

# Research Article: Study of Obstetric and Somatic History in Women with Discharge of Amniotic Fluid

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## Abstract

The article presents the results of a gynecological and somatic history. A gynecological history was burdened in 71.7% of the subjects: chronic inflammatory diseases of the appendages, and vagina in 37.7% diseases of the cervix in 25.5%, uterine fibroids in 5.7% and ovarian cysts in 2.8%. Overweight somatic history was 81.1% of pregnant women. The most frequent pathologies among the examined patients were: Iron deficiency anemia in 36.8%, and diseases of the urinary system in 10.4%. Clinical and anamnestic risk factors for pregnant women complicated by premature rupture discharge of amniotic fluid are a history of endometritis, pathological growth of conditionally pathogenic cervicovaginal microflora, chlamydia, nonspecific vaginal inflammation.

**Keywords:** chorioamnionitis; amniotic membrane; premature rupture of amniotic fluid; induction of labor

## Introduction

A large number of scientific studies have been devoted to the study of the problem of premature discharge of amniotic fluid, which addresses the issues of etiopathogenesis, clinic, diagnosis and methods of induction of labor. Studies of hemostasiological, biochemical, microbiological disorders observed in this pathology, hemodynamic disorders in the uterus and placenta, the role of growth factors in predicting miscarriage, the effect of infection on the development of premature discharge of amniotic fluid were carried out [1,2,3].

It was found that the microbial spectrum of the lower genital tract of the compared groups of pregnant women with and without premature rupture of amniotic fluid sharply differ from each other, while representatives of the indigenous vaginal microflora dominated in the control group, the proportion of pathogenic microorganisms in the main group and the comparison group sharply increased, reaching a percentage level indigenous microorganism, and sometimes superior to them. We believe that the presence of vaginal dysbiosis, increased and massive sowing of pathogenic creates an unfavorable background for pregnancy, infects the placenta, amniotic fluid and thereby leads to microbial contamination of the fetus, followed by infection [4,5,6].

Despite numerous scientific and practical studies in this area, the frequency of preterm birth does not decrease, and in some countries even grows, which necessitates further comprehensive studying and improvement of diagnostic and therapeutic measures. In the diagnosis of preterm birth, several biophysical and biochemical markers, an ultrasound assessment of the length of the uterine cervix, are used. Premature discharge of amniotic fluid in

preterm pregnancy was considered to be the most high-risk factor for the fetus and mother, as it determines the high level of perinatal and infant morbidity and mortality [7,8,9]. A complication of labor by premature rupture of membranes is one of the worst problems of modern obstetrics [10,11]. Premature rupture of membranes is the cause of initiation of childbirth in 8-92% of cases, depending on the period of pregnancy. The problem of preterm birth (PB) is the leading one in the structure of perinatal morbidity and mortality [12,13].

After PRAF, regular labor activity does not always develop, the anhydrous period (AP) in the premature period can be days or months, and this usually leads to complications in childbirth, the postpartum period, and affects the state of the mother and baby. Authors believe that wait-and-see tactics for premature rupture of membranes in the premature term are a risk factor for the development of choriodecidual and chorioamnionitis, and the histological study is the gold standard for diagnosing pathology of the placenta and chorioamnionitis [14,15,16].

The course of childbirth can lead to complications such as prolonged latent and active phases of labor, the development of hypoxia and infection of the mother and fetus. Chorioamnionitis, which worsens the course and outcome of labor, poses a great threat to the mother. The importance of studying this problem lies in the fact that there is no generally accepted tactic of conducting childbirth with an increase in the anhydrous interval [17,18]. Currently, there is no consensus on the effectiveness of the prophylactic prescription of antibacterial drugs and the choice of delivery method with increasing anhydrous interval. Consequently, the paramount task of domestic medical science practical health care is the development of management

tactics for deliveries with prenatal rupture of the membranes, in order to reduce infectious complications in puerperas and newborns [19,20].

Amniotic fluid, or amniotic fluid, is a biologically active environment surrounding the fetus. Throughout pregnancy, amniotic fluid performs a wide variety of functions, ensuring the normal functioning of the mother – placenta – fetus system.

