MATERNAL AND FETAL COMPLICATIONS of PROM

Maternal complications of PROM

1- Chorioamnionitis:

Definition:

Chorioamnionitis defined as infection of the chorioamnion & is thought to be both a cause & a consequence of PPROM ***(B.Magee et al., 2013)***.

Clinical chorioamnionitis is diagnosed when there is fever (37.8℃) plus any two of the following: maternal tachycardia, fetal tachycardia, uterine tenderness, foul odor of amniotic fluid or maternal leukocytosis. ***(Casey and Cox, 1997; Cunningham et al., 2010)***

Incidence:

Its incidence ranges from 4.2-10.5%. The occurrence of chorioamnionitis after PROM seems to be greater in hospital caring for low socioeconomic segments of population ***(Osmanagaoglu et al., 2004).***

Microbiology of chorioamnionitis:

Although the exact pathogenesis of amnionitis is unknown, data from several studies would indicate that these infections are similar to other pelvic infections, and so acute chorioamnionitis is polymicrobial in nature ***(Saji et al., 2000)***.

The microorganisms isolated from culture in study by ***(Silva et al., 2003)*** such as dipheroides, ureaplasma urealyticum and mycoplasma hominis were the same as those detected in cultures of maternal cervical secretion. This finding is in accordance with the ascending pathway of microbial invasion in PPROM suggested by other authors. The ascending infection seems to be the cause of chorioamnionitis, leading to premature delivery and PROM.

The following list shows organisms isolated from the amniotic fluid of women with acute chorioamnionitis.

Aerobic bacteria:

- Group B streptococci (GBS).
- Enterococci species.
- E. coli.

Anaerobic bacteria:

- Peptococci species.

- Peptostreptococci species.
- Clostridium species.

Others:

- Gardenella vaginalis.
- Mycoplasma hominis.
- Ureaplasma urealyticum.

(Kenyon et al., 2001)

Factors affecting the development of chorioamnionitis:

A) Latent period:

Latent period means latency from membrane rupture to delivery. It increases risk of intrauterine and neonatal infection and oligohydramnios. Few conditions carry higher risk of delivery soon after their onset. However, of those women with PPROM who are amenable to conservative management, approximately half will remain pregnant for at least 1 week after membrane rupture (***Mercer, 2004)***.

The median and mean latency periods increase with decreasing gestational age at membrane rupture, with approximately 25% remaining undelivered at least 1 month after membrane rupture when PPROM occurs before or near the limit of viability ***(Mercer, 2004)*** .

B) Bacterial inhibitory activity of amniotic fluid:

The antibacterial activity of the amniotic fluid appears after 30 weeks gestation, increasing until term, is diminished in recognized high risk group (malnutrition and low socioeconomic background), and might be directly influenced by a nutritional factor (zinc) ***(Yoon et al., 1998)***.

Contamination of amniotic fluid is probably common phenomenon and is usually controlled be host defenses. Clinical intra-amniotic infection with PROM occurs when these defenses fail ***(Malik et al., 1996)***.

C) Gestational age (GA):

The risk of infection increases with decreasing gestational age at time of membrane rupture, and with increasing duration of membrane rupture. It occurs in 2% of women with PROM at term. With PROM remote from term, chorioamnionitis is much more common, complicating about 10% of women ***(Ramsey et al., 2005)***.

D) Cervical incompetence:

Cervical incompetence is the inability of the uterine cervix to retain an intra- uterine pregnancy in absence of contraction or labor. Once the cervical barrier is breached, ascending infection may enter into the intra-uterine space causing stimulation of the inflammatory

process leading to further cervical ripening and exposure to infection which culminates of membrane rupture, myometrial contractility and preterm labor or any combination of these ***(Manju et al., 2006)***.

E) Intercourse:

Sayle at al. (2001) found no evidence that sexual activity in late pregnancy increased women's risk of PROM and or preterm delivery between 29 – 36 weeks gestation.

It was found that orgasm was an important cofactor with chorioamnionitis in the high frequency of PROM that follows intercourse. Also seminal ejaculate affects the chorioamnion by changing its properties leading to rupture with no change in the intra amniotic pressure ***(Naeye and Peters, 1997)***.

F) Residual amniotic fluid volume after PROM:

The frequency of chorioamnionitis in patients with PROM with qualitative amniotic fluid volume that measured 2 cm or more in vertical diameter was 9.2% versus 47.3% of the patient who had amniotic fluid volume that measured less than 1 cm in vertical diameter ***(Yoon et al., 1999)***.

