnancies) is called PROM, which develops in approximately 2-3% of all singleton pregnancies and 7.4% of twin pregnancies.[1,2] However, if rupture occurs before 37 weeks of gestation, this condition is called preterm premature rupture of membranes (PPROM), which occurs as a complication in approximately one-third of all preterm deliveries. The problem of premature rupture of membranes requires greater attention since the prevalence is quite large and has a tendency to increase at any time.[2]

The incidence of PPROM is associated with increased maternal and perinatal morbidity and mortality. Approximately one-third of women who experienced PPROM would experience potentially severe infections. Moreover, neonates will also be at a greater risk of morbidity and mortality related to PPROM than their mothers at up to 47.9%. On the other hand, asphyxia, hypoxia, umbilical cord prolapse, and pulmonary hypoplasia have been reported to play a role in neonatal death as a consequence of PROM.[2-4] There are two management strategies applied in the management of PROM, namely, active and expectant management.[1-5] Expectant management leads to prolonged antenatal hospitalization, while active management may require intensive care of the neonate for problems associated with prematurity.[5]

Since 2018, the Department of Obstetrics and Gynaecology Dr. Hasan Sadikin General Hospital has implemented an active management protocol at 34 weeks of gestation. However, there has been no research discussing the effectiveness of implementing this protocol. Thus, this study analysed the maternal and neonatal outcomes in PPROM at 34-36 weeks of gestation compared to PROM as local data that can support global data to provide an overview of the current protocol's effectiveness to develop better protocols for PROM and PPROM.

Material and Methods

Research Design

This was an observational study with a cross-sectional method by taking secondary data from the Department of Obstetrics and Gynaecology Dr. Hasan Sadikin Bandung. All methods were carried out in accordance with relevant guidelines and regulations after obtaining approval and recommendations from the Ethics Committee Review Board of Hasan Sadikin General Hospital – Faculty of Medicine, Padjadjaran University with reference number LB.02.01/X.6.5/046/2021. Since data collection was done through secondary data, no complaints may arise.

Authors collected data on clinical chorioamnionitis and maternal death as maternal outcomes as well as neonatal asphyxia and neonatal death as neonatal outcomes from patients diagnosed with premature rupture of membranes at 34-36 weeks of gestation and term gestation.

Research Subjects

The subjects of this study were taken from secondary data of pregnant women diagnosed with premature rupture of membranes at 34-36 weeks of gestation and term gestation in the Department of Obstetrics and Gynaecology Dr. Hasan Sadikin General Hospital Bandung during the period January 2019 to December 2021 who met the inclusion and exclusion criteria. Those populations that had a singleton alive fetus were included in this study. However, subjects who had incomplete secondary data in their medical record and uncontrolled comorbid history that could affect maternal or neonatal outcomes such as

uterine abnormalities, fetal growth restriction (FGR), fetal abnormalities, uterine myoma, hypertension in pregnancy, antepartum hemorrhage, uterine atony, gestational diabetes, chronic kidney disease, and chronic heart failure New York Heart Association (NYHA) II-IV that had been confirmed by clinical examination and supporting examinations by obstetricians and internal medicine specialists were excluded from this study.

Sampling Methods

The sampling technique in this study was simple random sampling using a random number in Microsoft Excel software with a list of patients in the medical record as a sample frame. This study required a minimum sample of 225 pregnant women with term gestation and 225 pregnant women with 34-36 weeks of gestation.[6]

Data Collection and Statistical Analysis
Statistical analysis was performed by:

1. The chi-square test was used if there was an expectation value of cells <5 to analyze the relationship between two categorical data.
2. A P-value of <0.05 was considered statistically significant. The data obtained were recorded in a special form and then processed using SPSS version 25.0 for Windows.

