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The rate of neonatal respiratory distress syndrome/transient tachypnea in the newborn and the amniotic lamellar body count in twin pregnancies compared with singleton pregnancies

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ABSTRACT

Background: Whether or not the period of fetal lung maturity differs between twin and singleton pregnancies has not been clarified. We examined whether or not fetal lung maturity and fetal lung absorption are achieved earlier in twin fetuses than in singleton fetuses.

Methods: We registered 454 singleton pregnancies and 398 twin pregnancies with no congenital abnormalities affecting the respiratory function or neonatal deaths. All patients were delivered by Caesarean section without labor between 24 and 38 gestational weeks. The amniotic fluid samples were analyzed immediately without centrifugation. A multiple logistic regression analysis was performed to explore the relationship between twin pregnancy and neonatal respiratory distress syndrome and transient tachypnea of the newborn (RDS/TTN).

Results: The rate of RDS/TTN in infants was significantly higher and the lamellar body counts (LBCs) significantly lower in singleton pregnancies than that in twin pregnancies ($P < .001$). According to a multivariate logistic regression analysis, twin pregnancy (odds ratio, 0.34; 95% confidence interval, 0.22–0.55) was a significant preventive factor for neonatal RDS/TTN.

Conclusions: We showed that twin fetuses experience more rapid lung maturation and lung fluid absorption than singleton fetuses, as confirmed by the higher LBC values in twin fetuses.

1. Introduction

Twin pregnancies are known to have a higher rate of preterm births and Caesarean sections (CSs) than singletons. Therefore, we should keep in mind that twin neonates are at a higher risk for respiratory disorders, such as respiratory distress syndrome (RDS) and transient tachypnea of the newborn (TTN), than singleton neonates [1]. RDS is caused by the inadequate production of pulmonary surfactant and it is a major cause of morbidity and mortality in preterm infants. The incidence of RDS increases with decreasing gestational age, and infants born before 30 weeks of gestation are at the greatest risk. Furthermore, > 40% of preterm deliveries result in TTN due to the delayed absorption and clearance of fetal alveolar fluid [2]. Although TTN is thought to be a benign, self-limiting condition, increasing data suggest that TTN increases the risk of bronchopulmonary dysplasia and chronic oxygen dependence, which can lead to asthmatic episodes early in life [3, 4].

The amniotic lamellar body count (LBC) is considered to be the most useful way of predicting fetal lung maturity at present. The LBC can be determined quickly and inexpensively, making it a cost-effective and convenient predictor for neonatal RDS [5, 6]. We previously reported that the amniotic LBC was useful for predicting neonatal RDS/TTN not only in singleton pregnancies [7, 8], but also in twin pregnancies [1, 2, 9], and the LBC cut-off was similar between singletons and twins.

However, whether or not the period of fetal lung maturity differs between twin and singleton pregnancies is unclear. It is believed that twin fetuses experience more rapid lung maturation than singleton fetuses [10]. However, this assumption has been challenged by conflicting data [11–13]. The purpose of this study was to examine whether or not fetal lung maturity and the development of fetal lung absorption

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are more rapid in twin fetuses than in singleton fetuses. We compared the rate of neonatal RDS/TTN and amniotic LBC values between twin pregnancies and singleton pregnancies. We then analyzed the relationship between twin pregnancies and neonatal RDS/TTN using a multivariate logistic regression analysis composed of several independent variables to adjust for any imbalance between the cases.

2. Materials and methods

2.1. Case registration

This retrospective study was conducted between July 2009 and December 2016 at our institutions. In the present study, no patients had any complications, such as heart disease, lung disease, blood disease, gastrointestinal disease, renal disease, autoimmune disorder, psychiatric disease, or endocrine disease before pregnancy and were delivered by Caesarean section without labor. We excluded cases in which the amniotic fluid could not be collected, and those whose amniotic fluid samples were contaminated with blood and/or meconium. We then retrospectively registered 454 singleton pregnancies and 398 twin pregnancies (796 neonates) comprising 218 dichorionic twin (DCT) and 180 monochorionic twin (MCT) pairs with no congenital abnormalities affecting the respiratory function, neonatal deaths, or complications (such as twin-twin transfusion syndrome). In twin pregnancy, chorionicity was determined by early ultrasound findings and confirmed by the placental pathology following delivery. All mothers provided their informed consent to participate in this study, which was approved by the Ethics Committee of Nagoya University Hospital.

