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Subclinical chorioamnionitis as an etiological factor in preterm deliveries

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Abstract
Objective: To determine the role of histological chorioamnionitis in preterm deliveries and to study its fetomaternal outcome.
Methods: Two hundred women in age group of 21 – 30 years were recruited for the study. Among these, 100 cases with gestational age ≥ 28 and < 37 weeks were taken as cases and 100 women with gestational age > 37 weeks as controls. Histopathologic examination of placenta was carried out after delivery in both the groups to look for evidence of chorioamnionitis or funisitis. Fetal outcome and maternal outcome was then noted and analysed.
Results: In cases, 49% subjects had evidence of histological chorioamnionitis (HCA) in their placenta and 26% subjects in controls had HCA (p=0.0007). The rates of neonatal complications were significantly higher in subjects with HCA both in cases as well as controls. Severe and high grade of histological chorioamnionitis was further associated with poor neonatal outcome. There was no significant difference between the maternal outcome of cases and controls.
Conclusion: Histological chorioamnionitis was significantly more prevalent in preterm deliveries and Neonates of patients with evidence of histologic chorioamnionitis are at higher risk for developing various neonatal complications.

Keywords: Preterm birth, histologic chorioamnionitis, funisitis

Introduction
The incidence of preterm birth continues to rise especially in developing countries. Among the number of known contributors for preterm birth chorioamnionitis which is inflammation of amnion, chorion and placenta has now been a well established cause for preterm labour. It can be clinical or subclinical i.e. histologic. Preterm labour may result from a fetal and/or maternal response to chorioamnionitis. Histological diagnosis occur after delivery and is based on semi-quantitative assessment of inflammatory cells in the chorioamniotic membranes, umbilical cord and placental disc. The majority of fetuses exposed to chorioamnionitis develop a systemic inflammatory response known as the fetal inflammatory response syndrome (FIRS). This is due to the fetus being in direct contact with infected amniotic fluid and/or inflammatory cell transfer from the uteroplacental circulation [1]. FIRS can itself be categorised as clinical or subclinical. Clinical FIRS is defined by a fetal plasma interleukin-6 >11 pg/mL whilst subclinical FIRS is defined histologically by funisitis and fetal vasculitis [1]. In the short term, very-low-birth weight infants born to mothers with clinical chorioamnionitis have 2 fold to 3 fold higher rates of respiratory distress syndrome, sepsis, and seizures compared with infants of similar birth weight born to uninfected mothers. Even preterm infants born to mothers with subclinical infection have higher rates of death within 24 hours of birth. In the long term, preterm infants of mothers with clinical chorioamnionitis have risk for cerebral palsy and for periventricular leukomalacia (The precursor lesion for cerebral palsy [2]. Though with technical advances in neonatal intensive care the survival rate of preterm infants has greatly increased but unfortunately, the proportion of surviving babies that develop long-term handicap has remained constant [3].
This study was an attempt to determine the role of histological chorioamnionitis in preterm deliveries and its feto-maternal outcome.

Methods

A one year prospective controlled study (unmatched) was conducted in the department of Obstetrics and Gynaecology in Indira Gandhi Medical College, Shimla from August 2014 to July 2015. The Study group included 100 cases (women admitted with spontaneous preterm labour in hospital) and 100 controls (women admitted with term labour), those who met the inclusion criteria. Cases were further divided into two groups according to gestational age:

Group 1- gestational age 28 to <32 weeks.
Group 2- ≥ 32 to < 37 weeks.
Approval was taken from the Ethics committee of the institute.

Cases

Inclusion criteria

- Gestational age ≥28 week to <37 week
- Singleton pregnancy
- Spontaneous onset
- Features of preterm labour
- Intact membranes

Exclusion criteria

- Gestational age <28 week
- Preterm premature rupture of membranes(PPROM)
- Clinically apparent chorioamnionitis
- Multiple pregnancy
- Fetal malformations & Intrauterine death
- Pregnancy complicated with medical disorders or obstetrical complications

Controls

Inclusion criteria

- Gestational age ≥ 37 week
- Singleton pregnancy
- Intact membranes

Exclusion criteria

- Gestational age <37 week
- Premature rupture of membranes (PROM)
- Clinically apparent chorioamnionitis
- Multiple pregnancy
- Fetal malformations & Intrauterine death
- Pregnancy complicated with medical disorders or obstetrical complications

After admission of the patient's detailed history and examination was done. Antibiotics were given to all as per standard protocol. Tocolytics were given for gestational age less than 34 weeks. Two doses of betamethasone were given 24 hours apart for all patients with gestational age less than 34 weeks.