Results
Subject Characteristics

In total, 770 samples consisting of 385 subjects in each group, met the inclusion and exclusion criteria of the study. All of the variables in subject characteristics were not normally distributed, so the test was continued using the Mann-Whitney test (Table 1). The maternal age of the 34-36 weeks gestation group had an average of 27.14 ± 6.44 years, and the term gestation age group had an average of 27.28 ± 6.55 years. There was no significant difference in maternal age between the 34-36 weeks gestation group and the term gestation group (P= 0.776). The neonatal weight at 34-36 weeks of gestation had an average of 2212 ± 339 grams, while the term gestational group had an average of 2868 ± 375 grams. Based on these data, neonates at term gestational age had a heavier body weight than those at 34-36 weeks of gestation. The difference in neonatal weight between each group was statistically significant (P=0.001). The APGAR score at 1 minute of the 34-36 weeks gestation group had an average of 6.64 ± 0.89, while the term gestational group had an average of 6.80 ± 0.76. There was a significant difference in the 1-minute APGAR score between each group (P=0.01). Moreover, the APGAR score at 5 minutes in the 34-36 weeks gestation group had an average of 8.60 ± 0.84, while the term gestational group had an average of 8.70 ± 0.91. There was also a significant difference in the APGAR score at 5 minutes between each group (P= 0.02). Since the table of etiology of deaths and risk factors was a > 2 x 2 type of table, the test was continued with the Pearson and Chi-square test. The etiology of death caused by sepsis in the 34-36 weeks of gestation group was 50%, and asphyxia was responsible for as many as 40% cases of deaths in this group. The relationship between the etiology of death and gestational age was not significant (P= 0.90). The risk factors for PROM at 34-36 weeks of gestation were urinary tract infection (UTI) in 45.7% of cases, coronavirus disease 2019 (COVID-19) in (in 10%), hepatitis B infection (in 30%), and 49% from fetal position and presentation abnormalities in 49%. The relationship between risk factors and gestational age was statistically significant (P=0.001).

Table 1 Subject Characteristics

Variables	Total	Gestational Age		P-value
		Term Gestation	34-36 Weeks of Gestation	
Maternal Age(years)				
Mean ± SD	27 ± 6.49	27 ± 6.55	27 ± 6.44	0.78
Median	26.00	26.00	26.00	
Min – Max	14.00-49.00	14.00-49.00	15.00-44.00	
Neonatal Weight(grams)				
Mean ± SD	2541 ± 485	2868 ± 375	2212 ± 339	0.001*
Median	2500	2830.00	2200.00	
Min – Max	1600.00-4470	1700-4425	1600-4470	
APGAR Score 1 Minute				
Mean ± SD	6.72 ± 0.83	6.80 ± 0.76	6.64 ± 0.89	0.01*
Median	7.00	7.00	7.00	
Min – Max	1.00-9.00	1.00-8.00	1.00-9.00	
APGAR Score 5 Minutes				
Mean ± SD	8.65 ± 0.88	8.70 ± 0.91	8.60 ± 0.84	0.02*
Median	9.00	9.00	9.00	
Min – Max	1.00-10.00	1.00-10.00	4.00-10.00	
Etiology of Deaths				
None	763	381(49.9,0%)	382(50.1%)	0.90
Sepsis	2	1(50.0%)	1(50.0%)	
Asphyxia	5	3(40.0%)	2(40.0%)	
Risk Factors				
None	573	261(45.5%)	312(54.5%)	0.001*
UTI	35	19(54.3%)	16(45.7%)	
COVID-19	50	45(90.0%)	5(10.0%)	
Hepatitis B	10	7(70.0%)	3(30.0%)	
Abnormal Position and Presentation	101	52(51.5%)	49(48.5%)	

*Note: For numerical data, the p-value was tested by unpaired T-test if the data were normally distributed with the alternative Mann-Whitney test if the data were not normally distributed. Categorical data p- values were calculated based on the chi-square test with the alternative exact Fisher test if the requirements of the chi-square test were not met. A P-value <0.05 was considered statistically significant.

**Abbreviation: APGAR (appearance, pulse, grimace, activity and respiration), UTI: urinary tract infection, COVID-19:coronavirus disease.*

Relationship between the Differences in Asphyxia Neonatorum Incidence at 34-36 Weeks of Gestation Group with Preterm Premature Rupture of Membrane Compared to Term Gestational Group with Premature Rupture of Membrane.

