

**PPROM**  
**Preterm Premature**  
**Rupture of Membranes**

<b>Bölüm</b>
<b>5</b>

**The evaluation of preterm infants, PPRM**  
**infants, by established SMILEYS Form, based**  
**on Steuernagel concept.**

**Prematür Erken Membran Rüptürü olgularının**  
**SMILEYS Formuna göre yorumu, Steuernagel**  
**bakışı temelinde\***

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*TR. Aradan geçen süre dikkate alındığında, SMILES Formu ile değerlendirilen çalışmanın yeniden irdelenmesi amaçlanmıştır. Daha önce yapılan çalışmaların yeniden gözden geçirilmesi, yeni fikirler ve görüşler sunabileceği ile, önceki konumunuzu da daha etkin göstermiş olacaktır. Form hakkındaki bilgi “ESTUDAM İnfeksiyon Dergisi: An inflammation form SMILEYS, for clinical use, grounded on Claus Steuernagel concept, 2018 (1): yayına Kabul edilmiştir”. NOT: Bu makale çift dil ile yazılmış olup, tercüme yapılmamıştır.*

*Eng. Once upon a time, the past, your studies that you done, will be then, discussed, the position where you were and now where your decision is. SMILES Form is evaluated under these circumstances at “ESTUDAM İnfeksiyon Dergisi: An inflammation form SMILEYS, for clinical use, grounded on Claus Steuernagel concept, 2018 (1): accepted for publication”. NB: This is a bilingual writing not a translation.*

**S**MILES formu, infeksiyon ve inflamasyon konusunda bir sorunu irdeleyerek, sorunun boyutu anlamında bir klinik fikir vermesi için oluşturulmuştur. Tüm parametreleri bir arada olması hedeflenmektedir. EMR bu Ünite de incelenmektedir.

Thus, SMILES Form for evaluation of inflammation and infection parameters altogether. PPRM is the one that is evaluated at this Unit.

## Özet

### **Prematür Erken Membran Rüptürü olgularının Steuernagel çizelgesinden dayanılarak hazırlanan Forma göre yorumu**

**Amaç:** EMR (Erken Membran Rüptürü), gebelikte karşılaşılan ve zarın zamanında önce patlaması, yarılması ile oluşan bir durum ile, bebeğin doğmak zorunda kalmasıdır. Bu durumun temel anlamda bir infeksiyon ve inflamasyon mekanizması olduğu, oluşturulan SMILES formu ile gösterilmeye edilmeye çalışılmıştır.

**Dayanaklar/Kaynaklar:** Claus Steuernagel Formun Web kaydı ile, Wikipedia'dan sorunların irdelenmesi ve Prag, Perinatoloji Kongresi Sözlü Sunum temel alınmıştır.

**Genel Yaklaşım:** Bu Formda, inflamasyon mekanizmaları IMBALANCE, doku sorunları FUNCTIONAL ve olayın ciddiyeti NOTABLE bir düzen içinde toplu olarak irdelenmekte, bulunan sorunlara göre elde edilen puanlar işlenmektedir. Bunların oluşumu mekanizmaya göre yerleştirilip, klinik elde edilenler arasında değerlendirme yapılmaktadır.

**Yaklaşım:** EMR olan ve olmayan ile, inflamasyon bulgusu olan ile olmayan karşılaştırması, hem gebe, hem bebeklerin verilerine göre irdelenmiş ve ayrıca klinik veya laboratuvaradaki şiddete göre de irdeleme yapılmıştır.

**Sonuç:** EMR'si olanlarda prematüre doğum %54,4, Sistemik inflamasyon cevap sendromu (SICS) %27,2, Mortalite, 6,6%, inflamasyon reaksiyonları %81,8, hafif sorunlar %77,7, ağır sorunlar 44,5 olup, sorun tanımlanmayanlar ise %18,2 olduğu gözlenmiştir.

**Yorum:** EMR olan gebelerin ve çocukların, oldukça karmaşık sorunları olduğu, bunların tek başına prematüre doğum ile bağdaştırılamayacağı anlaşılmaktadır. EMR bir inflamasyon sorundur denilebileceği düşünülmektedir.

**Anahtar Kelimeler:** Erken Membran Rüptürü, İnflamasyon, SMILES Formu

## Outline

### **The PPRM (Preterm Rupture of Early Membrane) is considered by Steuernagel grounding Form**

**AIM:** PPRM (Preterm, Premature Rupture of Membrane), is a serious problem at the pregnancy. This is condition, considered as inflammation and infection reasoning, as evaluated by SMILES Form.

**Grounding Aspects:** Claus Steuernagel Form, Wikipedia and Oral Presentation at Prague, Perinatology Congress evidences are considered.

**Introduction:** This form considers the inflammation mechanisms as IMBALANCE, tissue problems as; FUNCTIONAL, the severity of the problems as NOTABLE, under the individual confirmation at the same form, by given notes from 0 to 10.

**Notions:** The PPRM positive cases/pregnancies; preterm labour 54,4%, Systemic Inflammation Response Syndrome (SIRS) 27,2%, Mortality 6,6%, inflamasyon reactions 81,8%, minimal complaints 77,7%, severe problems 44,5%, thus, no noticeable findings 18,2%.

**Results and Conclusion:** The findings indicate that, PPRM is an inflammation Reaction.

evaluations not as some standard rules, evaluated for individual perspective, the most point of inflection time is the adolescent period. This period, from the childhood to the rest of life, makes the way of living, thus, love is the only positive developing aspect at all of them.

**Key Words:** PPRM and Inflammation Reactions, SMILES Form

## Giriş/Introduction

TR. EMR (Erken Membran Ruptürü) olan ve olmayan olguları geriye dönük, dosyalardan incelenmiş, formda sorunları olanların Neonatal anlamda da sorun yarattığı gözlenmiştir. Bu açıdan daha önce Sözel Bildiri olarak sunulan çalışmanın, yeniden irdelenmesi amaçlanmıştır. Amaçlanan tüm infeksiyon-inflamasyon parametrelerini birlikte ele alınabilmesini sağlamaktır.

Eng. Preterm Premature Rupture of Membranes, are not just a single complaint, effect to the Newborn infant, thus, a reasoning of cumulative problems. This Oral Presentation is discussed afterwards, for new evaluation perspective.

## Method / Metot

TR. EMR olan ve olmayan ve doğum yapmış annelerin dosyaları ile bebeklerin dosyaları hazırlanan SMILES formu temelinde incelenmiştir. Herhangi bir eliminasyon yapılmadan, 10 dosya alınarak değerlendirme yapılmıştır.

Sorunlu gebeliklerin Üniversite Perinatoloji Bilim Dalı ile Neonatoloji Yoğun Bakım Ünitesi olan Neonatoloji Bilim Dalında yüksek olması doğal karşılanmalıdır.

Eng. The pregnant women are taken and follow-up the deliveries, for two weeks. The women put it into two groups, PPRM positive and negative, without any eliminations or making any limitations. The charts are taken from the Eskişehir Osmangazi University, infants charts form Neonatology Department and women charts are taken Perinatology Department in cooperation. 100 charts of patients' charts are taken, by in order. 50 PPRM and 50 other deliveries.

The other group, negative for PPRM, pregnant women, have such more problems, might be due to the University Hospital Perinatology Department, mostly referred cases.

The Form SMILES

**CHART 1/A: Evaluation of the Inflammation by immunologic mechanisms, SMILES**

**CHART 1/B: Evaluation of the inflammation by immunologic mechanisms, SMILES**

**Figure/Şekil 1: İnflamasyonu çok yönlü formu / Findings at the Inflammation**

The forms for the evaluation perspectives are (SMILES);

- 1) S: Severity of the inflammation (NOTABLE)
- 2) M: Mechanisms of the inflammation (IMBALANCE)
- 3) I: Inflammation outcome: clinical findings (FUNCTIONAL)
- 4) L: FORM: Laboratory results
- 5) E: FORM: Estimation of the inflammation
- 6) S: FORM: Score, obtained, and evaluation

Değerlendirme SMILES Formu üzerinden yapılmıştır

- 1) S: Severity, İnflamasyonun Ciddiyet durumu (NOTABLE)
  - 2) M: İnflamasyon Mekanizmaları (IMBALANCE)
  - 3) I: İnflamasyonun klinik bulguları (FUNCTIONAL)
  - 4) L: FORM: Laboratuvar sonuçları
  - 5) E: FORM: İnflamasyonda öngörüler
- S: FORM: Skor, değerlendirme puanı

The severity (NOTABLE) of the results;

Clinical Findings according to Severity			Causative Tissue Reactions/Cellular Response				
LEVEL	Positive	CLINICAL INDICATION					
N	- 0	Negative result					
O	?	O level, not taken, not known the result					
T	+	Trigger level, Sub clinical, under required level					
A	++	Appearance of disease and/or laboratory results (Recorded level)					
B	+++	Brief evident, obvious level, diagnostic findings					
L	++++	Label of disease, indicative, diagnostic clinical and/or laboratory finds					
E	+++++	Excess, overindulgence, mortal					
			<b>Slight</b>	<b>1</b>	<b>2</b>	<b>4</b>	<b>6</b>
			<b>Moderate</b>	<b>3</b>	<b>4</b>	<b>6</b>	<b>8</b>
			<b>Severe</b>	<b>4</b>	<b>7</b>	<b>9</b>	<b>10</b>
				<b>Minimal</b>	<b>Recordable</b>	<b>Severe</b>	<b>Necrosis/shock</b>

**Figure 2:** Evidence or Causative Factor and Tissue Response

The inflammation Mechanisms. IMBALANCE	İnflamasyon Mekanizmaları (IMBALANCE)
1) I: Infection	1) I: İnfeksiyon
2) M: Mediatör Release	2) M: Mediatör Salınımı
3) B: Blood Coagulation	3) B: Kan Pıhtılaşması
4) A: Apoptosis	4) A: Apoptoz
5) L: Labile, super-antigen	5) L: Dengesiz, süper antijen, anafilaksi
6) A: Antigen Presentation	6) A: Antijen Sunumu
7) N: Neutrophil Activation	7) N: Nötrofil aktivasyonu
8) C: Complement System	8) C: Kompleman Sistemi
9) E: Effect on Tissue	9) E: Doku Etkileşimi

TR. İnflamasyon mekanizmaları tüm mekanizmaları içine alacak şekilde tanımlanmıştır. Bunun genel bilgi olarak sunumu, önceki Yayında iletilmektedir.

Bu verilerin dışında klasik veri olan şişme, kızarıklık, işlev kaybı ve ağrı ötesinde diğer anafilaksi gibi parametreler ile CRP gibi boyutlarda çizelge içinde mevcuttur. Bunlar da oluşumlara göre tanımlanmakta, kısaca uzmanlık, hekimlik boyutu gerekli olmaktadır.

Eng. The findings can be easily being added under the SMILES Form. Thus, this is a physician perspective is required. It is a professional chart for expert use.

## Physio-pathological stages, FUNCTIONAL/

Clinical Findings according to Severity		
1. F	Functional variations	Biological variation: Variations between the gestational ages and infants.
2. U	Unacceptable adaptation	Physiological adaptations try to control: Adaptation mechanisms, stimulus and feedback forced to control the body.
3. N	Non destructive disturbances	Functional disturbance: Increase in respiration, deep breathing, heart rate etc. No any injury. Metabolic activity increases.
4. C	Compensation period	Compensation: Compensatory phase of acidosis and alkalosis. Metabolic problems.
5. T	Tissue reactions started	Reaction of tissues started: Vasoconstriction, pooling, interstitial edema, central flowing of blood and systemic inflammatory reactions started.
6. I	Impairments noticed	Disturbances begin Cellular functions will be delayed, halted, ineffective and reactive states (e.g. Hypoxic Ischemic Encephalopathy (HIE) begin.
7. O	Oxidative Stress and Degeneration	Degeneration Vacuolar, hydropic cells and vasogenic edema develops. Histo-pathological findings are noticed. Changes in mitochondria
8. N	Noticeable findings	Clinical inflammation reactions are noticed: Fever, swelling, pain, etc are encountered.
9. A	Abnormal tissue reactions	Tissue reactions Tissue reactions, degenerations, hemorrhages, scleredema, cytostatic edema, Graft Versus Host, fibrosis.
10. L	Lysis Cell and/or tissue death	Cell and/or tissue death Lyses of erythrocytes, necrosis.

**Figure 3:** Stages of Clinical Findings and physio-pathological conditions

## Findings / Bulgular

TR. Bulgular konusunda irdeleme fazla yapılmayacaktır. Burada sorunlu olan gebelerinkine benzer sorunların tanımlandığı vurgusu belirgindir.

