

## Premature rupture of the membranes

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### Summary

Premature rupture of the membranes (= amniorrhea) occurs in 1% to 2% of all pregnancies and 30% of preterm births (earlier than 37 weeks) are due to the rupture of membranes. The rupture occurs if an imbalance between the resilience of the amnion and the pressure administered develops; this can have different reasons. An intact amnion with sufficient amniotic fluid is not only essential for the fetal development (lung, movement), but also protects the child from ascending infections. Regardless of the pregnancy week, an amniotic infection syndrome (AIS) clearly degrades the newborn's prognosis. The sensitivity of the laboratory parameters (e.g. interleukin-6 and procalcitonin), which can selectively detect a subclinical AIS, has yet to be proven by studies. Hence, depending on the pregnancy week, one has to decide whether to prolong the pregnancy, which would increase the risk for AIS and preterm birth.

### Introduction

A premature rupture of the membranes is defined as the rupture of the amnion after 37 weeks of gestation but prior to the first stage of labour. It occurs in 1% to 2% of pregnancies. In Germany, the English term PROM ("premature rupture of membranes") has increasingly been used for this phenomenon. In contrast, a preterm premature rupture of the membranes (PPROM) occurs before the 37<sup>th</sup> week of pregnancy and is the reason for 30% of preterm births. Differentiating between PROM and PPRM has mainly got therapeutic consequences, as it enables to decide on the appropriate intervention: prolonging pregnancy or initiating birth. Furthermore, PPRM is divided into subgroups in order to adapt therapy according to preterm birth risks.

Apart from a preterm rupture of the membranes, other forms of membranes rupture exist:

- Scheduled rupture of the membranes: rupture with completely opened cervix
- Preterm rupture of the membranes: rupture during opening period
- Upper rupture of the membranes: rupture above the lower eggpole, which stays intact.

## Physiology and Pathophysiology

The amniotic sac is composed of an inner and an outer membrane. The outer layer (chorion) is formed by trophoblasts, while the inner layer (amnion) is formed by embryoblasts. As a metabolic organ, it is part of the production and resorption of the amniotic fluid. Apart from the amniotic epithelium, the fetal kidney and the fetal lung produce the amniotic fluid. Resorption occurs via the amniotic sac and the gastrointestinal system when the fetus drinks the amniotic fluid.

Only a few ml of amniotic fluid are produced at the beginning of pregnancy but it increases when the fetus grows and can reach a liter at 36 weeks ga (gestational age). In the remaining weeks, the amount of amniotic fluid decreases. It has got a pH of 7.0 and is thus neutral.

Variances from the normal amount of amniotic fluid can give rise to maternal or fetal diseases. A hydramnios or polyhydramnios (Fig. 1) is defined as more than 2000ml of amniotic fluid. Reasons can be fetal swallowing disorders, esophageal atresia, tracheal stenosis, cerebral malformations and maternal diabetes. If the total amniotic fluid is less than 100ml, this is termed oligohydramnios. The absence of amniotic fluid is called anhydramnios. Reasons for a reduced amount of amniotic fluid can be, amongst others, pathologies of the fetal urogenital system (kidney malformations and renal aganesis, urogenital tract disorders). However, it is important to exclude a ROM in these cases.



Figure 1: Polyhydramnios

## Amniotic fluid index (AFI)

The AFI is determined by measuring the vertical height of the deepest pocket in each quadrant of the uterus, whereby excluding the umbilical and fetal parts from the area. The sum of the measurements is the AFI, the “Amniotic-Fluid-Index” (Table 1).

Table 1: Amniotic fluid index (AFI)

AFI	
< 5 cm	Oligohydramnios
5.0-18.0 cm	Normal amount of amniotic fluid
> 18.1 cm	Polyhydramnios

The amniotic sac surrounds the fetus and provides shelter from dehydration, compression of the umbilical cord, traumatic external influences and gives room for the child to move and grow. Besides, the amniotic fluid is necessary for the development of the lungs.

