

Peer Review History: Relationship between Premature Rupture of the Membrane and Cesarean Delivery: Case from Jakarta, Indonesia

Editor(s):

(1) Dr. Bagiu Iulia-Cristina, Assistant professor, Multidisciplinary Research Center on Antimicrobial Resistance, "Victor Babes" University of Medicine and Pharmacy, Romania.

Reviewers:

(1) Visweswara Rao Guthi, SVIMS, Sri Padmavathi Medical College for Women, India.

(2) Ritika Rocque, College of Nursing, All India Institute of Medical Sciences, India.

Additional Reviewers:

Open Peer Review Policy: [Click Here](#)

Specific Comment:

Average Peer review marks at initial stage: 8.5/10

Average Peer review marks at publication stage: 9/10

Peer Review History:

Stage 1 | Original Manuscript | [File 1](#) | NA

Stage 2 | Peer review report_1 (Visweswara Rao Guthi, India) | [File 1](#) | [File 2](#)

Stage 2 | Peer review report_2 (Ritika Rocque, India) | [File 1](#) | NA

Stage 2 | Revised_MS_v1_and_Feedback_v1 | [File 1](#) | [File 2](#)

Stage 3 | Comment_Editor_1_v1 | [File 1](#) | NA

Relationship Between Premature Rupture of The Membrane and Cesarean Delivery

Abstract

Premature rupture of membranes (PROM) is the spontaneous rupture of the membranes before the onset of signs of labor. It can occur both before term (<37 weeks) and after term (>37 weeks). *Caesarean delivery* is a surgical technique to deliver the fetus through an incision in the abdominal wall and uterine wall. This procedure is performed to minimize all complications from premature rupture of membranes. This study aims to determine the relationship between premature rupture of membranes and delivery of *sectio caesarea* at the UKI General Hospital in the 2019 period by using a descriptive content analysis method (analysis of medical records documents) with a cross-sectional approach and obtained 65 samples who experienced premature rupture of membranes. The results showed that 53 samples (81.55%) experienced premature rupture of membranes and performed *sectio caesarea*, while 12 samples (18.45%) had premature rupture of membranes but did not perform *sectio caesarea* with p-value = 0.001 ($p < 0.05$) from the results of the chi-square statistical test. From the results of the analysis, it was found that there was a relationship between premature rupture of membranes and delivery of *cesarean section* at the UKI General Hospital for the 2019 period. It is suggested that patients avoid the factors that can cause premature rupture of the membranes, which have been told by the doctor or health worker and the patient's family to support the patient to remind them to avoid factors that can cause premature rupture of the membranes.

Keywords: Premature rupture of membranes, *Cesarean Section*.

Introduction

Premature or premature rupture of membranes is the spontaneous rupture of the amniotic membranes before signs of labor occur. This condition can occur either before term (<37 weeks) or after term (>37 weeks). [1] The amniotic membranes function to produce amniotic fluid and protect the fetus from various kinds of infections. [2] Under normal circumstances, the membranes will rupture during labor. According to the World Health Organization, in 2014, the incidence of premature rupture of membranes or premature rupture of membranes ranged from 5-10% of all births. Preterm premature rupture of membranes occurs in 1% of all pregnancies, and 70% of premature rupture occurs at term. In 30% of cases, premature rupture of membranes is the cause of preterm birth. [3]

The incidence of premature rupture of membranes in Indonesia ranges from 4.5% - 6% of all pregnancies. In contrast, in the United States, premature rupture of membranes occurs in 120,000 pregnancies per year and is associated with a high risk to maternal, fetal, and neonatal safety [4]. Various studies in India explain that the incidence is 7-12% for premature rupture of membranes which 60-70% occurs in the long term. [5] The incidence of premature rupture of membranes in several hospitals in Indonesia is quite varied, including Sardjito Hospital at 5.3%, Hasan Sadikin Hospital at 5.05%, Cipto Mangunkusumo Hospital at 11.22%, Pringadi Hospital at 2.27%, and Kariadi Hospital which is equal to 5.10%. [6] Premature rupture of membranes has various complications for the mother and fetus that cause morbidity and mortality. Maternal complications include chorioamnionitis and fetal complications such as fetal distress, premature birth, and cord compression, to neonatal complications such as neonatal asphyxia and sepsis. This complication requires labor conditions to be ended quickly to save the mother and fetus.

Sectio Caesarea is a labor procedure performed to minimize all complications from premature rupture of membranes [7].

Sectio Caesarea is a surgical technique to deliver a fetus through an incision in the abdominal wall (laparotomy) and uterine wall (hysterectomy). Sectio Caesarea is one of the ten most commonly performed major surgeries. This medical procedure is needed to assist deliveries that cannot be carried out normally due to maternal health problems or fetal conditions [8].

According to Travassolo in 2010 stated that premature rupture of membranes with oligohydramnios is related to the duration of rupture of membranes, high rates of sectio caesarea, and low Apgar scores at birth.

In Indonesia, the number of caesarean section deliveries continues to increase. According to the Indonesian Demographic and Health Survey (IDHS) data, there was an increase in caesarean sections in Indonesia from 1991 to 2007, around 1.3-6.8 percent. [9] Meanwhile, the results of the Riskesdas report (basic health research) in 2013 found that 9.8% of deliveries were carried out by sectio caesarea in Indonesia, 2.3% of which were due to complications in pregnancy [10].

Research conducted by Andayasari et al. in 2014 stated that sectio caesarea deliveries in one government hospital and one private hospital in DKI Jakarta from January 2011-December 2011 reached 59.2%, and premature rupture of membranes contributed 31.4% to sectio deliveries caesarea [11]. Research conducted by Sumelung in 2014 stated that premature rupture of membranes was one of the factors that increased the incidence of sectio caesarea at Liub Kendage Hospital in 2015 [12].

Based on the background above, the researchers wanted to research the relationship between premature rupture of membranes and cesarean section delivery at UKI General Hospital in January-December 2019. The problem in this study was "Is there a relationship between premature rupture of membranes and cesarean delivery in UKI General Hospital period January-December 2019? The study aims to determine the incidence of premature rupture of membranes and sectio caesarea deliveries at UKI General Hospital from January to December 2019.

Literature Review

The amniotic sac (amniotic sac), which lines the amniotic cavity, consists of the amnion and chorion, which are tightly bound. The amniotic membrane is a flexible but tough avascular tissue. These avascular structures have an important role in pregnancy in humans. In many obstetric cases, rupture of the membranes at a young gestational age is the most common cause of preterm birth. The inner membrane communicating with the amniotic fluid consists of a single layer of cuboidal epithelium derived from the embryonic ectoderm. This epithelium is tightly attached to the basement membrane, which is connected to the interstitial layer containing collagen I, III, and V. The outer part of the membrane is mesenchymal tissue derived from the mesoderm. This layer of the amnion is connected to the chorion leave. The amnion's inner lining is microvilli which transfer fluids and metabolism. This layer produces metalloproteinase-1 inhibitory substances [13].

Mesenchymal cells function to produce collagen so that the membrane becomes flexible and strong. In addition, these tissues produce the cytokines IL-6, IL-8, and MCP-1 (monocyte chemoattractant protein-1); This substance is useful against bacteria. In addition, the amniotic membranes produce vasoactive substances: endothelin-1 (a vasoconstrictor) and PHRP (parathyroid hormone-related protein), a vasorelaxant. Thus, the amniotic membrane regulates blood circulation and local vascular tone. The amniotic membrane also covers the umbilical cord. Some of the fluid will also come from diffusion in the umbilical cord. The rupture of the membranes is related to the strength of the membranes. In smokers

and infections, the resistance of the membranes is weakening so that they break easily. In a normal pregnancy, there are few macrophages. At the time of birth, leukocytes will enter the amniotic fluid as a reaction to inflammation. There is no IL-1B in a normal pregnancy, but IL-1B will be found in preterm labor.

It is related to the occurrence of the infection process. Since the beginning of pregnancy, amniotic fluid has been formed. Amniotic fluid is a protector and cushion for protection while supporting growth. Osmolarity, sodium, urea, and creatinine levels do not differ from the mother's serum levels, meaning that the levels in the amniotic fluid are the result of diffusion from the mother. Amniotic fluid contains many fetal cells (lanugo, vernix caseosa) [14]. Macroscopically, the amnion is a thin layer (only 20% of the thickness of the fetal membranes) and is a transparent (translucent) structure. This amniotic membrane can easily be separated from the underlying chorion because the amnion is never completely fused with the chorion and is only passively attached by internal pressure from the amniotic fluid [15]. The amnion lacks blood vessels and obtains its required nutrients and oxygen supplied directly by diffusion from the surrounding amniotic fluid, fetal surface vessels, or the decidua [16]. The thickness of the amnion varies greatly due to changes in the amount of mucin and fluid contained in the spongy lining, which ranges from 80 - 120 μm [17].

The amniotic epithelium, the innermost amnion layer that leads to the fetus and surrounds the amniotic fluid, consists of a single layer of simple, squamous to cuboidal cells, with microvilli apical and attached to the basement membrane [18]. The amniotic epithelium secretes collagen types I, III, and IV, non-collagen glycoproteins such as laminin, nidogen, and fibronectin, forming a cell basement membrane thickness of nearly 1 μm . The stromal compactum layer varies greatly in thickness, is tightly adherent, and cannot be separated from the basement membrane. This layer is a microfibril-dense cell-free homogeneous layer. Collagen types I, III, and V, and elastic fibers of the compact layer, are secreted by the mesenchymal cells in the fibroblast layer beneath the compact layer [19], which form the main burden-carrying fibrous framework of the amnion. The main tensile strength of the amnion is provided by collagen, which is arranged in one direction, i.e., parallel to the amniotic epithelium [20]. The compact layer and fibroblasts are difficult to differentiate histologically. The fibroblast layer beneath the compact layer is the most complex and thickest layer of the amnion, consisting of cellular tissue within a loose collagen network with non-collagenous glycoproteins, proteoglycans, and type III collagen. Fibroblasts and macrophages (Hofbauer cells) have been identified within this layer. The spongy intermediate layer, also called the intermediate layer because it lies between the amnion and the chorion, is rich in proteoglycans and hyaluronate, which absorbs large amounts of water and forms a viscous layer that allows the amnion to slide over the chorion [21].

By this mechanism, this spongy coating makes it possible to absorb physical stress and to provide spontaneous short-term mechanical repair and defect closure systems. In addition, a circular fibrous structure is found in direct relation to the chorionic side, helping to adjust the lateral tension on the sliding surface between the amnion and chorion [22]. Occasionally, a potential space can be seen histologically in the spongy layer between the amnion and chorion. The space comprises loosely arranged collagen fibers that are sometimes oedematous and contain scattered fibroblasts and macrophages.

Development is between the embryonic cell mass and the trophoblast during the early implantation period. The small cells lining the inner surface of the trophoblast are called amniogenic cells, which are precursors of the amniotic epithelium. The amnion can be identified for the first time on embryo development's 7th or 8th day. It begins with the formation of a vesicle that develops into a small sac covering the dorsal surface of the embryo. As the amniotic sac enlarges, distention of the amniotic sac causes it to contact the

interior surface of the chorion leave. Apposition of the chorion and amnion near the end of the first trimester. In young pregnancies, amniotic fluid is an ultrafiltrate of maternal plasma formed by the amnion cells. In the second trimester of pregnancy, amniotic fluid is formed by extracellular diffusion through the fetal skin, so its composition is similar to fetal plasma. Furthermore, after the second trimester, fetal skin horn substance formation occurs and blocks the diffusion of fetal plasma so that most of the amniotic fluid is formed by; amniotic cells and fetal urine. Fetal kidneys start excreting urine from the age of 12 weeks, and after reaching the age of 18 weeks, they can excrete urine as much as 7-14 cc/day. Term fetuses produce urine 27 cc/hour or 650 ccs daily [23]. Thus, the composition that forms amniotic fluid follows a postulate that the increase in amniotic fluid is not linear.

After the gestational age exceeds 12 weeks, what participates in forming amniotic fluid is; fetal kidneys (so that urea, creatinine, and uric acid are found), desquamation of fetal skin (skin cells, lanugo hair, vernix caseosa), secretions from the fetal lungs, transudate from the surface of the placental amnion, hormones or hormone-like substances in the amniotic fluid. Meanwhile, regulating amniotic fluid is very important to maintain the amount regularly. The following three important components influence the setting: production produced by the amnion cells, the amount of urine produced, and the amount of amniotic fluid swallowed by the fetus. Amniotic fluid regulation in term pregnancy includes the amount taken by the fetus \pm 500-1000 ml, enters the lungs \pm 170 ml, and from the umbilical cord and amnion \pm 200-500 ml. At the same time, the amount of fluid released by the fetus into the amniotic cavity is from oral secretions \pm 25 ml, secretions from the respiratory tract \pm 170 ml, urine \pm 800-1200 ml, and transmembrane from the amnion \pm 10 ml. Thus, fetal urine appears to dominate the production of amniotic fluid, and the average regulation near term reaches 500 cc/day [24].

Amniotic fluid has an important role in supporting the process of pregnancy and childbirth. Throughout a normal pregnancy, the compartments of amniotic fluid provide space for the fetus to grow, move and develop. Without amniotic fluid, the uterus will contract and put pressure on the fetus; in cases where rupture of the membranes occurs early in the first trimester, the fetus may experience structural abnormalities, including facial distortion, reduction of limbs, and abdominal wall defects due to uterine compression [25]. Towards mid-pregnancy, the amniotic fluid becomes increasingly important for fetal development and growth, including lung development, so if there is insufficient amniotic fluid during mid-pregnancy, the fetus is often accompanied by pulmonary hypoplasia and continues to death. In addition, this fluid also has a protective role in the fetus. This liquid contains anti-bacterial agents and works to inhibit the growth of bacteria with potential pathogens. Amniotic fluid is a protective medium for the fetus to help with cervical dilation during labor and delivery. In addition, amniotic fluid also acts as a means of communication between the fetus and the mother. The maturity and readiness of the fetus for birth can be known from the fetal urine hormones excreted into the amniotic fluid [26].

Amniotic fluid can also be used as a diagnostic tool to see fetal growth and development abnormalities by conducting cell cultures or using a spectrometer. Other functions of amniotic fluid can also protect the fetus from trauma, as a medium for fetal musculoskeletal development, maintain fetal body temperature, equalize uterine pressure in parturition, clean the birth canal so that the baby is less infected, and maintain normal development and growth of the lungs and gastro tract intestinal [27]. Any wound on any body part will go through several stages: inflammation, proliferation, and maturation. Each phase involves many components and mechanisms, including the inflammatory, proliferative, and maturation phases. [28]

Premature rupture of the membranes is a condition in which the membranes rupture before labor or in part. Premature rupture of membranes can occur in term or preterm

pregnancies. Preterm Premature Rupture of the Membranes or premature rupture of membranes is the rupture of the membranes in patients with a gestational age of fewer than 37 weeks [29]. The incidence of premature rupture of membranes is 8% at term (> 37 weeks) and is associated with an increased risk of infection in the mother (chorioamnionitis, endometritis) and infection in the fetus (neonatal sepsis). Meanwhile, the incidence of preterm premature rupture of membranes is 3%, as a cause of 20-30% of preterm labor [30]. Two things broadly cause the causes of premature rupture of membranes, namely reduced membrane strength and increased intrauterine pressure or both factors. An infection can cause reduced membrane strength from the vagina and cervix. The factors influencing premature rupture of membranes are age, parity, smoking behavior, and history of premature rupture. Experiences experienced by mothers in labor with premature rupture of membranes can have a major influence on the mother when facing pregnancy conditions. The previous history of premature rupture of membranes is 2-4 times at risk of experiencing premature rupture of membranes again. In short, the pathogenesis of premature rupture of membranes results from a decrease in collagen content in the membrane, which triggers premature and preterm rupture of membranes. Women who have experienced premature rupture of membranes in pregnancies before delivery will be at greater risk in subsequent pregnancies than women who have never experienced premature rupture of membranes before because the composition of the membranes decreases in subsequent pregnancies.