Asphyxia accounted for 2.3% of cases in neonates born from pregnant women with term gestational age, while in the 34-36 weeks gestational age group, asphyxia was found in 2.1% of cases. There was no statistically significant relationship between gestational age and the incidence of neonatal asphyxia (P= 0.81). However, PROM pregnant women had a 1.13 fold higher risk (OR= 1.13, CI 95%) for neonatal asphyxia than the 34-36 weeks of gestation group. Thus, a gestational age of 34-36 weeks was associated with a lower risk of neonatal asphyxia, as shown in **Table 2**.

Relationship between the Differences in Early Neonatal Deaths at 34-36 Weeks of Gestation Group with Preterm Premature Rupture of Membrane Compared to Term Gestational Group with Premature Rupture of Membrane.

Term gestational age pregnant women with an early neonatal death occurred in as many as 1.0% of cases, while the 34-36 weeks of gestation group with early neonatal death occurred in as many as 0.8% of cases. PROM pregnant women had a higher risk 1.34 fold higher risk (OR= 1.34, CI 95%) for early neonatal death compared to the 34-36 weeks of gestation group. However, there was no statistically significant difference between gestational age and the incidence of early neonatal death (P= 0.70) (**Table 3**).

Relationship between the Differences in Clinical Chorioamnionitis at 34-36 Weeks of Gestation Group with Preterm Premature

Table 2 Relationship between the Differences in Asphyxia Neonatorum Incidence at 34-36 Weeks of Gestation Compared to the Term Gestational Group.

Variable	Total	Asphyxia		OR (95%CI)	P-value
		Yes	No		
Gestational Age					
Term gestation	385	9(2.3%)	376 (97.7%)	1.13(0.43-2.96)	0.81
34-36 weeks	385	8(2.1%)	377(97.9%)	Reff	

*Note: For numerical data, the p-value was tested by unpaired T-test if the data were normally distributed with the alternative Mann Whitney test if the data were not normally distributed. Categorical data p- values were calculated based on the chi-square test with the alternative exact Fisher test if the requirements of the chi square test were not met. A P-value <0.05 was considered statistically significant.

Table 3 Relationship between the Differences in Early Neonatal Deaths at 34-36 Weeks of Gestation Compared to the Term Gestational Group.

Variable	Total	Early Neonatal Death		OR (95%CI)	P-value
		Yes	No		
Gestational Age					
Term gestation	385	4(1.0%)	381(99.0%)	1.34(0,30-6,01)	0.70
34-36 weeks	385	3(0.8%)	382(99.2%)	Reff	

*Note: For numerical data, the p-value was tested by unpaired T-test if the data were normally distributed with the alternative Mann Whitney test if the data were not normally distributed. Categorical data p- values were calculated based on the chi-square test with the alternative exact Fisher test if the requirements of the chi-square test were not met. A P-value <0.05 was considered statistically significant

Table 4 Relationship between the Differences in Clinical Chorioamnionitis at 34-36 Weeks of Gestation Group Compared to Term Gestational Group.

Variable	Total	Chorioamnionitis		OR (95%CI)	P-value
		Yes	No		
Gestational Age					
Term gestation	385	4(1.0%)	381(99.0%)	4.03(0.45-36.24)	0.18
34-36 weeks	385	1(0.3%)	384 (99.7%)	Reff	

*Note: For numerical data, the p-value was tested by unpaired T-test if the data were normally distributed with the alternative Mann Whitney test if the data were not normally distributed. Categorical data p-values were calculated based on the chi-square test with the alternative exact Fisher test if the requirements of the chi-square test were not met.A P-value <0.05 was considered statistically significant.

Rupture of Membrane Compared to Term Gestational Group with Premature Rupture of Membrane.

Term gestational age pregnant women with clinical chorioamnionitis occurred as much as 1.0% of cases, while 34-36 weeks of gestation group with clinical chorioamnionitis occurred as much as 0.3% of cases. PROM pregnant women had a 4.03 fold higher risk (OR= 4.03, CI 95%) of developing clinical chorioamnionitis in the 34-36 weeks of gestation group (**Table 4**).

Relationship between the Differences in Maternal Deaths at 34-36 Weeks of Gestation Group with Preterm Premature Rupture of Membrane Compared to Term Gestational Group with Premature Rupture of Membrane.