Following delivery, the placenta was weighed and examined fresh for any macroscopic pathology according to a standard protocol. Thereafter, placenta was sent for histopathological examination in formalin 10% to the department of Pathology, IGMC Shimla. Tissue samples were obtained from each placenta including two sections from the umbilical cord, two 1-cm wide slices from the chorionic plate, four decidual sections from the placental disc, and a roll of membranes extending from the rupture point to placental margin. Placenta was then examined by Pathologist and histopathologic acute inflammation findings were evaluated according to a grading system modified from Salafia *et al.* [4].

Amnion and chorion-decidua

- Grade 1: Presence of one focus of at least five polymorphonuclear leukocytes.
- Grade 2: More than one focus of grade 1 inflammation or at least one focus of 5-20 polymorphonuclear leukocytes
- Grade 3: Multiple or confluent foci of grade 2
- Grade 4: Diffuse and dense acute inflammation

Umbilical cord

- Grade 1: Polymorphonuclear leukocytes within the inner third of the umbilical vein wall
- Grade 2: Polymorphonuclear leukocytes within the inner third of at least two umbilical vessel walls
- Grade 3: Polymorphonuclear leukocytes in perivascular Wharton jelly
- Grade 4: Panvasculitis and funisitis extending deep into Wharton jelly

Chorionic plate

- Grade 1: One focus of at least five polymorphonuclear leukocytes in subchorionic fibrin
- Grade 2: Multiple foci of grade 1 in subchorionic fibrin
- Grade 3: Few polymorphonuclear leukocytes in connective tissue or chorionic plate
- Grade 4: Numerous polymorphonuclear leukocytes in chorionic plate and chorionic vasculitis
- Chronic villitis was diagnosed in the presence of lymphoblast infiltration in chorionic villi.

Fetal outcome and maternal outcome was then noted and analysed in relation to histologic chorioamniotis.

Statistical analyses

A descriptive statistics was done for the baseline variables. All quantitative variables were estimated using measures of central location (mean, median) and measures of dispersion (standard deviation). Qualitative variables were described as frequencies and proportions. The results of the study were subjected to statistical analysis by Chi-square test (using Epi Info 7 Software) and ANOVA.

Results

Baseline demographic characteristics were similar among both the groups. [Table 1] In cases, 49% subjects had evidence of histological chorioamnionitis (HCA) in their placenta and 26% subjects in controls had HCA (p= 0.0007). Amongst cases in group 1, 81.2% subjects had HCA in comparison to 33.8% in group 2 ($p<0.05$). [Table 1] According to histologic grading, percentage of subjects with grade 3 and grade 4 chorioamnionitis was 12% vs 4% (p=0.037) and 13% vs 2% (p=0.003) in group 1 and group 2 respectively. Percentage of grade 1 and grade 2 did not differ significantly between cases and controls. Amongst cases incidence of grade 3 and grade 4 chorioamnionitis was 25.8% vs 5.8% (p=0.006) and 28.1% vs 5.8% (p=0.002) respectively. [Table 2]

Amongst 49 subjects with HCA in cases mean birth weight was 1462 grams, APGAR 4.82 and 7 at 1 minute and 5 minute respectively and in subjects without HCA, mean birth weight was1845 gram, APGAR at 1 & 5 minute was 6.11 & 8.22. Rate of admissions in NICU was higher 77.5% in cases with HCA and 37.2% in subjects without HCA. Higher number of neonatal complications was observed in subjects with HCA. 8.1% (4/49) of neonates died in subjects with HCA compared to none in subjects without HCA. In controls, 23% of NICU admissions were seen in subjects with HCA and only 8.1% neonates were

admitted in NICU in subjects without HCA. Neonatal complication rate was also higher in controls with HCA. In cases with chorioamnionitis, 8 (16.3%) neonates were admitted with EOS, 8 (16.3%) with RDS, 12 (24.4%) had neonatal jaundice, 4 (8.1%) had birth asphyxia, 3 (6.1%) had hypoglycemia and 3 (6.1%) had hypothermia. Whereas in subjects without evidence of histological chorioamnionitis, 2 (3.9%) were admitted with EOS, 3(5.8%) with RDS, 16 (11.7%) with NNJ, 3 (5.8%) had birth asphyxia, 2 (3.9%) had hypoglycemia and 3 (5.8%) had hypothermia. [Table 3]

In control group, mean birth weight of neonates born to subjects with or without chorioamnionitis was 2.534 & 2.687 kg respectively. Mean Apgar score at 1 and 5 minute was 6.68 and 8.72 respectively in those having chorioamnionitis and 6.7 and 8.92 in subjects without chorioamnionitis. 26 subjects in controls had evidence of chorioamnionitis. Out of these, 6 neonates were admitted in NICU. Same number of admissions were seen in subjects not having chorioamnionits. EOS, RDS, NNJ and birth asphyxia was present in 2 (7.6%), 1 (3.8%), 2 (7.6%) and 2 (7.6%) subjects respectively, in subjects with chorioamnionitis. In subjects without chorioamnionitis, 1 (1.3%), 1 (1.3%), 1 (1.3%) and 2 (2.6%) neonates had EOS, RDS, NNJ, hypoglycemia and hypothermia respectively. [Table 3]