The rupture of membranes in labor is generally caused by repeated uterine contractions and stretching. The membranes rupture because, in certain areas, biochemical changes occur, which cause the inferior membranes to become brittle, not because the entire membranes are fragile. There is a balance between synthesis and degradation of the extracellular matrix. Changes in structure, cell number, and collagen catabolism cause collagen activity to change and cause the membranes to rupture. Collagen degradation is mediated by matrix metalloproteinases inhibited by tissue-specific and protease inhibitors. The membranes' integrity is due to a combination of low metalloproteinase activity and relatively higher concentrations of tissue inhibitors metalloproteinase-1. Microorganisms that infect the membranes of the membranes can form protease enzymes accompanied by an inflammatory response from the membranes, thereby affecting the balance of metalloproteinases and tissue inhibitors metalloproteinase-1, which causes a weakening of the tension of the membranes and rupture of the membranes hemolytic, and staphylococcus. In addition, closer to the delivery time, the balance between metalloproteinase and tissue inhibitors metalloproteinase-1 leads to proteolytic degradation of the extracellular matrix and fetal membranes. This proteolytic degradation activity increases towards delivery. The amniotic membranes are very strong in young pregnancies. In the third trimester, the membranes rupture easily. The weakening of the strength of the membranes is related to the enlargement of the uterus, uterine contractions, and fetal movements. In the last trimester, biochemical changes occur in the amniotic membranes so that the rupture of the membranes at term is physiological. Premature rupture of membranes in preterm pregnancy is caused by external factors such as infections that spread from the vagina [31].

Premature rupture of membranes greatly affects complications and length of labor. In the 1st stage of labor, the fetal membranes and the presenting part of the fetus act to open the upper part of the vagina. However, after the rupture of the membranes, the changes in the pelvic floor are all produced by the pressure exerted by the presenting part of the fetus so that the hydrostatic action of the fetal membranes causes cervical dilatation. If the membranes have ruptured, the lowest part of the fetus that attaches to the cervix and forms the lower uterine segment functions the same. It will result in one of the complications of premature rupture of membranes, namely the long labor process, so sectio caesarea is the only option in this condition [32].

Another complication of mothers with premature rupture of membranes that causes morbidity and mortality is chorioamnionitis. This infection causes inflammation of the amniotic fluid, amniotic membranes, or fetus, and this condition causes mothers with premature rupture of membranes to have symptoms of fever, fundal tenderness, tachycardia, fetal tachycardia, and smelly amniotic fluid. This condition is one of the complications feared to occur if a mother with premature rupture of membranes does not end her pregnancy immediately [33].

A study in Iran reported that out of 536 cases of premature rupture of membranes, 28% were performed by sectio caesarea. Other researchers concluded that sectio caesarea reached 26.6% in India in patients with premature rupture of membranes [34]. It is due to complications from premature membrane rupture, including fetal distress, malpresentation, narrow pelvis, failed induction, and the maternal complication of chorioamnionitis. Apart from that, other complications that led to the decision to perform sectio caesarea in mothers with premature rupture of membranes were complications of neonatal asphyxia and sepsis [35]. There is a relationship between fetal distress and decreased amniotic fluid volume. The more critical the fetus is. It was found that babies with premature rupture of membranes >12 hours had a 12 times greater risk of experiencing unfavorable outcomes, so it can be concluded that at term KPD, pregnancy termination should be carried out at least 6-12 hours from the onset of premature rupture of membranes.

Research Method

This type of research uses a descriptive analysis research method with a cross-sectional approach. This study used secondary data from UKI General Hospital medical records for the January-December 2019 period. The location for collecting research data was carried out in the UKI General Hospital medical records section. The time of execution, collection, and implementation of the research was carried out from August 2020 – October 2020. The population for this study was patients who gave birth at the UKI General Hospital for the period January-December 2019. The sample was part of the population that had met the inclusion criteria, namely patients who gave birth on indications of Premature rupture of membranes at UKI General Hospital during January-December 2019. The Central Statistics Agency in Indonesia stated that the total population of Indonesia was 271,066,400 in 2019. The World Health Organization reported that as many as 17,655 mothers gave birth in Indonesia in 2019. The number of samples in this study was at least 65 people. Data collection was carried out at the UKI General Hospital medical record section. Furthermore, medical record data following the research variables will be recorded. All data obtained will be filtered again according to the inclusion and exclusion criteria set so that data is produced that will be used in the results of this study. Data collected through medical records are processed using the IBM SPSS (Statistical for Social Science) program for Windows edition 25.0 and the Microsoft Office Excel 2016 program.

Result and Discussion

Data were obtained from the medical records of all patients with premature rupture of membranes delivered by cesarean section and normal delivery at UKI General Hospital for January-December 2019. The total sample was 65 patients.

Table 1. Characteristics of the sample by age

Age	Frequency	Percentage %
< 30 Tahun	15	23,1%
≥30 Tahun	50	76,9%
Total	65	100%

Table 1 shows the characteristics of the study sample based on age, which found 15 patients (23.1%) aged <30 years, while 50 patients (76.9%) were aged ≥ 30 years.

Table 2. Sample characteristics based on parity

Parity	Frequency	Percentage %
Primigravida	25	38,5%
Multigravida	40	61,5%
Total	65	100%

Table 2 shows the characteristics of the study sample based on parity, where there were 25 patients with primigravidas (38.5%), while multigravidas had 40 patients (61.5%).

Table 3. Sample characteristics based on gestational age

Gynecological Age	Frequency	Percentage %
< 37 Weeks	12	18,5%
≥ 37 Weeks	53	81,5%
Total	65	100%

Table 3 shows the characteristics of the study sample based on gestational age, which was found at gestational age <37 weeks in 12 patients (18.5%), while gestational age ≥ 37 weeks were found in 53 patients (81.5%).

Table 4. Sample characteristics based on BMI (Body Mass Index)

BMI	Frequency	Percentage %
< 30	17	26,2%
≥ 30	48	73,8%
Total	65	100%

Table 4 shows the characteristics of the study sample based on BMI (Body Mass Index), where there were 17 patients (26.2%) with a BMI <30, while 48 patients (73.8%) had a BMI ≥ 30 .

Table 5. Sample characteristics based on the history of premature rupture of membranes

History of premature rupture of membranes	Frequency	Percentage %
Ever	40	61,5%
Never	25	38,5%
Total	65	100%

Table 5 shows the characteristics of the study sample based on a history of premature rupture of membranes, in which 40 patients (61.5%) had a history of premature rupture of membranes, while 25 patients had never had premature rupture of membranes (38.5%)).

Table 6. Characteristics of the sample based on the APGAR SCORE

Apgar Score	Frequency	Percentage %
< 7	46	70,8%
≥ 7	19	29,2%
Total	65	100%

Table 6 shows the characteristics of the study sample based on the Apgar Score, where there were 46 patients (70.8%) with an APGAR SCORE <7, while 19 patients (29.2%) had an Apgar Score \geq 7.

Table 7. Sample characteristics based on birth weight

Birth Weight	Frequency	Percentage %
< 3 Kg	20	30,8%
\geq 3 Kg	45	69,2%
Total	65	100%

Table 7 shows the characteristics of the study sample based on birth weight, in which 20 patients (30.8%) had babies with birth weight <3 kg, while 45 patients (69.2%) had babies with birth weights \geq 3 kg.

Table 8. The relationship between premature rupture of membranes and sectio caesarea delivery

Gynecological Age		Type of Childbirth				Total	P-value
		Sectio	n (%)	No Sectio	n (%)		
Premature rupture of membranes	< 37 Weeks	7	10,76%	5	7,69%	12(18,45%)	0,001
	\geq 37 Weeks	50	76,92%	3	4,63%	53 (81,55%)	
Total		57	87,68%	8	12,32%	65 (100%)	

Table 8 shows the characteristics of the study sample based on the gestational age of mothers who experienced premature rupture of membranes and the type of delivery performed. It was found that mothers with gestational age <37 weeks experienced premature rupture of membranes and performed sectio caesarea in 7 patients (10.76%), whereas mothers with gestational age \geq 37 weeks experienced premature rupture of membranes but did not perform a cesarean section in 5 patients (7.69%). Meanwhile, 50 patients (76.92%) had premature rupture of membranes, and 50 patients (76.92%) had premature rupture of membranes and 37 weeks of gestational age \geq 37 weeks of mothers who had premature rupture of membranes without having a caesarean section. (4.63%), and the P-value is 0.001.

The study results found that the age group that experienced premature rupture of membranes was the most in the age group \geq 30 years, with as many as 50 patients (76.9%). It follows the theory where according to Sudarto, a mother who gives birth at the age of 35 and over can affect her reproductive system because her reproductive organs have begun to reduce their ability and elasticity in accepting pregnancy, affecting the process of embryogenesis. The amniotic membranes will be thinner, facilitating premature rupture [36]. Based on the results of the study, it was found that a woman with multigravida experienced premature rupture of membranes in 40 patients (61.5%). It is following the theory according to Kacerovky, women who have given birth several times accompanied by close pregnancy intervals can be at risk of experiencing premature rupture of membranes in their next pregnancy. It is because pregnancies are too frequent, affecting the embryogenesis process. The amniotic membranes become thinner, so they break easily prematurely. In addition, there is also a theory that the more parity, the easier it is for amnion infection to occur due to damage to the cervical structure in previous deliveries [37].

Based on the study's results, 53 pregnant women experienced premature rupture of membranes when their gestational age was \geq 37 weeks (81.5%). According to Popowski, it follows the theory that most premature rupture of membranes occurs at gestational age \geq 37 weeks. Premature rupture of membranes occurs nearing delivery due to an increase in matrix metalloproteinase which tends to cause the membranes to rupture, in addition to an increase

in matrix metalloproteinase, uterine enlargement, uterine contractions, and fetal movements occur [38].

From the results of the study, it was found that pregnant women who had a BMI (Body Mass Index) ≥ 30 had premature rupture of membranes, and 48 patients (73.8%) had a cesarean section. An increase in Body Mass Index ≥ 30 has a great risk for a normal delivery because, in a normal delivery, there will be a delay in the first stage of the active phase and the second stage. After all, the mother who is obese will have a narrow birth canal due to the accumulation of fat, making it difficult for the baby to come out, and a sectio caesarea must be carried out immediately [39].

The history that mothers have experienced in labor with the incidence of premature rupture of membranes can have a big influence on the mother when facing pregnancy conditions. Based on the amount of research data, it was found that 40 patients (61.5%) had a history of premature rupture of membranes in previous deliveries. According to Morgan, it follows the theory that patients with a previous history of premature rupture of membranes are at risk of 2-4 times experiencing premature rupture of membranes again. In short, the pathogenesis of premature membrane rupture results from a decrease in collagen content in the membrane, which triggers premature rupture membranes.

Women who have experienced premature rupture of membranes during pregnancy or before delivery are at greater risk in their next pregnancy than women who have never experienced premature rupture of membranes before because the composition of the membranes becomes fragile. The collagen content decreases in subsequent pregnancies [40]. The APGAR SCORE is a practical method systematically used to assess a baby as soon as possible after birth. What is assessed is heart rate, respiratory effort, muscle tone, skin color, and reaction to stimulation (response to stimuli), namely by inserting a catheter into the nostril after the airway has been cleaned when the new baby is born.

From the results of this assessment, it can be seen whether the baby is normal (APGAR score 7-10), moderate-mild asphyxia (APGAR score 4-6), or the baby has severe asphyxia (APGAR score 0-3). The characteristics of the sample based on the APGAR SCORE showed that patients who gave birth with premature rupture of membranes and their babies had an APGAR SCORE <7 . There were 46 patients (70.8%). It follows the theory according to Ni Wayan and Melania, where with the rupture of the membranes, there will be prolapse of the funiculi / descent of the umbilical cord, which will cause the neonatorum to experience hypoxia and asphyxia (lack of oxygen in the baby) which will result in compression of the umbilical cord, respiratory distress. The baby will be at risk of having a low APGAR SCORE (<7) [41].

Mechanical stretching, such as in a large baby's weight, can cause stretching of the membranes and can cause premature rupture of the membranes. It is also supported by the data results where there is an increase in the number of patients who experience premature rupture of membranes with a baby weighing > 3.5 kg by 1.6%, while babies weighing > 4 Kg were 2.4%. Based on the study's results, with birth weight ≥ 3 Kg and experiencing premature rupture of membranes were 45 patients (69.2%). It follows the theory according to Zelop, where mechanically stretching the fetal membranes will increase the production of prostaglandin E2 and Interleukin-8 in the amnion, also increasing the activity of MMP-1 in the membranes. Interleukin-8 produced from amnion and chorion cells is chemotactic towards neutrophils and stimulates collagenase activity, which disrupts the balance of synthesis and degradation of the extracellular matrix, which ultimately causes the rupture of the membranes.

Prostaglandin E2 increases uterine irritability, decreases membrane collagen synthesis, and increases the production of MMP-1 and MMP-3 by fibroblasts. The production of interleukin-8 and prostaglandin E2 from the amnion indicates that biochemical changes in the

membranes can be initiated by physical forces or by stretching the membranes, suggesting that mechanical forces cause premature rupture of membranes [42].

The results of the research on the relationship between premature rupture of membranes and sectio caesarea delivery obtained a value of $P = 0.001$ ($P < 0.05$) which means there is a relationship between premature rupture of membranes and sectio caesarea delivery where this is following the theory, according to Barbara, pregnant women with indications of ruptured membranes Early pregnancy will cause the amount of amniotic fluid to decrease and the risk of having a normal delivery. Babies born will also have an increased risk of morbidity and mortality. The risk of infection in the mother is also quite high, so it will increase morbidity and mortality, so the action of cesarean section is expected to reduce maternal morbidity and mortality and improve infant outcomes.

Conclusion

From the results of the research that was described in the previous chapter, the following conclusions were drawn: a) the prevalence of premature rupture of membranes at UKI General Hospital carrying out sectio caesarea in the January-December 2019 period was 57 patients (87.68%), while those who did not perform sectio caesarea in 8 patients (12.32%), and b) based on the Chi-square test, there was a significant relationship between premature rupture of membranes and sectio caesarea ($P=0.001$). Thus, it is hoped that health workers and health institutions as health workers can help educate patients about the factors that can cause premature rupture of membranes so that patients can take preventive action to prevent premature rupture membranes. In addition, it is recommended that patients avoid factors that can cause premature rupture of a membrane that doctors or health workers have told, and the patient's family can support patients to remind them to avoid factors that can cause premature rupture of membranes.