PRAF occurs if the stability of the amnion pressure decreases, which can have different reasons. An intact amnion with a sufficient amount of amniotic fluid is necessary not only for the development of the fetus (lungs, movements), but also protects the fetus from an ascending infection. Of course, this may be a consequence of the mechanical stress of the membrane. For example, during childbirth, with multiple pregnancy or polyhydramnios. However, a possible cause may be a decrease in the resistance of the amnion [21,22].

The American College of Obstetricians and Gynecologists (ACOG) indicates the following risk factors leading to this complication of gestation: the presence in the past of pregnancy (s) that ended prematurely with PRAF; inflammatory diseases of the genital organs of the mother and intra-amniotic infection; isthmocervical insufficiency; instrumental medical intervention; bad habits and diseases of the mother; abnormalities in the development of the uterus and multiple pregnancy; some diseases of the mother; injuries [6,9].

One of the most unfavorable complications encountered in threatening preterm delivery is premature rupture of the amniotic fluid (PRAF). For a period of up to 37 weeks, the frequency of PRAF before the onset of labor is 8–10% of cases. PRAF complicates 2–4% of all singleton and 7–20% of multiple pregnancies [23]. Timely diagnosis of this complication will allow treatment and improve the prognosis for the mother and fetus. The clinical picture of PRAF depends on the degree of damage to the membranes. When the fetal bladder ruptures, a large amount of fluid is released that is not associated with urination. The situation is more complicated due to microscopic cracks, amniotic fluid flows literally drop by drop. Against the background of increased vaginal secretion during pregnancy, excess fluid often goes unnoticed. A woman may note that in the supine position there is more discharge.

The addition of infection leads to the development of chorioamnionitis and is characterized by fever, chills, tachycardia in the mother and fetus, soreness of the uterus upon palpation and purulent discharge from the cervix during examination [24]. The onset of labor and the latent period after PRAF are determined by the gestational age at the time of outflow [5,7,9]. The frequency of complications and their severity depend on the period of pregnancy when the amniotic fluid was poured out, and on the management tactics of the pregnant woman by medical personnel. So, PRAF in the early term 4 times increases the mortality of newborns [4,5].

The main complication of PRAF is, first and foremost, infection, then compression of the umbilical cord, premature detachment of the normally located placenta, prematurity. There are maternal risks (amniotic infection syndrome - AIS), sepsis, uterine postpartum hypotension, fever and endomyometritis in puerperia) and fetal risks (preterm birth, neonatal sepsis, pulmonary hypoplasia, fetal respiratory distress syndrome, contracture and deformity) [1]. The term “amniotic infection syndrome” in foreign literature is akin to the generally accepted signs of chorioamnionitis. Signs of AIS include: sensitivity to pressure of the winding, foul-smelling amniotic fluid, increased contractions. In parallel with an increase in body temperature (more than 38°C), tachycardia usually develops (more than 100 beats per minute); with cardiotocography of the fetus - tachycardia with loss of acceleration and a decrease in visible oscillations.

It is emphasized that PRAF for the mother can be complicated in the postpartum period by endomyometritis, postpartum sepsis (septicemia), postpartum hemorrhage, venous thrombosis.