The reasons for a rupture of the membranes lie, on the one hand, in the mechanical stress applied on the membrane, e. g. during labour, multiple pregnancies or polyhydramnios. Apart from mechanical stress however, another possible reason is the decreased resistance of the amnion. Beginning at 20 weeks gestation, a lower synthesis of collagen (reduction in collagen-mRNA) and a reduced production of collagen-stabilizing enzymes, such as lysyloxidase, catabolize the amniotic sac. Another mechanism is the increased destruction of collagen by specific matrix metalloproteinases (MMPs), mainly MMP-1, -8 and -9. These bind to specific tissue inhibitors (TIMP). During normal pregnancy, the balance of TIMPs to the mentioned MMPs is towards the tissue inhibitors, thereby stabilizing the membranes. Labour or chorioamnionitis lead to an imbalance towards matrix metalloproteinases. An increased collagenolysis results in the destruction of the amnion, and consequently a reduced resistance of the membranes.

One major reason for a PROM is an ascending vaginal infection (Table 2). Pathophysiologically, the infection leads to the production of cytokines and prostaglandines (E<sub>2</sub> and F<sub>2</sub>) and, via a cascade of an increased production of matrix-metalloproteinases, to an increased collagenolysis. Furthermore, an infection increases labour and maturation of the cervix.

Table 2: Chorionamnionitis: most frequent bacteria

- Type B streptococci
- E. coli
- Fusobacteria
- Peptostreptococci
- Bacterioides
- Ureaplasma urealyticum

Further risk factors for a PROM include vaginal bleedings in the first trimester, smoking and a preterm birth or a PROM in the patient's history (Table 3). The incidence of ROMs following intrauterine interventions (amniocentesis, chorionic villus sampling, cordocentesis and fetal surgery) lies at 1 in 150 to 1 in 3000. Especially if the ROM correlates with an amniocentesis, the probability for a spontaneous re-storation of the amniotic sac increases. For all PPROMS, the spontaneous closure rate lies at 0% to 15%.

Table 3: Risk factors for a PPROM

- Bacterial vaginosis
- Multiple pregnancy
- Polyhydramnios
- Preterm contractions
- Bleeding in the first trimester
- Nicotine abuse
- Preterm birth or PPROM in the patient's history

### Diagnosis

The anamnesis usually includes a sudden or increased vaginal fluid loss. This might or might not correlate with contractions. The differential diagnosis includes increased fluor due to the pregnancy itself or a vaginosis. Often, the patients falsely interpret it as an involuntary loss of urine, caused by the pressure applied by the fetus on the maternal bladder.

In order to monitor the contractions and the wellbeing of the child, a CTG in a horizontal position should be recorded. An abdominal ultrasound in order to document the child's position and estimate the amount of amniotic fluid remaining can be carried out. However, a sufficient amount of amniotic fluid does not exclude a rupture of membranes. Likewise, missing amniotic fluid does not confirm diagnosis. In order to prevent an iatrogenic infection, the speculum has got to be sterilized prior to the examination.

In 90% of the cases, the rupture of membranes can be detected by the visible loss of amniotic fluid (if necessary, with flocculus vernix) from the endocervical canal. Simultaneously, a bacteriological (microbiology and native) and a chlamydia smear have to be taken from the endocervical canal. Even if the percentage of false-negative results is high, a targeted antibiotherapy can be carried out in case of a positive result. Palpation of the cervix should always be avoided in a PPRM. In order to diagnose cervical insufficiency, transvaginal ultrasound is better than digital examinations during the preterm birth period.

If, by using specula, the ROM can neither be confirmed nor excluded, supplementary tests can help. Tiny amounts of amniotic fluid change the physiological pH in the vagina from acid (pH 4.2) to alkaline (pH of the amniotic fluid is 7.0). Litmus paper, nitrazine or bromothymol blue will stain blue when in contact with the amniotic fluid. The sensitivity of diagnosing a PROM via the pH lies at 94%, the negative predictive value at 93%, the specificity at 63% and the positive predictive value at 69%. Thus, this method has got few false-negative but numerous false-positive results.

In addition, the detection of certain proteins in the cervical or vaginal liquid can indicate to a ROM.

### IGFBP-1 ("insulin-like growth factor binding protein-1")

The IGFBP-1 is a 25 kDa protein that is produced in the fetal liver and in the decidua. In the amniotic fluid, it has a concentration of 10.5 to 350 mg/l. In contrast, in the maternal serum, it only has a concentration of 60 µg/l. Monoclonal antibodies against IGFBP-1 can detect the protein in vaginal secretions in a ROM. The result takes approximately five to ten minutes, depending on the manufacturer. The sensitivity and the negative predictive value lie at almost 100%, the specificity and the positive predictive value at 80%.