Adverse effects of chorioamnionitis:

1- Adverse maternal effects:

- *Maternal mortality:*

Di naro et al. (2003) reported no maternal death in 29 women with chorioamnionitis.

Lahra and Jeffery (2004) reported no maternal death in (2076/3928) with histologic chorioamnionitis.

- *Maternal morbidity:*

Although mortality from acute amnionitis is rare, significant maternal morbidity may still occur when CS is required. About 11% of patients with amnionitis delivered by CS may require additional antimicrobial therapy for persistent serious pelvic infection, while about 4.5% of them may require debridement and drainage of subcutaneous wound infections. In patient with amnionitis delivered vaginally, about 1.5% requires additional therapy ***(Murtha et al., 2000)***.

Patient delivered by CS are more liable for major complications as pelvic abscess and pelvis septic thrombophlebitis. Patients who have chorioamnionitis of some duration, which has not been appropriate managed, may develop Gram negative septicemia and septic shock ***(Casey and Cox, 1997)***.

2- Adverse fetal and neonatal effects:

- *Fetal and neonatal mortality:*

Premature rupture of membranes continues to be leading cause of neonatal morbidity and mortality. It occurs in approximately 2 – 8% of the pregnancies but it is associated with 20% of prenatal death. Complications include maternal and fetal infection, preterm labor, asphyxia and if earlier in pregnancy pulmonary hypoplasia and anatomical distortion as a result of amniotic band ***(Nova Flores et al., 2003)***.

- *Fetal and neonatal morbidity:*

Sepsis, mostly caused by group B streptococcus, is one of the most serious acute morbidities result from PROM especially at an early gestational age before 29 weeks ***(Mercer, 2003)***.

About 24% of the neonates have either congenital pneumonia or septicemia. Other complications such as asphyxia, intracranial hemorrhage, necrotizing enterocolitis and seizures are uncommon in infant of mothers with intra-amniotic infection. ***(Lewis et al., 1996)***

Diagnosis of chorioamnionitis:

I- Clinical criteria:

Clinical chorioamnionitis is diagnosed when there is fever (>37.8° C) plus any two of the following: maternal

tachycardia (>100 beats per minute), fetal tachycardia (>160 beats per minute), foul odor, vaginal discharge or uterine tenderness. However clinical symptoms and signs are frequently inconsistent or subtle, and many affected women are virtually symptom free ***(Wiwanitkit, 2005)***.

William et al. (2005) found that fever is the only reliable indicator for clinical chorioamnionitis.

A temperature of 38℃ or more accompanying ruptured membranes implies infection.

II- Laboratory criteria:

A- Tests performed on maternal blood:

1- Total leukocytic count:

Normal pregnancy is associated with leucocytic changes causing a significant rise in number of these cells; therefore, the ability of this serum marker in the diagnosis of intra-amniotic infection may be limited. Sensitivity and specificity of the results are quite varied and are dependent on leukocyte level ***(Carroll et al., 1998)***.

2- C-Reactive protein (CRP):

In a study by ***Nowak et al. (2000),*** to analyze the efficacy of serum CRP, ESR and maternal white

blood cell count serial elevations in the prediction of chorioamnionitis in case of PROM. It was concluded that CRP was found to be most reliable indicator of histological chorioamnionitis and indicated the presence of intra-amniotic infection earlier than ESR or WBC.

An elevated CRP concentration in vaginal fluid is a risk factor in intra-amniotic inflammation / infection and impending preterm delivery in PPROM ***(Shim et al., 2005).***

3- ESR:

During pregnancy there is increased of globulin and fibrinogen and this will falsely increase the ESR so that the use of this marker to detect chorioamnionitis is not feasible ***(De Dooy et al., 2001)***.

4- Serum cytokines:

Bacterial colonization of the choriodecidual interface induces production of pro-inflammatory cytokines that in turn lead to neutrophil activation, synthesis and release of uterotonins such as prostaglandins and metalloproteinases ***(Park et al., 2005).***

They are protein mediators exist in numerous tissues and organs involved in regulation of physiological processes such as chemotaxis, cell proliferation and inflammation. Serum level of interleukin-6 is significantly higher in mother with chorioamnionitis than in those without ***(Von Minckwitz et al., 2000)***.