Eng. The findings are discussed under the form SMILES. When considered the complaints of the pregnant women, they are diversity as noticed. Thus, mother indicates less problems, but, infants have a lot.

### The Complaints/Sorunlar

TR. Bulguları olan annelerin sadece EMR olması ve %10 altında yakınma göstermeleri tanımlanan sorunların pre-eklampsi ve diyabet gibi tüm sistemleri etkilediği ve hematolojik sorunlarında önemli boyut olduğu gösterilmektedir. Ancak bunların EMR açıklamaktan uzaktır, onda bir olması ile başka boyutlara bakılmasını gerekli kılmaktadır.

Genel yenidoğan sorunlarına bakılınca: solunum sistemi, karaciğer, nörolojik, hematolojik ve gelişme geriliği olduğu görülmektedir. Kısaca tüm vücut yapısını etkilemektedir. Anomali görülmesini, bu sorun ile bağlamak çok akılcı olmayacaktır, ancak Gastro-intestinal sistem ve gangliyon oluşumundaki gerilik boyutu da dikkate alınmalıdır.

Gebede az problem tanımlansa bile, bu problemler sorunlar açanlardan olmaktadır. Çocuklardaki sorunların geniş yoğunlukta olması bu kanıyı desteklemektedir EMR bulgusu olmayan annelere/gebelere de bakılacak olunursa; benzer neticelerin olduğu görülmektedir.

Eng. Eclampsia-Preeclampsia must be a combination of problems. Thus, Diabetic/glucose intolerance is also a major problem, leads lot problems to infants

When considering the problems, it seems that, all might be a result or reasoning of inflammation reactions. Thus, several organ System involved.



## Comparison of PPROM (-) and (+) mothers &amp; infants / EMR (-) ve (+) anne-bebek sorunları

PROM POZİTİVE (n 44)				PROM NEGATİVE (n 56)							
MOTHERS		INFANTS		MOTHERS		INFANTS					
Findings	n-%	Findings	n-%	Findings	n-%	Findings	n-%				
Early	Preeclampsia Hematological Diabetic	4-9.1 4-9.1 1-2.3	Early	Preterm Resp Problems RDS, MAS Bilirubinemia SIRS, sepsis Neurological Metabolic Hematological Mortality IUGR Anomaly	24-54.5 23-52.2 17-38.6 16-36.3 12-27.2 8-18.2 6-13.6 6-13.6 6-13.6 3-6.8 2-4.5	Early	Urinary Infec Preeclampsia Rh/rh Hematological Diabetic Metabolic Asthma Cardiac Prob Hepatitis Ablatio Placenta Oligohydramnios	7-12.5 5-9.0 3-5.4 2-3.6 2-3.6 1-1.8 1-1.8 1-1.8 1-1.8 1-1.8 1-1.8	Early	Bilirubinemia Preterm Resp Problems Anomaly, Down RDS, MAS SIRS, sepsis ROP LGA Mortality Neurological Metabolic Prob Hematological Hidrops IUGR	21-37.6 18-32.2 11-19.7 10-17.9 6-10.74 6-10.74 5-9.0 5-9.0 4-7.2 3-5.4 3-5.4 2-3.6 2-3.6 1-1.8
1-2 w		1-2 w		1-2 w		1-2 w					
Late		Late	Conjunctivitis Diaper Dermatitis Hirschprung	1-2.3 1-2.3 1-2.3	Late		Late	Recurrent infections	1-1.8		

\* Preterm deliveries in PROM + 54.5 to Negative 32.2%  
 \* SIRS/sepsis in PROM + 27.2 to Negative 10.7%  
 \* Mortality in PROM + 6.6 to Negative 7.2%

Figure/Şekil 4: Gebelikte-doğum sonu sorunlar / Women-infant problems

## Yorum/Comment

TR. EMR saptanan gebelerde genel sistemik inflamasyon kanıtı olan pre-eklampsi gözlenmiştir. Üriner infeksiyon EMR gebelerde beklenirken, EMR olmayanda olması da semptomlarda uygunluk boyutu yoktur. Bu açıdan değerlendirmelerin özgün yerine genel yapılması daha anlamlı olacaktır.

Prematür doğumun daha yüksek olması ile solunum problemlerin fazla olması beklenen boyuttur. Mortalite benzerdir.

- Preterm doğumlar: EMR'si olan gebelerde %54,5 iken negatiflerde %32,2'dir
- SIRS/sepsis tanımlanma oranı: EMR'si olan gebelerde %27,2 iken negatiflerde %10,7'dir
- Solunum Sorunları: EMR'si olan gebelerde %82,2 iken negatiflerde %28,6'dir
- Mortalite Oranları: EMR'si olan gebelerde %6,6 iken negatiflerde %7,2'dir

Eng. There are nearly no differences seen, between the PPROM positive and negative infants. Let's consider some aspects:

- Preterm deliveries: PROM positive 54,5%, versus PROM negative 32,2%
- SIRS/Sepsis: PROM positive 27,2%, versus PROM negative 10,7%
- Respiratory Problems: PROM positive 82,2%, versus PROM negative 28,6%
- Mortality: PROM positive 6,6%, versus PROM negative 7.2%

Pulmonary maturation is mostly affected at PPROM. Thus, other problems are nearly same. Prematurity ration is 32.2/54.5, thus, respiratory problems are 28,6/82,2. Estimation might be, 57,2% for respiratory problems, thus nearly doubled, means PPROM.

## Sonuç/Conclusion

TR. EMR diğer preterm doğumlarda olduğu gib benzer sorunlar yaratmaktadır.

EMR yine inflamasyon olarak irdelemenin kavranması açısından yararlı olacağı anlaşılmaktadır. .

Eng. Even without PPROM one, the findings are nearly similar the findings. The predicts and findings are nearly common on the degree of the inflammation. We must confirm more knowledge, on PPROM for the exact decision make.

## Bilgi sorgulama/Knowledge on PPROM

### Premature rupture of membranes (Wikipedia)

**Premature rupture of membranes (PROM)**, or **pre-labor rupture of membranes**, is a condition that can occur in [pregnancy](#). It is defined as [rupture of membranes](#) (breakage of the [amniotic sac](#)), commonly called breaking of the mother's water(s), more than 1 hour before the onset of [labor](#).<sup>[1]</sup> The sac (consisting of 2 [membranes](#), the [chorion](#) and [amnion](#)) contains [amniotic fluid](#), which surrounds and protects the [fetus](#) in the [uterus](#) (womb). After rupture, the amniotic fluid leaks out of the uterus, through the [vagina](#).

Women with PROM usually experience a painless gush of fluid leaking out from the vagina, but sometimes a slow steady leakage occurs instead.

When premature rupture of membranes occurs at or after 37 weeks completed [gestational age](#) (full-term or term), there is minimal risk to the fetus and labor typically starts soon after.

If rupture occurs before 37 weeks, it is called preterm premature rupture of membranes (PPROM), and the fetus and mother are at greater risk for complications. PPROM causes one-third of all preterm births,<sup>[2]</sup> and babies born preterm (before 37 weeks) can suffer from the complications of prematurity, including death.

Premature rupture of the membranes provides a path for bacteria to enter the womb and puts both the mother and fetus at risk for life-threatening infection. Low levels of fluid around the fetus also increase the risk of [umbilical cord compression](#) and can interfere with lung and body formation in early pregnancy.<sup>[2]</sup>

Women who suspect they might have experienced premature rupture of membranes should be evaluated promptly in the hospital to determine whether a rupture of membranes has indeed occurred, and to be treated appropriately to avoid infection and other complications.

### Yorum/Comment

TR. Zarın. 2 membranı olduğu; koriyon ve amnion ise, bu ikisinin patlaması için, zarın esnekliği gibi yapısında bir değişikliğin olması gerekir. Doğumda bile bıçak ile patlatılması oldukça zor olan bir zarın kolaylıkla patlaması, zarın bir nedenle tutulduğu, eski çarşaflarda olduğu gibi, zayıflaması ve patlaması gereklidir. Bunun immün sistemde olan, genellikle nötrofil aktivasyonu ile beklediğimiz bir doku hasarı yapan mekanizma akla getirmektedir. Kısaca olgularımızda gözlenen pre-eklampsi acaba buna neden olabilir mi, sorusu sorulmalıdır.

Eng. There are two membranes; amnion and chorion. There must a reason for losing the strengthened these membranes. If we considered eclampsia or/and preeclampsia as a main reasoning at our cases, we must discuss this condition too.

### Classification

- Premature rupture of membranes (PROM): when the fetal membranes rupture early, at least one hour before labor has started.<sup>[3]</sup>
- Prolonged PROM: a case of premature rupture of membranes in which more than 24 hours has passed between the rupture and the onset of labor.<sup>[4]</sup>
- Preterm Premature Rupture of Membranes (PPROM): premature rupture of membranes that occurs before 37 weeks.
- Midtrimester PPROM or Pre-viable PPROM: premature rupture of membranes that occurs before 24 weeks completed gestational age of the fetus. Before this age, the fetus cannot survive outside of the mother's womb.<sup>[5]</sup>

### Yorum/Comment

TR. Zarın bir güç, basınç veya doğum eylemi ile patlaması değil, spontan patlaması olup, doğumun da bir gün kadar geç başlaması ile tanı konulmaktadır.

Eng. The concept is, membrane not rupture because of the pressure. The labor will be after 24 hours, meaning, PPROM triggered the labor.



## Signs and symptoms ...

### Risk factors

The cause of premature rupture of membranes (PROM) is not clearly understood, but the following are risk factors that have been shown to increase the chance of it happening. In many cases, however, no risk factor is identified.<sup>[6]</sup>

- Infections: [urinary tract infection](#), [sexually transmitted diseases](#), lower genital infections (ex: [Bacterial Vaginosis](#)),<sup>[3]</sup> infections within the amniotic sac membranes<sup>[1]</sup>
- Cigarette smoking during pregnancy<sup>[6]</sup>
- Illicit drug use during pregnancy<sup>[1]</sup>
- Having had PROM or preterm delivery in previous pregnancies<sup>[3]</sup>
- [Hydramnios](#): too much amniotic fluid<sup>[4]</sup>
- [Multiple gestation](#): being pregnant with two or more fetuses at one time<sup>[3]</sup>
- Having had episodes of bleeding anytime during the pregnancy<sup>[3]</sup>
- Invasive procedures (ex: [amniocentesis](#))<sup>[4]</sup>
- Nutritional deficits<sup>[6]</sup>
- [Cervical insufficiency](#): having a short or prematurely dilated cervix during pregnancy<sup>[4]</sup>
- Low socioeconomic status<sup>[6]</sup>
- Being underweight<sup>[6]</sup>

### Yorum/Comment

TR. Zarın erken delinme, patlamasının nedeninin sıklıkla medikal girişimler dışında, inflamasyon nedenli olduğu görülmektedir.

Eng. The accused parameters will not be satisfied for me, all can be united under some condition, as inflammation will be more prone for them. All the above parameters can lead inflammation reactions.

### Pathophysiology[edit]

10-week-old human fetus surrounded by amniotic fluid and fetal membranes

#### Weakened fetal membranes[edit]

Fetal membranes likely break because they become weak and fragile. This weakening is a normal process that typically happens at term as the body prepares for labor and delivery. But, this can be a problem when it occurs pre-term (before 37 weeks). The natural weakening of fetal membranes is thought to be due to one or a combination of the following. In premature rupture of membranes, these processes are activated too early:

- [Cell death](#): when cells undergo programmed cell death, they release chemical markers that are detected in higher concentrations in cases of PPROM.
- Poor assembly of [collagen](#): collagen is a molecule that gives fetal membranes their strength. In cases of PPROM, proteins that bind and cross-link collagen to increase its tensile strength are altered.
- Breakdown of collagen: collagen is broken down by enzymes called [matrix metalloproteinases \(MMPs\)](#), which are found at higher levels in PPROM amniotic fluid, this MMPs will break down the strength-bearing collagen, so [Prostaglandin](#) production will be synthesised in high amount to prompt the uterine contraction and cervical ripening . Matrix metalloproteinases are inhibited by [tissue inhibitors of matrix metalloproteinases \(TIMPs\)](#) which are found at lower levels in PPROM amniotic fluid.<sup>[6]</sup>

### Yorum/Comment

TR. Zar a) hücre ölümü, b) Kollajen gücünün zayıflaması, c) Kollajen yapının bozulması ve bazı enzimatik reaksiyonların olması ile lenfositlerin tetiklenerek inflamasyon nedeni olduğu belirtilebilir.