It must be emphasized that prenatal discharge is associated with 40% of preterm births and, as a result, is often the cause of the neonatal morbidity of mortality [13]. Three main causes of neonatal mortality are associated with PRAF in preterm pregnancy: immaturity of organs and systems, sepsis and lung hypoplasia. PRAF poses a risk to the mother primarily due to chorioamnionitis. The connection between an ascending infection from the lower parts of the genital tract PPAF is proved. Every third patient with PRAF in preterm pregnancy has positive results of inoculation of contents from the genital tract, moreover, studies have shown the possibility of bacteria penetrating through intact membranes. There are many publications discussing the identification of fetuses with intrauterine infection (IUI), the prophylactic use of antibiotics, tocolytics and corticosteroids, and optimal gestational age for delivery. It is known that the likelihood of development of labor activity during amniotic fluid effusion is directly dependent on the gestational period: the shorter the period, the longer the period before the development of regular labor activity (latent period). The initiation of perinatal morbidity in most cases are intrauterine infections, prenatal and premature rupture of membranes, ranging from 24% to 36% of all births [2,7]. Premature discharge of amniotic fluid is closely associated with perinatal infection, increasing by 10 times the risk of neonatal sepsis, high perinatal and infant mortality, as well as the risk of purulent-septic complications of the mother. Often there was a history of viral infection; isthmio-cervical insufficiency; uterine malformations; uterine hyperextension due to polyhydramnios, multiple pregnancy, fetal macrosomia; surgery during pregnancy, especially on abdominal organs, or trauma. Note also the role in the Genesis of rupture of membranes in the II trimester of pregnancy factors such as race or ethnicity, access to health care. Factors that contribute to premature discharge of amniotic fluid at different stages of pregnancy remain not fully understood.

## Objective

The study the causal factors, as well as obstetric and perinatal outcomes of labor in women with premature rupture of membranes and tactics of labor.

## Material And Methods

The material of study was the history of the birth of 106 pregnant women who have births complicated by premature rupture of membranes in the period from 32-36 weeks of gestation, delivery in the Bukhara regional perinatal center for the period 2017-2019 years. Studied somatic anamnesis data, obstetrical and gynecological status of all postpartum women. Collecting anamnesis carefully studied for the present and previous pregnancies, childbirth and the postpartum period. Laboratory parameters, the state of vaginal flora, the degree of readiness of the birth canal on the bishop scale according to indications (bleeding, congenital malformations of the fetus, antenatal fetal death, signs of chorioamnionitis, inconclusive fetal condition) were also analyzed. Ultrasound examination of the uterus and fetus was also performed.

## Results And Discussion

The median age was 26.5 year. All women had a history of pregnancy with a combination of obstetric, gynecological and somatic diseases. Among patients with premature rupture of membranes 20.7% (22 women) had low socio-economic status; 11.3% (11 women) bad habits (drug and nicotine addiction), 20.7% (22 women) occupational hazards and 30.2% (32 women) burdened heredity.

In most cases, combinations of several pathologies were revealed. Table 1 shows the obstetric history.

Table 1

**Obstetrics history of examined women (n = 106)**

Parity assessment			Total In groups	Total
Nulliparous	Pregnant	26(60,5%)	43 (40,6%)	106 (100%)
	History of abortion	6 (14%)		
	Spontaneous miscarriage	11(25,6%)		
Multiparous	Multiparous	20 (31,7%)	63 (59,4%)	
	Childbirth + artifactabortion	18(28,6%)		
	Childbirth + Spontaneous miscarriage	25(39,7%)		

The table shows that the parity prevailed repeated births (63 women), which amounted to 59.4%. Almost every third woman who gave birth (28.6%) had a history of artificial abortion. Reproductive losses such as non-developing pregnancy and spontaneous miscarriages occurred in both groups. Pregnancy ended prematurely in 81 women, which was 76.4%. In 25 women, pregnancy was prolonged to full term (23.6%).

The study of gynecological history of the examined showed that more than half of 76 (71.7%) pregnant women had a complicated history. 27 women (25.5%) reported genital diseases: mainly cervicitis - in 26 (24.5%), chronic

inflammatory diseases of the appendages and vagina - in 40 (37.7%). Sexually transmitted infections (chlamydia, herpes, ureaplasma) were diagnosed in 8 (7.5%). Retention ovarian formations (cysts) were diagnosed in 3 women (2.8%). Cervical diathermocoagulation for erosions was performed in 13.2% of cases (14 women). Various surgical interventions in the genital organs in the anamnesis were in 11 women, which was 10.4% of cases. Below are the data of the somatic status of the examined women.