High interleukin-6 (IL-6) concentrations are associated with microbial invasion of amniotic fluid, chorioamnionitis and preterm delivery. IL-6 has a better diagnostic value for these complications than other markers that are studied in the amniotic fluid which include gram staining, glucose levels, white blood cells and leukocyte count ***(Annells et al., 2004)***.

IL-6 and IL-8 are elevated in maternal serum and amniotic fluid in patients with premature rupture of membranes with microbial invasion of amniotic cavity before development of clinical symptoms and signs of chorioamnionitis ***(Jacabsson et al., 2003)***.

Comparative study done by ***Hatzidaki et al. (2005)*** included 58 neonates who were born after PPROM and 51 control neonates. IL-6 levels were measured in umbilical cord blood, maternal blood during delivery and in neonatal blood taken on the 4^{th}

day of life. IL-6 concentrations in maternal blood, cord blood and neonatal blood were significantly higher in neonates with sepsis, compared with those without sepsis. Choosing 108.5 pg/ml as a cut-off value of IL-6 in umbilical cord blood for neonatal sepsis resulted in sensitivity 90%, a specificity 97.4%, a positive predictive value 94.7%, and negative predictive value 94.0%.

Witt et al. (2005) collected amniotic fluid, placental tissue and amniotic membranes, during preterm cesarean sections, for bacterial culture. In addition, they determined IL-8 concentrations in maternal serum, amniotic fluid and cord blood and correlated them with the various intra-amniotic pathogens isolated by bacterial culture. IL-8 concentrations were determined in amniotic fluid in 107 cases, in cord blood in 185 cases and in maternal blood in 158 cases. Women with intra-amniotic ureaplasma urealyticum infection had significantly higher amniotic fluid concentration of IL-8 than those without.

5- Serum complement activity:

Serum complement levels are found to be decreased in case of PPROM than the normal pregnancies because

of the presence of subclinical infection ***(Malik et al., 1996).***

6- *Serum neutrophil granule products:*

Lan et al. (2003) included 52 patient between 24 and 34 weeks gestation with PPROM in their study. Fifty-two control subjects between 25 and 30 weeks gestation were recruited for baseline defensin and lactoferrin levels. Mean defensin levels on admission in patients without histologic chorioamnionitis were compared with patients in whom histologic chorioamnionitis developed (520ng/ml vs. 9163ng/ml). The same relationship was not demonstrated for lactoferrin. With use a defensin value of 1500 ng/ml on admission, the sensitivity is 76% and the specificity is 94% in predicting histologic chorioamnionitis.

7- Serum soluble intercellular adhesion molecules I:

Zou et al. (2004) studied 55 pregnant women with PROM, including 18 pregnant women with PPROM and also 20 normal ELISA for soluble intracellular adhesion molecule I. Chorioamnionitis was histologically confirmed after delivery. The results revealed that (1) Maternal serum level of soluble intracellular adhesion molecule I and CRP were

significantly higher in women with PROM than those without it; (2) Maternal serum levels of soluble intercellular adhesion molecules I and CRP were significantly higher in women with chorioamnionitis than those without it; (3) The sensitivity, specificity, positive predictive value and negative predictive value of maternal serum soluble intercellular adhesion molecules I (cutoff 104.7 ng/ml) for diagnosing chorioamnionitis were 100%, 91.2%, 87.5%, 100% while sensitivity, specificity, positive predictive value and negative predictive value of CRP (cutoff 1.03 mg/dl) were 81.0%, 73.5%, 65.4%, 86.2%.

B-Tests performed on amniotic fluid:

- *Gram stain of amniotic fluid:*

  It is found that Gram stain is 80% sensitive and 91% specific

in detecting intra-amniotic infection when the result is interpreted as positive with either organisms or leukocytes, as compared with a sensitivity of 45% and specificity of 97% when the result is interpreted a positive only for the presence of organisms ***(Hussy et al., 2001)***.

Romero et al. (2000) found that, a positive gram stain has 93.3% positive predictive value and negative gram stain has 85.4% negative predictive value. The accuracy of the test depends on the concentration of bacteria at time of sampling.

- *WBCs in the amniotic fluid:*

Elevated C-reactive protein, white blood cell count and granulocyte band forms in the maternal blood have been shown to correlate with subclinical amnionitis and preterm birth ***(Steinborn, 2000)***.

WBC count of 15.000/ml or greater, band cell percentage greater than 10%, C-reactive protein greater than 10mg/ml are associated with preterm labor, with at least one parameter elevated suggesting the presence of infection as a cause ***(Atorbe and Czaj, 2004)***.