There were no maternal deaths in either group. Therefore, the analysis could not be carried out because there was no comparison group in this study.

Discussion

In this study, term pregnant women with PROM had a 1.128 fold higher risk (OR= 1.13, CI 95%) for neonatal asphyxia than the 34-36 weeks of gestation group. It was found that PROM could increase the risk of asphyxia four times higher.[7-11] However, in this study, there was no significant difference in the incidence of neonatal asphyxia between 34-36 weeks of gestation and term gestational age. These findings correlate with lung maturation that has only been completed above 34 weeks of gestation. A study conducted by Bond et al found that the incidence of respiratory distress syndrome, hyperbilirubinemia, and necrotizing enterocolitis decreased at ≥34 weeks of gestation.[12-15] PROM pregnant women had a 1.34 fold higher risk of early neonatal death compared to the 34-36 weeks of gestation group. However, there was no statistically significant difference between gestational age and the incidence of early neonatal death. There were a total of seven early neonatal deaths; three babies at 34-36 weeks of gestation and four babies at term gestational age. Five babies died due to asphyxia, while two other babies died due to neonatal sepsis. This could have occurred since PROM or PPROM can increase the incidence of sepsis and asphyxia.[16-23] Moreover, there was a possible correlation between COVID-19 and the term group (PROM), although it was not statistically significant. During this pandemic health emergency, maternal and foetal outcomes worsened globally. There are still limited data indicating that SARS-CoV-2 infection in COVID-19 causes higher levels of adverse perinatal outcomes, including neonatal death measured in infected pregnant women compared to noninfected pregnant women.[24-25] Some case reports and case series have identified that there is an increased risk of perinatal death in mothers who tested positive for SARS-CoV-2 during the

pandemic. Most of these studies referred to the effect of the virus on the placenta and inflammation, leading to fetal growth restriction and inducing perinatal death, including neonatal death.26-30

PROM pregnant women had a 4.03 fold higher risk (OR= 4.03, CI 95%) of developing clinical chorioamnionitis in the 34-36 weeks of gestation group. Risk factors in term groups included 32% of cases compared to only 19 cases in PPROM, thus the incidence of complications with risk factors in the PROM group was higher than that in the PPROM group. Moreover, PROM subjects in this study had a higher prevalence of COVID-19 and hepatitis, which were nine times and more than two times higher than the PPROM group, respectively. COVID-19 and hepatitis were more likely to have an association with the incidence of chorioamnionitis, which was 4.03 times higher in term pregnant women with PROM than in PPROM groups.[31-33] Patients with COVID-19 are at increased risk of PROM, which may result in immediate risks and subsequent problems, including maternal or neonatal infection. One of the possible explanations from previous studies regarding this association was the activation of a series of mediators and biochemical pathways of inflammation, such as macrophages or IL-6, in the PROM and premature delivery that were also found in COVID-19, which had a higher prevalence in the PROM group in this study. Among other cytokines, IL-6, is of major importance because there is evidence that circulating IL-6 levels are closely linked to the severity of COVID-19 and could lead to PROM in pregnant women.[34-36] Maternal prepregnancy hepatitis B virus infection as a comorbidity was independently associated with an increased risk of preterm birth, the risk of preterm birth, and other adverse pregnancy outcomes in addition to mother-to-child transmission) in women infected with hepatitis B virus and should not be neglected. Pregnant women could have a high hepatitis B virus DNA load that could affect immunity, leading to adverse outcomes such as PROM.[37-38]

Maternal deaths are divided into two categories; directly and indirectly related to childbirth. In this study, there were no maternal deaths in the data, so an analysis could not be carried out because there was no comparison group.

Study Limitations

This study has several limitations (1) This study was conducted retrospectively based on medical record data. The study would be better if it was carried out prospectively to provide better results; thus, it could be used as a comparison in patients undergoing active or expectant management. (2) This study did not consider the duration of premature rupture of membranes, which would affect the outcome of the study. (3) Furthermore, for maternal morbidities such as chorioamnionitis, it was necessary to definitively establish a diagnosis through histopathological examination.