(Table 2)

**Somatic status of examined women (n = 106)**

Nosology of diseases	abs	(%)	Total
Anemia	82	77,4	106 (100%)
Thyroid Diseases	44	41,5	
Gastrointestinal tract diseases (gastritis, pancreatitis)	7	6,6	
Diseases of the cardiovascular system (hypertension, hypotension, varicose veins)	13	12,3	
Urinary system diseases (pyelonephritis, urolithiasis, cystitis)	31	29,2	
ENT diseases of the organs (tonsillitis, sinusitis)	61	57,5	
Infectious diseases transferred during a real pregnancy (ARI, exacerbation of sinusitis)	28	26,4	
Broncho-pulmonary diseases (bronchitis, bronchial asthma)	3	2,8	
Myopia	17	16	
Other	11	10,4	

All pregnant women with premature discharge of amniotic fluid had a history of somatic impairment. The structure of extragenital diseases was dominated by anemia, diseases of the thyroid gland and urinary system, as well as diseases of the ENT organs and gastrointestinal tract

The results of the vaginal microbiocenosis and detection of the presence of pathogens were assessed by analyzing vaginal secretions on the flora. Smear sampling is made from the mucous membrane of the vagina, cervix or urethra.

The second degree of purity had 31 women (29.2 per cent), in which the contents of the vagina had acid reaction (pH=5-5,5) with vaginal cells and sticks Dederleyn to a lesser extent, a lot of bacteria type commatariabill

(anaerobic curved in the form of a comma coli), many epithelial cells, there were some white blood cells

The third degree of purity was found in 58 women (54,7%), in which vaginal secretions were weakly alkaline reaction (pH 6,0-6,5), vaginal sticks were in small numbers, dominated commatariabill and anaerobic Streptococcus, there were many cocci with the presence of a large number of leukocytes.

17 women (16%) were diagnosed with grade 4 vaginal smear purity, which had a weakly alkaline reaction, with no vaginal rods. Commatariabill were in the minority, motley dominated the bacterial flora, anaerobic cocci, bacilli, there were few Trichomonas or other specific infectious agents, the mass of leukocytes.

According to the National standard management of patients with premature discharge of amniotic fluid to all expectant mothers initiated antibiotic therapy (pill erythromycin at 500 mg every 8 hours) with the purpose of prophylaxis of purulent-septic complications in the fetus. In order to prevent respiratory distress syndrome appointed: intramuscular injection of dexamethasone 8 mg every 8 hours within 3 days. The threat of premature birth, tocolytic therapy with Tab Nifedipine 10 mg every 15 minutes to five tablets.

At the gestation period from 28 to 34 weeks, the priority was considered to be a waiting-active tactic, the purpose of which was: to prevent the development of clinically and histologically significant chorioamnionitis. In 28 (26.4%) of mothers in the dynamics of expectant management withheld in connection with the accession of signs of chorioamnionitis or strict

contraindications to prolongation of pregnancy (bleeding, malformations of the fetus, antenatal death of the fetus, the inconclusive status of the fetus), what was the indication for the beginning of labor induction.

The following signs were considered parameters increase the risk of chorioamnionitis: an increase in leukocytes more than 15-20% of the original level, neutrophils and especially C-reactive protein, the presence of negative dynamics of the functional state of the system mother—placenta—fetus (reduction of amniotic fluid index, a decrease in cranial index, the negative dynamics when Doppler in middle brain artery of the fetus). Before labor induction conducted a study to assess the maturity of the cervix on a scale of Bishop.

#### Bishop Cervical Maturity Assessment

Signs	Points			
	0	1	2	3
Disclosure	<1	1-2	3-4	>5
Length (length)	>4cm	2-4cm	1-2cm	<1cm
Consistency	Dense	Average	Soft	-
Neck position	Back	Centered	-	-
The preceding part	-3 or higher	-2	-1 or 0	+1 or lower

As can be seen from the table, the assessment was carried out according to 5 criteria.