References

- [1] Caughey AB, Robinson JN, Norwitz ER. Contemporary diagnosis and management of preterm premature rupture of membranes. *Reviews in obstetrics and gynecology*. 2008;1(1):11.
- [2] Menon R, Richardson LS. Preterm prelabor rupture of the membranes: a disease of the fetal membranes. In *Seminars in perinatology* 2017 Nov 1 (Vol. 41, No. 7, pp. 409-419). WB Saunders.
- [3] Fitriyani F, Yuliana Lubis Y. Determinant factors in premature rupture of membranes. *Health Media Journal*. 2018 Nov 16;11(1):053-61.
- [4] Syarwani TI, Tendean HM, Wantania JJ. Overview of Premature Ruptured Membranes (PROM) in Prof. Dr. RD Kandou Manado in 2018. *Medical Scope Journal*. 2020;1(2).
- [5] Susan Blossia E. A Prospective Cross Sectional study on CRP Levels in Antenatal Women with Prelabor Rupture of Membrane and CRP Levels in Women with Normal Labor (Doctoral dissertation, Christian Medical College, Vellore).
- [6] Rohmawati N, Wijayanti Y. Premature rupture of membranes at Ungaran Regional General Hospital. *HIGEIA (Journal of Public Health Research and Development)*. 2018 Feb 1;2(1):23-32.
- [7] Venancyana MC, Indrayani T, Lubis R. Analysis Of Factors Affecting Pregnant Mothers In Making Decisions For Caesarean Section Childbirth Plan At Tc Hillers Hospital, Sikka Regency, Year 2022. *International Journal Of Multi Science*. 2022 Aug 25;3(02):7-17.

- [8] Waang WW, Kusumawati PD. Analysis of Deep Breath Relaxation Techniques for Post SC Patients with Pain. *Journal of Health Science Community*. 2022 Nov 15;3(2):97-101.
- [9] BP Statistics. Indonesia Demographic and Health Survey Report.
- [10] Suparmi S, Kusumawardhani N, Susiloretni KA. Sub-national inequality of caesarean sections in urban-rural areas of Indonesia. In *Proceedings of the international conference on public health 2018* (Vol. 4, No. 1, pp. 23-32).
- [11] Hardiyanti R. Use of Prophylactic Antibiotics in Sectio Caesarea Patients. *Journal of Health Science and Physiotherapy*. 2020 Jan 7;2(1):96-105.
- [12] Ulfa EN. Factors related to delivery by sectio caesarea at the Karsa Husada Batu general hospital in 2020 (Doctoral dissertation, Maulana Malik Ibrahim State Islamic University).
- [13] Machtejevienė E. Peptide pattern of amniotic fluid and its correlation with protein composition of fetal membranes: the search for new potential biomarkers to predict preterm premature rupture of membranes:[Rankraštis]: doctoral dissertation: biomedical sciences, medicine (06B).
- [14] Brace RA, Anderson DF, Cheung CY. Regulation of amniotic fluid volume: mathematical model based on intramembranous transport mechanisms. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*. 2014 Nov 15;307(10):R1260-73.
- [15] Cohen MC, Scheimberg I, Hutchinson JC. Anatomy and Pathology of the Placental Membranes. *Benirschke's Pathology of the Human Placenta*. 2022:281-343.
- [16] Founds SA, Baker B. Fetal and Placental Development and Functioning. *Core Curriculum for Maternal-Newborn Nursing E-Book*. 2022 Oct 14:28.
- [17] POLZIN WJ, BRADY K. Mechanical factors in the etiology of premature rupture of the membranes. *Clinical obstetrics and gynecology*. 1991 Dec 1;34(4):702-14.
- [18] Mamede AC, Carvalho MJ, Abrantes AM, Laranjo M, Maia CJ, Botelho MF. Amniotic membrane: from structure and functions to clinical applications. *Cell and tissue research*. 2012 Aug;349:447-58.
- [19] Country IK, KFM SO. Matrix Metalloproteinases in Premature Ruptured Membrane. *deependpublish*; 2021 May 1.
- [20] Yunus M, Sos S, Hatijar S. Textbook of Midwifery Care in Pregnancy.
- [21] Macedo BM. Exploração das Membranas Fetais para Aplicações de Engenharia dos Tecidos (Doctoral dissertation).
- [22] Haller C. Evaluation of human fetal membrane sealing (Doctoral dissertation, University of Zurich).
- [23] Ferselina L. Case Study of Handling Newborns with Cloudy Amniotic Water in Mrs. Vdi Pmb Komariah, Sst Lampung Selatan (Doctoral dissertation, Tanjungkarang Health Polytechnic).
- [24] Fahimah WF. Literature Review: Factors Causing Premature Rupture of Water.
- [25] Trance MG. Continuing Midwifery Care for Mrs. EB at the Kaputu Community Health Center April 13 to June 10 2019 (Doctoral dissertation, Kupang Ministry of Health Polytechnic).
- [26] Liley AW. Disorders of amniotic fluid. In *Fetal-placental disorders* 1972 Jan 1 (pp. 157-206). Academic Press.

- [27] Henny Sulistyawati SS, Zulfa Hanum SS, Keb M, Meikawati PR, SiTS S, Rosdianto NO, ST S, Keb M, Muayah SS, Ety Apianti SK. Textbook for Postpartum DIII Midwifery Volume I. Mahakarya Citra Utama Group; 2022 Sep 15.
- [28] Monika P, Waiker PV, Chandraprabha MN, Rangarajan A, Murthy KN. Myofibroblast progeny in wound biology and wound healing studies. *Wound Repair and Regeneration*. 2021 Jul;29(4):531-47.
- [29] Ma'roef M, Putri AP. The Relationship of Leukocyturia on The Incidence of Prominent Rupture of The Membrane in Preterm Pregnancy at The General Hospital of The University of Muhammadiyah Malang. *Medical Science*. 2019 Dec 21;15(2):139-45.
- [30] Sari DS. Relationship between Multiple Pregnancy and Fetal Abnormalities with Premature Rupture of the Membranes at the Prabumulih Regional General Hospital in 2019. *Abdurahman Health Journal*. 2020 Sep 25;9(2):56-63.
- [31] Margono RS, Sukrisno A, Nugrohowati N, Lestari W. Relationship between a premature rupture of membranes and the increase of leucocyte levels in pregnant women during the COVID-19 pandemic. *Journal of Traditional Midwifery and Health*. 2021 Oct 25:127-34.
- [32] Putri RS. Application of the Pelvic Rocking Technique on the Gymball Against the Progress of 1st Stage Labor Ny. T At PMB Eliana Putriani, Str. South Lampung Regency (Doctoral dissertation, Tanjungkarang Health Polytechnic).
- [33] Sprong KE, Mabenge M, Wright CA, Govender S. Ureaplasma species and preterm birth: current perspectives. *Critical reviews in microbiology*. 2020 Mar 3;46(2):169-81.
- [34] Ulfa EN. Factors related to delivery by sectio caesarea at the Karsa Husada Batu general hospital in 2020 (Doctoral dissertation, Maulana Malik Ibrahim State Islamic University).
- [35] Marlyana DM, Nurwahyuni A, Wibowo A. Neonate Outcome And Response Time For Emergency Cesarean Section: A Scoping Review. *Journal of Medicine and Health: Scientific Publication of the Faculty of Medicine, Sriwijaya University*. 2023 Jan 19;10(1):125-40.
- [36] Motiec TD, Trisnawati I, Handayani IF, Darwanti J. Description of the Case of Premature Ruptured Membranes in Mothers at the Purwasari Karawang Maternity Hospital in 2020 (Doctoral dissertation, Health Polytechnic of the Ministry of Health, Bandung).
- [37] Wahyuni R. Factors causing premature rupture of membranes in women giving birth at the general hospital in the Sumbawa Besar area. *Journal of Health and Science*. 2020 Mar 28;3(2):26-33.
- [38] Dea D, Riana E, Khairunisa D. Midwifery care for women giving birth with premature rupture of membranes in the independent practice of Midwife Ida Apianti Pontianak (Doctoral dissertation, Polytechnic'Aisyiyah Pontianak).
- [39] Mendez-Figueroa H, Bicocca MJ, Bhalwal AB, Wagner SM, Chauhan SP, Barta MF. Preterm cesarean delivery for nonreassuring fetal heart rate tracing: Risk factors and predictability of adverse outcomes. *European Journal of Obstetrics & Gynecology and Reproductive Biology*. 2022 Sep 1;276:207-12.
- [40] IM's daughter, Ismiyatun N. Early detection of high-risk pregnancies. *JKM (Journal of Public Health) Main Scholar*. 2020 Sep 4;8(1):40-51.

[41] Yuliani NW, Wahyuningsih M. Differences in Apgar Values in the First Minutes of Newborns with Premature Rupture of Membranes and Normal Rupture of Membranes in Yogyakarta City Hospital. In Proceedings of the National Seminar on Multidisciplinary Sciences 2019 Apr 3 (Vol. 1, No. 1).

[42] Leimert KB, Xu W, Princ MM, Chemtob S, Olson DM. Inflammatory amplification: a central tenet of uterine transitions for labor. *Frontiers in Cellular and Infection Microbiology*. 2021 Aug 19;11:660983.

UNDER PEER REVIEW

Review Form 1.7

Journal Name:	Asian Journal of Research in Infectious Diseases
Manuscript Number:	Ms_AJRID_97587
Title of the Manuscript:	Relationship Between Premature Rupture of The Membrane and Cesarean Delivery
Type of the Article	Original research with secondary data

General guideline for Peer Review process:

This journal's peer review policy states that **NO** manuscript should be rejected only on the basis of '**lack of Novelty**', provided the manuscript is scientifically robust and technically sound. To know the complete guideline for Peer Review process, reviewers are requested to visit this link:

(<https://www.journalajrid.com/index.php/AJRID/editorial-policy>)

PART 1: Review Comments

	Reviewer's comment	Author's comment (if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)
Compulsory REVISION comments 1. Is the manuscript important for scientific community? (Please write few sentences on this manuscript) 2. Is the title of the article suitable? (If not please suggest an alternative title) 3. Is the abstract of the article comprehensive? 4. Are subsections and structure of the manuscript appropriate? 5. Do you think the manuscript is scientifically correct? 6. Are the references sufficient and recent? If you have suggestion of additional references, please mention in the review form. (Apart from above mentioned 6 points, reviewers are free to provide additional suggestions/comments)	Yes Can add place of study and source of data in the title. Abstract should be structured as background, aims, methods, results and discussion and conclusions. Review of literature is not required as per journal style. Yes Check references citation. Some references are not as per journal style.	
Minor REVISION comments 1. Is language/English quality of the article suitable for scholarly communications?	Yes	
Optional/General comments		

PART 2:

	Reviewer's comment	Author's comment (if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)
Are there ethical issues in this manuscript?	(If yes, Kindly please write down the ethical issues here in details)	

Reviewer Details:

Name:	Visweswara Rao Guthi
Department, University & Country	SVIMS, Sri Padmavathi Medical College for Women, India

Relationship Between Premature Rupture of The Membrane and Cesarean Delivery

Comment [VRG1]: Can add place of study and source of data in the title

Abstract

Comment [VRG2]: Abstract should be structured as background, aims, methods, results and discussion and conclusions

Premature rupture of membranes (PROM) is the spontaneous rupture of the membranes before the onset of signs of labor. It can occur both before term (<37 weeks) and after term (> 37 weeks). *Caesarean delivery* is a surgical technique to deliver the fetus through an incision in the abdominal wall and uterine wall. This procedure is performed to minimize all complications from premature rupture of membranes. This study aims to determine the relationship between premature rupture of membranes and delivery of *sectio caesarea* at the UKI General Hospital in the 2019 period by using a descriptive content analysis method (analysis of medical records documents) with a cross-sectional approach and obtained 65 samples who experienced premature rupture of membranes. The results showed that 53 samples (81.55%) experienced premature rupture of membranes and performed *sectio caesarea*, while 12 samples (18.45%) had premature rupture of membranes but did not perform *sectio caesarea* with $p\text{-value} = 0.001$ ($p < 0.05$) from the results of the chi-square statistical test. From the results of the analysis, it was found that there was a relationship between premature rupture of membranes and delivery of *cesarean section* at the UKI General Hospital for the 2019 period. It is suggested that patients avoid the factors that can cause premature rupture of the membranes, which have been told by the doctor or health worker and the patient's family to support the patient to remind them to avoid factors that can cause premature rupture of the membranes.

Keywords: Premature rupture of membranes, *Cesarean Section*.

Introduction

Premature or premature rupture of membranes is the spontaneous rupture of the amniotic membranes before signs of labor occur. This condition can occur either before term (<37 weeks) or after term (>37 weeks). [1] The amniotic membranes function to produce amniotic fluid and protect the fetus from various kinds of infections. [2] Under normal circumstances, the membranes will rupture during labor. According to the World Health Organization, in 2014, the incidence of premature rupture of membranes or premature rupture of membranes ranged from 5-10% of all births. Preterm premature rupture of membranes occurs in 1% of all pregnancies, and 70% of premature rupture occurs at term. In 30% of cases, premature rupture of membranes is the cause of preterm birth. [3]

The incidence of premature rupture of membranes in Indonesia ranges from 4.5% - 6% of all pregnancies. In contrast, in the United States, premature rupture of membranes occurs in 120,000 pregnancies per year and is associated with a high risk to maternal, fetal, and neonatal safety [4]. Various studies in India explain that the incidence is 7-12% for premature rupture of membranes which 60-70% occurs in the long term. [5] The incidence of premature rupture of membranes in several hospitals in Indonesia is quite varied, including Sardjito Hospital at 5.3%, Hasan Sadikin Hospital at 5.05%, Cipto Mangunkusumo Hospital at 11.22%, Pringadi Hospital at 2.27%, and Kariadi Hospital which is equal to 5.10%. [6] Premature rupture of membranes has various complications for the mother and fetus that cause morbidity and mortality. Maternal complications include chorioamnionitis and fetal complications such as fetal distress, premature birth, and cord compression, to neonatal complications such as neonatal asphyxia and sepsis. This complication requires labor conditions to be ended quickly to save the mother and fetus.

Sectio Caesarea is a labor procedure performed to minimize all complications from premature rupture of membranes [7].

Sectio Caesarea is a surgical technique to deliver a fetus through an incision in the abdominal wall (laparotomy) and uterine wall (hysterectomy). Sectio Caesarea is one of the ten most commonly performed major surgeries. This medical procedure is needed to assist deliveries that cannot be carried out normally due to maternal health problems or fetal conditions [8].

According to Travassolo in 2010 stated that premature rupture of membranes with oligohydramnios is related to the duration of rupture of membranes, high rates of sectio caesarea, and low Apgar scores at birth.

In Indonesia, the number of caesarean section deliveries continues to increase. According to the Indonesian Demographic and Health Survey (IDHS) data, there was an increase in caesarean sections in Indonesia from 1991 to 2007, around 1.3-6.8 percent. [9] Meanwhile, the results of the Riskesdas report (basic health research) in 2013 found that 9.8% of deliveries were carried out by sectio caesarea in Indonesia, 2.3% of which were due to complications in pregnancy [10].

Research conducted by Andayasari et al. in 2014 stated that sectio caesarea deliveries in one government hospital and one private hospital in DKI Jakarta from January 2011-December 2011 reached 59.2%, and premature rupture of membranes contributed 31.4% to sectio deliveries caesarea [11]. Research conducted by Sumelung in 2014 stated that premature rupture of membranes was one of the factors that increased the incidence of sectio caesarea at Liub Kendage Hospital in 2015 [12].

Based on the background above, the researchers wanted to research the relationship between premature rupture of membranes and cesarean section delivery at UKI General Hospital in January-December 2019. The problem in this study was "Is there a relationship between premature rupture of membranes and cesarean delivery in UKI General Hospital period January-December 2019? The study aims to determine the incidence of premature rupture of membranes and sectio caesarea deliveries at UKI General Hospital from January to December 2019.