Conclusions

The APGAR score between the PPROM and PROM groups was not significantly different. PROM pregnant women had a higher risk of 1.13 times for neonatal asphyxia, 1.34 times for early neonatal death (which may also be associated with the higher cases of COVID-19 and hepatitis B in the PROM group compared to the PPROM group), and 4.03 times to develop clinical chorioamnionitis compared to the 34 -36 weeks of gestation group. There were no maternal deaths in this study.

References

1. Assefa, N., Berhe, H., Girma, F. *et al*. Risk factors of premature rupture of membranes in public hospitals at Mekele city, Tigray, a case control study. *BMC*

Pregnancy Childbirth **18**, 386. https://doi.org/10.1186/s12884-018-2016-6 (2018).
2. Menon R, Richardson LS. Preterm prelabor rupture of the membranes: A disease of the fetal membranes. *Semin Perinatol*. **41**:409-419; 10.1053/j.semperi.2017.07.012. PMID: 28807394; PMCID: PMC5659934. (2017).
3. Sari IM, Adisasmita AC, Prasetyo S, Amelia D, Purnamasari R. Effect of premature rupture of membranes on preterm labor: a case-control study in Cilegon, Indonesia. *Epidemiol Health*. **42**:e2020025; 10.4178/epih.e2020025. PMID: 32422694; PMCID: PMC7340614 (2020).
4. Czikk MJ, McCarthy FP, Murphy KE. Chorioamnionitis: From pathogenesis to treatment. Clin Microbiol Infect [Internet]. *European Society of Clinical Infectious Diseases*. **17(9)**:1304–11. http://dx.doi.org/10.1111/j.1469- 0691.2011.03574.x. (2011)
5. Murtha AP, Sinclair T, Hauser ER, Swamy GK, Herbert WN, Heine RP. Maternal serum cytokines in preterm premature rupture of membranes. *Obstet Gynecol*. Jan;**109(1)**:121-7; 10.1097/01.AOG.0000250474.35369.12. PMID: 17197597. (2007).
6. Martius JA, Steck T, Oehler MK, Wulf KH. Risk factors associated with preterm (<37+0 weeks) and early preterm birth (<32+0 weeks): univariate and multivariate analysis of 106 345 singleton births from the 1994 statewide perinatal survey of Bavaria. *Eur J Obstet Gynecol Reprod Biol*. **80(2):**183-9; 10.1016/s0301-2115(98)00130-4. PMID: 9846665. (1998).
7. Bouvier D, Forest JC, Blanchon L, *et al*. Risk Factors and Outcomes of Preterm Premature Rupture of Membranes in a Cohort of 6968 Pregnant Women Prospectively Recruited. *J Clin Med*. **8(11)**:1987; 10.3390/jcm8111987. PMID: 31731659; PMCID: PMC6912547. (2019).
8. Ghafoor S. Current and Emerging Strategies for Prediction and Diagnosis of Prelabour Rupture of the Membranes: A Narrative Review. Malays *J Med Sci*. **28(3)**:5-17. 10.21315/mjms2021.28.3.2. Jun 30. PMID: 34285641; PMCID: PMC8260062. (2021).
9. American College of Obstetrics and Gynaecology (ACOG). Prelabor Rupture of Membranes. *Obstet Gynecol.* **133(76)**:168–86. 10.1097/AOG.0000000000003700. (2019)
10. Laptook AR. Birth Asphyxia and Hypoxic-Ischemic Brain Injury in the Preterm Infant. *Clin Perinatol*. **43(3)**:529-45; 10.1016/j.clp.2016.04.010; PMID: 27524452. (2016).
11. Bayih WA, Tezera TG, Alemu AY, *et al*. Prevalence and determinants of asphyxia neonatorum among live births at Debre Tabor General Hospital, North Central Ethiopia: a cross-sectional study. *Afr Health Sci*. **21(1)**:385-396; 10.4314/ahs.v21i1.49; PMID: 34394321; PMCID: PMC8356583. (2021).
12. Wlodkowic D, Telford W, Skommer J, Darzynkiewicz Z. Apoptosis and beyond: cytometry in studies of programmed cell death. *Methods Cell Biol*; **103**:55-98; 10.1016/B978-0-12-385493-3.00004-8. PMID: 21722800; PMCID: PMC3263828. (2011).
13. Ghomian N, Hafizi L, Takhti Z. The role of vitamin C in prevention of preterm premature rupture of membranes. *Iran Red Crescent Med J*; **15(2)**:113-6; 10.5812/ircmj.5138. PMID: 23682322; PMCID: PMC3652497. (2013).
14. Hassanzadeh A, Paknahad Z, Khoigani MG. The relationship between macro- and micro-nutrients intake and risk of preterm premature rupture of membranes in pregnant women of Isfahan. *Adv Biomed Res*. **26(5)**:155; 10.4103/2277-