It was revealed that 40.6% of the examined pregnant women had the parameters of disclosure, length, consistency, position of the cervix and the state of the preposterous part of the fetus with scores up to 5, which was assessed as "immature cervix" of uterine. And in 61.3% of women, the birth canal was assessed as "mature cervix" of uterine. Accordingly, the tactics of further management was chosen according to the Protocol of the Regional Perinatal Center. In pregnant women with "immature" cervix in combination with obstetric complications, according to the protocol, induction of labor with Tab Glandine E2, 3 mg per 1 tablet per vaginal after informed consent of the pregnant woman and relatives was proposed. A conversation was held about possible complications of labor excitation. Fetal heartbeat and uterine activity were monitored during induction. The birth canal was reassessed after 8 hours to clarify the need for continued induction. Pregnant women with "mature" cervix, the delivery was conducted in a wait and see tactic to cast regular labor or a Council of physicians decided on labor induction oxytocin. 67.8% of pregnant women delivered through the natural birth canal. The tactics of pregnancy management and the choice of delivery method were discussed in each case collectively by a Council of doctors. With the beginning of the regular labor activity, the antibiotic is replaced in the injectable form. Given the high sensitivity of vaginal and cervical bacteria to ampicillin, we prefer to use this antibacterial drug in women with premature discharge of amniotic fluid.

The nature of labor activity was controlled on the basis of partograms. In the management of labor complicated by premature discharge of amniotic fluid—maintained control of hemodynamic parameters, to the body every 4 hours, a blood leukocytosis, 1 per day, general blood analysis (coagulation, C-reactive protein, leukocyte intoxication index, urinalysis, blood group and Rh affiliation, analysis of vaginal discharge (smear), ultrasound of the uterus and fetus, the overall status of mothers.

In case of critical conditions threatening the lives of women (severe preeclampsia, eclampsia, failure of the scar after the cesarean section), severe obstetric pathology, with the immaturity of the cervix with the accession of

chorioamnionitis, absence of conditions for urgent delivery the doctors decided the question of surgical births.

#### Summary

- Thus, in the process of retrospective study of birth histories, it was found that the main factors contributing to premature discharge of amniotic fluid are burdened obstetric, gynecological and somatic history, which occurred in all cases of the study. The most common background pathology was anemia, diseases of the urinary system and infections suffered during this pregnancy.
- Premature outpouring of amniotic fluid as a consequence of pathological growth of conditionally pathogenic cervico-vaginal microflora in 26.4% of cases was the cause of chorioamnionitis, which contributed to a significant increase in the specific frequency of obstetric pathologies.

#### References

- Hotamova, M. T., & Tosheva, I. I. (2019). Aspects of the management of labor at antenatal discharge of amniotic fluid. *Tibbiotda yangi kun*, (2), 292-295.
- Ikhtiyarova, G. A., Dustova, N. K., & Tosheva, I. I. (2020). KurbanovaZ. Sh, Navruzova NO "Clinical manifestations of COVID-19 coronavirus infection in pregnant women, measures for pregnancy and childbirth" Methodical recommendation.
- Ikhtiyarova, G. A., Kilicheva, V., Rozikova, D., & Tosheva, I. (2018). Microbiological changes in pregnancy with antenatal death of fetus. *Journal of research in health science*, 1(2), 18-22.
- Ikhtiyarova, G. A., Tosheva, I. I., & Narzulloeva, N. S. (2017). Causes of fetal loss syndrome at different gestation times. *Asian Journal of Research*, (3), 3.
- Ikhtiyarova, G. A., Tosheva, I. I., Aslonova, M. J., & Dustova, N. K. (2020). Prenatal rupture of amnion membranes as A risk of development of obstetrics pathologies. *European Journal of Molecular and Clinical Medicine*, 7(7), 530-535.