### fFN (fetal fibronectin)

The fetal fibronectin is a 500 kD glycoprotein, which is produced in the chorion and in the placenta. Its concentration in the amniotic fluid is five to tenfold higher than in the maternal plasma. The protein is also detected via monoclonal antibodies and the result also takes five to ten minutes. This method has got a sensitivity and negative predictive value of nearly 100%, however, it has a low specificity of only 70% and with only 74% a lower positive predictive value than the IGFBP-1 does.

The "gold standard" in the diagnosis of a PROM is the amniocentesis with instillation of a colouring agent. Due to the possible side effects (fetal intestinal necrosis and haemolytic anemia), methylen blue is no longer used. Instead, indigokarmin is the alternative. Because of being an invasive method that can lead to severe complications, this method has been rejected by many clinics. However, by combining the above-mentioned non-invasive methods, a

rupture of membranes can be securely diagnosed. The “gold standard” thus only carries historical value.

### Complications due to PROM

The risks for a newborn (Table 4) in a PROM partly arise because of the insufficient amniotic fluid and the missing protection from ascending infections when the amniotic sac is defective which can ultimately result in a preterm birth. Depending on the gestational age, a risk-adapted therapy concept has got to be developed for every case. Undoubtedly, a neonatal sepsis preceded by an amniotic infection will significantly exacerbate neonatal morbidity and mortality independent of gestational age. Thus, the signs for an amniotic infection syndrome have to be identified early and, if it is diagnosed, pregnancy has got to be terminated.

The two major respiratory problems for the newborn are pulmonary hypoplasia due to insufficient amniotic fluid and the respiratory distress syndrome (RDS), triggered by preterm birth. The missing amniotic fluid not only disturbs the development of the fetal lungs, but also affects the child’s ability to move freely within the uterus. Especially when a PROM occurs in early pregnancy and if the pregnancy is prolonged over several weeks, there is a significant risk for contractures and deformities.

The major maternal risk (Table 4) caused by a PROM is a spreading infection that can eventually lead to a sepsis. Due to the infection, the risk for postpartal atonia, endomyometritis as well as fever in the puerperium increases. Sporadically, an early placental abruption occurs.

Table 4: Maternal and fetal risks in PROM

Maternal risks	Fetal risks
Amniotic infection syndrome	Preterm birth
Sepsis	Neonatal sepsis
Placental abruption	Pulmonary hypoplasia
Postpartal atonia	Respiratory distress syndrome
Fever and endomyometritis in puerperium	Contractures and deformities

### Amniotic infection syndrome (AIS)

Maternal and neonatal morbidity/mortality increases significantly with an amniotic infection. Thus, in an ROM, the focus lays on the surveillance of the respective clinical parameters in order to rapidly detect the infection and take the appropriate precautions.

Clinically, a pressure-sensitive uterus with a foul-smelling amniotic fluid loss and increasing contractions can diagnose the AIS. Parallel to a rise in temperature ( $> 38\text{ }^{\circ}\text{C}$ ), the mother usually develops tachycardia ( $> 100\text{ bpm}$ ). In the CTG, a fetal tachycardia with a loss of accelerations and reduced oscillation is visible.

In order to early diagnose an AIS, laboratory check-ups have to be performed regularly in order to examine the above named clinical parameters. A leucocytosis ( $> 15\ 000/\mu\text{l}$ ) and a rise in CRP can be signs for an infection. However, these clinical and biochemical parameters appear only very late in the course of the infection, whereby not correlating with the actual onset of the infection. Thus, an early detection of the infection is impossible with these parameters.

This becomes especially apparent when histopathologically inspecting the placenta after delivery in a PPROM. In 1% to 2% of cases, the infection becomes visible. In literature, the rate of primary newborn sepsis after a PROM lies between 4% and 6%.

Interleukin-6 as well as procalcitonin from maternal serum rises earlier than the CRP and can be used for an early diagnosis of a subclinical infection. However, more studies have to be carried out in order to justify their clinical benefit.