9175.188949. PMID: 27713876; PMCID: PMC5046777. (2016).
15. Gupta S, Malik S, Gupta S. Neonatal complications in women with premature rupture of membranes (PROM) at term and near term and its correlation with time lapsed since PROM to delivery. *Tropical Doctor*. **50(1)**:8-11. doi:10.1177/0049475519886447. (2020).
16. Merenstein GB, Weisman LE. Premature rupture of the membranes: neonatal consequences. *Semin Perinatol*. **20(5)**:375-80; 10.1016/s0146-0005(96)80004-8. PMID: 8912991. (1996).
17. Blumenfeld YJ, Lee HC, Gould JB, et al. The effect of preterm premature rupture of membranes on neonatal mortality rates. *Obstet Gynecol*. **116(6)**:1381-1386. 10.1097/AOG.0b013e3181fe3d28. PMID: 21099606. (2010).
18. Zhang H, Wang LU, Wang J, Hei J, Ruan C. Premature rupture of the fetal membrane combined with subclinical chorioamnionitis negatively affects pregnancy outcomes by a mechanism associated with reduced levels of matrix metalloproteinase-2. *Exp Ther Med*; **10(2)**:561-566. *10.3892/etm.2015.2559*. (2015).
19. Fahey JO. Clinical management of intra-amniotic infection and chorioamnionitis: a review of the literature. *J Midwifery Womens Health*. **53(3)**:227-235; 10.1016/j.jmwh.2008.01.001. PMID: 18455097. (2008).
20. Bond DM, Middleton P, Levett KM, *et al*. Planned early birth versus expectant management for women with preterm prelabour rupture of membranes prior to 37 weeks' gestation for improving pregnancy outcome. *Cochrane Database Syst Rev*;**3(3)**:CD004735; *10.1002/14651858.CD004735.pub4*. PMID: 28257562; PMCID: PMC6464692. (2017).
21. Endale T, Fentahun N, Gemada D, Hussen MA. Maternal and fetal outcomes in term premature rupture of membrane. *World J Emerg Med*. **7(2)**:147-52; 10.5847/wjem.j.1920-8642.2016.02.011. PMID: 27313811; PMCID: PMC4905872. (2016).
22. Enjamo M, Deribew A, Semagn S, Mareg M. Determinants of Premature Rupture of Membrane (PROM) Among Pregnant Women in Southern Ethiopia: A Case-Control Study. *Int J Womens Health*. **31(14)**:455-466; 10.2147/IJWH.S352348. PMID: 35386937; PMCID: PMC8979419. (2022).
23. Stancu SMK, Ash LK, Smeding C, Alwan MA. Predictors of Caesarean Delivery in Preterm Premature Rupture of Membranes. *Open Access Maced J Med Sci*. **7(7)**:1124-1128; 10.3889/oamjms.2019.250. PMID: 31049093; PMCID: PMC6490484. (2019).
24. Hekimoğlu B, Aktürk Acar F. Effects of covid-19 pandemic period on neonatal mortality and morbidity. *Pediatrics & Neonatology*. **63(1)**:78–83. 10.1016/j.pedneo.2021.08.019. (2022).
25. Vousden N, Bunch K, Morris E, *et al.* The incidence, characteristics and outcomes of pregnant women hospitalized with symptomatic and asymptomatic SARS-CoV-2 infection in the UK from March to September 2020: A national cohort study using the UK Obstetric Surveillance System (UKOSS). *PLoS One*. **16(5)**:e0251123. 10.1371/journal.pone.0251123. PMID: 33951100; PMCID: PMC8099130. (2021).
26. Pathirathna ML, Samarasekara BPP, Dasanayake TS, Saravanakumar P, Weerasekara I. Adverse Perinatal Outcomes in COVID-19 Infected Pregnant Women: A Systematic Review and Meta-Analysis. *Healthcare (Basel)*. **10(2)**:203. *10.3390/healthcare10020203*. (2022).
27. Kazemi SN, Hajikhani B, Didar H, *et*