It was observed that in cases only 6(6%) subjects developed puerperial pyrexia while none developed puerperial sepsis. Amongst controls, 3(3%) subjects developed pyrexia, puerperial sepsis was not seen in any patient. In group1, 4(12.5%) subjects had puerperial pyrexia and2 (2.9%) subjects in group 2 had puerperial pyrexia. The difference was not significant. [Table 4]

Discussion

Chorioamnionitis is the most frequent diagnosis on placental pathology reports and represents the presence of intramniotic infection [5, 6]. Acute inflammatory lesion of the placenta is defined as infiltration of neutrophils into chorion, amnion (termed as chorioamnionitis) or villus (termed as villitis) [7]. Funisitis represents the histological counterpart of fetal inflammatory response syndrome [8]. Amongst cases and controls no significant difference was observed between subjects with and without HCA in respect to mean age, socioeconomic status, residential background and gravidity of the subjects. In cases, 22.4% subjects with HCA and 7.8% subjects without HCA had history of previous preterm delivery ($p<0.05$). The previous history of preterm birth is a known major risk factor for preterm delivery. The risk increases with increase in number of previous preterm deliveries.

Histologic chorioamnionitis was more common in cases when compared to controls and was more severe in terms of degree of invasion of placental tissues (49 vs 26%). Incidence was much higher in cases as compared to controls. It was comparable to study of Sherman *et al.* [9] and study of Holzman *et al.* [10]. Relationship between histologic chorioamnionitis and preterm birth is well established, especially in cases where infective agents have been identified as primary cause. Histologic chorioamniotis was inversely related to gestational age at birth and its presence increased the risk of proven neonatal sepsis and long term sequelae. Higher the grade of chorioamnionitis, more was the risk of neonatal complications seen.

In present study, amongst cases mean birth weight of neonates of subjects with and without histological chorioamnionitis was 1.462 and 1.845 grams respectively. This was due to lower gestational age in subjects with evidence of histological chorioamnionitis. Birth weight was less in studies by Ellimian *et al.* [11] and Erdemir *et al.* [12] as the gestational age of subjects in their studies was lower than that of subjects in the present study. In study by Erdemir *et al.* [12] the gestational age was less than 35 weeks and it included extreme preterm cases also. Mean gestational age of patients with histological chorioamnionitis in their study was 30.1±6.9 weeks. Also in study by Ellimian *et al.* [11] mean gestational age of subjects with histological chorioamnionitis was 27.8±3.1 weeks which was less than that in the present study.

In present study, mean Apgar score of neonate at 1 minute and 5 minutes in cases with and without histological chorioamnionitis was 4.82 vs 6.11 and 7.0 vs 8.22 minutes respectively. In addition, mean Apgar score at 1 and 5 minutes were lower in cases in comparison to controls. Majority of the cases having evidence of histological chorioamnionitis belonged to gestational age group 28 to < 32 weeks, hence had lower APGAR scores. Also histologically percentage of Grade 3 and Grade 4 chorioamnionitis was higher between gestational age 28 to < 32 weeks.

The percentage of neonates admitted in neonatal intensive care unit in subjects with or without histological chorioamnionitis was 77.5 and 37.2 % respectively the difference being significant statistically. Similarly, significant difference was observed for early onset sepsis which was seen in 16.3% of neonates with evidence of histological chorioaminonitis and in 7.6 % of neonates without histological chorioamnionitis. The percentage of early onset sepsis was very high in study of Ellimian *et al.* [11]. It may be because the lesser gestational age of subjects in their study which included extreme preterm and subjects< 34 weeks and hence more risk of premature lungs where as in our study more number of subjects were in moderate to late preterm group than very preterm group and subjects with extreme preterm labour were excluded.

There was no significant difference between the maternal outcome of cases and controls. 6% of the cases developed pyrexia compared to 3% of controls. None of the subjects presented with puerperal sepsis.

Neonates of patients with evidence of histologic chorioamnionitis are at higher risk for developing various neonatal complications. For the treatment and management of those complications better and well equipped NICU facilities should be provided in order to reduce morbidity and mortality.

Conclusion

The presence of histological chorioamnionitis was significantly more found in preterm deliveries and neonates of such women were at higher risk for various neonatal complications. No significant difference was observed between the maternal outcome of cases and controls.

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