- *Amniotic fluid culture :*

Amniotic fluid culture for aerobic an anaerobic organisms, with its inherent 24-72 hours delay in result reporting, must be performed to identify specific organisms involved and aid in proper antibiotic prescription when indicated. Culture technique must be as aseptic as possible, so trans-

abdominal amniocentesis may be used for collection of amniotic fluid sample ***(Naef et al., 1998)***.

- *Leukocyte elastase test:*

The amniotic fluid neutrophil elastase had the best screening efficiency in predicting histologic chorioamnionitis. Using amniotic fluid cut-off level of 0.15 microg/ml for neutrophil elastase and 250 IU/ml for LDH, the sensitivity, specificity, positive and negative predictive value for histologic chorioamnionitis were 88.9% versus 84.1%, 73.3% versus 66.7%, 90.9% versus 88.1% and 68.8% versus 58.8% respectively. So amniotic neutrophil elastase and LDH are useful marker in predicting histologic chorioamnionitis ***(Kidokoro et al., 2006).***

The concentration of nitric oxide, interleukin-6 and leukocyte elastase in AF were all higher in chorioamnionitis cases rather than in normal pregnant women ***(Daoud et al., 2006).***

- *Amniotic fluid glucose concentration:*

Buhimschi et al. (2006) identified the use of vaginal amniotic fluid (VAF) glucose measurements in predicting infection of the amniotic fluid retrieved by Trans-abdominal amniocentesis in women with

PPROM. Glucose concentration for paired abdominal-vaginal AF samples was determined. They concluded that VAF glucose measurement has less than 5mg/dl have a predictive value but low sensitivity for detection of intra-amniotic infection in women with PPROM.

- *The limulus amebocyte lysate assay:*

The test is used to detect bacterial endotoxins. This test is 87.5% sensitive and 99% specific ***(Benedetto et al., 2006).***

- *Amniotic fluid nitric oxide metabolites:*

Daoud et al. (2006) assessed levels of nitric oxide and cytokines in amniotic fluid obtained from 12 patients with severe chorioamnionitis and 89 patients undergoing diagnostic amniocentesis. The concentrations of nitric oxide, IL-6 and leukocyte elastase were all higher in sever chorioamnionitis than in normal pregnant women.

Elevation of total nitrate and nitrate concentration in vaginal secretions has been shown to accompany PROM, and that it precedes preterm delivery ***(Nakatsuka et al., 2000).***

- *Amniotic fluid granulocyte colony stimulating factor (G-CSF):*

Hoskins et al. (1997) they concluded that: 1- Amniotic fluid G-CSF level is elevated in chorioamnionitis. 2- An amniotic fluid G-CSF level >2000pg/ml is a strong positive predicator of chorioamnionitis. 3- Elevated amniotic fluid G-CSF level appear to be more reliable in predicting chorioamnionitis than any other single test currently used in clinical practice.

C-Ultrasonography:

1- *Amniotic fluid volume:*

Vermillion et al. (2000) performed a non concurrent prospective study included a total 225 patients with PROM; 131 were included in group 1 (AFI<5cm) and 94 in group 2 (AFI>5cm), univariate analysis demonstrated that patients in group 1 had a significant increase in the frequency of clinical chorioamnionitis (P<001). In the multiple logistic regression of clinical analysis incorporating risk factors for prenatal infections, an AFI<5cm was the only risk factor that demonstrate significant independent association with clinical chorioamnionitis (P=0.024).

Amniotic fluid index of <5cm after PROM was found to be associated with higher rates of positive

amniotic fluid culture results , clinical and histological chorioamnionitis and higher level of amniotic fluid interleukin-6, interleukin-1 and tumor necrosis factor ***(Yoon et al., 1999).***

2- Fetal biophysical profile (BPP):

Fetal biophysical profile (non-stress test, fetal breathing movements, fetal movements and fetal tone) has been described as an early predicator of fetal infection in patients with PROM and no clinical signs of infection or labor. In patients whose last biophysical scores were 7 or less, the frequency of infection was 93.7%, whereas the frequency of infection was only 2.7% with biophysical scores of 8 or more ***(David et al., 1999).***

Ghidini et al. (2000) studied 166 pregnant women with PROM and found that neither abnormal BPP score within 24 hours of delivery nor abnormal results of its individual component indicated histologic evidence of intra-uterine infection. They found no single BPP parameter correlated with the severity of intra-uterine infection, even the most sensitive component, e.g., non stress test, would miss at least one

third of cases of intra-uterine infection (false negative), whereas even the most specific component, i.e., absent fetal tone, would result in false-positive rate of at least 8%, with consequent unnecessary delivery of uninfected neonates at low gestational age.