Eng. A) Cell death, B) loosening the collagen strength, and/or C) breakdown the collagen structure, must be some enzymatic reactions, which must be triggered from especially lymphocytes, causing such effects.

### Infection

Infection and inflammation likely explains why membranes break earlier than they are supposed to. In studies, bacteria have been found in the amniotic fluid from about one-third of cases of PROM. Often, testing of the amniotic fluid is normal, but a subclinical infection (too small to detect) or infection of maternal tissues next to the amniotic fluid, may still be contributing. In response to infection, the body creates inflammation by making chemicals (ex: [cytokines](#)) that weaken the fetal membranes and put them at risk for rupture.<sup>[6]</sup> Premature rupture of membranes is also a risk factor in the development of [neonatal infection](#).

## Yorum/Comment

TR. Zarın parçalanmasının infeksiyon ve inflamasyona bağlı olması açık ifadelerle belirtilmektedir.

Eng. The infection is a reasoning or a causative factor. After some period is passed, secondary infection is obvious. Even taken cultures are really a cause? PCR studies must confirm reality. There must be some time for making EMR, effects on the membrane. My assume; infection cultured ration  $1/3^{rd}$ , secondary cultures, depending the time, each division of the bacteria require 20 minutes, geometric growth, so needs 6-8 hours, afterwards 12-24 hours for infection. Thus, the main cause of bacteria might be  $1/3^{rd}$  cultured one, means  $1/10^{th}$  for all the cases. Thus inflammation mediators, cytokines, interleukins and other parameters must be nearly all of them.

### Genetics

Many genes play a role in inflammation and collagen production, therefore inherited genes may play a role in predisposing a person to PROM.<sup>[6]</sup>

### Diagnosis ...

Extra tests ...

False positives ...

Differential diagnosis ...

## Yorum/Comment

TR. Zarın genetik olarak zayıf olma durumu olsa da, bunu temel açıklayıcı olamayacağı belirgindir.

Eng. The blasting of the membrane, flowing of the fluid, is really a chock for the mother. Pregnancy is hoping to have healthy newborn; thus, problems are waiting, day and night, not quite sure about the outcome of the infant. False alarming will be a best happening entire her life. Thus, some reasons are worse, than expected.

### Prevention

Women who have had premature rupture of membranes (PROM) are more likely to experience it in future pregnancies.<sup>[1]</sup> There is not enough data to recommend a way to specifically prevent future PROM. However, any woman that has had a history of preterm delivery, because of PROM or not, is recommended to take [progesterone supplementation](#) to prevent preterm birth recurrence.<sup>[1][4]</sup>

### Management

... As of 2012, the Royal College of Obstetricians and Gynaecologists advised, based on expert opinion and not clinical evidence, that attempted delivery during maternal instability, increases the rates of both [fetal death](#) and [maternal death](#), unless the source of instability is an [intrauterine infection](#).<sup>[8]</sup>

... At any age, if the fetal well-being appears to be compromised, or if intrauterine infection is suspected, the baby should be delivered quickly by [artificially stimulating labor \(induction of labor\)](#).<sup>[1][5]</sup>

## Yorum/Comment

TR. Zarın patlamasının önlenmesi açısından infeksiyon ve doal olarak inflamasyonun engellenmesi önemlidir.

Eng. The evaluation is from bird-view. The discussion grounding on the findings, just following the road. Not making some controlling, just follow, and making the treatment. The only way of early estimations with hope is cortisone ([Steroids before birth](#): corticosteroids ([betamethasone](#)) given to the mother of a baby at risk of being born prematurely can speed up fetal lung development and reduce the risk of death of the infant, [respiratory distress syndrome](#), [brain bleeds](#), and [bowel death](#).<sup>[1]</sup>), thus, requires some time for efficient of this drug, medicine. This is a paradox, infection versus maturation as considered, as “the use of [tocolytic medications](#) to prevent labor contractions is controversial. On the one hand, this can delay delivery and allow the fetus more time to develop and benefit from [antenatal corticosteroid medication](#), on the other hand it increases the risk of infection/[chorioamnionitis](#). The use of tocolysis has not shown to benefit mom or baby and currently there is not enough data to recommend or discourage its use in the case of preterm PROM.<sup>[1][2]’</sup> .

**PROM at term**

... If a woman strongly does not want to be induced, watchful waiting is an acceptable option as long as there is no sign of infection, the fetus is not in distress, and she is aware and accepts the risks of prolonged PROM.<sup>[1]</sup> There is not enough data to show that the use of prophylactic antibiotics (to prevent infection) is beneficial for mothers or babies at or near term. Because of the potential side effects and development of antibiotic resistance, the use of antibiotics without the presence of infection is not recommended in this case.<sup>[9]</sup>

**PPROM greater than 34 weeks**

When the fetus is premature (< 37 weeks), the risk of being born prematurely must be weighed against the risk of prolonged membrane rupture. As long as the fetus is 34 weeks or greater, delivery is recommended as if the baby was term (see above).<sup>[1][3]</sup>

**PPROM less than 34 weeks**

Before 34 weeks, the fetus is at a much higher risk of the complications of prematurity. Therefore, as long as the fetus is doing well, and there are no signs of infection or [placental abruption](#), watchful waiting (expectant management) is recommended.<sup>[1]</sup>

...

**Yorum/Comment**

TR. Zarın delinmesi doğrudan enfeksiyona bağlı değil, inflamasyonun oluşması etkin olmaktadır. PCR ile saptanma oranı 1/10 iken, 3/10 bakteri üretebilir, ancak tanısal boyut inflamasyon mekanizmaları ile açıklanabilir.

Eng. The thought that I estimated, this is a natural way of expulsion of a fetus, by inflammation mechanisms. Early means, the maturation is not confirmed, the reactions are so extensive, diffuse, thus, cannot be survived even in utero. When maturation over 36 gestational age, the maturation is nearly complete, thus problems of the infants will be less, apart of the other inflammation reactions, might be lower than the early one.

**Recommended**

- **Monitoring for infection:**
- **Steroids before birth:** corticosteroids ([betamethasone](#)) given to the mother of a baby at risk of being born prematurely can speed up fetal lung development and reduce the risk of death of the infant, [respiratory distress syndrome](#), [brain bleeds](#), and [bowel death](#).<sup>[1]</sup> It is recommended that mothers receive one course of corticosteroids between 24 and 34 weeks when there is a risk of preterm delivery. In cases of PPRM these medications do not increase the risk of infection even though steroids are known to suppress the immune system. ...
- **Magnesium sulfate:** ...
- **Latency Antibiotics:** The time from rupture of membranes to labor is termed the latency period, and there is an inverse relationship between gestational age and the length of latency, meaning that the earlier the rupture, the longer it will take for labor to begin naturally.<sup>[3]</sup> As expected, antibiotics given to mothers that experience PPRM serve to protect against infections during this lengthened latency period. Additionally, antibiotics increase the time that babies stay in the womb. Antibiotics don't seem to prevent death or make a difference in the long-term (years after the baby is born). But, because of the short-term benefits, routine use of antibiotics in PPRM is still recommended.<sup>[1]</sup> The [American College of Obstetricians and Gynecologists](#) (ACOG) recommends a seven-day course of intravenous [ampicillin](#) and [erythromycin](#) followed by oral [amoxicillin](#) and erythromycin if watchful waiting is attempted before 34 weeks.<sup>[1]</sup> [Amoxicillin-clavulanic acid](#) increases the risk of fetal bowel death ([necrotizing enterocolitis](#)) and should be avoided in pregnancy.<sup>[1]</sup>
- **Prophylactic Antibiotics:** If a woman is colonized with group B strep, than the typical use of antibiotics during labor is recommended to prevent transmission of this bacteria to the fetus, regardless of earlier treatments.<sup>[1]</sup>

**Controversial or not recommended**

- **Preventative tocolysis (medications to prevent contractions):** ...
- **Therapeutic tocolysis (medications to stop contractions):** ...
- **Amnioinfusion:** ...
- **Home care:** ...
- **Sealing membranes after rupture:** Infection is the major risk associated with PROM and PPRM.<sup>[14]</sup> By closing the ruptured membranes, it is hoped that there would be a decrease in infection, as well as encouraging the re-accumulation of amniotic fluid in the uterus to protect the fetus and allow for further lung development. When compared to the current standard of care, both mechanical sealing and stimulating the mother's immune system to repair the membranes (immunological sealing) fail to provide strong evidence of improved maternal or neonatal outcomes.<sup>[15]</sup>

### Pre-viable PPROM

Before 24 weeks, a fetus is not viable meaning it cannot live outside the mother. In this case, either watchful waiting at home or an induction of labor done.<sup>[1]</sup>

Because the risk of infection is so high, the mother should check her temperature often and return to the hospital if she develops any signs or symptoms of infection, labor, or vaginal bleeding. These women are typically admitted to the hospital once their fetus reaches 24 weeks and then managed the same as women with PPROM before 34 weeks (discussed above). When possible, these deliveries should take place in a hospital that has expertise in the management of the potential maternal and neonatal complications, and has the necessary infrastructure in place to support the care of these patients (ie. neonatal intensive care unit).<sup>[1,6]</sup> Antenatal corticosteroids, latency antibiotics, magnesium sulfate, and tocolytic medications are not recommended until the fetus reaches viability (24 weeks).<sup>[1]</sup> In cases of pre-viable PPROM, chance of survival of the fetus is between 15-50%, and the risk of chorioamnionitis is about 30%.<sup>[4]</sup>

### Chorioamnionitis

**Chorioamnionitis** is a bacterial infection of the fetal membranes, which can be life-threatening to both mother and fetus. Women with PROM at any age are at high risk of infection because the membranes are open and allow bacteria to enter. Women are checked often (usually every 4 hours) for signs of infection: fever ( > 38 °C/100.5 °F), uterine pain, fast maternal heart rate (>100 beats per minute), fast fetal heart rate (>160 beats per minute), or foul smelling amniotic fluid.<sup>[6]</sup> Elevated white blood cells are not a good way to predict infection because they are normally high in labor.<sup>[4]</sup> If infection is suspected, artificial induction of labor is started at any gestational age and broad antibiotics are given. **Cesarean section** should not be automatically done in cases of infection, and should only be reserved for the usual fetal emergencies.<sup>[4]</sup>

### Outcomes ...

#### Infection (any age)

At any gestational age, an opening in the fetal membranes provides a route for bacteria to enter the womb. This can lead to **chorioamnionitis** (an infection of the fetal membranes and amniotic fluid) which can be life-threatening to both the mother and fetus.<sup>[3]</sup> The risk of infection increases the longer the membranes remain open and baby undelivered.<sup>[1]</sup> Women with preterm PROM will develop an intramniotic infection 15-25% of the time, and the chances of infection increase at earlier gestational ages.<sup>[1]</sup>

#### Pre-term birth (before 37 weeks)

#### Fetal development (before 24 weeks)

#### PROM after second-trimester amniocentesis

... Compared to spontaneous PROM, about 70% of women will have normal amniotic fluid levels within one month, and about 90% of babies will survive.<sup>[1]</sup>

### Epidemiology

PROM occurs in about 10-12% of all births in the United States.<sup>[1][3][4]</sup> Of all term pregnancies (> 37 weeks) about 8% are complicated by PROM,<sup>[6]</sup> 20% of these become prolonged PROM.<sup>[4]</sup> About 30% of all preterm deliveries (before 37 weeks) are complicated by PPROM, and rupture of membranes before viability (before 24 weeks) occurs in less than 1% of all pregnancies.<sup>[1]</sup> Since there are significantly fewer preterm deliveries than term deliveries, the number of PPROM cases make up only about 5% of all cases of PROM.<sup>[4]</sup>

### Yorum/Comment

TR. Zarın patlaması açısından çoklu vurgu olsa da, tümü inflamasyon tanımında bütünleşmektedirler.

Eng. There are several diverse and different problems, means the infant must be taken care in Intensive Care Unit of the Newborn and needs Neonatology Proficiency.

### Sonuç /Conclusion

TR. Zarın patlaması, doğal olarak çok zor ve imkansız gibi olduğu, doğumda bıçak ile patlatmak bile zor iken, onun delik deşik olarak, kolay yırtılması, inflamasyon sonucunu belirttiğini en doğrusu olacaktır.

Eng. The Premature Rupture of the Membranes is somehow, a life and death border. Careful and know what to do, is main and only way to go. Thus, requires special and professionally acting Intensive Care Unit, with all the medical staff.