al. COVID-19 and cause of pregnancy loss during the pandemic: A systematic review. *PLoS One* ;**16(8):**e0255994; *10.1371/journal.pone.0255994*. PMID: 34379700; PMCID: PMC8357105. (2021).
28. Juan J, Gil MM, Rong Z, *et al*. Effect of coronavirus disease 2019 (COVID-19) on maternal, perinatal and neonatal outcome: systematic review. *Ultrasound Obstet Gynecol*. **56(1)**:15-27. 10.1002/uog.22088. PMID: 32430957; PMCID: PMC7276742. (2020).
29. Chmielewska B, Barratt I, Townsend R, *et al*. Effects of the COVID-19 pandemic on maternal and perinatal outcomes: a systematic review and meta-analysis. *Lancet Glob Health.* **9(6)**:e759–e772. 10.1016/S2214-109X(21)00079-6. (2021).
30. Allotey J, Stallings E, Bonet M, et al; for PregCOV-19 Living Systematic Review Consortium. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. *BMJ*. **370**:m3320; *10.1136/bmj.m3320.* PMID: 32873575; PMCID: PMC7459193. (2020).
31. Bayih WA, Yitbarek GY, Aynalem YA, *et al*. Prevalence and associated factors of birth asphyxia among live births at Debre Tabor General Hospital, North Central Ethiopia. *BMC Pregnancy Childbirth* ;**20(1)**:653. 10.1186/s12884-020-03348-2. PMID: 33115413; PMCID: PMC7594464. (2020).
32. Bayih WA, Tezera TG, Alemu AY, *et al*. Prevalence and determinants of asphyxia neonatorum among live births at Debre Tabor General Hospital, North Central Ethiopia: a cross-sectional study. *Afr Health Sci*. **21(1)**:385-396. 10.4314/ahs.v21i1.49. PMID: 34394321; PMCID: PMC8356583. (2021).
33. Gupta S, Malik S, Gupta S. Neonatal complications in women with premature rupture of membranes (PROM) at term and near term and its correlation with time lapsed since PROM to delivery. Trop Doct. **50(1)**:8-11. 10.1177/0049475519886447. PMID: 31726941. (2020).
34. Martinez-Perez, O., Prats Rodriguez, P., Muner Hernandez, M. *et al.* The association between SARS-CoV-2 infection and preterm delivery: a prospective study with a multivariable analysis. *BMC Pregnancy Childbirth* **21**:273. https://doi.org/10.1186/s12884-021-03742-4. (2021).
35. Mirbeyk M, Saghazadeh A, Rezaei N. A systematic review of pregnant women with COVID-19 and their neonates. Arch Gynecol Obstet. **304(1)**:5-38. 10.1007/s00404-021-06049-z. (2021).
36. Soy, M., Keser, G., Atagündüz, P. *et al.* Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. *Clin Rheumatol* **39:**2085–2094. https://doi.org/10.1007/s10067-020-05190-5. (2020).
37. Liu J, Zhang S, Liu M, *et al*. Maternal pre-pregnancy infection with hepatitis B virus and the risk of preterm birth: a population-based cohort study. *Lancet Glob Health*. **5(6)**:e624-e632. 10.1016/S2214-109X(17)30142-0. PMID: 28495266. (2017).
38. Huang QT, Wei SS, Zhong M, *et a*l. Chronic hepatitis B infection and risk of preterm labor: a meta-analysis of observational studies. *J Clin Virol*. 61(1):3-8. 10.1016/j.jcv.2014.06.006. PMID: 24973811. (2014).