European Journal of Obstetrics & Gynecology and Reproductive Biology 214 (2017) 1–5

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Full length article

The placental factor in spontaneous preterm birth in twin vs. singleton pregnancies☆,☆☆

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ARTICLE INFO

Article history:
Received 12 January 2017
Received in revised form 8 April 2017
Accepted 18 April 2017
Available online xxx

Keywords:
Placental pathology
Preterm delivery
Singletons
Multiple pregnancy
Twins
Inflammatory lesions
Neonatal sepsis

ABSTRACT

Objective: The association between infection and inflammatory response in singleton preterm birth (PTB) is well established, yet, less is known about PTB in twins. We aimed to compare the placental component and pregnancy outcome in pregnancies complicated with PTB of singletons vs. twin deliveries. We hypothesized that due to different underlying mechanisms, placental inflammatory lesions will be more prevalent in placentas derived from singleton pregnancies than twins.

Study design: Labor characteristics, neonatal outcome and placental histopathology reports of spontaneous PTB at 24–33$^{6}/_{7}$ weeks, from 1/2008–12/2015, were reviewed.

Results: were compared between dichorionic-diamniotic twin deliveries (twins group) and singleton deliveries (singleton group) matched for gestational age. Excluded from the study medically indicated deliveries, due to preeclampsia or fetal growth restriction, and monochorionic twins. Placental lesions were classified to maternal vascular supply lesions, fetal vascular supply lesions, and maternal (MIR) and fetal (FIR) inflammatory responses. Composite neonatal outcome was defined as one or more of early complications: respiratory distress, necrotizing enterocolitis, sepsis, blood transfusion, ventilation, seizures, intra-ventricular hemorrhage, hypoglycemia, phototherapy, or death.

Results: The twins group (n = 72) was characterized by higher maternal BMI (p = 0.009), and higher rates of assisted reproductive techniques (56.2% vs. 17.8%, $p < 0.001$) and cesarean deliveries (75.3% vs. 32.8%, $p < 0.001$) as compared to the singleton group (n = 72). Placentas from the singleton group were characterized by higher rate of MIR, 58.9% vs. 19.2%, ($p < 0.001$), FIR, 31.5% vs. 3.4%, ($p < 0.001$), retro-placental hemorrhage, 26% vs. 8.9% ($p < 0.001$), and vascular lesions related to maternal malperfusion, 28.8% vs. 9.6%, ($p < 0.001$), as compared to placentas from the twins group. Higher rate of neonatal sepsis was observed in the singleton group as compared to the twins group, 24.7% vs. 4.1%, $p < 0.001$, respectively. By logistic regression analyses retro-placental hemorrhage, placental maternal vascular malperfusion lesions, MIR, FIR and neonatal sepsis were found to be independently associated with singleton PTB: aOR 3.4, 95% CI 2.1–6.9, $p < 0.001$, aOR = 3.1, 95% CI 1.8–7.2, $p < 0.001$, aOR = 2.9, 95% CI 1.4–7.8, $p < 0.001$, aOR = 4.9, 95% CI 2.3–6.9, $p < 0.001$, and aOR = 4.8, 95% CI 2.3–6.7, $p < 0.001$ respectively.

Conclusion: Placentas from singleton PTBs are characterized by higher rate of inflammatory and malperfusion lesions. The lack of these findings in twins PTBs suggests different factors that participate in the development of preterm birth in twins, such as over-distension of the uterus and up regulation of oxytocin receptors.

Introduction

The correlation between histological chorioamnionitis and preterm birth (PTB) has been studied thoroughly, establishing the concept and the mechanism of infection as a major factor contributing to PTB [1]. However, accumulating evidence based on placental pathology, amniotic fluid cultures, and bacterial rDNA polymerase chain reaction (PCR) studies suggests that infection

☆ This study was presented at the SMFM's 37th annual meeting in Las-Vegas, Nevada, January 23–28 2017.

☆☆ The study was conducted in Holon, Israel.

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http://dx.doi.org/10.1016/j.ejogrb.2017.04.035
0301-2115/

may be less common cause of PTB than previously suspected, especially after 32 weeks of gestation. Instead, many cases of spontaneous PTB appear to be caused by poor utero-placental perfusion, similar to preeclampsia and fetal growth restriction [2–4].

One of the major contributors for PTB is multiple pregnancies and mostly twin pregnancies, as a result of the increase in use of ovulation induction treatments and assisted reproductive technology [5]. Twins as well as singletons preterm deliveries [6], are associated with adverse perinatal outcome including short-term complications attributed to immature organ systems (respiratory, intestinal, and cerebral) [7] as well as long-term neurodevelopmental disorders, such as cerebral palsy, intellectual disabilities, vision and hearing impairments [8].

It has been suggested that PTB that is associated with multiple pregnancies has a different natural history than singleton pregnancies, and perhaps different mechanisms participate in the development of preterm twins'labor. [9] Since placental histological inflammation is known to be strongly associated with mortality and morbidity in preterm infants [10,11], differentiating between the mechanisms participating in the development of PTB, in twins as in singletons pregnancy, has a prognostic importance. Yet, data on placental pathology in relation to preterm birth in twins are limited [12]. Therefore, we aimed to fill this gap and to compare the placental histopathology lesions in pregnancies complicated with spontaneous PTB of singleton vs. twins, and to correlate these differences with neonatal outcome.