### Pre-eclampsia (Wikipedia)

**Pre-eclampsia (PE)** is a disorder of **pregnancy** characterized by the onset of **high blood pressure** and often a significant amount of **protein in the urine**.<sup>[1][8]</sup> The condition begins after 20 **weeks of pregnancy**.<sup>[2][3]</sup> In severe disease there may be **red blood cell breakdown**, a **low blood platelet count**, impaired liver function, kidney dysfunction, **swelling**, **shortness of breath due to fluid in the lungs**, or visual disturbances.<sup>[2][3]</sup> Pre-eclampsia increases the risk of poor outcomes for both the mother and the baby.<sup>[3]</sup> If left untreated, it may result in **seizures** at which point it is known as **eclampsia**.<sup>[2]</sup>

Risk factors for pre-eclampsia include [obesity](#), prior [hypertension](#), older age, and [diabetes mellitus](#).<sup>[2][4]</sup> It is also more frequent in a woman's first pregnancy and if she is carrying twins.<sup>[2]</sup> The underlying mechanism involves abnormal [formation of blood vessels in the placenta](#) amongst other factors.<sup>[2]</sup> Most cases are diagnosed before delivery. Rarely, pre-eclampsia may begin in the [period after delivery](#).<sup>[3]</sup> While historically both high blood pressure and protein in the urine were required to make the diagnosis, some definitions also include those with hypertension and any associated organ dysfunction.<sup>[3][9]</sup> Blood pressure is defined as high when it is greater than 140 mmHg [systolic](#) or 90 mmHg [diastolic](#) at two separate times, more than four hours apart in a woman after twenty weeks of pregnancy.<sup>[3]</sup> Pre-eclampsia is routinely screened for during [prenatal care](#).<sup>[10][11]</sup> Recommendations for prevention include: [aspirin](#) in those at high risk, [calcium supplementation](#) in areas with low intake, and treatment of prior hypertension with medications.<sup>[4][5]</sup> In those with pre-eclampsia delivery of the baby and [placenta](#) is an effective treatment.<sup>[4]</sup> When delivery becomes recommended depends on how severe the pre-eclampsia and how far along in pregnancy a person is.<sup>[4]</sup> [Blood pressure medication](#), such as [labetalol](#) and [methyldopa](#), may be used to improve the mother's condition before delivery.<sup>[6]</sup> [Magnesium sulfate](#) may be used to prevent eclampsia in those with severe disease.<sup>[4]</sup> Bedrest and salt intake have not been found to be useful for either treatment or prevention.<sup>[3][4]</sup> Pre-eclampsia affects 2–8% of pregnancies worldwide.<sup>[4]</sup> [Hypertensive disorders of pregnancy](#) (which include pre-eclampsia) are one of the most common causes of death due to pregnancy.<sup>[9]</sup> They resulted in 46,900 deaths in 2015.<sup>[7]</sup> Pre-eclampsia usually occurs after 32 weeks; however, if it occurs earlier it is associated with worse outcomes.<sup>[6]</sup> Women who have had pre-eclampsia are at increased risk of [heart disease](#) and [stroke](#) later in life.<sup>[10]</sup> The word eclampsia is from the Greek term for lightning.<sup>[12]</sup> The first known description of the condition was by [Hippocrates](#) in the 5th century BC.<sup>[12]</sup>

## Yorum/Comment

TR. Pre eklampsi konusunda da inflamasyonun önemi belirginidir. Zarın erken patlamasının gerekçesi de aynı mekanizma olması, beklenmesi doğaldır.

Eng. This problem is one of the most precautions to take, at the Obstetrics. So broad perspective, so different causative and grounding aspects, that can be lead plural problems, and be swift at the knowledge, by the only person, the woman, the pregnant.

## Signs and symptoms ...

### Causes

There is no definitive known cause of pre-eclampsia, though it is likely related to a number of factors. Some of these factors include:<sup>[2][10]</sup>

- Abnormal [placentation](#) (formation and development of the placenta)
- Immunologic factors
- Prior or existing maternal pathology – pre-eclampsia is seen more at a higher incidence in individuals with preexisting [hypertension](#), obesity, [antiphospholipid antibody syndrome](#), and those with history of pre-eclampsia
- Dietary factors, e.g. calcium supplementation in areas where dietary calcium intake is low has been shown to reduce the risk of pre-eclampsia<sup>[4]</sup>
- Environmental factors, e.g. air pollution<sup>[13]</sup>

Those with long term [high blood pressure](#) have a risk 7 to 8 times higher than those without.<sup>[14]</sup>

Physiologically, research has linked pre-eclampsia to the following physiologic changes: alterations in the interaction between the maternal immune response and the placenta, placental injury, [endothelial](#) cell injury, altered vascular reactivity, oxidative stress, imbalance among [vasoactive](#) substances, decreased intravascular volume, and [disseminated intravascular coagulation](#).<sup>[10][15]</sup>

While the exact cause of pre-eclampsia remains unclear, there is strong evidence that a major cause predisposing a susceptible woman to pre-eclampsia is an abnormally implanted placenta.<sup>[2][10]</sup> This abnormally implanted placenta may result in poor uterine and placental perfusion, yielding a state of hypoxia and increased oxidative stress and the release of anti-angiogenic proteins along with inflammatory mediators into the maternal plasma.<sup>[10]</sup> A major consequence of this sequence of events is generalized [endothelial](#) dysfunction.<sup>[11]</sup> The abnormal implantation may stem from the maternal [immune system](#)'s response to the placenta, specifically a lack of established [immunological tolerance in pregnancy](#). Endothelial dysfunction results in hypertension and many of the other symptoms and complications associated with pre-eclampsia.<sup>[2]</sup> Those with pre-eclampsia may have a lower risk of breast cancer.<sup>[16]</sup>

Abnormal chromosome 19 microRNA cluster (C19MC) impairs extravillous trophoblast cell invasion to the spiral arteries, causing high resistance, low blood flow, and low nutrient supply to the fetus.<sup>[17][18][19]</sup>

## Yorum/Comment

TR. Anormal plasental işlev aynı şekilde, EMR içinde bir gerekçedir.

Eng. Controlling the endothelial dysfunction is not so easy, and each pregnant has several different perspectives, so you must select, which window is the one, for pass, not see, be taken control of the problem.

Placental function prime important, formation and development must be at least satisfactory. This problem might be grounding genetic, environmental and also immunological tolerance state or



active rejection is started. Endothelial injury, oxidative stress, poor blood supply, inflammation of the immune cells; leucocytes, especially lymphocytes, triggering of several immune reactions at numerous immune mechanisms.

#### Risk factors ...

#### Pathogenesis

Although much research into mechanism of pre-eclampsia has taken place, its exact pathogenesis remains uncertain. Pre-eclampsia is thought to result from an abnormal placenta, the removal of which ends the disease in most cases.<sup>[2]</sup> During normal pregnancy, the placenta vascularizes to allow for the exchange of water, gases, and solutes, including nutrients and wastes, between maternal and fetal circulations.<sup>[15]</sup> Abnormal development of the placenta leads to poor placental perfusion. The placenta of women with pre-eclampsia is abnormal and characterized by poor trophoblastic invasion.<sup>[15]</sup> It is thought that this results in oxidative stress, hypoxia, and the release of factors that promote endothelial dysfunction, inflammation, and other possible reactions.<sup>[1][15][25]</sup>

The clinical manifestations of pre-eclampsia are associated with general endothelial dysfunction, including vasoconstriction and end-organ ischemia.<sup>[15]</sup> Implicit in this generalized endothelial dysfunction may be an imbalance of [angiogenic](#) and [anti-angiogenic](#) factors.<sup>[2]</sup> Both circulating and placental levels of [soluble fms-like tyrosine kinase-1](#) (sFlt-1) are higher in women with pre-eclampsia than in women with normal pregnancy.<sup>[15]</sup> sFlt-1 is an anti-angiogenic protein that antagonizes [vascular endothelial growth factor](#) (VEGF) and [placental growth factor](#) (PlGF), both of which are proangiogenic factors.<sup>[10]</sup> Soluble [endoglin](#) (sEng) has also been shown to be elevated in women with pre-eclampsia and has anti-angiogenic properties, much like sFlt-1 does.<sup>[15]</sup>

Both sFlt-1 and sEng are upregulated in all pregnant women to some extent, supporting the idea that hypertensive disease in pregnancy is a normal pregnancy adaptation gone awry. As natural killer cells are intimately involved in placentation and placentation involves a degree of [maternal immune tolerance](#) for a foreign placenta, it is not surprising that the maternal immune system might respond more negatively to the arrival of some placentae under certain circumstances, such as a placenta which is more invasive than normal. Initial maternal rejection of the placental cytotrophoblasts may be the cause of the inadequately remodeled [spiral arteries](#) in those cases of pre-eclampsia associated with shallow implantation, leading to downstream hypoxia and the appearance of maternal symptoms in response to upregulated sFlt-1 and sEng.

Oxidative stress may also play an important part in the pathogenesis of pre-eclampsia. The main source of reactive oxygen species (ROS) is the enzyme [xanthine oxidase](#) (XO) and this enzyme mainly occurs in the liver. One hypothesis is that the increased purine catabolism from placental hypoxia results in increased ROS production in the maternal liver and release into the maternal circulation that causes endothelial cell damage.<sup>[26]</sup>

Abnormalities in the maternal [immune system](#) and insufficiency of [gestational immune tolerance](#) seem to play major roles in pre-eclampsia. One of the main differences found in pre-eclampsia is a shift toward [Th<sub>1</sub> responses](#) and the production of [IFN- \$\gamma\$](#) . The origin of IFN- $\gamma$  is not clearly identified and could be the [natural killer cells](#) of the uterus, the placental dendritic cells modulating responses of [T helper cells](#), alterations in synthesis of or response to regulatory molecules, or changes in the function of [regulatory T cells](#) in pregnancy.<sup>[27]</sup> Aberrant immune responses promoting pre-eclampsia may also be due to an altered fetal allorecognition or to inflammatory triggers.<sup>[27]</sup> It has been documented that fetal cells such as fetal [erythroblasts](#) as well as [cell-free fetal DNA](#) are increased in the maternal circulation in women who develop pre-eclampsia. These findings have given rise to the hypothesis that pre-eclampsia is a disease process by which a placental lesion such as hypoxia allows increased fetal material into the maternal circulation, that in turn leads to an [immune response](#) and endothelial damage, and that ultimately results in pre-eclampsia and eclampsia.

One hypothesis for vulnerability to pre-eclampsia is the maternal-fetal conflict between the maternal organism and fetus.<sup>[28]</sup> After the first trimester trophoblasts enter the spiral arteries of the mother to alter the spiral arteries and thereby gain more access to maternal nutrients.<sup>[28]</sup> Occasionally there is impaired trophoblast invasion that results in inadequate alterations to the uterine spiral arteries.<sup>[28]</sup> It is hypothesized that the developing embryo releases biochemical signals that result in the woman developing hypertension and pre-eclampsia so that the fetus can benefit from a greater amount of maternal circulation of nutrients due to increased blood flow to the impaired placenta.<sup>[28]</sup> This results in a conflict between maternal and fetal fitness and survival because the fetus is invested in only its survival and fitness while the mother is invested in this and subsequent pregnancies.<sup>[28]</sup>

Another evolutionary hypothesis for vulnerability to pre-eclampsia is the idea of ensuring pair-bonding between the mother and father and paternal investment in the fetus.<sup>[29]</sup> Researchers posit that pre-eclampsia is an adaptation for the mother to terminate investment in a fetus that might have an unavailable paternal donor, as determined by repeated semen exposure of the paternal donor to the mother.<sup>[29]</sup> Various studies have shown that women who frequently had exposure to partners' semen before conception had a reduced risk of pre-eclampsia.<sup>[29]</sup> Also, subsequent pregnancies by the same paternal donor had a reduced risk of pre-eclampsia while subsequent pregnancies by a different paternal donor had a higher risk of developing pre-eclampsia.<sup>[29]</sup>

In normal early embryonic development, the outer epithelial layer contains cytotrophoblast cells, a stem cell type found in the trophoblast that later differentiates into the fetal placenta. These cells differentiate into many placental cells types, including extravillous trophoblast cells. Extravillous trophoblast cells are an invasive cell type which remodel the maternal spiral arteries by replacing the maternal epithelium and smooth muscle lining the spiral arteries causing artery dilation. This prevents maternal vasoconstriction in the spiral arteries and allows for continued blood and nutrient supply to the growing fetus with low resistance and high blood flow.<sup>[17]</sup>

In pre-eclampsia, abnormal expression of chromosome 19 microRNA cluster (C19MC) in placental cell lines reduces extravillous trophoblast migration.<sup>[18][30]</sup> Specific microRNAs in this cluster which might cause abnormal spiral artery invasion include miR-520h, miR-520b, and 520c-3p. This impairs extravillous trophoblast cells invasion to the maternal spiral arteries, causing high resistance and low blood flow and low nutrient supply to the fetus.<sup>[17]</sup>

## Yorum/Comment

TR. Risk faktörleri de aynı şekilde EMR gerekçesine de uymaktadır.