Literature Review

The amniotic sac (amniotic sac), which lines the amniotic cavity, consists of the amnion and chorion, which are tightly bound. The amniotic membrane is a flexible but tough avascular tissue. These avascular structures have an important role in pregnancy in humans. In many obstetric cases, rupture of the membranes at a young gestational age is the most common cause of preterm birth. The inner membrane communicating with the amniotic fluid consists of a single layer of cuboidal epithelium derived from the embryonic ectoderm. This epithelium is tightly attached to the basement membrane, which is connected to the interstitial layer containing collagen I, III, and V. The outer part of the membrane is mesenchymal tissue derived from the mesoderm. This layer of the amnion is connected to the chorion leave. The amnion's inner lining is microvilli which transfer fluids and metabolism. This layer produces metalloproteinase-1 inhibitory substances [13].

Mesenchymal cells function to produce collagen so that the membrane becomes flexible and strong. In addition, these tissues produce the cytokines IL-6, IL-8, and MCP-1 (monocyte chemoattractant protein-1); This substance is useful against bacteria. In addition, the amniotic membranes produce vasoactive substances: endothelin-1 (a vasoconstrictor) and PHRP (parathyroid hormone-related protein), a vasorelaxant. Thus, the amniotic membrane regulates blood circulation and local vascular tone. The amniotic membrane also covers the umbilical cord. Some of the fluid will also come from diffusion in the umbilical cord. The rupture of the membranes is related to the strength of the membranes. In smokers

Comment [VRG3]: This can be reframed. All three sentences are look like similar.

Comment [VRG4]: This is not required for this journal

and infections, the resistance of the membranes is weakening so that they break easily. In a normal pregnancy, there are few macrophages. At the time of birth, leukocytes will enter the amniotic fluid as a reaction to inflammation. There is no IL-1B in a normal pregnancy, but IL-1B will be found in preterm labor.

It is related to the occurrence of the infection process. Since the beginning of pregnancy, amniotic fluid has been formed. Amniotic fluid is a protector and cushion for protection while supporting growth. Osmolarity, sodium, urea, and creatinine levels do not differ from the mother's serum levels, meaning that the levels in the amniotic fluid are the result of diffusion from the mother. Amniotic fluid contains many fetal cells (lanugo, vernix caseosa) [14]. Macroscopically, the amnion is a thin layer (only 20% of the thickness of the fetal membranes) and is a transparent (translucent) structure. This amniotic membrane can easily be separated from the underlying chorion because the amnion is never completely fused with the chorion and is only passively attached by internal pressure from the amniotic fluid [15]. The amnion lacks blood vessels and obtains its required nutrients and oxygen supplied directly by diffusion from the surrounding amniotic fluid, fetal surface vessels, or the decidua [16]. The thickness of the amnion varies greatly due to changes in the amount of mucin and fluid contained in the spongy lining, which ranges from 80 - 120 μm [17].

The amniotic epithelium, the innermost amnion layer that leads to the fetus and surrounds the amniotic fluid, consists of a single layer of simple, squamous to cuboidal cells, with microvilli apical and attached to the basement membrane [18]. The amniotic epithelium secretes collagen types I, III, and IV, non-collagen glycoproteins such as laminin, nidogen, and fibronectin, forming a cell basement membrane thickness of nearly 1 μm . The stromal compactum layer varies greatly in thickness, is tightly adherent, and cannot be separated from the basement membrane. This layer is a microfibril-dense cell-free homogeneous layer. Collagen types I, III, and V, and elastic fibers of the compact layer, are secreted by the mesenchymal cells in the fibroblast layer beneath the compact layer [19], which form the main burden-carrying fibrous framework of the amnion. The main tensile strength of the amnion is provided by collagen, which is arranged in one direction, i.e., parallel to the amniotic epithelium [20]. The compact layer and fibroblasts are difficult to differentiate histologically. The fibroblast layer beneath the compact layer is the most complex and thickest layer of the amnion, consisting of cellular tissue within a loose collagen network with non-collagenous glycoproteins, proteoglycans, and type III collagen. Fibroblasts and macrophages (Hofbauer cells) have been identified within this layer. The spongy intermediate layer, also called the intermediate layer because it lies between the amnion and the chorion, is rich in proteoglycans and hyaluronate, which absorbs large amounts of water and forms a viscous layer that allows the amnion to slide over the chorion [21].

By this mechanism, this spongy coating makes it possible to absorb physical stress and to provide spontaneous short-term mechanical repair and defect closure systems. In addition, a circular fibrous structure is found in direct relation to the chorionic side, helping to adjust the lateral tension on the sliding surface between the amnion and chorion [22]. Occasionally, a potential space can be seen histologically in the spongy layer between the amnion and chorion. The space comprises loosely arranged collagen fibers that are sometimes oedematous and contain scattered fibroblasts and macrophages.

Development is between the embryonic cell mass and the trophoblast during the early implantation period. The small cells lining the inner surface of the trophoblast are called amniogenic cells, which are precursors of the amniotic epithelium. The amnion can be identified for the first time on embryo development's 7th or 8th day. It begins with the formation of a vesicle that develops into a small sac covering the dorsal surface of the embryo. As the amniotic sac enlarges, distention of the amniotic sac causes it to contact the

interior surface of the chorion leave. Apposition of the chorion and amnion near the end of the first trimester. In young pregnancies, amniotic fluid is an ultrafiltrate of maternal plasma formed by the amnion cells. In the second trimester of pregnancy, amniotic fluid is formed by extracellular diffusion through the fetal skin, so its composition is similar to fetal plasma. Furthermore, after the second trimester, fetal skin horn substance formation occurs and blocks the diffusion of fetal plasma so that most of the amniotic fluid is formed by; amniotic cells and fetal urine. Fetal kidneys start excreting urine from the age of 12 weeks, and after reaching the age of 18 weeks, they can excrete urine as much as 7-14 cc/day. Term fetuses produce urine 27 cc/hour or 650 ccs daily [23]. Thus, the composition that forms amniotic fluid follows a postulate that the increase in amniotic fluid is not linear.

After the gestational age exceeds 12 weeks, what participates in forming amniotic fluid is; fetal kidneys (so that urea, creatinine, and uric acid are found), desquamation of fetal skin (skin cells, lanugo hair, vernix caseosa), secretions from the fetal lungs, transudate from the surface of the placental amnion, hormones or hormone-like substances in the amniotic fluid. Meanwhile, regulating amniotic fluid is very important to maintain the amount regularly. The following three important components influence the setting: production produced by the amnion cells, the amount of urine produced, and the amount of amniotic fluid swallowed by the fetus. Amniotic fluid regulation in term pregnancy includes the amount taken by the fetus \pm 500-1000 ml, enters the lungs \pm 170 ml, and from the umbilical cord and amnion \pm 200-500 ml. At the same time, the amount of fluid released by the fetus into the amniotic cavity is from oral secretions \pm 25 ml, secretions from the respiratory tract \pm 170 ml, urine \pm 800-1200 ml, and transmembrane from the amnion \pm 10 ml. Thus, fetal urine appears to dominate the production of amniotic fluid, and the average regulation near term reaches 500 cc/day [24].

Amniotic fluid has an important role in supporting the process of pregnancy and childbirth. Throughout a normal pregnancy, the compartments of amniotic fluid provide space for the fetus to grow, move and develop. Without amniotic fluid, the uterus will contract and put pressure on the fetus; in cases where rupture of the membranes occurs early in the first trimester, the fetus may experience structural abnormalities, including facial distortion, reduction of limbs, and abdominal wall defects due to uterine compression [25]. Towards mid-pregnancy, the amniotic fluid becomes increasingly important for fetal development and growth, including lung development, so if there is insufficient amniotic fluid during mid-pregnancy, the fetus is often accompanied by pulmonary hypoplasia and continues to death. In addition, this fluid also has a protective role in the fetus. This liquid contains anti-bacterial agents and works to inhibit the growth of bacteria with potential pathogens. Amniotic fluid is a protective medium for the fetus to help with cervical dilation during labor and delivery. In addition, amniotic fluid also acts as a means of communication between the fetus and the mother. The maturity and readiness of the fetus for birth can be known from the fetal urine hormones excreted into the amniotic fluid [26].

Amniotic fluid can also be used as a diagnostic tool to see fetal growth and development abnormalities by conducting cell cultures or using a spectrometer. Other functions of amniotic fluid can also protect the fetus from trauma, as a medium for fetal musculoskeletal development, maintain fetal body temperature, equalize uterine pressure in parturition, clean the birth canal so that the baby is less infected, and maintain normal development and growth of the lungs and gastro tract intestinal [27]. Any wound on any body part will go through several stages: inflammation, proliferation, and maturation. Each phase involves many components and mechanisms, including the inflammatory, proliferative, and maturation phases. [28]

Premature rupture of the membranes is a condition in which the membranes rupture before labor or in part. Premature rupture of membranes can occur in term or preterm

pregnancies. Preterm Premature Rupture of the Membranes or premature rupture of membranes is the rupture of the membranes in patients with a gestational age of fewer than 37 weeks [29]. The incidence of premature rupture of membranes is 8% at term (> 37 weeks) and is associated with an increased risk of infection in the mother (chorioamnionitis, endometritis) and infection in the fetus (neonatal sepsis). Meanwhile, the incidence of preterm premature rupture of membranes is 3%, as a cause of 20-30% of preterm labor [30]. Two things broadly cause the causes of premature rupture of membranes, namely reduced membrane strength and increased intrauterine pressure or both factors. An infection can cause reduced membrane strength from the vagina and cervix. The factors influencing premature rupture of membranes are age, parity, smoking behavior, and history of premature rupture. Experiences experienced by mothers in labor with premature rupture of membranes can have a major influence on the mother when facing pregnancy conditions. The previous history of premature rupture of membranes is 2-4 times at risk of experiencing premature rupture of membranes again. In short, the pathogenesis of premature rupture of membranes results from a decrease in collagen content in the membrane, which triggers premature and preterm rupture of membranes. Women who have experienced premature rupture of membranes in pregnancies before delivery will be at greater risk in subsequent pregnancies than women who have never experienced premature rupture of membranes before because the composition of the membranes decreases in subsequent pregnancies.

The rupture of membranes in labor is generally caused by repeated uterine contractions and stretching. The membranes rupture because, in certain areas, biochemical changes occur, which cause the inferior membranes to become brittle, not because the entire membranes are fragile. There is a balance between synthesis and degradation of the extracellular matrix. Changes in structure, cell number, and collagen catabolism cause collagen activity to change and cause the membranes to rupture. Collagen degradation is mediated by matrix metalloproteinases inhibited by tissue-specific and protease inhibitors. The membranes' integrity is due to a combination of low metalloproteinase activity and relatively higher concentrations of tissue inhibitors metalloproteinase-1. Microorganisms that infect the membranes of the membranes can form protease enzymes accompanied by an inflammatory response from the membranes, thereby affecting the balance of metalloproteinases and tissue inhibitors metalloproteinase-1, which causes a weakening of the tension of the membranes and rupture of the membranes hemolytic, and staphylococcus. In addition, closer to the delivery time, the balance between metalloproteinase and tissue inhibitors metalloproteinase-1 leads to proteolytic degradation of the extracellular matrix and fetal membranes. This proteolytic degradation activity increases towards delivery. The amniotic membranes are very strong in young pregnancies. In the third trimester, the membranes rupture easily. The weakening of the strength of the membranes is related to the enlargement of the uterus, uterine contractions, and fetal movements. In the last trimester, biochemical changes occur in the amniotic membranes so that the rupture of the membranes at term is physiological. Premature rupture of membranes in preterm pregnancy is caused by external factors such as infections that spread from the vagina [31].

Premature rupture of membranes greatly affects complications and length of labor. In the 1st stage of labor, the fetal membranes and the presenting part of the fetus act to open the upper part of the vagina. However, after the rupture of the membranes, the changes in the pelvic floor are all produced by the pressure exerted by the presenting part of the fetus so that the hydrostatic action of the fetal membranes causes cervical dilatation. If the membranes have ruptured, the lowest part of the fetus that attaches to the cervix and forms the lower uterine segment functions the same. It will result in one of the complications of premature rupture of membranes, namely the long labor process, so sectio caesarea is the only option in this condition [32].

Another complication of mothers with premature rupture of membranes that causes morbidity and mortality is chorioamnionitis. This infection causes inflammation of the amniotic fluid, amniotic membranes, or fetus, and this condition causes mothers with premature rupture of membranes to have symptoms of fever, fundal tenderness, tachycardia, fetal tachycardia, and smelly amniotic fluid. This condition is one of the complications feared to occur if a mother with premature rupture of membranes does not end her pregnancy immediately [33].

A study in Iran reported that out of 536 cases of premature rupture of membranes, 28% were performed by sectio caesarea. Other researchers concluded that sectio caesarea reached 26.6% in India in patients with premature rupture of membranes [34]. It is due to complications from premature membrane rupture, including fetal distress, malpresentation, narrow pelvis, failed induction, and the maternal complication of chorioamnionitis. Apart from that, other complications that led to the decision to perform sectio caesarea in mothers with premature rupture of membranes were complications of neonatal asphyxia and sepsis [35]. There is a relationship between fetal distress and decreased amniotic fluid volume. The more critical the fetus is. It was found that babies with premature rupture of membranes >12 hours had a 12 times greater risk of experiencing unfavorable outcomes, so it can be concluded that at term KPD, pregnancy termination should be carried out at least 6-12 hours from the onset of premature rupture of membranes.

Research Method

This type of research uses a descriptive analysis research method with a cross-sectional approach. This study used secondary data from UKI General Hospital medical records for the January-December 2019 period. The location for collecting research data was carried out in the UKI General Hospital medical records section. The time of execution, collection, and implementation of the research was carried out from August 2020 – October 2020. The population for this study was patients who gave birth at the UKI General Hospital for the period January-December 2019. The sample was part of the population that had met the inclusion criteria, namely patients who gave birth on indications of Premature rupture of membranes at UKI General Hospital during January-December 2019. The Central Statistics Agency in Indonesia stated that the total population of Indonesia was 271,066,400 in 2019. The World Health Organization reported that as many as 17,655 mothers gave birth in Indonesia in 2019. The number of samples in this study was at least 65 people. Data collection was carried out at the UKI General Hospital medical record section. Furthermore, medical record data following the research variables will be recorded. All data obtained will be filtered again according to the inclusion and exclusion criteria set so that data is produced that will be used in the results of this study. Data collected through medical records are processed using the IBM SPSS (Statistical for Social Science) program for Windows edition 25.0 and the Microsoft Office Excel 2016 program.

Comment [VRG5]: Explain the procedure for sample size estimation

Result and Discussion

Data were obtained from the medical records of all patients with premature rupture of membranes delivered by cesarean section and normal delivery at UKI General Hospital for January-December 2019. The total sample was 65 patients.

Table 1. Characteristics of the sample by age

Age	Frequency	Percentage %
< 30 Tahun	15	23,1%
≥30 Tahun	50	76,9%
Total	65	100%

Comment [VRG6]: 23.1% instead of 23,1% and 76.9% instead of 76,9%

Table 1 shows the characteristics of the study sample based on age, which found 15 patients (23.1%) aged <30 years, while 50 patients (76.9%) were aged ≥30 years.

Table 2. Sample characteristics based on parity

Parity	Frequency	Percentage %
Primigravida	25	38,5%
Multigravida	40	61,5%
Total	65	100%

Comment [VRG7]: Like above

Table 2 shows the characteristics of the study sample based on parity, where there were 25 patients with primigravidas (38.5%), while multigravidas had 40 patients (61.5%).

Comment [VRG8]: were

Table 3. Sample characteristics based on gestational age

Gynecological Age	Frequency	Percentage %
< 37 Weeks	12	18,5%
≥ 37 Weeks	53	81,5%
Total	65	100%

Comment [VRG9]: Like above

Table 3 shows the characteristics of the study sample based on gestational age, which was found at gestational age <37 weeks in 12 patients (18.5%), while gestational age ≥37 weeks were found in 53 patients (81.5%).