Materials and methods

Labor characteristics, neonatal outcome and placental histopathology reports of spontaneous deliveries of dichorionic-diamniotic twins between 24 and $33^{6}/_{7}$ weeks of gestation, from January 2008 to December 2015, in a single university hospital, were reviewed.

Excluded from the study monochorionic-diamniotic or monochorionic-monoamniotic twins, stillbirths, and medically indicated deliveries due to preeclampsia, or if one or both twins were small for gestational age (SGA). SGA was defined as actual birth-weight $\leq$10th percentile for gestational age using the updated local growth charts [13].

The study group (twins group) was matched to singletons (singleton group) in a 1:1 ratio for the year of delivery and gestational age ($\pm$3 days).

Approval was obtained from the institutional ethics committee.

Data collection

The following data were collected from the women's' medical and surgical files: age, gestational age at delivery, gravidity, parity, pregnancies achieved by assisted reproductive techniques, either ovulation induction or in-vitro fertilization (ART), mode of delivery, pre-pregnancy body mass index (BMI, kg/m^2), pre-gestational diabetes mellitus (DM, PGDM), gestational diabetes mellitus (GDM), thrombophilia defined as any thrombophilia, inherited or acquired, that necessitated thromboprophylaxis according to the practice bulletins of the American College of Obstetricians and Gynecologists [14,15], smoking, and steroids administration. Women were considered to receive antenatal corticosteroids if they received two dose of intramuscular Betamethasone 12 mg, 24 h apart, prior to delivery [16].

In all cases, gestational age was determined according to last menstrual period and confirmed by first-trimester ultrasound. Gestational age was corrected when there was a disparity of $\geq$7 days between the last menstrual period and the dating according to the first trimester ultrasound [17].

Immediately after birth, all neonates were examined by pediatricians. Birth-weight percentile for gestational age was assigned using the updated local growth charts [13]. Small for gestational age (SGA) was defined as actual birth-weight $\leq$10th percentile for gestational age. The following information was collected from the neonatal records: neonatal hospitalization, sepsis (positive blood or cerebrospinal fluid culture), need for blood transfusion, the need for phototherapy, respiratory distress syndrome, need for mechanical ventilation or support, necrotizing enterocolitis, intraventricular hemorrhage (all grades), hypoxic ischemic encephalopathy, seizures, and death.

Placental pathology

As part of our departmental protocol, in every case of PTB placentas are sent for histopathological evaluation. Placental pathology examinations were performed using our standard protocol by a single pathologist (author L.S). Placental lesions were classified according to the criteria adopted by the Society for Pediatric Pathology [18,19] as previously reported by us [20]. Briefly, placental weight was determined 24 h after delivery (untrimmed and fixed). From each placenta six tissue samples were embedded in paraffin blocks for microscopic assessment: one role of the free membranes, (chorion and amnion with attached decidua capsularis), one at the cord insertion, one from central tissue that appeared abnormal on gross examination, two from normally appearing central tissue, and one at the margin visible abnormal areas on gross examination. In addition, a section of umbilical cord was sampled.

Placentas derived from di-chorionic twins pregnancies were examined and reported as two separate placentas (Therefore, technically, were matched in a 2:1 ratio to the singleton placentas).

Lesions of maternal vascular supply included: placental hemorrhages (marginal, and retro-placental), vascular changes associated with maternal malperfusion [acute atherosis and mural hypertrophy (decidual arteriopathy)], and villous changes associated with maternal malperfusion (increased syncytial knots, villous agglutination, increased intervillous fibrin deposition, distal villous hypoplasia, and villous infarcts).

Lesions of fetal vascular supply included findings consistent with fetal thrombo-occlusive disease (FTOD): vascular lesions (thrombosis of the chorionic plate and stem villous vessels) and villous changes (villous stromal-vascular karyorrhexis, and avascular villi).

Findings consistent with chorioamnionitis were defined by the presence of an inflammatory neutrophil infiltrate at two or more sites on the chorionic plate and extra-placental membrane. Maternal inflammatory response (MIR), was divided into three stages; stage 1–characterized by the presence of a few scattered neutrophils in the subchorionic space; stage 2–characterized by many neutrophils [11–30 per high power field (HPF)] in the lower half of the chorionic plate; and stage 3–characterized by dense infiltrates of neutrophils (>30 per HPF) throughout the chorionic plate. Fetal inflammatory response (FIR) was also divided into 3 stages: stage 1–early, umbilical phlebitis; stage 2–intermediate, umbilical arteritis; and stage 3–concentric umbilical perivasculitis (necrotizing funisitis).

Villitis of unknown etiology or chronic villitis, defined as lymphohistiocytic inflammation localized to the stroma of terminal villi but often extending to the small vessels of upstream villi, was recorded separately.