Eng. Treatment is not so easy, thus, be ready for the severe problems. Pre-eclampsia is discussed even the grounding facts, because of PPRM and pre-eclampsia might be similar reasoning.

So, the placenta of women with pre-eclampsia is abnormal and characterized by poor trophoblastic invasion, is a causative factor of; oxidative stress, hypoxia, and the release of factors that promote endothelial dysfunction, inflammation, and other possible reactions.

Thus, natural killer cells are awakening, stimulated, involved in some degree of [maternal immune tolerance](#) for a foreign fetus, the fetal placental section. Such as a placenta which is more invasive than normal, Graft versus Host reaction, maternal rejection of the placental cytotrophoblasts may be the cause of the inadequately remodeled [spiral arteries](#) in those cases of pre-eclampsia associated with shallow implantation, leading to downstream hypoxia and the appearance of maternal symptoms. Same factors might be as reasoning of PPRM, as noticed also preeclampsia in such pregnant mothers.

Oxidative stress mostly reasoning or expecting process, for the pathogenesis of pre-eclampsia. Means endothelial damage, leads inflammation reactions.

The fact is indicated as; “Abnormalities in the maternal [immune system](#) and insufficiency of [gestational immune tolerance](#) seem to play major roles in pre-eclampsia.”

### Diagnosis ...

Diagnostic criteria ...

Predictive tests ...

Differential diagnosis ...

## Yorum/Comment

TR. Zarın patlayabilmesi için, kendisinin incelenmesi, zedelenmesi ve zaten patlayacak şekilde gelmesi gereklidir.

Eng. Diagnosis is seeming simple, but, the result for the medication will not be so sure on it.

### Prevention

#### Diet

... Supplementation with a balanced protein and energy diet does not appear to reduce the risk of pre-eclampsia.<sup>[36]</sup> Further, there is no evidence that changing [salt](#) intake has an effect.<sup>[37]</sup>

#### Aspirin

Taking [aspirin](#) is associated with a 1% to 5% reduction in pre-eclampsia and a 1% to 5% reduction in premature births in women at high risk.<sup>[51][42]</sup> The [World Health Organization](#) recommends low-dose aspirin for the prevention of pre-eclampsia in women at high risk and recommends it be started before 20 weeks of pregnancy.<sup>[39]</sup> The [United States Preventive Services Task Force](#) recommends a low-dose regimen for women at high risk beginning in the 12th week.<sup>[43]</sup> Benefits are less if started after 16 weeks.<sup>[44]</sup>

#### Physical activity

There is insufficient evidence to recommend either exercise<sup>[45]</sup> or strict bedrest<sup>[46]</sup> as preventive measures of pre-eclampsia.

#### Smoking cessation

In low-risk pregnancies, the association between cigarette [smoking](#) and a reduced risk of pre-eclampsia has been consistent and reproducible across epidemiologic studies. High-risk pregnancies (those with pregestational diabetes, chronic hypertension, history of pre-eclampsia in a previous pregnancy, or multifetal gestation) showed no significant protective effect. The reason for this discrepancy is not definitively known; research supports speculation that the underlying pathology increases the risk of preeclampsia to such a degree that any measurable reduction of risk due to smoking is masked.<sup>[47]</sup> However, the damaging effects of smoking on overall health and pregnancy outcomes outweighs the benefits in decreasing the incidence of preeclampsia.<sup>[10]</sup> It is recommended that smoking be stopped prior to, during and after pregnancy.<sup>[48]</sup> Studies suggest that marijuana use in the months prior to or during the early stages of pregnancy may interfere with normal placental development and consequently increase the risk of preeclampsia.<sup>[49][50]</sup>

## Yorum/Comment

TR. Sigara gibi faktörler ile aspirinin olumlu etkisi, yine inflamasyon mekanizmalarını belirtmektedir.

Eng. The effect of aspirin may be a signal for the inflammation predict. Thus smoking has negative adverse effect on pregnancy.

### Treatment ...

Blood pressure ...

Prevention of eclampsia ...

### Epidemiology

Pre-eclampsia affects approximately 2–8% of all pregnancies worldwide.<sup>[1][2][54]</sup> The incidence of pre-eclampsia has risen in the USA since the 1990s, possibly as a result of increased prevalence of predisposing disorders, such as chronic hypertension, diabetes, and obesity.<sup>[10]</sup>

Pre-eclampsia is one of the leading causes of maternal and perinatal morbidity and mortality worldwide.<sup>[1]</sup> Nearly one-tenth of all

## Yorum/Comment

TR. Zarın patlaması ile pre-eklampsia benzer oranlarda gözlenmektedir.

Eng. The more worse eclampsia will be protecting by curing preeclampsia.

### Complications

Complications of pre-eclampsia can affect both the mother and the fetus. Acutely, pre-eclampsia can be complicated by [eclampsia](#), the development of [HELLP syndrome](#), hemorrhagic or ischemic [stroke](#), liver damage and dysfunction, [acute kidney injury](#), and [acute respiratory distress syndrome](#) (ARDS).<sup>[6][15]</sup>

...

Eclampsia ...

HELLP Syndrome

[HELLP syndrome](#) is defined as [hemolysis](#) (microangiopathic), elevated liver enzymes (liver dysfunction), and low platelets ([thrombocytopenia](#)). This condition may occur in 10–20% of patients with severe pre-eclampsia and eclampsia<sup>[10]</sup> and is associated with increased maternal and fetal morbidity and mortality. In 50% of instances, HELLP syndrome develops preterm, while 20% of cases develop in late gestation and 30% during the post-partum period.<sup>[6]</sup>

Long term...

**History** The word [eclampsia](#) is from the Greek term for lightning.<sup>[12]</sup> The first known description of the condition was by [Hippocrates](#) in the 5th century BC.<sup>[12]</sup>

An outdated medical term for pre-eclampsia is [toxemia](#) of pregnancy, a term that originated in the mistaken belief that the condition was caused by [toxins](#).<sup>[67]</sup>

### Research

Some studies have suggested the importance of a woman's [immunological tolerance](#) to her baby's father, as the baby and father share genetics. There is tentative evidence that ongoing exposure either by vaginal or oral sex to the same semen that resulted in the pregnancy decreases the risk of pre-eclampsia.<sup>[68]</sup> As one early study described, "although pre-eclampsia is a disease of first pregnancies, the protective effect of multiparity is lost with change of partner".<sup>[69]</sup> The study also concluded that although women with changing partners are strongly advised to use condoms to prevent sexually transmitted diseases, "a certain period of sperm exposure within a stable relation, when pregnancy is aimed for, is associated with protection against pre-eclampsia".<sup>[69]</sup>

Several other studies have since investigated the decreased incidence of pre-eclampsia in women who had received blood transfusions from their partner, those with long preceding histories of sex without barrier contraceptives, and in women who had been regularly performing [oral sex](#).<sup>[70]</sup>

Having already noted the importance of a woman's [immunological tolerance](#) to her baby's paternal genes, several Dutch reproductive biologists decided to take their research a step further. Consistent with the fact that human immune systems tolerate things better when they enter the body via the mouth, the Dutch researchers conducted a series of studies that confirmed a surprisingly strong correlation between a diminished incidence of pre-eclampsia and a woman's practice of oral sex, and noted that the protective effects were strongest if she swallowed her partner's semen.<sup>[70][71]</sup> A team from the [University of Adelaide](#) has also investigated to see if men who have fathered pregnancies which have ended in [miscarriage](#) or pre-eclampsia had low seminal levels of critical immune modulating factors such as [TGF-Beta](#). The team has found that certain men, dubbed "dangerous males", are several times more likely to father pregnancies that would end in either pre-eclampsia or [miscarriage](#).<sup>[68]</sup> Among other things, most of the "dangerous males" seemed to lack sufficient levels of the seminal immune factors necessary to induce [immunological tolerance](#) in their partners.<sup>[72]</sup>

As the theory of immune intolerance as a cause of pre-eclampsia has become accepted, women who with repeated pre-eclampsia, miscarriages, or [in vitro fertilization](#) failures could potentially be administered key immune factors such as [TGF-beta](#) along with the father's foreign proteins, possibly either orally, as a sublingual spray, or as a vaginal gel to be applied onto the vaginal wall before intercourse.<sup>[68]</sup>

## Yorum/Comment

TR. İncelemeler, tüm gözlemlerin aynı, inflamasyonu işaret ettiğini göstermektedir.

Eng. The reactions can be overcome by the reducing of immunological tolerance.

## Sonuç/Conclusion

TR. Zarın patlama gereksesi inflamasyon işlevinin sonucudur denilebilir.

Eng. The eclampsia thus, first preeclampsia is a result of the immunological tolerance is lessened and over. The mechanism seems to me as graft versus host reaction.

## Eclampsia (Wikipedia)

**Eclampsia** is the onset of [seizures](#) (convulsions) in a woman with [pre-eclampsia](#).<sup>[1]</sup> Pre-eclampsia is a disorder of [pregnancy](#) in which there is [high blood pressure](#) and either large amounts of [protein in the urine](#) or other organ dysfunction.<sup>[7][8]</sup> Onset may be before, during, or after [delivery](#).<sup>[1]</sup> Most often it is during the second half of pregnancy.<sup>[1]</sup> The seizures are of the [tonic-clonic](#) type and typically last about a minute.<sup>[1]</sup> Following the seizure there is typically either a [period of confusion](#) or [coma](#).<sup>[1]</sup> Complications include [aspiration pneumonia](#), [cerebral hemorrhage](#), [kidney failure](#), and [cardiac arrest](#).<sup>[1]</sup> Pre-eclampsia and eclampsia are part of a larger group of conditions known as [hypertensive disorders of pregnancy](#).<sup>[1]</sup> Recommendations for prevention include [aspirin](#) in those at high risk, [calcium supplementation](#) in areas with low intake, and treatment of prior hypertension with medications.<sup>[2][3]</sup> Exercise during pregnancy may also be useful.<sup>[1]</sup> The use of intravenous or intramuscular [magnesium sulfate](#) improves outcomes in those with eclampsia and is generally safe.<sup>[4][9]</sup> This is true in both the [developed](#) and [developing world](#).<sup>[4]</sup> Breathing may need to be supported.<sup>[1]</sup> Other treatments may include blood pressure medications such as [hydralazine](#) and emergency delivery of the baby either vaginally or by [cesarean section](#).<sup>[1]</sup> Pre-eclampsia is estimated to affect about 5% of deliveries while eclampsia affects about 1.4% of deliveries.<sup>[5]</sup> In the developed world rates are about 1 in 2,000 deliveries due to improved medical care.<sup>[1]</sup> Hypertensive disorders of pregnancy are one of the most common causes of death in pregnancy.<sup>[10]</sup> They resulted in 46,900 deaths in 2015.<sup>[6]</sup> Around one percent of women with eclampsia die.<sup>[1]</sup> The word eclampsia is from the Greek term for lightning.<sup>[11]</sup> The first known description of the condition was by [Hippocrates](#) in the 5th century BCE.<sup>[11]</sup>

### Signs and symptoms ...

Onset ...

Complications ...

Risk factors ...

Mechanism

The presence of a [placenta](#) is required, and eclampsia resolves if it is removed.<sup>[30]</sup> Reduced blood flow to the placenta (placental [hypoperfusion](#)) is a key feature of the process. It is accompanied by increased sensitivity of the maternal vasculature to agents which cause constriction of the small arteries, leading to reduced blood flow to multiple organs. Also, an activation of the [coagulation](#) cascade may lead to [microthrombi](#) formation, which can further impair blood flow. Thirdly, increased [vascular permeability](#) results in the shift of [extracellular fluid](#) from the blood to the [interstitial space](#), with further reduction in blood flow, and [edema](#). These events lead to hypertension; renal, pulmonary, and hepatic dysfunction; and cerebral edema with cerebral dysfunction and convulsions.<sup>[30]</sup> Before symptoms appear, increased platelet and [endothelial activation](#)<sup>[30]</sup> may be detected.