Table 4. Sample characteristics based on BMI (Body Mass Index)

BMI	Frequency	Percentage %
< 30	17	26,2%
≥ 30	48	73,8%
Total	65	100%

Comment [VRG10]: Like above

Table 4 shows the characteristics of the study sample based on BMI (Body Mass Index), where there were 17 patients (26.2%) with a BMI <30, while 48 patients (73.8%) had a BMI ≥30.

Table 5. Sample characteristics based on the history of premature rupture of membranes

History of premature rupture of membranes	Frequency	Percentage %
Ever	40	61,5%
Never	25	38,5%
Total	65	100%

Comment [VRG11]: Like above

Table 5 shows the characteristics of the study sample based on a history of premature rupture of membranes, in which 40 patients (61.5%) had a history of premature rupture of membranes, while 25 patients had never had premature rupture of membranes (38.5%)).

Table 6. Characteristics of the sample based on the APGAR SCORE

Apgar Score	Frequency	Percentage %
< 7	46	70,8%
≥ 7	19	29,2%
Total	65	100%

Comment [VRG12]: Like above

Table 6 shows the characteristics of the study sample based on the Apgar Score, where there were 46 patients (70.8%) with an APGAR SCORE <7, while 19 patients (29.2%) had an Apgar Score \geq 7.

Table 7. Sample characteristics based on birth weight

Birth Weight	Frequency	Percentage %
< 3 Kg	20	30,8%
\geq 3 Kg	45	69,2%
Total	65	100%

Table 7 shows the characteristics of the study sample based on birth weight, in which 20 patients (30.8%) had babies with birth weight <3 kg, while 45 patients (69.2%) had babies with birth weights \geq 3 kg.

Table 8. The relationship between premature rupture of membranes and sectio caesarea delivery

Gynecological Age		Type of Childbirth				Total	P-value
		Seccio	n (%)	No Seccio	n (%)		
Premature rupture of membranes	< 37Weeks	7	10,76%	5	7,69%	12(18,45%)	0,001
	\geq 37Weeks	50	76,92%	3	4,63%	53 (81,55%)	
Total		57	87,68%	8	12,32%	65 (100%)	

Table 8 shows the characteristics of the study sample based on the gestational age of mothers who experienced premature rupture of membranes and the type of delivery performed. It was found that mothers with gestational age <37 weeks experienced premature rupture of membranes and performed sectio caesarea in 7 patients (10.76%), whereas mothers with gestational age <37 weeks experienced premature rupture of membranes but did not perform a cesarean section in 5 patients (7.69%). Meanwhile, 50 patients (76.92%) had premature rupture of membranes, and 50 patients (76.92%) had premature rupture of membranes and 37 weeks of gestational age \geq 37 weeks of mothers who had premature rupture of membranes without having a caesarean section. (4.63%), and the P-value is 0.001.

The study results found that the age group that experienced premature rupture of membranes was the most in the age group \geq 30 years, with as many as 50 patients (76.9%). It follows the theory where according to Sudarto, a mother who gives birth at the age of 35 and over can affect her reproductive system because her reproductive organs have begun to reduce their ability and elasticity in accepting pregnancy, affecting the process of embryogenesis. The amniotic membranes will be thinner, facilitating premature rupture [36]. Based on the results of the study, it was found that a woman with multigravida experienced premature rupture of membranes in 40 patients (61.5%). It is following the theory according to Kacerovky, women who have given birth several times accompanied by close pregnancy intervals can be at risk of experiencing premature rupture of membranes in their next pregnancy. It is because pregnancies are too frequent, affecting the embryogenesis process. The amniotic membranes become thinner, so they break easily prematurely. In addition, there is also a theory that the more parity, the easier it is for amnion infection to occur due to damage to the cervical structure in previous deliveries [37].

Based on the study's results, 53 pregnant women experienced premature rupture of membranes when their gestational age was \geq 37 weeks (81.5%). According to Popowski, it follows the theory that most premature rupture of membranes occurs at gestational age \geq 37 weeks. Premature rupture of membranes occurs nearing delivery due to an increase in matrix metalloproteinase which tends to cause the membranes to rupture, in addition to an increase

in matrix metalloproteinase, uterine enlargement, uterine contractions, and fetal movements occur [38].

From the results of the study, it was found that pregnant women who had a BMI (Body Mass Index) ≥ 30 had premature rupture of membranes, and 48 patients (73.8%) had a cesarean section. An increase in Body Mass Index ≥ 30 has a great risk for a normal delivery because, in a normal delivery, there will be a delay in the first stage of the active phase and the second stage. After all, the mother who is obese will have a narrow birth canal due to the accumulation of fat, making it difficult for the baby to come out, and a sectio caesarea must be carried out immediately [39].

The history that mothers have experienced in labor with the incidence of premature rupture of membranes can have a big influence on the mother when facing pregnancy conditions. Based on the amount of research data, it was found that 40 patients (61.5%) had a history of premature rupture of membranes in previous deliveries. According to Morgan, it follows the theory that patients with a previous history of premature rupture of membranes are at risk of 2-4 times experiencing premature rupture of membranes again. In short, the pathogenesis of premature membrane rupture results from a decrease in collagen content in the membrane, which triggers premature rupture membranes.

Comment [VRG13]: Cite Reference

Women who have experienced premature rupture of membranes during pregnancy or before delivery are at greater risk in their next pregnancy than women who have never experienced premature rupture of membranes before because the composition of the membranes becomes fragile. The collagen content decreases in subsequent pregnancies [40]. The APGAR SCORE is a practical method systematically used to assess a baby as soon as possible after birth. What is assessed is heart rate, respiratory effort, muscle tone, skin color, and reaction to stimulation (response to stimuli), namely by inserting a catheter into the nostril after the airway has been cleaned when the new baby is born.

From the results of this assessment, it can be seen whether the baby is normal (APGAR score 7-10), moderate-mild asphyxia (APGAR score 4-6), or the baby has severe asphyxia (APGAR score 0-3). The characteristics of the sample based on the APGAR SCORE showed that patients who gave birth with premature rupture of membranes and their babies had an APGAR SCORE <7 . There were 46 patients (70.8%). It follows the theory according to Ni Wayan and Melania, where with the rupture of the membranes, there will be prolapse of the funiculi / descent of the umbilical cord, which will cause the neonatorum to experience hypoxia and asphyxia (lack of oxygen in the baby) which will result in compression of the umbilical cord, respiratory distress. The baby will be at risk of having a low APGAR SCORE (<7) [41].

Mechanical stretching, such as in a large baby's weight, can cause stretching of the membranes and can cause premature rupture of the membranes. It is also supported by the data results where there is an increase in the number of patients who experience premature rupture of membranes with a baby weighing > 3.5 kg by 1.6%, while babies weighing > 4 Kg were 2.4%. Based on the study's results, with birth weight ≥ 3 Kg and experiencing premature rupture of membranes were 45 patients (69.2%). It follows the theory according to Zelop, where mechanically stretching the fetal membranes will increase the production of prostaglandin E2 and Interleukin-8 in the amnion, also increasing the activity of MMP-1 in the membranes. Interleukin-8 produced from amnion and chorion cells is chemotactic towards neutrophils and stimulates collagenase activity, which disrupts the balance of synthesis and degradation of the extracellular matrix, which ultimately causes the rupture of the membranes.

Comment [VRG14]: Cite reference

Prostaglandin E2 increases uterine irritability, decreases membrane collagen synthesis, and increases the production of MMP-1 and MMP-3 by fibroblasts. The production of interleukin-8 and prostaglandin E2 from the amnion indicates that biochemical changes in the

membranes can be initiated by physical forces or by stretching the membranes, suggesting that mechanical forces cause premature rupture of membranes [42].

The results of the research on the relationship between premature rupture of membranes and sectio caesarea delivery obtained a value of $P = 0.001$ ($P < 0.05$) which means there is a relationship between premature rupture of membranes and sectio caesarea delivery where this is following the theory, according to Barbara, pregnant women with indications of ruptured membranes Early pregnancy will cause the amount of amniotic fluid to decrease and the risk of having a normal delivery. Babies born will also have an increased risk of morbidity and mortality. The risk of infection in the mother is also quite high, so it will increase morbidity and mortality, so the action of cesarean section is expected to reduce maternal morbidity and mortality and improve infant outcomes.

Conclusion

From the results of the research that was described in the previous chapter, the following conclusions were drawn: a) the prevalence of premature rupture of membranes at UKI General Hospital carrying out sectio caesarea in the January-December 2019 period was 57 patients (87.68%), while those who did not perform sectio caesarea in 8 patients (12.32%), and b) based on the Chi-square test, there was a significant relationship between premature rupture of membranes and sectio caesarea ($P=0.001$). Thus, it is hoped that health workers and health institutions as health workers can help educate patients about the factors that can cause premature rupture of membranes so that patients can take preventive action to prevent premature rupture membranes. In addition, it is recommended that patients avoid factors that can cause premature rupture of a membrane that doctors or health workers have told, and the patient's family can support patients to remind them to avoid factors that can cause premature rupture of membranes.

Comment [VRG15]: Is it prevalence or incidence?

References

- [1] Caughey AB, Robinson JN, Norwitz ER. Contemporary diagnosis and management of preterm premature rupture of membranes. Reviews in obstetrics and gynecology. 2008;1(1):11.
- [2] Menon R, Richardson LS. Preterm prelabor rupture of the membranes: a disease of the fetal membranes. In Seminars in perinatology 2017 Nov 1 (Vol. 41, No. 7, pp. 409-419). WB Saunders.
- [3] Fitriyani F, Yuliana Lubis Y. Determinant factors in premature rupture of membranes. Health Media Journal. 2018 Nov 16;11(1):053-61.
- [4] Syarwani TI, Tendean HM, Wantania JJ. Overview of Premature Ruptured Membranes (PROM) in Prof. Dr. RD Kandou Manado in 2018. Medical Scope Journal. 2020;1(2).
- [5] Susan Blossia E. A Prospective Cross Sectional study on CRP Levels in Antenatal Women with Prelabor Rupture of Membrane and CRP Levels in Women with Normal Labor (Doctoral dissertation, Christian Medical College, Vellore).
- [6] Rohmawati N, Wijayanti Y. Premature rupture of membranes at Ungaran Regional General Hospital. HIGEIA (Journal of Public Health Research and Development). 2018 Feb 1;2(1):23-32.
- [7] Venancyana MC, Indrayani T, Lubis R. Analysis Of Factors Affecting Pregnant Mothers In Making Decisions For Caesarean Section Childbirth Plan At Tc Hillers Hospital, Sikka Regency, Year 2022. International Journal Of Multi Science. 2022 Aug 25;3(02):7-17.

- [8] Waang WW, Kusumawati PD. Analysis of Deep Breath Relaxation Techniques for Post SC Patients with Pain. *Journal of Health Science Community*. 2022 Nov 15;3(2):97-101.
- [9] BP Statistics. Indonesia Demographic and Health Survey Report.
- [10] Suparmi S, Kusumawardhani N, Susiloretni KA. Sub-national inequality of caesarean sections in urban-rural areas of Indonesia. In *Proceedings of the international conference on public health 2018* (Vol. 4, No. 1, pp. 23-32).
- [11] Hardiyanti R. Use of Prophylactic Antibiotics in Sectio Caesarea Patients. *Journal of Health Science and Physiotherapy*. 2020 Jan 7;2(1):96-105.
- [12] Ulfa EN. Factors related to delivery by sectio caesarea at the Karsa Husada Batu general hospital in 2020 (Doctoral dissertation, Maulana Malik Ibrahim State Islamic University).
- [13] Machtejevienė E. Peptide pattern of amniotic fluid and its correlation with protein composition of fetal membranes: the search for new potential biomarkers to predict preterm premature rupture of membranes:[Rankraštis]: doctoral dissertation: biomedical sciences, medicine (06B).
- [14] Brace RA, Anderson DF, Cheung CY. Regulation of amniotic fluid volume: mathematical model based on intramembranous transport mechanisms. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*. 2014 Nov 15;307(10):R1260-73.
- [15] Cohen MC, Scheimberg I, Hutchinson JC. Anatomy and Pathology of the Placental Membranes. *Benirschke's Pathology of the Human Placenta*. 2022:281-343.
- [16] Founds SA, Baker B. Fetal and Placental Development and Functioning. *Core Curriculum for Maternal-Newborn Nursing E-Book*. 2022 Oct 14:28.
- [17] POLZIN WJ, BRADY K. Mechanical factors in the etiology of premature rupture of the membranes. *Clinical obstetrics and gynecology*. 1991 Dec 1;34(4):702-14.
- [18] Mamede AC, Carvalho MJ, Abrantes AM, Laranjo M, Maia CJ, Botelho MF. Amniotic membrane: from structure and functions to clinical applications. *Cell and tissue research*. 2012 Aug;349:447-58.
- [19] Country IK, KFM SO. Matrix Metalloproteinases in Premature Ruptured Membrane. *deepublish*; 2021 May 1.
- [20] Yunus M, Sos S, Hatijar S. Textbook of Midwifery Care in Pregnancy.
- [21] Macedo BM. Exploração das Membranas Fetais para Aplicações de Engenharia dos Tecidos (Doctoral dissertation).
- [22] Haller C. Evaluation of human fetal membrane sealing (Doctoral dissertation, University of Zurich).
- [23] Ferselina L. Case Study of Handling Newborns with Cloudy Amniotic Water in Mrs. Vdi Pmb Komariah, Sst Lampung Selatan (Doctoral dissertation, Tanjungkarang Health Polytechnic).
- [24] Fahimah WF. Literature Review: Factors Causing Premature Rupture of Water.
- [25] Trance MG. Continuing Midwifery Care for Mrs. EB at the Kaputu Community Health Center April 13 to June 10 2019 (Doctoral dissertation, Kupang Ministry of Health Polytechnic).
- [26] Liley AW. Disorders of amniotic fluid. In *Fetal-placental disorders* 1972 Jan 1 (pp. 157-206). Academic Press.