Another problem of laboratory diagnostics lies in the RDS prophylaxis (respiratory distress syndrome) with glucocorticoids that is necessary in a PPROM occurring earlier than 34 weeks pregnancy. The glucocorticoids can have influence on the laboratory parameters (leucocytosis), at least during lung maturation.

### Therapy

The therapeutic goal when dealing with a PROM is the prevention of an AIS. If the PPROM occurs before 34 weeks gestation, a prolongation of pregnancy is indicated in order to prevent preterm birth associated morbidity. Below, different tactics on the management of PROM depending on the gestational age are outlined. The basis is the AWMF guideline (015/029) "Recommendations for the management of PROM" (analogous to the guidelines of the German society for Gynecology and Obstetrics, DGGG) (Fig. 2).

Prophylactic antibiotherapy reduces the risk for developing AIS and thus maternal and neonatal morbidity, and can attain the prolongation of pregnancy. In the case of a manifest or beginning AIS or in severely immunocompromised pregnant women, an immediate delivery is indicated.

Studies have not yet been able to prove, which antibiotic is best suitable and how long antibiotherapy would have to be carried out. In the first place, this therapy is aimed at B streptococci (GBS) and E. coli. Penicillin G should be administered at an introductory dose of 5 million units with a subsequent dose of 2.5 million units every four hours until birth. Alternatively, ampicillin or cefazolin can be used.

If the preterm rupture of membranes occurs before 37 weeks gestation, an antibiotherapy independent of the GBS status should be initiated. After 37 weeks of gestation, the antibacterial therapy can be initiated 18 hours after PROM in case of a negative GBS smear and missing signs for AIS.

Between 24 (in seldom cases 23) and 34 weeks gestation, RDS prophylaxis with a 12 mg intramuscular injection of bethamethason twice within the first 24 hours has got to be administered. The advantage of a simultaneous tocolysis until the lung maturation is concluded (48 h) has been proven. From 23 weeks of gestation onwards, the pregnant woman has got to be transferred to a perinatal center.