6. Ixtiyarova, G. A., & Ashurova, N. G. (2017). Tosheva I. I. Predgravidary preparation of women with a high group of perinatal risks and inflammatory diseases of the genitals. *European Journal of Research-Vienna, Austria*, (9-10), 53-62.
7. Mavlyanova, N. N., Ixtiyarova, G. I., Tosheva, I. I., & Aslonova, M. Zh., Narzullaeva NS The State of the Cytokine Status in Pregnant Women with Fetal Growth Retardation. *Journal of Medical-Clinical Research & Reviews*. ISSN, 18-22.
8. Tosheva II, Ikhtiyarova GA Cytokine Profile Changing in Pregnant Women with Chorioamnionitis// *Open Access Journal of Gynecology-2021*.6(4): 000227. P.1-6.
9. Tosheva, I. I., & Ikhtiyarova, G. A. (2019). Obstetric complications in pregnant women with premature discharge of amniotic fluid. *Biologiya va tibbiyot muammolari*, 42(115), 146-149.
10. Tosheva, I. I., Ikhtiyarova, G. A., & Aslonova, M. J. (2019). Introduction Of Childbirth In Women With The Discharge Of Amniotic Fluid With Intrauterine Fetal Death. *Problems and solutions of advanced scientific research*, 1(1), 417-424.
11. Ашурова Н.Г., Тошева И.И., Кудратова Д. Состояние готовности родовых путей у рожениц с дородовым разрывом плодных оболочек. *Репродуктивная медицина* 2 (35) 2018: 32–35.
12. Магзумова Н.М., Ихтиярова Г.А., Тошева И.И. Роль акушерского анамнеза в развитии хориоамнионита. *Проблемы биологии и медицины* № 1.1(126). 2021:169–171.
13. Магзумова, Н. М., Ихтиярова, Г. А., Тошева, И. И., & Адизова, С. Р. (2019). Микробиологические изменения в плаценте у беременных с дородовым излитием околоплодных вод. *Инфекция, иммунитет и фармакология*, (5), 158-162.
14. Нарзуллаева, Н. С., Тошева, И. И., Мирзоева, М. Р., & Ихтиярова, Д. Ф. (2018). Клинические и иммунологические аспекты миомы матки в сочетании с различными инфекциями. *Редакционная коллегия*, 232.
15. Тошева И.И., Ашурова Н.Г., Рахматуллаева М.М. Акушерские осложнения при длительном безводном периоде. *Хабаршысы вестник* № 1(85). 2019:115–118.
16. Тошева И.И., Ашурова Н.Г., Ихтиярова Г.А. Разрыв плодных оболочек в недоношенном сроке, как фактор развития акушерских осложнений//*Журнал Проблемы биологии и медицины*. - 2020. - №1. - С.76-79.
17. Тошева И.И., Ихтиярова Г.А. Дифференцированные подходы к методам родоразрешения при хориоамнионите. *Вестник оперативной хирургии и топографической анатомии* № 1 (01), Том 1, ISSN 2713–3273. 2020: 25–29.
18. Тошева И.И., Каримовова Г.К., Адисова С.Р. Изучение пбариçин акуерских осложнний наафона излити околоплодных вод в донашенном сроке. *Vestnik Tashkentkooy medicinckooy akademii*. 2020:170-171.
19. Тошева И.И., Мусаходжаева Д.А., Магзумова Н.М. Родовозбуждение при антенатальной гибели плода у женщин с излитием околоплодных вод и внутриутробной инфекцией. *Теоретической и клинической медицины* Том 1, № 6 2021: 111–113.
20. Тошева, И. И., & Ашурова, Н. Г. (2019). Исходы родов у беременных с преждевременным излитием околоплодных вод. *Вестник Дагестанской государственной медицинской академии*, (4), 34-37.
21. Тошева, И. И., & Ихтиярова, Г. А. (2020). Исходы беременности при преждевременном разрыве плодных оболочек. *РМЖ. Мать и дитя*, 3(1), 16-19.
22. Тошева, И. И., & Ихтиярова, Г. А. (2020). Патоморфология последов, осложнения беременности, родов и исходы новорожденных с дородовым излитием околоплодных вод. *Opinion leader*, (2), 56-60.
23. Тошева, И. И., Ихтиярова, Г. А., & Аслонова, М. Ж. (1999). Современные методы индукции родов у женщин с отхождением околоплодных вод с внутриутробными инфекциями. *Инфекция, иммунитет и фармакология*, 254.
24. Тошева, И., Ашурова, Н., & Ихтиярова, Г. (2020). Разрыв плодных оболочек в недоношенном сроке, как фактор развития акушерских осложнений. *Журнал вестник врача*, 1(1), 77-80.



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