- [27] Henny Sulistyawati SS, Zulfa Hanum SS, Keb M, Meikawati PR, SiTS S, Rosdianto NO, ST S, Keb M, Muayah SS, Ety Aprianti SK. Textbook for Postpartum DIII Midwifery Volume I. Mahakarya Citra Utama Group; 2022 Sep 15.
- [28] Monika P, Waiker PV, Chandraprabha MN, Rangarajan A, Murthy KN. Myofibroblast progeny in wound biology and wound healing studies. *Wound Repair and Regeneration*. 2021 Jul;29(4):531-47.
- [29] Ma'roef M, Putri AP. The Relationship of Leukocyturia on The Incidence of Prominent Rupture of The Membrane in Preterm Pregnancy at The General Hospital of The University of Muhammadiyah Malang. *Medical Science*. 2019 Dec 21;15(2):139-45.
- [30] Sari DS. Relationship between Multiple Pregnancy and Fetal Abnormalities with Premature Rupture of the Membranes at the Prabumulih Regional General Hospital in 2019. *Abdurahman Health Journal*. 2020 Sep 25;9(2):56-63.
- [31] Margono RS, Sukrisno A, Nugrohowati N, Lestari W. Relationship between a premature rupture of membranes and the increase of leucocyte levels in pregnant women during the COVID-19 pandemic. *Journal of Traditional Midwifery and Health*. 2021 Oct 25:127-34.
- [32] Putri RS. Application of the Pelvic Rocking Technique on the Gymball Against the Progress of 1st Stage Labor Ny. T At PMB Eliana Putriani, Str. South Lampung Regency (Doctoral dissertation, Tanjungkarang Health Polytechnic).
- [33] Sprong KE, Mabenge M, Wright CA, Govender S. Ureaplasma species and preterm birth: current perspectives. *Critical reviews in microbiology*. 2020 Mar 3;46(2):169-81.
- [34] Ulfa EN. Factors related to delivery by sectio caesarea at the Karsa Husada Batu general hospital in 2020 (Doctoral dissertation, Maulana Malik Ibrahim State Islamic University).
- [35] Marlyana DM, Nurwahyuni A, Wibowo A. Neonate Outcome And Response Time For Emergency Cesarean Section: A Scoping Review. *Journal of Medicine and Health: Scientific Publication of the Faculty of Medicine, Sriwijaya University*. 2023 Jan 19;10(1):125-40.
- [36] Motiec TD, Trisnawati I, Handayani IF, Darwanti J. Description of the Case of Premature Ruptured Membranes in Mothers at the Purwasari Karawang Maternity Hospital in 2020 (Doctoral dissertation, Health Polytechnic of the Ministry of Health, Bandung).
- [37] Wahyuni R. Factors causing premature rupture of membranes in women giving birth at the general hospital in the Sumbawa Besar area. *Journal of Health and Science*. 2020 Mar 28;3(2):26-33.
- [38] Dea D, Riana E, Khairunisa D. Midwifery care for women giving birth with premature rupture of membranes in the independent practice of Midwife Ida Apianti Pontianak (Doctoral dissertation, Polytechnic'Aisyiyah Pontianak).
- [39] Mendez-Figueroa H, Bicocca MJ, Bhalwal AB, Wagner SM, Chauhan SP, Bartal MF. Preterm cesarean delivery for nonreassuring fetal heart rate tracing: Risk factors and predictability of adverse outcomes. *European Journal of Obstetrics & Gynecology and Reproductive Biology*. 2022 Sep 1;276:207-12.
- [40] IM's daughter, Ismiyatun N. Early detection of high-risk pregnancies. *JKM (Journal of Public Health) Main Scholar*. 2020 Sep 4;8(1):40-51.

[41] Yuliani NW, Wahyuningsih M. Differences in Apgar Values in the First Minutes of Newborns with Premature Rupture of Membranes and Normal Rupture of Membranes in Yogyakarta City Hospital. In Proceedings of the National Seminar on Multidisciplinary Sciences 2019 Apr 3 (Vol. 1, No. 1).

[42] Leimert KB, Xu W, Princ MM, Chemtob S, Olson DM. Inflammatory amplification: a central tenet of uterine transitions for labor. *Frontiers in Cellular and Infection Microbiology*. 2021 Aug 19;11:660983.

UNDER PEER REVIEW

Review Form 1.7

Journal Name:	Asian Journal of Research in Infectious Diseases
Manuscript Number:	Ms_AJRID_97587
Title of the Manuscript:	Relationship Between Premature Rupture of The Membrane and Cesarean Delivery
Type of the Article	

General guideline for Peer Review process:

This journal's peer review policy states that **NO** manuscript should be rejected only on the basis of '**lack of Novelty**', provided the manuscript is scientifically robust and technically sound. To know the complete guideline for Peer Review process, reviewers are requested to visit this link:

(<https://www.journalajrid.com/index.php/AJRID/editorial-policy>)

PART 1: Review Comments

	Reviewer's comment	Author's comment <i>(if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)</i>
<u>Compulsory</u> REVISION comments 1. Is the manuscript important for scientific community? (Please write few sentences on this manuscript) 2. Is the title of the article suitable? (If not please suggest an alternative title) 3. Is the abstract of the article comprehensive? 4. Are subsections and structure of the manuscript appropriate? 5. Do you think the manuscript is scientifically correct? 6. Are the references sufficient and recent? If you have suggestion of additional references, please mention in the review form. <u>(Apart from above mentioned 6 points, reviewers are free to provide additional suggestions/comments)</u>	YES YES YES YES YES YES	
<u>Minor</u> REVISION comments 1. Is language/English quality of the article suitable for scholarly communications?	Language should be revised Check spellings and grammar	
<u>Optional/General</u> comments	Follow author guidelines	

PART 2:

	Reviewer's comment	Author's comment (if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)
Are there ethical issues in this manuscript?	(If yes, Kindly please write down the ethical issues here in details)	

Reviewer Details:

Name:	Ritika Rocque
Department, University & Country	College of Nursing, All India Institute of Medical Sciences, India

Relationship Between Premature Rupture of The Membrane and Cesarean Delivery: Case from Jakarta, Indonesia

Abstract

Premature rupture of membranes (PROM) is the spontaneous rupture of the membranes before the onset of signs of labor. It can occur both before term (<37 weeks) and after term (>37 weeks). *Cesarean delivery* is a surgical technique to deliver the fetus through an incision in the abdominal wall and uterine wall. This procedure is performed to minimize all complications from premature rupture of membranes. This study aims to determine the relationship between premature rupture of membranes and delivery of *sectio caesarea* at the UKI General Hospital in the 2019 period by using a descriptive content analysis method (analysis of medical records documents) with a cross-sectional approach and obtained 65 samples who experienced premature rupture of membranes. The results showed that 53 samples (81.55%) experienced premature rupture of membranes and performed *sectio caesarea*, while 12 samples (18.45%) had premature rupture of membranes but did not perform *sectio caesarea* with p-value = 0.001 ($p < 0.05$) from the results of the chi-square statistical test. From the results of the analysis, it was found that there was a relationship between premature rupture of membranes and delivery of *cesarean section* at the UKI General Hospital for the 2019 period. It is suggested that patients avoid the factors that can cause premature rupture of the membranes, which have been told by the doctor or health worker and the patient's family to support the patient to remind them to avoid factors that can cause premature rupture of the membranes.

Keywords: Premature rupture of membranes, *Cesarean Section*.

Introduction

Premature or premature rupture of membranes is the spontaneous rupture of the amniotic membranes before signs of labor occur. This condition can occur either before term (<37 weeks) or after term (>37 weeks). [1] The amniotic membranes function to produce amniotic fluid and protect the fetus from various kinds of infections. [2] Under normal circumstances, the membranes will rupture during labor. According to the World Health Organization, in 2014, the incidence of premature rupture of membranes or premature rupture of membranes ranged from 5-10% of all births. Preterm premature rupture of membranes occurs in 1% of all pregnancies, and 70% of premature rupture occurs at term. In 30% of cases, premature rupture of membranes is the cause of preterm birth. [3]

The incidence of premature rupture of membranes in Indonesia ranges from 4.5% - 6% of all pregnancies. In contrast, in the United States, premature rupture of membranes occurs in 120,000 pregnancies per year and is associated with a high risk to maternal, fetal, and neonatal safety [4]. Various studies in India explain that the incidence is 7-12% for premature rupture of membranes which 60-70% occurs in the long term. [5] The incidence of premature rupture of membranes in several hospitals in Indonesia is quite varied, including Sardjito Hospital at 5.3%, Hasan Sadikin Hospital at 5.05%, Cipto Mangunkusumo Hospital at 11.22%, Pringadi Hospital at 2.27%, and Kariadi Hospital which is equal to 5.10%. [6] Premature rupture of membranes has various complications for the mother and fetus that cause morbidity and mortality. Maternal complications include chorioamnionitis and fetal complications such as fetal distress, premature birth, and cord compression, to neonatal complications such as neonatal asphyxia and sepsis. This

complication requires labor conditions to be ended quickly to save the mother and fetus. Sectio Caesarea is a labor procedure performed to minimize all complications from premature rupture of membranes [7].

Sectio Caesarea is a surgical technique to deliver a fetus through an incision in the abdominal wall (laparotomy) and uterine wall (hysterectomy). Sectio Caesarea is one of the ten most commonly performed major surgeries. This medical procedure is needed to assist deliveries that cannot be carried out normally due to maternal health problems or fetal conditions [8].

According to Travassolo in 2010 stated that premature rupture of membranes with oligohydramnios is related to the duration of rupture of membranes, high rates of sectio caesarea, and low Apgar scores at birth.

In Indonesia, the number of caesarean section deliveries continues to increase. According to the Indonesian Demographic and Health Survey (IDHS) data, there was an increase in caesarean sections in Indonesia from 1991 to 2007, around 1.3-6.8 percent. [9] Meanwhile, the results of the Riskesdas report (basic health research) in 2013 found that 9.8% of deliveries were carried out by sectio caesarea in Indonesia, 2.3% of which were due to complications in pregnancy [10].

Research conducted by Andayasari et al. in 2014 stated that sectio caesarea deliveries in one government hospital and one private hospital in DKI Jakarta from January 2011-December 2011 reached 59.2%, and premature rupture of membranes contributed 31.4% to sectio deliveries caesarea [11]. Research conducted by Sumelung in 2014 stated that premature rupture of membranes was one of the factors that increased the incidence of sectio caesarea at Liub Kendage Hospital in 2015 [12].

Based on the background above, the researchers wanted to research the relationship between premature rupture of membranes and cesarean section delivery at UKI General Hospital in January-December 2019. The problem in this study was "Is there a relationship between premature rupture of membranes and cesarean delivery in UKI General Hospital period January-December 2019? The study aims to determine the incidence of premature rupture of membranes and sectio caesarea deliveries at UKI General Hospital from January to December 2019.

Literature Review

The amniotic sac (amniotic sac), which lines the amniotic cavity, consists of the amnion and chorion, which are tightly bound. The amniotic membrane is a flexible but tough avascular tissue. These avascular structures have an important role in pregnancy in humans. In many obstetric cases, rupture of the membranes at a young gestational age is the most common cause of preterm birth. The inner membrane communicating with the amniotic fluid consists of a single layer of cuboidal epithelium derived from the embryonic ectoderm. This epithelium is tightly attached to the basement membrane, which is connected to the interstitial layer containing collagen I, III, and V. The outer part of the membrane is mesenchymal tissue derived from the mesoderm. This layer of the amnion is connected to the chorion leave. The amnion's inner lining is microvilli which transfer fluids and metabolism. This layer produces metalloproteinase-1 inhibitory substances [13].

Mesenchymal cells function to produce collagen so that the membrane becomes flexible and strong. In addition, these tissues produce the cytokines IL-6, IL-8, and MCP-1 (monocyte chemoattractant protein-1); This substance is useful against bacteria. In addition, the amniotic membranes produce vasoactive substances: endothelin-1 (a vasoconstrictor) and PHRP (parathyroid hormone-related protein), a vasorelaxant. Thus, the amniotic membrane regulates blood circulation and local vascular tone. The amniotic membrane also covers the umbilical cord. Some of the fluid will also come from diffusion in the umbilical

cord. The rupture of the membranes is related to the strength of the membranes. In smokers and infections, the resistance of the membranes is weakening so that they break easily. In a normal pregnancy, there are few macrophages. At the time of birth, leukocytes will enter the amniotic fluid as a reaction to inflammation. There is no IL-1B in a normal pregnancy, but IL-1B will be found in preterm labor.

It is related to the occurrence of the infection process. Since the beginning of pregnancy, amniotic fluid has been formed. Amniotic fluid is a protector and cushion for protection while supporting growth. Osmolarity, sodium, urea, and creatinine levels do not differ from the mother's serum levels, meaning that the levels in the amniotic fluid are the result of diffusion from the mother. Amniotic fluid contains many fetal cells (lanugo, vernix caseosa) [14]. Macroscopically, the amnion is a thin layer (only 20% of the thickness of the fetal membranes) and is a transparent (translucent) structure. This amniotic membrane can easily be separated from the underlying chorion because the amnion is never completely fused with the chorion and is only passively attached by internal pressure from the amniotic fluid [15]. The amnion lacks blood vessels and obtains its required nutrients and oxygen supplied directly by diffusion from the surrounding amniotic fluid, fetal surface vessels, or the decidua [16]. The thickness of the amnion varies greatly due to changes in the amount of mucin and fluid contained in the spongy lining, which ranges from 80 - 120 μm [17].

The amniotic epithelium, the innermost amnion layer that leads to the fetus and surrounds the amniotic fluid, consists of a single layer of simple, squamous to cuboidal cells, with microvilli apical and attached to the basement membrane [18]. The amniotic epithelium secretes collagen types I, III, and IV, non-collagen glycoproteins such as laminin, nidogen, and fibronectin, forming a cell basement membrane thickness of nearly 1 μm . The stromal compactum layer varies greatly in thickness, is tightly adherent, and cannot be separated from the basement membrane. This layer is a microfibril-dense cell-free homogeneous layer. Collagen types I, III, and V, and elastic fibers of the compact layer, are secreted by the mesenchymal cells in the fibroblast layer beneath the compact layer [19], which form the main burden-carrying fibrous framework of the amnion. The main tensile strength of the amnion is provided by collagen, which is arranged in one direction, i.e., parallel to the amniotic epithelium [20]. The compact layer and fibroblasts are difficult to differentiate histologically. The fibroblast layer beneath the compact layer is the most complex and thickest layer of the amnion, consisting of cellular tissue within a loose collagen network with non-collagenous glycoproteins, proteoglycans, and type III collagen. Fibroblasts and macrophages (Hofbauer cells) have been identified within this layer. The spongy intermediate layer, also called the intermediate layer because it lies between the amnion and the chorion, is rich in proteoglycans and hyaluronate, which absorbs large amounts of water and forms a viscous layer that allows the amnion to slide over the chorion [21].

By this mechanism, this spongy coating makes it possible to absorb physical stress and to provide spontaneous short-term mechanical repair and defect closure systems. In addition, a circular fibrous structure is found in direct relation to the chorionic side, helping to adjust the lateral tension on the sliding surface between the amnion and chorion [22]. Occasionally, a potential space can be seen histologically in the spongy layer between the amnion and chorion. The space comprises loosely arranged collagen fibers that are sometimes oedematous and contain scattered fibroblasts and macrophages.

Development is between the embryonic cell mass and the trophoblast during the early implantation period. The small cells lining the inner surface of the trophoblast are called amniogenic cells, which are precursors of the amniotic epithelium. The amnion can be identified for the first time on embryo development's 7th or 8th day. It begins with the formation of a vesicle that develops into a small sac covering the dorsal surface of the

embryo. As the amniotic sac enlarges, distention of the amniotic sac causes it to contact the interior surface of the chorion leave. Apposition of the chorion and amnion near the end of the first trimester. In young pregnancies, amniotic fluid is an ultrafiltrate of maternal plasma formed by the amnion cells. In the second trimester of pregnancy, amniotic fluid is formed by extracellular diffusion through the fetal skin, so its composition is similar to fetal plasma. Furthermore, after the second trimester, fetal skin horn substance formation occurs and blocks the diffusion of fetal plasma so that most of the amniotic fluid is formed by; amniotic cells and fetal urine. Fetal kidneys start excreting urine from the age of 12 weeks, and after reaching the age of 18 weeks, they can excrete urine as much as 7-14 cc/day. Term fetuses produce urine 27 cc/hour or 650 ccs daily [23]. Thus, the composition that forms amniotic fluid follows a postulate that the increase in amniotic fluid is not linear.