3- Umbilical Artery Doppler:

Bacteria in the amniotic fluid may cause vasospasm of umbilical vessels. However, Doppler measurement of systolic-diastolic ratio (S/D) of the umbilical artery doesn't predict clinical chorioamnionitis in patients with PROM (***Leo et al., 2002).***

2- Postpartum endometritis:

Incidence:

It is the most common obstetric infection. It affect approximately 1-3% of women delivered vaginally and 10-30% of those delivered with CS ***(Casey and Cox, 1997).***

Causes:

Postpartum endometritis is a polymicrobial ascending infection by organisms that constitute the normal vaginal flora,

usually a mixture of aerobic and anaerobic organisms. The most common isolated organisms involve group B streptococci, gardenella vaginalis, E. coli and mycoplasma ***(Benitz et al., 2000)***.

Diagnosis:

The most important element in the diagnosis is development of fever. The temperature should exceed 38°C on two occasions 4 hours apart, lower abdominal pain, foul vaginal discharge. The pelvic examination will reveal extremely tender uterus and foul smelling lochia. Laboratory investigations usually show leukocytosis. Blood culture will be positive in approximately 10% of the cases ***(Casey and Cox, 1997)***.

3- **Placenta abruption**:

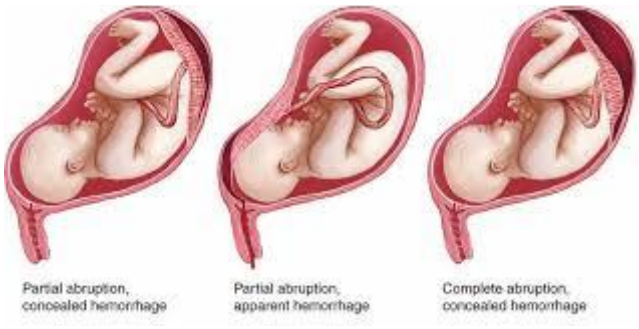


Fig.(5): Types of placenta abruption.

The separation of the placenta from its site of implantation before delivery has been variously called abruptio placenta, placenta abruption and in Great Britain, accidental hemorrhage (***Cunningham et al., 2010)***.

Holmgren et al. (1997) found that the incidence of abruption-placenta in the women with singleton pregnancies less than 24 weeks gestation who had ruptured membranes for at least 24 hours was 5.6% significantly higher than the 1.47% observed among women in the control group.

Fetal and neonatal complications of PROM

1- Preterm labor:

Preterm birth is one of the major clinical problems in obstetrics and neonatology as it is associated with prenatal mortality, serious neonatal morbidity and in some cases childhood disability. It is reported that 60-80% of all neonatal mortality and morbidity is due to preterm birth ***(Roy et al., 2006)***.

Spontaneous preterm birth account for around 70% of all preterm birth and is either due to preterm labor or preterm rupture of membranes (***Nina et al., 2005)***.

There are several factors associated with preterm birth: multiple gestation, previous preterm birth, maternal/fetal complications, low socioeconomic status, drug use and assisted reproduction all increase the rate of preterm birth ***(Timothy, 2006)***.

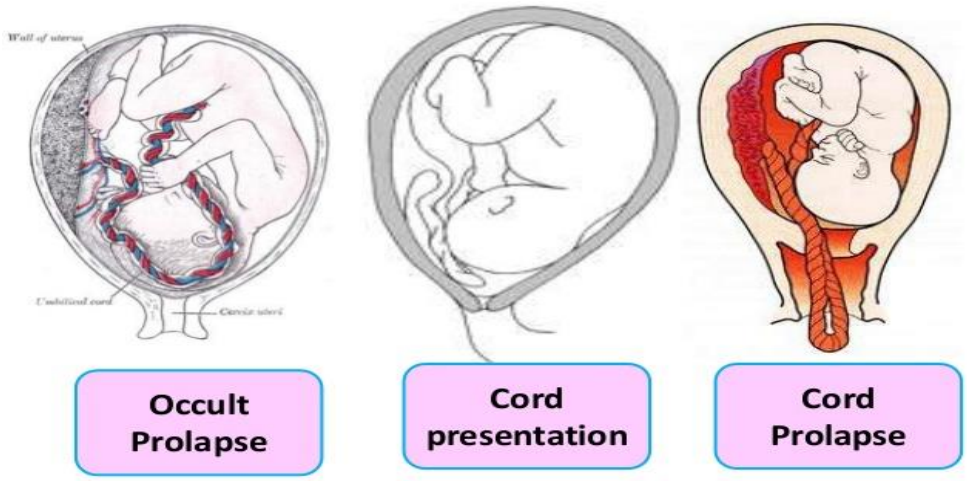
Because PPROM is associated with early delivery and prenatal infection, it is a potential risk factor for long term neurological morbidity. Cerebral palsy and cystic periventricular