Placental hypoperfusion is linked to abnormal modelling of the fetal–maternal placental interface that may be immunologically mediated.<sup>[30]</sup> The invasion of the [trophoblast](#) appears to be incomplete.<sup>[31]</sup> The placenta produces the potent vasodilator [adrenomedullin](#): it is reduced in pre-eclampsia and eclampsia.<sup>[32]</sup> Other vasodilators are also reduced, including [prostacyclin](#), [thromboxane A2](#), [nitric oxide](#), and [endothelins](#), also leading to vasoconstriction.<sup>[33]</sup>

Eclampsia is a form of [hypertensive encephalopathy](#): cerebral [vascular resistance](#) is reduced, leading to increased blood flow to the brain, [cerebral edema](#) and resultant convulsions.<sup>[34]</sup> An eclamptic convulsion usually does not cause chronic brain damage unless [intracranial haemorrhage](#) occurs.<sup>[35]</sup>

Diagnosis ...

Vital signs ...

Laboratory testing ...

Differential diagnosis ...

Prevention ...

Treatment ...

Delivery ...

Monitoring ...

Etymology ...

## Yorum/Comment

TR. Eklampsi de ek olarak tansiyon gibi sorunlar da eklenmekte, beyin işlevleri de bozulmaktadır. EMR ile tanımlanan faktörlere benzemektedir.

Eng. The reasoning is not placental toxins, thus, placental reaction to the fetus, as lowering the immune tolerance, thus, leading several inflammation reactions. These parameters mostly influence the infant, and the findings at the newborn infants, even the immaturity is an adverse reaction of this immune response.

Placenta is the target organ, first, not direct have an immunological relation with the zygote, thus, obtains energy and other nutrition by themselves. Becoming a mother of the blasto-cell/ovum/new embryo, placenta requires the changing, maturation etc. The reduction of the blood flow, the oxidation and vital important factors if insufficient, several modulation is started. Endothelial activation, fibrinolytic activity and coagulation steps, invasion of several kind of white cells. The invasion of trophoblast appear to be incomplete to the uterine cavity. Vasodilatations, and [prostacyclin](#), [thromboxane A2](#), [nitric oxide](#), and [endothelins](#), also leading to vasoconstriction.

All means some inflammation mechanisms is going to be active, leading PPROM another problem, far away tissue problems, as; of [hypertensive encephalopathy](#): cerebral [vascular resistance](#) is reduced, leading to increased blood flow to the brain, [cerebral edema](#) and resultant convulsions, and [intracranial haemorrhage](#).

## Sonuç/Conclusion

TR. EMR bir inflamasyon reaksiyonu, mekanizmasıdır.

Eng. Under the knowledge based confirmation, the problems are uniquely inflammation I discussed. Thus, in collaboration of all of them, is identified they are all on one, as PROM or other pregnancy outcomes. IL-6 and IL-8 transferred by blood circulation, so, if the level is high and produced by neutrophils, so we can have noticed their reactions all over the body. As in anaphylaxis.

## The Complaints/Sorunlar

TR. Zarın erken patlaması, prematürede sorunlar oluşturduğu için yaşamsal önemli olmaktadır. Bu açıdan gebelikteki gelişimin boyutu çok öne çıkmaktadır.

TR. Bulguları olan annelerin sadece EMR olması ve %10 altında yakınma göstermeleri tanımlanan sorunların pre-eklampsi ve diyabet gibi tüm sistemleri etkilediği ve hematolojik sorunlarında önemli boyut olduğu gösterilmektedir. Ancak bunların EMR açıklamaktan uzaktır, onda bir olması ile başka boyutlara bakılmasını gerekli kılmaktadır.

Genel yenidoğan sorunlarına bakılınca: solunum sistemi, karaciğer, nörolojik, hematolojik ve gelişme geriliği olduğu görülmektedir. Kısaca tüm vücut yapısını etkilemektedir. Anomali görülmesini, bu sorun ile bağlamak çok akılcı olmayacaktır, ancak Gastro-intestinal sistem ve gangliyon oluşumundaki gerilik boyutu da dikkate alınmalıdır.

Eng. When considered the complaints of the pregnant women, they are diversity as noticed. Thus, mother indicates less problems, but, infants have a lot.

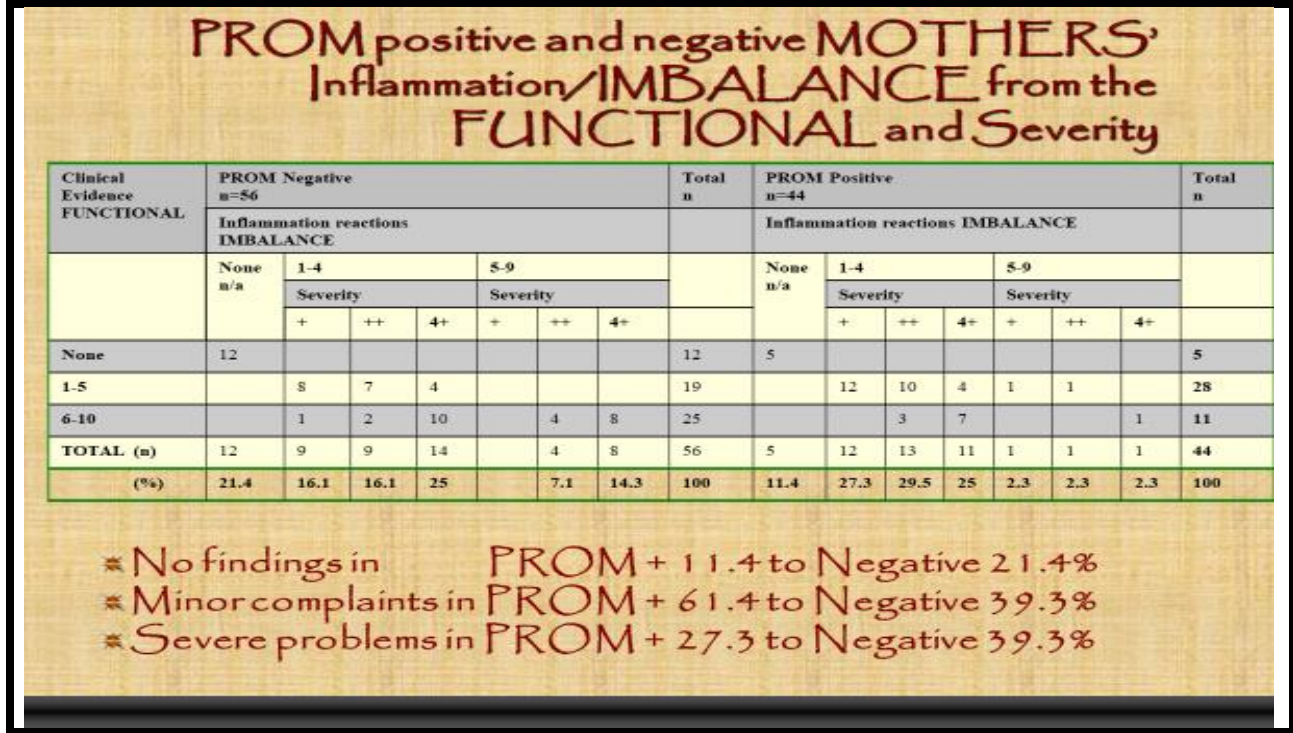
The problems at mothers are about nearly 10-20 percent, so low than expected. This is far away of the grounding of the PPROM. Means, the immunologic tolerance, the suppression of the reactions, thus, as major effective ones as preeclampsia and diabetes is more obvious than the condition.

Blood glucose level is somehow, over 180-200mg/dL (10mOsmol/L) is mentioned as diabetes, thus the molecular weight is 18, so, even 10 mOsmol is recordable factor for the evaluation. But, as in electrolyte imbalances, (+/-) 2 is easily tolerable, (+/-) 5-8 is for starting the problem. For the human



body, 140 mg/dL and over cause some problems, even passed to urine. This effect mainly to the fetus, transferring the glucose, increase the insulin level, thus, insulin is not passed from the placenta, and hyperinsulinemia state to the fetus. Pancreas is over production insulin, hypersecretion, like insulinoma state. Even required 3-4 months to reduce the hyperplasia of beta cells. Therefore, this is not a glucose metabolism, this is complete body metabolisms and all other functions, as seen obesity at the grown human.

**MOTHER/PREGNANT:** IMBALANCE of inflammation, from FUNCTIONAL of Tissue Reactions / İnflamasyon Mekanizmaları (IMBALANCE) olması ile Doku Reaksiyonları (FUNCTIONAL)



**Figure/Şekil 5:** Functionality /Women problems

#### Yorum/Comment

TR. EMR bulgusu olmayan annelere/gebelere de bakılacak olunursa; benzer neticelerin olduğu görülmektedir.

Eng. The two groups are nearly similar in appearance. Thus, especially the neutrophil activation is not being prone at the PPROM negative ones. How we assume, the other reaction mechanism is more obvious than the tissue concept. This is something like Graft versus Host reactions. Like aphthous verdicts due to the immune problems. The nut caused aphthous lesions, due to the membrane attack complex. Fixed drug eruption is also a complex, due to an antigen especially select a special place for ulcerous finding.

#### Inflammation mechanisms and Tissue Reactions

Eng. Mothers-infant's comparison, as PROM positive and PROM negative considerations as;

- No findings: PROM positive cases: 11,4%, PROM Negative ones: 21,4%
- Minor Complaints: PROM positive cases: 61,4%, PROM Negative ones: 39,3%
- Severe Problems: PROM positive cases: 27,3%, PROM Negative ones: 39,3%

Comment; even one third (1/3<sup>rd</sup>) have severe problems (27,3 to 39,3).

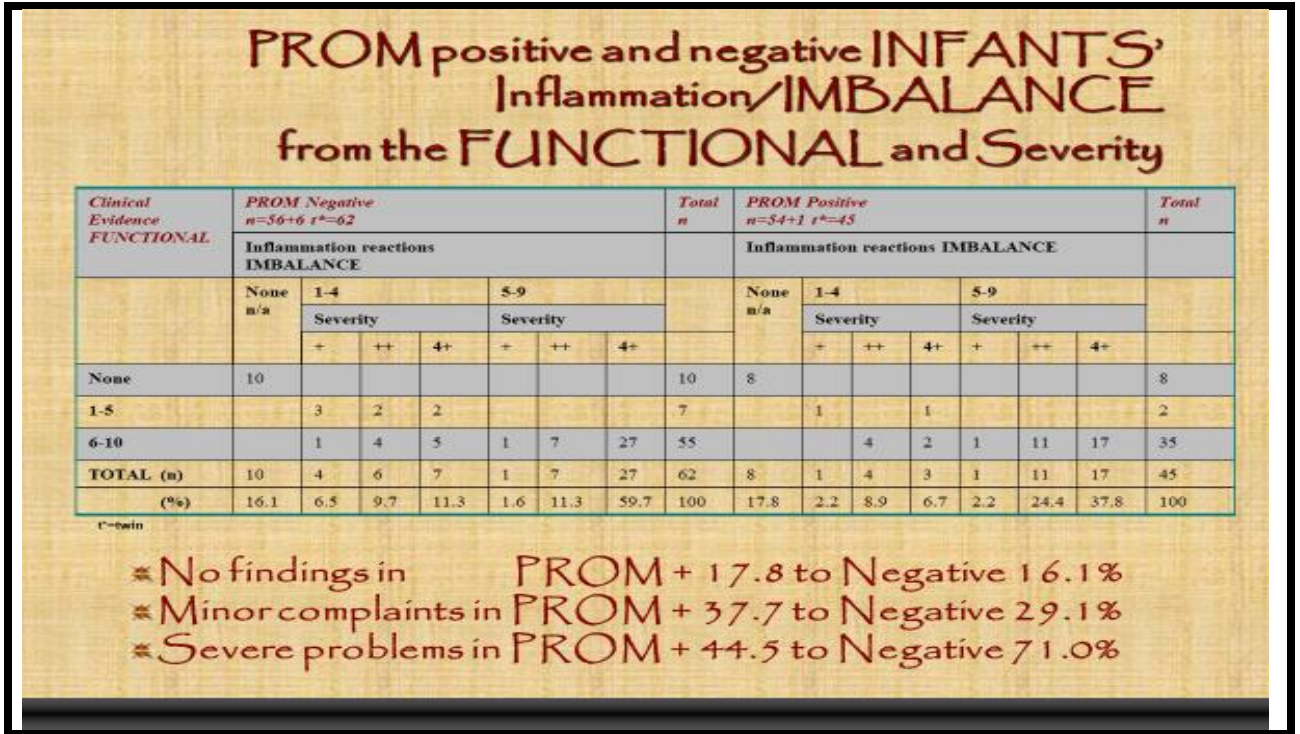
### Yorum/Comment

Bebeklerde de sorunlar önemli boyuttadır.