After the gestational age exceeds 12 weeks, what participates in forming amniotic fluid is; fetal kidneys (so that urea, creatinine, and uric acid are found), desquamation of fetal skin (skin cells, lanugo hair, vernix caseosa), secretions from the fetal lungs, transudate from the surface of the placental amnion, hormones or hormone-like substances in the amniotic fluid. Meanwhile, regulating amniotic fluid is very important to maintain the amount regularly. The following three important components influence the setting: production produced by the amnion cells, the amount of urine produced, and the amount of amniotic fluid swallowed by the fetus. Amniotic fluid regulation in term pregnancy includes the amount taken by the fetus \pm 500-1000 ml, enters the lungs \pm 170 ml, and from the umbilical cord and amnion \pm 200-500 ml. At the same time, the amount of fluid released by the fetus into the amniotic cavity is from oral secretions \pm 25 ml, secretions from the respiratory tract \pm 170 ml, urine \pm 800-1200 ml, and transmembrane from the amnion \pm 10 ml. Thus, fetal urine appears to dominate the production of amniotic fluid, and the average regulation near term reaches 500 cc/day [24].

Amniotic fluid has an important role in supporting the process of pregnancy and childbirth. Throughout a normal pregnancy, the compartments of amniotic fluid provide space for the fetus to grow, move and develop. Without amniotic fluid, the uterus will contract and put pressure on the fetus; in cases where rupture of the membranes occurs early in the first trimester, the fetus may experience structural abnormalities, including facial distortion, reduction of limbs, and abdominal wall defects due to uterine compression [25]. Towards mid-pregnancy, the amniotic fluid becomes increasingly important for fetal development and growth, including lung development, so if there is insufficient amniotic fluid during mid-pregnancy, the fetus is often accompanied by pulmonary hypoplasia and continues to death. In addition, this fluid also has a protective role in the fetus. This liquid contains anti-bacterial agents and works to inhibit the growth of bacteria with potential pathogens. Amniotic fluid is a protective medium for the fetus to help with cervical dilation during labor and delivery. In addition, amniotic fluid also acts as a means of communication between the fetus and the mother. The maturity and readiness of the fetus for birth can be known from the fetal urine hormones excreted into the amniotic fluid [26].

Amniotic fluid can also be used as a diagnostic tool to see fetal growth and development abnormalities by conducting cell cultures or using a spectrometer. Other functions of amniotic fluid can also protect the fetus from trauma, as a medium for fetal musculoskeletal development, maintain fetal body temperature, equalize uterine pressure in parturition, clean the birth canal so that the baby is less infected, and maintain normal development and growth of the lungs and gastro tract intestinal [27]. Any wound on any body part will go through several stages: inflammation, proliferation, and maturation. Each phase involves many components and mechanisms, including the inflammatory, proliferative, and maturation phases. [28]

Premature rupture of the membranes is a condition in which the membranes rupture

before labor or in part. Premature rupture of membranes can occur in term or preterm pregnancies. Preterm Premature Rupture of the Membranes or premature rupture of membranes is the rupture of the membranes in patients with a gestational age of fewer than 37 weeks [29]. The incidence of premature rupture of membranes is 8% at term (> 37 weeks) and is associated with an increased risk of infection in the mother (chorioamnionitis, endometritis) and infection in the fetus (neonatal sepsis). Meanwhile, the incidence of preterm premature rupture of membranes is 3%, as a cause of 20-30% of preterm labor [30]. Two things broadly cause the causes of premature rupture of membranes, namely reduced membrane strength and increased intrauterine pressure or both factors. An infection can cause reduced membrane strength from the vagina and cervix. The factors influencing premature rupture of membranes are age, parity, smoking behavior, and history of premature rupture. Experiences experienced by mothers in labor with premature rupture of membranes can have a major influence on the mother when facing pregnancy conditions. The previous history of premature rupture of membranes is 2-4 times at risk of experiencing premature rupture of membranes again. In short, the pathogenesis of premature rupture of membranes results from a decrease in collagen content in the membrane, which triggers premature and preterm rupture of membranes. Women who have experienced premature rupture of membranes in pregnancies before delivery will be at greater risk in subsequent pregnancies than women who have never experienced premature rupture of membranes before because the composition of the membranes decreases in subsequent pregnancies.

The rupture of membranes in labor is generally caused by repeated uterine contractions and stretching. The membranes rupture because, in certain areas, biochemical changes occur, which cause the inferior membranes to become brittle, not because the entire membranes are fragile. There is a balance between synthesis and degradation of the extracellular matrix. Changes in structure, cell number, and collagen catabolism cause collagen activity to change and cause the membranes to rupture. Collagen degradation is mediated by matrix metalloproteinases inhibited by tissue-specific and protease inhibitors. The membranes' integrity is due to a combination of low metalloproteinase activity and relatively higher concentrations of tissue inhibitors metalloproteinase-1. Microorganisms that infect the membranes of the membranes can form protease enzymes accompanied by an inflammatory response from the membranes, thereby affecting the balance of metalloproteinases and tissue inhibitors metalloproteinase-1, which causes a weakening of the tension of the membranes and rupture of the membranes hemolytic, and staphylococcus. In addition, closer to the delivery time, the balance between metalloproteinase and tissue inhibitors metalloproteinase-1 leads to proteolytic degradation of the extracellular matrix and fetal membranes. This proteolytic degradation activity increases towards delivery. The amniotic membranes are very strong in young pregnancies. In the third trimester, the membranes rupture easily. The weakening of the strength of the membranes is related to the enlargement of the uterus, uterine contractions, and fetal movements. In the last trimester, biochemical changes occur in the amniotic membranes so that the rupture of the membranes at term is physiological. Premature rupture of membranes in preterm pregnancy is caused by external factors such as infections that spread from the vagina [31].

Premature rupture of membranes greatly affects complications and length of labor. In the 1st stage of labor, the fetal membranes and the presenting part of the fetus act to open the upper part of the vagina. However, after the rupture of the membranes, the changes in the pelvic floor are all produced by the pressure exerted by the presenting part of the fetus so that the hydrostatic action of the fetal membranes causes cervical dilatation. If the membranes have ruptured, the lowest part of the fetus that attaches to the cervix and forms the lower uterine segment functions the same. It will result in one of the complications of premature rupture of membranes, namely the long labor process, so sectio caesarea is the

only option in this condition [32].

Another complication of mothers with premature rupture of membranes that causes morbidity and mortality is choriamnionitis. This infection causes inflammation of the amniotic fluid, amniotic membranes, or fetus, and this condition causes mothers with premature rupture of membranes to have symptoms of fever, fundal tenderness, tachycardia, fetal tachycardia, and smelly amniotic fluid. This condition is one of the complications feared to occur if a mother with premature rupture of membranes does not end her pregnancy immediately [33].

A study in Iran reported that out of 536 cases of premature rupture of membranes, 28% were performed by sectio caesarea. Other researchers concluded that sectio caesarea reached 26.6% in India in patients with premature rupture of membranes [34]. It is due to complications from premature membrane rupture, including fetal distress, malpresentation, narrow pelvis, failed induction, and the maternal complication of chorioamnionitis. Apart from that, other complications that led to the decision to perform sectio caesarea in mothers with premature rupture of membranes were complications of neonatal asphyxia and sepsis [35]. There is a relationship between fetal distress and decreased amniotic fluid volume. The more critical the fetus is. It was found that babies with premature rupture of membranes >12 hours had a 12 times greater risk of experiencing unfavorable outcomes, so it can be concluded that at term KPD, pregnancy termination should be carried out at least 6-12 hours from the onset of premature rupture of membranes.

Research Method

This type of research uses a descriptive analysis research method with a cross-sectional approach. This study used secondary data from UKI General Hospital medical records for the January-December 2019 period. The location for collecting research data was carried out in the UKI General Hospital medical records section. The time of execution, collection, and implementation of the research was carried out from August 2020 – October 2020. The population for this study was patients who gave birth at the UKI General Hospital for the period January-December 2019. The sample was part of the population that had met the inclusion criteria, namely patients who gave birth on indications of Premature rupture of membranes at UKI General Hospital during January-December 2019. The Central Statistics Agency in Indonesia stated that the total population of Indonesia was 271,066,400 in 2019. The World Health Organization reported that as many as 17,655 mothers gave birth in Indonesia in 2019. The number of samples in this study was at least 65 people. Data collection was carried out at the UKI General Hospital medical record section. Furthermore, medical record data following the research variables will be recorded. All data obtained will be filtered again according to the inclusion and exclusion criteria set so that data is produced that will be used in the results of this study. Data collected through medical records are processed using the IBM SPSS (Statistical for Social Science) program for Windows edition 25.0 and the Microsoft Office Excel 2016 program.

Result and Discussion

Data were obtained from the medical records of all patients with premature rupture of membranes delivered by cesarean section and normal delivery at UKI General Hospital for January-December 2019. The total sample was 65 patients.

Table 1. Characteristics of the sample by age

Age	Frequency	Percentage %
< 30 Tahun	15	23.1%
≥30 Tahun	50	76.9%

Total	65	100%
--------------	----	------

Table 1 shows the characteristics of the study sample based on age, which found 15 patients (23.1%) aged <30 years, while 50 patients (76.9%) were aged ≥ 30 years.

Table 2. Sample characteristics based on parity

Parity	Frequency	Percentage %
Primigravida	25	38.5%
Multigravida	40	61.5%
Total	65	100%

Table 2 shows the characteristics of the study sample based on parity, where there were 25 patients with primigravidas (38.5%), while multigravidas had 40 patients (61.5%).

Table 3. Sample characteristics based on gestational age

Gynecological Age	Frequency	Percentage %
< 37 Weeks	12	18.5%
≥ 37 Weeks	53	81.5%
Total	65	100%

Table 3 shows the characteristics of the study sample based on gestational age, which was found at gestational age <37 weeks in 12 patients (18.5%), while gestational age ≥ 37 weeks were found in 53 patients (81.5%).

Table 4. Sample characteristics based on BMI (Body Mass Index)

BMI	Frequency	Percentage %
< 30	17	26.2%
≥ 30	48	73.8%
Total	65	100%

Table 4 shows the characteristics of the study sample based on BMI (Body Mass Index), where there were 17 patients (26.2%) with a BMI <30, while 48 patients (73.8%) had a BMI ≥ 30 .

Table 5. Sample characteristics based on the history of premature rupture of membranes

History of premature rupture of membranes	Frequency	Percentage %
Ever	40	61.5%
Never	25	38.5%
Total	65	100%

Table 5 shows the characteristics of the study sample based on a history of premature rupture of membranes, in which 40 patients (61.5%) had a history of premature rupture of membranes, while 25 patients had never had premature rupture of membranes (38.5%)).

Table 6. Characteristics of the sample based on the APGAR SCORE

Apgar Score	Frequency	Percentage %
< 7	46	70.8%
≥ 7	19	29.2%

Total	65	100%
--------------	-----------	-------------

Table 6 shows the characteristics of the study sample based on the Apgar Score, where there were 46 patients (70.8%) with an APGAR SCORE <7, while 19 patients (29.2%) had an Apgar Score \geq 7.

Table 7. Sample characteristics based on birth weight

Birth Weight	Frequency	Percentage %
< 3 Kg	20	30.8%
\geq 3 Kg	45	69.2%
Total	65	100%

Table 7 shows the characteristics of the study sample based on birth weight, in which 20 patients (30.8%) had babies with birth weight <3 kg, while 45 patients (69.2%) had babies with birth weights \geq 3 kg.

Table 8. The relationship between premature rupture of membranes and sectio caesarea delivery

Gynecological Age		Type of Childbirth				Total	<i>p-value</i>
		<i>Sectio</i>	n (%)	No <i>Sectio</i>	n (%)		
Premature rupture of membranes	< 37 Weeks	7	10,76%	5	7,69%	12(18.45%)	0,001
	\geq 37 Weeks	50	76,92%	3	4,63%	53 (81.55%)	
Total		57	87,68%	8	12,32%	65 (100%)	

Table 8 shows the characteristics of the study sample based on the gestational age of mothers who experienced premature rupture of membranes and the type of delivery performed. It was found that mothers with gestational age <37 weeks experienced premature rupture of membranes and performed sectio caesarea in 7 patients (10.76%), whereas mothers with gestational age <37 weeks experienced premature rupture of membranes but did not perform a cesarean section in 5 patients (7.69%). Meanwhile, 50 patients (76.92%) had premature rupture of membranes, and 50 patients (76.92%) had premature rupture of membranes and 37 weeks of gestational age \geq 37 weeks of mothers who had premature rupture of membranes without having a cesarean section. (4.63%), and the P-value is 0.001.

The study results found that the age group that experienced premature rupture of membranes was the most in the age group \geq 30 years, with as many as 50 patients (76.9%). It follows the theory where according to Sudarto, a mother who gives birth at the age of 35 and over can affect her reproductive system because her reproductive organs have begun to reduce their ability and elasticity in accepting pregnancy, affecting the process of embryogenesis. The amniotic membranes will be thinner, facilitating premature rupture [36]. Based on the results of the study, it was found that a woman with multigravida experienced premature rupture of membranes in 40 patients (61.5%). It is following the theory according to Kacerovsky, women who have given birth several times accompanied by close pregnancy intervals can be at risk of experiencing premature rupture of membranes in their next pregnancy. It is because pregnancies are too frequent, affecting the embryogenesis process. The amniotic membranes become thinner, so they break easily prematurely. In addition, there is also a theory that the more parity, the easier it is for amnion infection to occur due to damage to the cervical structure in previous deliveries [37].

Based on the study's results, 53 pregnant women experienced premature rupture of membranes when their gestational age was \geq 37 weeks (81.5%). According to Popowski, it follows the theory that most premature rupture of membranes occurs at gestational age \geq 37 weeks. Premature rupture of membranes occurs nearing delivery due to an increase in matrix

metalloproteinase which tends to cause the membranes to rupture, in addition to an increase in matrix metalloproteinase, uterine enlargement, uterine contractions, and fetal movements occur [38].

From the results of the study, it was found that pregnant women who had a BMI (Body Mass Index) ≥ 30 had premature rupture of membranes, and 48 patients (73.8%) had a cesarean section. An increase in Body Mass Index ≥ 30 has a great risk for a normal delivery because, in a normal delivery, there will be a delay in the first stage of the active phase and the second stage. After all, the mother who is obese will have a narrow birth canal due to the accumulation of fat, making it difficult for the baby to come out, and a sectio caesarea must be carried out immediately [39].

The history that mothers have experienced in labor with the incidence of premature rupture of membranes can have a big influence on the mother when facing pregnancy conditions. Based on the amount of research data, it was found that 40 patients (61.5%) had a history of premature rupture of membranes in previous deliveries. According to Morgan, it follows the theory that patients with a previous history of premature rupture of membranes are at risk of 2-4 times experiencing premature rupture of membranes again. In short, the pathogenesis of premature membrane rupture results from a decrease in collagen content in the membrane, which triggers premature rupture membranes.

Women who have experienced premature rupture of membranes during pregnancy or before delivery are at greater risk in their next pregnancy than women who have never experienced premature rupture of membranes before because the composition of the membranes becomes fragile. The collagen content decreases in subsequent pregnancies [40]. The APGAR SCORE is a practical method systematically used to assess a baby as soon as possible after birth. What is assessed is heart rate, respiratory effort, muscle tone, skin color, and reaction to stimulation (response to stimuli), namely by inserting a catheter into the nostril after the airway has been cleaned when the new baby is born.

From the results of this assessment, it can be seen whether the baby is normal (APGAR score 7-10), moderate-mild asphyxia (APGAR score 4-6), or the baby has severe asphyxia (APGAR score 0-3). The characteristics of the sample based on the APGAR SCORE showed that patients who gave birth with premature rupture of membranes and their babies had an APGAR SCORE <7 . There were 46 patients (70.8%). It follows the theory according to Ni Wayan and Melania, where with the rupture of the membranes, there will be prolapse of the funiculi / descent of the umbilical cord, which will cause the neonatorum to experience hypoxia and asphyxia (lack of oxygen in the baby) which will result in compression of the umbilical cord, respiratory distress. The baby will be at risk of having a low APGAR SCORE (<7) [41].