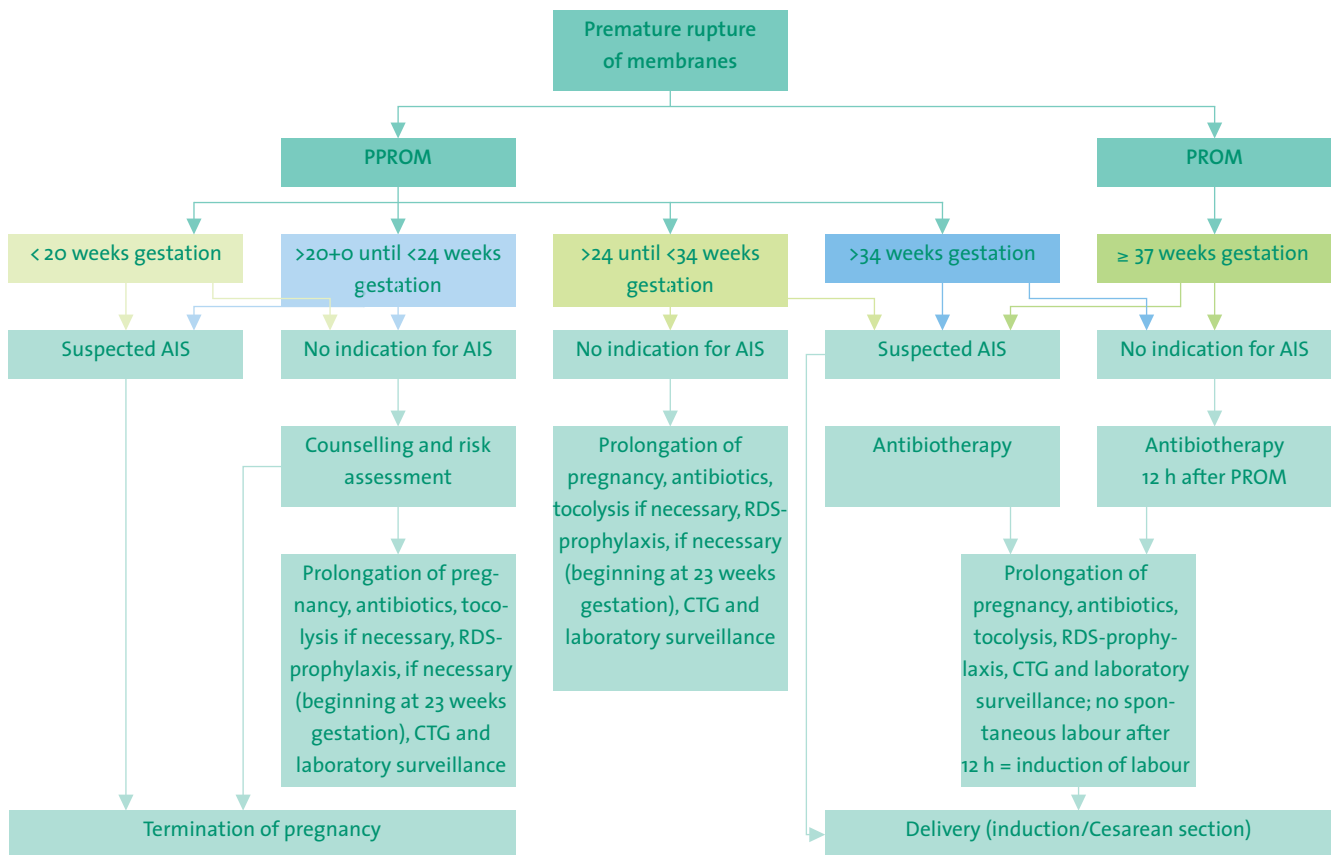


Figure 2: Treatment guidelines in preterm rupture of membranes

### Procedure at less than 20 weeks gestational age

If there are no clues for an AIS, expectant management is possible. However, CRP levels and white blood cell counts should be checked regularly. If, in a PROM with a persisting oligohydramnios or anhydramnios, a spontaneous closure of the amniotic sac is improbable (after approximately 7 to 10 days), a decision together with the patient has to be taken, whether or not to end the pregnancy.

### Procedure at 20 to 24 weeks gestational age

By regular check-ups of the respective inflammatory parameters, expectant management is possible. Advantages of an antibiotherapy have not been proven yet, but it is still recommended. An RDS prophylaxis can already take place beginning at 23 weeks gestational age after an individual case discussion with all involved specialists including a thorough discussion and agreement with the patient. Tocolysis should only be administered when in labour.

### Procedure at more than 24 completed weeks of gestation until 34 weeks gestational age

If there is no suspicion for an amniotic infection, lung maturation induction takes place under tocolysis. The use of an immediate prophylactic antibiotherapy is indicated. Daily check-ups of initially unobtrusive inflammatory parameters (white blood cell count and CRP) are advisable. When having reached 34 weeks gestation, an active induction of labour or a cesarean is indicated.

### Procedure in > 34 weeks gestational age

In a PROM before 37 weeks gestation, antibiotherapy is immediately initiated. After 37 weeks gestation and no sign for AIS, the use of antibiotics can be considered 18 hours after the event. If, within 12 to 24 hours after a ROM no spontaneous labour has occurred, the active induction of labour is indicated.

The AWMF-guideline provides instructions. However, we have to consider that not all recommendations are based on evident studies, and that in the case of insufficient data, expert opinion was added. Especially between 30 and 34 weeks gestation, the data is scarce. Small studies could show that after 30 weeks gestation and after lung maturation has been completed (48 h), a subsequent delivery by selective cesarean section raises perinatal survival to almost 100%. Neonatal morbidity is, compared to a prolonged pregnancy with histologically proven chorioamnionitis, significantly lower. Thus, induction of labour is also reasonable at 32 weeks gestation after having completed lung maturation.

The goal should be to prevent infections with severe fetal and maternal risks. This can be prevented by an active induction of labour in PPRM. In contrast, expectant management consists in the administration of antibiotics, glucocorticoids and tocolysis. This procedure reduces morbidity caused by preterm birth; however, it implies an increased risk for infection. Laboratory parameters that could detect an infection have not been introduced into clinical routine yet.

### Prophylactic antibiotics in the rupture of membranes

#### Is the use of antibiotics during pregnancy justified?

#### Results of the ORACLE-1 and-2 studies

The data of the ORACLE study (Great Britain), published in the Lancet in 2001, shows that in PROM and also in imminent preterm birth, the prognosis of the newborn is improved by the use of erythromycin. Ever since, the use of antibiotics in pregnant women has increased.