leukomalacia has been linked to the presence of amnionitis, which is commonly seen with PPROM ***(Wu and Colford, 2000)***.

Several studies were done to attempt the prediction of preterm labor among patients with PPROM. Patients with PPROM and an AFI of <5cm were found to have spontaneous preterm delivery within 24-40 hours more frequently when compared to those with AFI>5cm ***(Park et al., 2001)***.

2- <u>Umbilical cord prolapse:</u>

Prolapse of the umbilical cord to a level at or below the presenting part exposes the cord to intermittent compression that compromises the fetal circulation. Depending on the duration and intensity of compression, may lead to fetal hypoxia, brain damage and death ***(Karen Kish et al., 2003)***.



<u>Fig.(6):</u> cord presentation and cord prolapse.

3- <u>Fetal and neonatal infection:</u>

Neonatal sepsis at term has an incidence of about 1/500 newborn. On the other hand, after prolonged PROM this incidence increase significantly. In cases of chorioamnionitis, this reaches 3-5% following PPROM ***(Bacchi et al., 2004)***.

The timing of clinical presentation is characterized by being in the first 6 days of life with majority presenting on the first day. Early onset neonatal sepsis is usually evident in the first few hours of life. The following risk factors much enhance the development of early onset neonatal sepsis:

1- Gestational age less than 37 weeks i.e., prematurity.
2- Intrapartum temperature of 38° C or higher.
3- ROM 18 or more hours before delivery.
4- Genital tract colonization with pathogenic organism is group B streptococci (GBS).

(Paul, 2001)

Neonatal sepsis is diagnosed if blood, urine or cerebrospinal fluid cultures are positive or if X-ray findings are consistent with pneumonia. Cord blood sample is also used for diagnosis of neonatal infection (leukocytosis and +ve C-reactive protein). Mortality rate in neonatal sepsis may reach 50% ***(Naeye and Peters, 1997)***.

4- <u>Prenatal asphyxia and fetal distress:</u>

Fetal distress requiring operative delivery or resulting in low 5-minutes Apgar scores is seen in 2% to 20% of PROM

patients. It may be due to abruption placenta, cord prolapse and cord compression (***Mercer, 2003)***.

5- <u>Respiratory distress syndrome (RDS):</u>

Respiratory distress syndrome (RDS) is the most common serious complication after PROM at any gestational age ***(Cunningham et al., 2010).***

To provide blood gas exchange after birth, the infant's lungs must rapidly fill with air while being cleared of fluid and the volume of blood that perfuse the lungs must increase remarkably. Some of the fluid is expressed as the chest is compressed during vaginal delivery, and the remainder is absorbed through the pulmonary lymphatics. Sufficient surfactant synthesized by type II pneumocytes, is essential to stabilize the air-expanded alveoli by lowering surface tension and thereby preventing lung collapse during expiration. If surfactant is inadequate, respiratory distress develops, and hyaline membranes form in distal bronchioles and alveoli. Because of this, respiratory distress in the newborn is also termed hyaline membrane disease ***(Cunningham et al., 2010)***.

6- <u>Brain damage:</u>

There is increased evidence demonstrating a relationship between intrauterine infection and the development of

intraventricular hemorrhage and periventricular leukomalacia with subsequent occurrence of cerebral palsy, which is thought to be mediated through the generation of pro-inflammatory cytokines in the case of chorioamnionitis. ***(Svigos, 2001)***

Long term neurological outcomes also increase in those born after maternal infection ***(Bacchi et al., 2004)***.

7- <u>Compression deformities:</u>

Normal infants may suffer the consequences of early onset severely diminished amniotic fluid. Adhesion between the amnion may entrap fetal parts and cause serious deformities, including amputation. Moreover, subjected to pressure from all sides, musculoskeletal deformities such as clubfoot are observed frequently ***(Cunningham et al., 2010).***

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