Mechanical stretching, such as in a large baby's weight, can cause stretching of the membranes and can cause premature rupture of the membranes. It is also supported by the data results where there is an increase in the number of patients who experience premature rupture of membranes with a baby weighing > 3.5 kg by 1.6%, while babies weighing > 4 Kg were 2.4%. Based on the study's results, with birth weight ≥ 3 Kg and experiencing premature rupture of membranes were 45 patients (69.2%). It follows the theory according to Zelop, where mechanically stretching the fetal membranes will increase the production of prostaglandin E2 and Interleukin-8 in the amnion, also increasing the activity of MMP-1 in the membranes. Interleukin-8 produced from amnion and chorion cells is chemotactic towards neutrophils and stimulates collagenase activity, which disrupts the balance of synthesis and degradation of the extracellular matrix, which ultimately causes the rupture of the membranes.

Prostaglandin E2 increases uterine irritability, decreases membrane collagen synthesis, and increases the production of MMP-1 and MMP-3 by fibroblasts. The production of

interleukin-8 and prostaglandin E2 from the amnion indicates that biochemical changes in the membranes can be initiated by physical forces or by stretching the membranes, suggesting that mechanical forces cause premature rupture of membranes [42].

The results of the research on the relationship between premature rupture of membranes and sectio caesarea delivery obtained a value of $P = 0.001$ ($P < 0.05$) which means there is a relationship between premature rupture of membranes and sectio caesarea delivery where this is following the theory, according to Barbara, pregnant women with indications of ruptured membranes Early pregnancy will cause the amount of amniotic fluid to decrease and the risk of having a normal delivery. Babies born will also have an increased risk of morbidity and mortality. The risk of infection in the mother is also quite high, so it will increase morbidity and mortality, so the action of cesarean section is expected to reduce maternal morbidity and mortality and improve infant outcomes.

Conclusion

From the results of the research that was described in the previous chapter, the following conclusions were drawn: a) the prevalence of premature rupture of membranes at UKI General Hospital carrying out sectio caesarea in the January-December 2019 period was 57 patients (87.68%), while those who did not perform sectio caesarea in 8 patients (12.32%), and b) based on the Chi-square test, there was a significant relationship between premature rupture of membranes and sectio caesarea ($P=0.001$). Thus, it is hoped that health workers and health institutions as health workers can help educate patients about the factors that can cause premature rupture of membranes so that patients can take preventive action to prevent premature rupture membranes. In addition, it is recommended that patients avoid factors that can cause premature rupture of a membrane that doctors or health workers have told, and the patient's family can support patients to remind them to avoid factors that can cause premature rupture of membranes.

Ethical Approval:

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

Consent

As per international standard or university standard, patient(s) written consent has been collected and preserved by the author(s).

References

- [1] Cughey AB, Robinson JN, Norwitz ER. Contemporary diagnosis and management of preterm premature rupture of membranes. Reviews in obstetrics and gynecology. 2008;1(1):11.
- [2] Menon R, Richardson LS. Preterm prelabor rupture of the membranes: a disease of the fetal membranes. In Seminars in perinatology 2017 Nov 1 (Vol. 41, No. 7, pp. 409-419). WB Saunders.
- [3] Fitriyani F, Yuliana Lubis Y. Determinant factors in premature rupture of membranes. Health Media Journal. 2018 Nov 16;11(1):053-61.
- [4] Syarwani TI, Tendean HM, Wantania JJ. Overview of Premature Ruptured Membranes (PROM) in Prof. Dr. RD Kandou Manado in 2018. Medical Scope Journal. 2020;1(2).
- [5] Susan Blossia E. A Prospective Cross Sectional study on CRP Levels in Antenatal Women with Prelabor Rupture of Membrane and CRP Levels in Women with Normal Labor (Doctoral dissertation, Christian Medical College, Vellore).

- [6] Rohmawati N, Wijayanti Y. Premature rupture of membranes at Ungaran Regional General Hospital. HIGEIA (Journal of Public Health Research and Development). 2018 Feb 1;2(1):23-32.
- [7] Venancyana MC, Indrayani T, Lubis R. Analysis Of Factors Affecting Pregnant Mothers In Making Decisions For Caesarean Section Childbirth Plan At Tc Hillers Hospital, Sikka Regency, Year 2022. International Journal Of Multi Science. 2022 Aug 25;3(02):7-17.
- [8] Waang WW, Kusumawati PD. Analysis of Deep Breath Relaxation Techniques for Post SC Patients with Pain. Journal of Health Science Community. 2022 Nov 15;3(2):97-101.
- [9] BP Statistics. Indonesia Demographic and Health Survey Report.
- [10] Suparmi S, Kusumawardhani N, Susiloretni KA. Sub-national inequality of caesarean sections in urban-rural areas of Indonesia. In Proceedings of the international conference on public health 2018 (Vol. 4, No. 1, pp. 23-32).
- [11] Hardiyanti R. Use of Prophylactic Antibiotics in Sectio Caesarea Patients. Journal of Health Science and Physiotherapy. 2020 Jan 7;2(1):96-105.
- [12] Ulfa EN. Factors related to delivery by sectio caesarea at the Karsa Husada Batu general hospital in 2020 (Doctoral dissertation, Maulana Malik Ibrahim State Islamic University).
- [13] Machtejevienė E. Peptide pattern of amniotic fluid and its correlation with protein composition of fetal membranes: the search for new potential biomarkers to predict preterm premature rupture of membranes:[Rankraštis]: doctoral dissertation: biomedical sciences, medicine (06B).
- [14] Brace RA, Anderson DF, Cheung CY. Regulation of amniotic fluid volume: mathematical model based on intramembranous transport mechanisms. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology. 2014 Nov 15;307(10):R1260-73.
- [15] Cohen MC, Scheimberg I, Hutchinson JC. Anatomy and Pathology of the Placental Membranes. Benirschke's Pathology of the Human Placenta. 2022:281-343.
- [16] Founds SA, Baker B. Fetal and Placental Development and Functioning. Core Curriculum for Maternal-Newborn Nursing E-Book. 2022 Oct 14:28.
- [17] POLZIN WJ, BRADY K. Mechanical factors in the etiology of premature rupture of the membranes. Clinical obstetrics and gynecology. 1991 Dec 1;34(4):702-14.
- [18] Mamede AC, Carvalho MJ, Abrantes AM, Laranjo M, Maia CJ, Botelho MF. Amniotic membrane: from structure and functions to clinical applications. Cell and tissue research. 2012 Aug;349:447-58.
- [19] Country IK, KFM SO. Matrix Metalloproteinases in Premature Ruptured Membrane. deepublish; 2021 May 1.
- [20] Yunus M, Sos S, Hatijar S. Textbook of Midwifery Care in Pregnancy.
- [21] Macedo BM. Exploração das Membranas Fetais para Aplicações de Engenharia dos Tecidos (Doctoral dissertation).
- [22] Haller C. Evaluation of human fetal membrane sealing (Doctoral dissertation, University of Zurich).
- [23] Ferselina L. Case Study of Handling Newborns with Cloudy Amniotic Water in Mrs. Vdi Pmb Komariah, Sst Lampung Selatan (Doctoral dissertation, Tanjungkarang Health Polytechnic).
- [24] Fahimah WF. Literature Review: Factors Causing Premature Rupture of Water.

- [25] Trance MG. Continuing Midwifery Care for Mrs. EB at the Kaputu Community Health Center April 13 to June 10 2019 (Doctoral dissertation, Kupang Ministry of Health Polytechnic).
- [26] Liley AW. Disorders of amniotic fluid. In *Fetal-placental disorders* 1972 Jan 1 (pp. 157-206). Academic Press.
- [27] Henny Sulistyawati SS, Zulfa Hanum SS, Keb M, Meikawati PR, SiTS S, Rosdianto NO, ST S, Keb M, Muayah SS, Ety Aprianti SK. Textbook for Postpartum DIII Midwifery Volume I. Mahakarya Citra Utama Group; 2022 Sep 15.
- [28] Monika P, Waiker PV, Chandraprabha MN, Rangarajan A, Murthy KN. Myofibroblast progeny in wound biology and wound healing studies. *Wound Repair and Regeneration*. 2021 Jul;29(4):531-47.
- [29] Ma'roef M, Putri AP. The Relationship of Leukocyturia on The Incidence of Prominent Rupture of The Membrane in Preterm Pregnancy at The General Hospital of The University of Muhammadiyah Malang. *Medical Science*. 2019 Dec 21;15(2):139-45.
- [30] Sari DS. Relationship between Multiple Pregnancy and Fetal Abnormalities with Premature Rupture of the Membranes at the Prabumulih Regional General Hospital in 2019. *Abdurahman Health Journal*. 2020 Sep 25;9(2):56-63.
- [31] Margono RS, Sukrisno A, Nugrohowati N, Lestari W. Relationship between a premature rupture of membranes and the increase of leucocyte levels in pregnant women during the COVID-19 pandemic. *Journal of Traditional Midwifery and Health*. 2021 Oct 25:127-34.
- [32] Putri RS. Application of the Pelvic Rocking Technique on the Gymball Against the Progress of 1st Stage Labor Ny. T At PMB Eliana Putriani, Str. South Lampung Regency (Doctoral dissertation, Tanjungkarang Health Polytechnic).
- [33] Sprong KE, Mabenge M, Wright CA, Govender S. Ureaplasma species and preterm birth: current perspectives. *Critical reviews in microbiology*. 2020 Mar 3;46(2):169-81.
- [34] Ulfa EN. Factors related to delivery by sectio caesarea at the Karsa Husada Batu general hospital in 2020 (Doctoral dissertation, Maulana Malik Ibrahim State Islamic University).
- [35] Marlyana DM, Nurwahyuni A, Wibowo A. Neonate Outcome And Response Time For Emergency Cesarean Section: A Scoping Review. *Journal of Medicine and Health: Scientific Publication of the Faculty of Medicine, Sriwijaya University*. 2023 Jan 19;10(1):125-40.
- [36] Motiec TD, Trisnawati I, Handayani IF, Darwanti J. Description of the Case of Premature Ruptured Membranes in Mothers at the Purwasari Karawang Maternity Hospital in 2020 (Doctoral dissertation, Health Polytechnic of the Ministry of Health, Bandung).
- [37] Wahyuni R. Factors causing premature rupture of membranes in women giving birth at the general hospital in the Sumbawa Besar area. *Journal of Health and Science*. 2020 Mar 28;3(2):26-33.
- [38] Dea D, Riana E, Khairunisa D. Midwifery care for women giving birth with premature rupture of membranes in the independent practice of Midwife Ida Apianti Pontianak (Doctoral dissertation, Polytechnic'Aisyiyah Pontianak).

[39] Mendez-Figueroa H, Bicocca MJ, Bhalwal AB, Wagner SM, Chauhan SP, Bartal MF. Preterm cesarean delivery for nonreassuring fetal heart rate tracing: Risk factors and predictability of adverse outcomes. *European Journal of Obstetrics & Gynecology and Reproductive Biology*. 2022 Sep 1;276:207-12.

[40] IM's daughter, Ismiyatun N. Early detection of high-risk pregnancies. *JKM (Journal of Public Health) Main Scholar*. 2020 Sep 4;8(1):40-51.

[41] Yuliani NW, Wahyuningsih M. Differences in Apgar Values in the First Minutes of Newborns with Premature Rupture of Membranes and Normal Rupture of Membranes in Yogyakarta City Hospital. In *Proceedings of the National Seminar on Multidisciplinary Sciences 2019 Apr 3 (Vol. 1, No. 1)*.

[42] Leimert KB, Xu W, Princ MM, Chemtob S, Olson DM. Inflammatory amplification: a central tenet of uterine transitions for labor. *Frontiers in Cellular and Infection Microbiology*. 2021 Aug 19;11:660983.

UNDER PEER REVIEW

Review Form 1.7

Journal Name:	Asian Journal of Research in Infectious Diseases
Manuscript Number:	Ms_AJRID_97587
Title of the Manuscript:	Relationship Between Premature Rupture of The Membrane and Cesarean Delivery
Type of the Article	

General guideline for Peer Review process:

This journal's peer review policy states that **NO** manuscript should be rejected only on the basis of '**lack of Novelty**', provided the manuscript is scientifically robust and technically sound. To know the complete guideline for Peer Review process, reviewers are requested to visit this link:

(<https://www.journalajrid.com/index.php/AJRID/editorial-policy>)

PART 1: Review Comments

	Reviewer's comment	Author's comment (if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)
Compulsory REVISION comments		
1. Is the manuscript important for scientific community? (Please write few sentences on this manuscript)	YES	Thanks
2. Is the title of the article suitable? (If not please suggest an alternative title)	YES	
3. Is the abstract of the article comprehensive?	YES	Thanks
4. Are subsections and structure of the manuscript appropriate?	YES	
5. Do you think the manuscript is scientifically correct?	YES	
6. Are the references sufficient and recent? If you have suggestion of additional references, please mention in the review form. (Apart from above mentioned 6 points, reviewers are free to provide additional suggestions/comments)	YES	
Minor REVISION comments		
1. Is language/English quality of the article suitable for scholarly communications?	Language should be revised Check spellings and grammar	Language revised
Optional/General comments	Follow author guidelines	Done

PART 2:

	Reviewer's comment	Author's comment (if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)
Are there ethical issues in this manuscript?	(If yes, Kindly please write down the ethical issues here in details)	

Review Form 1.7

Journal Name:	Asian Journal of Research in Infectious Diseases
Manuscript Number:	Ms_AJRID_97587
Title of the Manuscript:	Relationship Between Premature Rupture of The Membrane and Cesarean Delivery
Type of the Article	Original research with secondary data

General guideline for Peer Review process:

This journal's peer review policy states that **NO** manuscript should be rejected only on the basis of '**lack of Novelty**', provided the manuscript is scientifically robust and technically sound. To know the complete guideline for Peer Review process, reviewers are requested to visit this link:

(<https://www.journalajrid.com/index.php/AJRID/editorial-policy>)

PART 1: Review Comments

	Reviewer's comment	Author's comment (if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)
<u>Compulsory</u> REVISION comments 1. Is the manuscript important for scientific community? (Please write few sentences on this manuscript) 2. Is the title of the article suitable? (If not please suggest an alternative title) 3. Is the abstract of the article comprehensive? 4. Are subsections and structure of the manuscript appropriate? 5. Do you think the manuscript is scientifically correct? 6. Are the references sufficient and recent? If you have suggestion of additional references, please mention in the review form. <u>(Apart from above mentioned 6 points, reviewers are free to provide additional suggestions/comments)</u>	Yes Can add place of study and source of data in the title. Abstract should be structured as background, aims, methods, results and discussion and conclusions. Review of literature is not required as per journal style. Yes Check references citation. Some references are not as per journal style.	Added Noted Done revision
<u>Minor</u> REVISION comments 1. Is language/English quality of the article suitable for scholarly communications?	Yes	Thanks
<u>Optional/General</u> comments		

PART 2:

	Reviewer's comment	Author's comment (if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)
Are there ethical issues in this manuscript?	(If yes, Kindly please write down the ethical issues here in details)	

Editor's Comment:

The manuscript can be published.

Editor's Details:

Dr. Bagiu Iulia-Cristina

Assistant professor, Multidisciplinary Research Center on Antimicrobial Resistance, "Victor Babes"
University of Medicine and Pharmacy, Romania.