These results have been questioned in follow-up studies. The ORACLE Children Study I could show that the number of children aged seven having functional limitations is similar in the group treated with antibiotics and the group without antibiotic treatment following PROM. The "ORACLE Children Study II" examined children whose mothers had been treated with antibiotics during pregnancy but had had no signs for a PROM. In this case, the children of pregnancies that had been treated with antibiotics had a higher percentage of cerebral palsy (3.3% in antibiotic children compared to 1.9% in the control group).

These results can be explained by an increased resistance due to the frequent use of antibiotics as well as the insufficient dosage. The dosage was high enough to maintain pregnancy, but too low to eliminate all bacteria.

With our current knowledge, pregnancy can be prolonged by the administration of antibiotics in a PROM and the differential administration of antibiotics in the absence of PROM.

### Keywords

Pregnancy, PROM, amniotic infection, preterm birth

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#### Conflict of interest

The author declares that there is no conflict of interest as defined by the guidelines of the International Committee of Medical Journal Editors (ICMJE; [www.icmje.org](http://www.icmje.org)).

#### Manuscript information

Submitted on: 26.02.2009

Accepted on: 03.03.2009



# CME-Continuing Medical Education

## Premature rupture of the membranes

### Question 1

Which statement concerning PPRM is true?

- a. It occurs at 37 weeks gestation.
- b. In 30% of cases, it is the reason for preterm birth.
- c. It is always accompanied by preterm labor.
- d. Determining the AFI (amniotic fluid index) confirms the diagnosis.
- e. Immediate antibiotics is indicated.

### Question 2

Which statement concerning the AFI (amniotic fluid index) is correct?

- a. It is determined via transvaginal ultrasound.
- b. When determining the AFI, only the depth of the biggest pocket of fluid is measured.
- c. An AFI of 5.0 to 18.0 cm is the normal amniotic fluid amount.
- d. The AFI is one possibility to diagnose AIS.
- e. None of the statements is correct.

### Question 3

A preterm rupture of membranes following amniocentesis:

- a. is an indication for immediately terminating pregnancy,
- b. spontaneously closes in 10% to 15% of cases,
- c. is an indication for an immediate tocolysis,
- d. is a sign for a normal outcome of pregnancy,
- e. none of the statements is correct.

### Question 4

Diagnosis of a preterm rupture of membranes is possible by:

1. speculum examination
2. bacterial smear
3. palpation of the cervix
4. IGFBP-1 (“insulin-like growth factor binding protein-1”) detection, if necessary

- a. Statement 1 is correct.
- b. Statement 3 is correct.
- c. Statements 1 and 3 are correct.
- d. Statements 1, 2 and 4 are correct.
- e. No statement is correct.

### Question 5

The amniotic infection syndrome (AIS):

- a. does not bear any maternal risks,
- b. ought to be a reason to prolong pregnancy,
- c. is safely diagnosed by the CRP,
- d. can be excluded by a negative smear,
- e. is compatible with a spontaneous birth.

### Question 6

Which of the antibiotics should not be used as a prophylaxis of AIS?

- a. Penicillin G
- b. Cefazolin
- c. Doxycycline
- d. Erythromycin
- e. Ampicillin

### Question 7

In a rupture of membranes prior to 24 weeks gestation, the following procedure is *wrong*:

- a. Transfer to a perinatal center
- b. RDS prophylaxis
- c. Antibiosis
- d. Misoprostol
- e. CTG control

### Question 8

Lung maturation (RDS prophylaxis):

- a. is also induced between 34 and 37 weeks gestation
- b. consists of 2 x 12 mg Betamethason within 24 hours
- c. does not change any laboratory parameters
- d. should be induced from 20 weeks gestation onwards
- e. has got no side effects

### Question 9

No reason for an oligohydramnios is/are:

- a. PPRM
- b. congenital urinary tract anomalies
- c. esophageal atresia
- d. placental insufficiency
- e. urinary tract disorders

### Question 10

The IGFBP-1 (“insulin-like growth factor binding protein-1”):

- a. is produced in the fetal liver
- b. is detectable in the mother’s serum in high concentrations
- c. found in vaginal fluid is a 100% confirmation of the rupture of membranes
- d. is a 500 kD glycoprotein
- e. None of the statements is correct.