Eng. Infant's comparison, as PROM positive and PROM negative considerations as;

- No findings: PROM positive cases: 17,8%, PROM Negative ones: 16,1%
- Minor Complaints: PROM positive cases: 37,7%, PROM Negative ones: 29,1%
- Severe Problems: PROM positive cases: 44,5%, PROM Negative ones: 71,0%

**INFANTS:** FUNCTIONAL of Inflammation to Severity of the conditions (NOTABLE) / İnflamasyon reaksiyonları (IMBALANCE) ile olguların ciddiyeti (NOTABLE)



**Figure/Şekil 6:** Functionality /infant problems

### Yorum/Comment

Bebeklerde de sorunlar önemli boyuttadır.

Eng. Infant's comparison, as PROM positive and PROM negative considerations as;

- No findings: PROM positive cases: 17,8%, PROM Negative ones: 16,1%
- Minor Complaints: PROM positive cases: 37,7%, PROM Negative ones: 29,1%
- Severe Problems: PROM positive cases: 44,5%, PROM Negative ones: 71,0%

When comparison as:

- **No Findings PROM (+) Mother, 11,4%, Infant, 17,8%**
- **Minor: PROM (+) Mother, 61,4%, Infant, 37,7%**
- **Severe: PROM (+) Mother, 27,3%, Infant, 44,5%**
- **Complaints: PROM (-) Mother, 39,3%, Infant, 16,1%**

### Yorum/Comment

TR. Sorunlar her iki grupta da, inflamasyon parametreleri olması ile yüksektir.

Eng. Due to the severity of the conditions, means; the problems are so multiple and wide, thus, minor complaints, therefore, the recordable and be obvious complaints and findings must be noticed, at these findings.

PROM positive and/or negative Infants, comparison by Inflammation (IMBALANCE)/ tissue reactions (FUNCTIONAL) and severity.

When considering the Inflammation and NOTABLE; Mothers-infant's comparison, as PROM positive and PROM negative considerations as;

- Positive PROM, inflammation YES, 81,8%,
- Negative PROM, inflammation YES, 78,3%

Comment; so Obvious.

### Comparison of PROM positive and negative with other inflammation positive to negative

**The comparison of PROM positive and negative mothers' and infant's interactions, from the inflammation/IMBALANCE**

MOTHERS (n-%) PROM		INFANTS (n-%) Inflammation reactions IMBALANCE		
		YES	NO	TOTAL
Positive		36 – (81.8%)	8 – (18.2%)	44 – (100%)
Negative		46 – (82.1%)	10 – (17.9%)	56 – (100%)
	Other Inflammation YES	36 – (94.7%) [78.3%]	2 – ( 5.3%) [20%]	38 – (100%) [67.9%]
	Other Inflammation NO	10 – (66.7) [21.7%]	8 – (33.3) [80%]	18 – (100%) [32.1%]
Total (n-%)		46 – (82.1%) [100%]	10 – (17.9) [100%]	56 – (100%) [100%]

**Figure/Şekil 7:** Imbalance-doğum sonu sorunlar/Women-infant problems

## Some References/Bazı Kaynaklar

- 1) [Mogami H<sup>1</sup>](#), [Kishore AH<sup>1</sup>](#), [Word RA](#). **Collagen Type 1 Accelerates Healing of Ruptured Fetal Membranes.** [Sci Rep](#). 2018 Jan 12;8(1):696.

Pregnant mouse model to test the efficacy of collagen type 1 gel for healing of the prematurely ruptured fetal membranes. Ruptured fetal membranes resulted in 40% closure, injection of collagen type 1 improved closure rates to 90% within 72 h. NOT: TR. Yara iyileşmesinde kolagen verilenlerde 540, 72 saat sonra %90 faydası olmuştur.

Eng. The matrix, macrophages of the M2 wound healing phenotype were entrapped in the collagen layer, meaning an inflammation response.

- 2) [Schneider H<sup>1</sup>](#). **Placental Dysfunction as a Key Element in the Pathogenesis of Preeclampsia.** [Dev Period Med](#). 2017;21(4):309-316.

Placental pathology is associated with major pregnancy disorders and the concept of the Great Placental Syndromes encompasses disorders of placentation, such as preeclampsia with and without fetal growth restriction, preterm labor,



preterm premature rupture of membranes, late spontaneous abortion, and placental abruption. Preeclampsia is divided between the early and late onset variety and placental dysfunction is a central feature in the pathogenesis of both. In the early onset type, syncytiotrophoblastic stress seems to be related to an inherent defect of the trophoblast. Vascular protection of early placental development is replaced by vascular dysfunction. In late onset preeclampsia, maternal factors, such as genotypic predisposition to endothelial disease, and an impairment of antioxidant defence with a limited capacity of the maternal clearing system to cope with the increasing charge of apoptotic cell debris, are at the center of pathogenesis. Syncytiotrophoblastic stress in late pregnancy has been related to molecular senescence and late onset preeclampsia may be viewed as an exaggeration of normal placental ageing.

NOT: TR. Plasental fonksiyon bozukluęu ile trofoblastik aktivite etkin olmaktadır.

Eng. The basic inflammation concepts at the center of pathogenesis are; a) an impairment of antioxidant defense b) with a limited capacity of the maternal clearing system c) to cope with the increasing charge of apoptotic cell debris d) meaning, Syncytiotrophoblastic stress.

- 3) [Rodríguez-Trujillo A<sup>1</sup>](#), [Ríos J<sup>2,3</sup>](#), [Ángeles MA<sup>1</sup>](#), [Posadas DE<sup>1</sup>](#), [Murillo C<sup>1</sup>](#), [Rueda C<sup>1</sup>](#), [Botet F<sup>1</sup>](#), [Bosch J<sup>4</sup>](#), [Vergara A<sup>4</sup>](#), [Gratacós E<sup>1,5</sup>](#), [Palacio M<sup>1,5</sup>](#), [Cobo T<sup>1,5</sup>](#) Influence of perinatal inflammation on the neurodevelopmental outcome of premature infants. *J Matern Fetal Neonatal Med.* 2017 Nov 16:1-9.

To evaluate the influence of perinatal inflammation on neurodevelopmental outcome of premature infants; Among 98 infants evaluated, 22% had an abnormal score. Amniotic fluid interleukin-6 levels and early-onset sepsis (EOS) were independent factors of an altered ASQ-3 with delivery <26.0 weeks being the strongest predictor. In premature infants, the presence of (intra amniotic inflammation) IAI, delivery <26.0 weeks and EOS were found to be independent factors of an altered ASQ-3

NOT: TR. IL-6 yükseklięi ve sepsis gelişmesi inflamasyon belirtisidir.

NOTE: The basic findings as IL-6 and Early Onset of Sepsis indicated the inflammation mechanism.

- 4) [Modi BP<sup>1</sup>](#), [Teves ME<sup>2</sup>](#), [Pearson LN<sup>3</sup>](#), [Parikh HI<sup>4</sup>](#), [Haymond-Thornburg H<sup>2</sup>](#), [Tucker JL<sup>2</sup>](#), [Chaemsaitong P<sup>5</sup>](#), [Gomez-Lopez N<sup>5,6,7,8</sup>](#), [York TP<sup>1,2</sup>](#), [Romero R<sup>5,6,7,8</sup>](#), [Strauss JF 3rd<sup>1,2</sup>](#) Mutations in fetal genes involved in innate immunity and host defense against microbes increase risk of preterm premature rupture of membranes (PPROM). *Mol Genet Genomic Med.* 2017 Nov;5(6):720-729. doi: 10.1002/mgg3.330. Epub 2017 Aug 23.

Infection and inflammation of the fetal membranes is commonly found associated with PPRM. We conclude that rare damaging mutations in innate immunity and host defense genes, the majority being heterozygous, are more frequent in neonates born of pregnancies complicated by PPRM. These findings suggest that the risk of preterm birth in African-Americans may be conferred by mutations in multiple genes encoding proteins involved in dampening the innate immune response or protecting the host against microbial infection and microbial products.

NOT: TR. Genomdaki etkileşimin doęal immüniteyi azaltmaktadır.

NOTE: The genomic DNA from neonates, with PPRM birth, reducing the innate immune response.

- 5) [Kumar D<sup>1</sup>](#), [Moore RM<sup>1</sup>](#), [Mercer BM<sup>2</sup>](#), [Mansour JM<sup>3</sup>](#), [Mesiano S<sup>2</sup>](#), [Schatz F<sup>4</sup>](#), [Lockwood CJ<sup>4</sup>](#), [Moore JJ<sup>5</sup>](#) In an in-vitro model using human fetal membranes, 17- $\alpha$  hydroxyprogesterone caproate is not an optimal progestogen for inhibition of fetal membrane weakening. *Am J Obstet Gynecol.* 2017 Dec;217(6):695.e1-695.e14.

Tumor necrosis factor-alpha and thrombin both weakened fetal membranes (43% and 62%, respectively) and increased granulocyte-macrophage colony-stimulating factor levels (3.7- and 5.9-fold, respectively).

NOT: TR. Steroidler etkisinin farklı olduęu vurgusu vardır. Steroidler immün cevaptaki farklı rolleri bilinmektedir.

NOTE: We speculate that progestogens other than 17-alpha hydroxyprogesterone caproate may be more efficacious in preventing preterm premature rupture of the fetal membranes-related spontaneous preterm birth.

- 6) [Mogami H<sup>1</sup>](#), [Hari Kishore A<sup>1</sup>](#), [Akqul Y<sup>2</sup>](#), [Word RA<sup>3</sup>](#) Healing of Preterm Ruptured Fetal Membranes. [Sci Rep.](#) 2017 Oct 13;7(1):13139.

Preterm premature rupture of membrane (pPROM) is associated with 30-40% of preterm births. Infection is considered a leading cause of pPROM due to increased levels of proinflammatory cytokines in amniotic fluid. Only 30%, however, are positive for microbial organisms by amniotic fluid culture. Interestingly, in some pregnancies complicated by preterm premature rupture of membranes (pPROM), membranes heal spontaneously and pregnancy continues until term.

Here, we investigated mechanisms of amnion healing. Using a preclinical mouse model, we found that small ruptures of the fetal membrane closed within 72 h whereas healing of large ruptures was only 40%. Small rupture induced transient upregulation of cytokines whereas large ruptures elicited sustained upregulation of proinflammatory cytokines in the fetal membranes. Fetal macrophages from amniotic fluid were recruited to the wounded amnion where macrophage adhesion molecules were highly expressed.

NOT: TR. Epitel mesenşimal geçiř, epitel göçünün amnion mekanizmasını etkilemektedir.

NOTE: The recruited macrophages released limited and well-localized amounts of IL-1 $\beta$  and TNF which facilitated epithelial-mesenchymal transition (EMT) and epithelial cell migration. Arg1 + macrophages dominated within 24 h. Migration and healing of the amnion mesenchymal compartment, however, remained compromised. These findings provide novel insights regarding unique healing mechanisms of amnion.

- 7) [Vandenbroucke L<sup>1,2,3,4</sup>](#), [Doyen M<sup>3,4</sup>](#), [Le Lous M<sup>2,4</sup>](#), [Beuchée A<sup>1,4,5</sup>](#), [Loget P<sup>6</sup>](#), [Carrault G<sup>1,3,4</sup>](#), [Pladys P<sup>1,3,4,5</sup>](#). Chorioamnionitis following preterm premature rupture of membranes and fetal heart rate variability. [PLoS One.](#) 2017 Sep 25;12(9):e0184924.

These results show differences in fetal heart rate variability, suggesting that fetal computerized cardiotocography (cCTG) could be used clinically to diagnose chorioamnionitis during the pPROM latency period.

NOTE: Fetal cardio is also affected.

NOT: TR. Etkileřim sistematik olmakta, kardiyak etkisi de gözlenmektedir.

- 8) [Toprak E<sup>1</sup>](#), [Bozkurt M<sup>2</sup>](#), [Dinçgeç Çakmak B<sup>3</sup>](#), [Özçimen EE<sup>1</sup>](#), [Silahlı M<sup>4</sup>](#), [Ender Yumru A<sup>5</sup>](#), [Çalıřkan E<sup>6</sup>](#). **Platelet-to-lymphocyte ratio: A new inflammatory marker for the diagnosis of preterm premature** The platelet-to-lymphocyte ratio (PLR) might be a cost effective, easy to use, and practical marker for the early diagnosis of pPROM, which can help to determine the appropriate waiting time for delivery and provide maternal and fetal well-being.

NOTE: The platelets and lymphocytes are both inflammation cells.

NOT: TR. Trombositler ve lenfositlerin etkilenmesi de immün etkileřimi göstermektedir.

- 9) [Gomez-Lopez N<sup>1</sup>](#), [Romero R<sup>2</sup>](#), [Plazyo O<sup>3</sup>](#), [Schwenkel G<sup>3</sup>](#), [Garcia-Flores V<sup>3</sup>](#), [Unkel R<sup>3</sup>](#), [Xu Y<sup>3</sup>](#), [Leng Y<sup>3</sup>](#), [Hassan SS<sup>3</sup>](#), [Panaitescu B<sup>3</sup>](#), [Cha J<sup>4</sup>](#), [Dey SK<sup>4</sup>](#). Preterm labor in the absence of acute histologic chorioamnionitis is characterized by cellular senescence of the chorioamniotic membranes. [Am J Obstet Gynecol.](#) 2017 Nov;217(5):592.e1-592.e17.

In the absence of acute histologic chorioamnionitis, signs of cellular senescence are present in the chorioamniotic membranes from women who underwent spontaneous preterm labor compared to those who delivered preterm in the absence of labor. However, the chorioamniotic membranes from women who underwent spontaneous labor at term did not show consistent signs of cellular senescence in the absence of histologic chorioamnionitis. These results suggest that different pathways are implicated in the pathological and physiological processes of labor.

NOTE: The basic findings; (1) there were differences between the term in labor and preterm in labor groups at expressed genes; (2) they are closely related to the tumor suppressor protein (TP53) pathway; (3) the expression of TP53 was down-regulated; (4) the expression of CDKN1A (gene coding for p21) was up-regulated in the term in (5) the expression of the cyclin kinase CDK2 and cyclins CCNA2, CCNB1, and CCNE1 was down-regulated in the preterm in labor; (6) the concentration of TP53 was lower in the preterm in labor group than in the preterm no labor and term in labor groups; (7) the senescence-associated  $\beta$ -galactosidase activity was greater in the preterm in labor group than in the preterm no labor and term in labor groups; (8) the concentration of phospho-S6 ribosomal protein was reduced in the term in labor group compared to its nonlabor counterpart, but no differences were observed between the preterm in labor and preterm no labor groups; and (9) no significant differences were observed in relative telomere



length among the study groups (term no labor, term in labor, preterm no labor, and preterm in labor).

NOT: TR. Bazı farklılıkların gösterilmesi, inflamasyonda ki etkileşimi vurgulamaktadır.

- 10) [Musilova I](#)<sup>1</sup>, [Kacerovsky M](#)<sup>1,2</sup>, [Stepan M](#)<sup>1</sup>, [Bestvina T](#)<sup>1</sup>, [Pliskova L](#)<sup>3</sup>, [Zednikova B](#)<sup>4</sup>, [Jacobsson B](#)<sup>5,6</sup>. **Maternal serum C-reactive protein concentration and intra-amniotic inflammation in women with preterm prelabor rupture of membranes.** [PLoS One](#). 2017 Aug 16;12(8):e0182731.

The maternal serum CRP cutoff value of 17.5 mg/L was the best level to identify the presence of both microbial invasion of the amniotic cavity (MIAC) and intra-amniotic inflammation (IAI). with sensitivity of 47%, specificity of 96%, positive predictive value of 42%, negative predictive value of 96%, and the positive likelihood ratio of 10.9

NOTE: The CRP is also a good indication of infection.

NOT: TR. CRP immün mekanizmanın bir verisidir.

- 11) [Wu T](#)<sup>1</sup>, [Shi J](#), [Bao S](#), [Qu Y](#), [Mu DZ](#). [Effect of premature rupture of membranes on maternal infections and outcome of preterm infants]. [Zhongguo Dang Dai Er Ke Za Zhi](#). 2017 Aug;19(8):861-865.

**OBJECTIVE:**

To investigate the effect of premature rupture of membranes (PROM) on maternal infections and outcome of preterm infants. PROM duration  $\geq 72$  hours significantly increases the risk of placental infection in mothers and it is an independent risk factor for pneumonia and intracranial hemorrhage in preterm infants.

NOTE: Colonisation is important for secondary infection.

NOT: TR. Mikropların koloni olması önemlidir. Daha önce olması, mikrobuñ önce olması anlamındadır ve geç olması da bulaşım doğumda olduđu verisidir.

## Discussion and Conclusion

### Yorum/Comment

TR. Zarın patlaması ile pre-eklampsi gibi konularda temel oluşumun inflamasyon mekanizması olduđu görülmektedir.

Eng. The cases, the pregnant women are taken in considerations, and put it into two groups, PPRM positive and negative, not making any limitations. From a University Hospital, Eskişehir Osmangazi, Neonatology Department and Perinatology Department in cooperation. 100 charts of patients are taken, by in order. 50 PPRM and 50 other deliveries, thus not have PPRM. Just discrimination by positive or negative PPRM.

The other group, negative for PPRM, pregnant women, have such more problems, might be due to the University Hospital Perinatology Department, mostly referred cases.

When we consider PPRM or other inflammation reactions, the problems were; 81,8 and 82,1%.

When negative from infant's findings, the ratio is 18,2 to 17,9%

This can lead us, as the conclusion, if there will be an inflammation reaction at the pregnancy, the infant will ve more than 80% will be ill or problems. So be ready for care and precautions, that you must b-formerly taken in consideration.

### PPROM Negative Mother-Infant/EMR olmayan anne-bebek sorunları

#### Yorum/Comment

TR. Zar patlayanlarda %81,8'inde sorunlar ile diđer inflamasyonda olanlarda da %78,3 oranında sorun olmaktadır.

Eng. Mothers-infant's comparison, as PROM positive and PROM negative considerations as;

- Positive PROM, inflammation YES, 81,8%,

- Negative PROM, inflammation YES, 78,3%

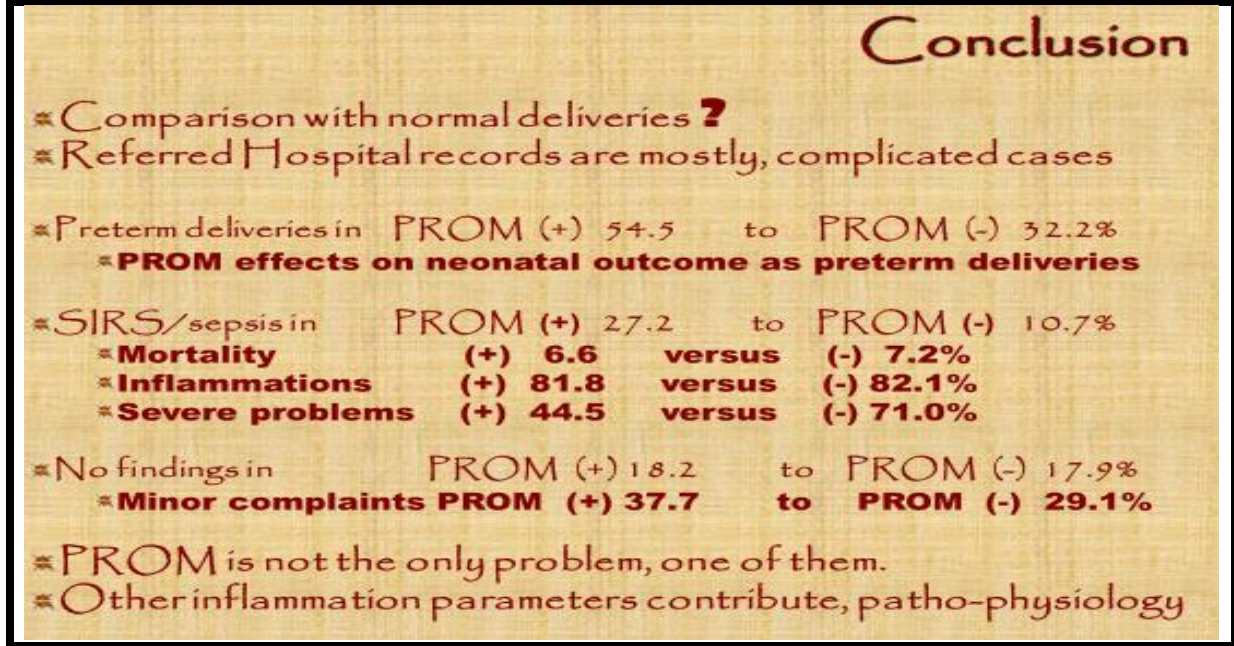
Comment; so Obvious.

Eng. Mothers-infant's comparison, as PROM positive and PROM negative considerations as;

- Negative PROM, inflammation NO, 17,9,8%,
- Negative İnflammation, inflammation NO, 33,3%

Comment; if problem is encountered, consider other than inflammation.  
here are two

## Comparison between the deliveries/EMR olan olmayan gebeliklerin karşılaştırması



**Figure/Şekil 8:** Gebelikte-doğum sonu bebek izleminde sorunlar /Women-infant problems in general

### Yorum/Comment

TR. İnflamasyon parametreleri olanlarda sorun oluşması belirgindir.

Eng. Pregnancy is a stranger in your body, growing and developing, by mother, taken all from her, without any limitations, only for gain and gain concept.

The immunological tolerance is obvious, also suppressed by the immune products from mother. Thus, at the day of 26-30, thymus is encountered, 31-35 days, large lymphatic vessels are noticeable, 36-40 days, lymphatic pattern at 51-55 days, spleen is seen. (Reference: RJ. Lemire, J.D. Loeser, R.W. Leech, E.C. Alvord. Normal and Abnormal Development of the Human Nervous System. Harper and Row Publishers, Hagerstown, Maryland, 1975). At 15<sup>th</sup> gestational week, some relations and cooperation is newly started, thus immune tolerance is noticeable. If there are reactions started, the tissue, placenta is an area of conflict, leading preeclampsia, eclampsia and [Chorioamnionitis](#) etc.

PPROM is one of the inflammation reaction, thus it is not the only one, other causative factors also influence the baby and required Neonatology Intensive Care Unit transferring. When considering the cases at the Perinatal and Neonatal Department, such conditions are more.

## General Comparison

Eng. PROM positive and PROM negative considerations as;

- Preterm Deliveries: PROM positive cases: 54,5%, PROM Negative ones: 32,2%  
PROM effects preterm deliveries, as statistically as expected
- SIRS (Systemic Inflammation Response Syndrome)/Sepsis outcome:
  - Total: PROM positive cases: 27,2%, PROM Negative ones: 10,7%
  - Mortality: PROM positive cases: 6,6%, PROM Negative ones: 7,2%
  - Inflammation Reactions: PROM positive cases: 81,8%, PROM Negative ones: 82,1%
  - Minor Complaints: PROM positive cases: 77,7%, PROM Negative ones: 29,1%
  - Severe Problems: PROM positive cases: 44,5%, PROM Negative ones: 71,0%
- No findings: PROM positive cases: 18,2%, PROM Negative ones: 17,9%

Statistical evaluation is not only a indicator. Each person is different and inflammation reactions can be targeting one mechanism and be so severe to leading death, mostly as anaphylaxis. There might be chain reaction, so, e aware of the mechanisms, for reducing and stopping or halting the mechanisms or influences, thus, for overcome clinically overt and not be harm to body homo balance, status. Blood is a transferring media cytokines, mediators and leukotrienes, so local solution may be the best, if you can.

## Son Vurgu / Last Comment

TR. Zarin patlaması ve birçok gebelik sorunlarının bir bakıma Greft versus Host gibi, inflamasyon mekanizması ile oluştuğu belirtilmektedir. Bu açıdan gebeliklerde bu mekanizmaların sorgulanması yerinde olacaktır. Bebeklerin daha sonraki boyutlarını da anlaşılır kılacaktır.

Eng. Estimation is important to overcome the pathological problems, not to cure and treat, thus, solve it before it becomes a problem. Care and serve and precautions for warnings is quite necessary. In order to estimate the organ system and pathophysiologic outcome of the preterm, the best approach, treatment can be established. After sepsis is noticeable hard to be treatment, even death is prone.

PPROM, will be considered as a complex problem, like a cluster of reactions that will be, a trigger of a problem chain. Mostly seems to be a neutrophil on tissue, as seen chorioamnionitis and preeclampsia as noticed.

Thus, as noticed, PPRM is one of the prenatal inflammation reaction.