2.2. Measuring the LBC

Amniotic fluid samples were obtained between 24 and 38 gestational weeks. The samples were analyzed without centrifugation in accordance with the standardized methodology for the LBC previously reported by Neerhof et al. [5]. To measure the LBC precisely, we used the following strategy: First, amniotic fluid samples were obtained from the amniotic sac during Caesarean section. We then measured the LBC using amniotic fluid without vaginal or cervical mucus. Second, we did not use amniotic fluid samples contaminated with blood and/or meconium because blood and meconium in amniotic fluid can increase the LBC, even though the effect of blood and meconium on the LBC is reported to be marginal [5, 14]. Third, after sampling the amniotic fluid, we transferred the fluid to a clear test tube and then flushed the platelet channel without centrifugation. Finally, we processed the specimen through the cell counter and recorded the platelet count as the LBC. The LBC (/μl) was determined using the platelet channel on an automated hematology analyzer (Sysmex SF-3000; Sysmex Corp.); the procedure took no > 30 min, and only 1 ml of amniotic fluid was required to measure the LBC [1, 2, 7–9]. To ensure the accuracy of our machines, our institutions take the following management measures: First, calibration is performed by the manufacturer each year. Second, quality control by an outsider is performed several times a year. Finally, we measure the count of artificial blood cells with two different concentrations twice a day. Blood cell histograms of both the platelets in the blood and lamellar bodies in the amniotic fluid are shown in Fig. 1.

2.3. Clinical characteristics and the diagnosis of RDS/TTN

Neonatal data, including gestational age at delivery, birth weight, sex, umbilical pH, and respiratory outcomes (RDS, TTN), were extracted. The clinical characteristics of the mother, such as pregnancy-induced hypertension and gestational diabetes mellitus (GDM), were documented in order to assess factors that might influence the risk of neonatal respiratory complications. The diagnoses of RDS and TTN were established by neonatologists based on the combination of the clinical signs, clinical course and chest radiography findings [7]. The radiological criteria for TTN were perihilar streaking, increased lung volumes with flat diaphragms, mild cardiomegaly, and fluid in the interlobar fissure and/or pleural space. The radiological criteria for RDS consisted of a diffuse reticulogranular ground-glass pattern with air bronchograms and a decreased lung volume [7, 8]. The neonatologists were blinded to the LBC data.

2.4. Statistical analyses

The data were entered into a computerized spreadsheet (Excel 2010; Microsoft). The Statistical Package for the Social Sciences software program was used for the data analysis (V.24.0). The values are expressed as the mean ± standard deviation (SD). After using the Shapiro-Wilk test to assess the normality of the data, the Mann-Whitney *U* test was used to compare continuous variables between 2 groups, with Student's *t*-test used as appropriate. The χ^2 test or Fisher's exact test was used for comparisons of categorical variables. A multiple logistic regression analysis was performed to explore the relationship between twin pregnancy and neonatal RDS/TTN in unadjusted models, and factors such as maternal age, fetal sex, nulliparity, gestational age at delivery, birth weight SD, umbilical cord pH < 7.15, fetal growth restriction, pregnancy-induced hypertension, diabetes mellitus, and maternal betamethasone were included in the multivariate models. The results of all regression models are reported as adjusted mean differences with 95% CIs (95%CI). A $P < 0.05$ was considered to be significant.

3. Results

3.1. Maternal and neonatal characteristics

The cases enrolled in this study were separated into groups of singleton and twin pregnancies; twin pregnancy was then further separated into groups according to the chorionicity: DCT or MCT. The maternal and neonatal characteristics of each group are shown in Table 1. In this study, the gestational age at delivery ranged from 24 to 38 weeks. The maternal age, gestational age at delivery, umbilical artery pH, and neonatal body weight SD value were significantly lower in twin pregnancies than that in singletons ($P < 0.001$). The rate of nulliparity and fetal growth restriction was significantly higher in twin pregnancies than in singletons ($P < 0.001$).

3.2. LBC and fetal respiratory outcomes

The LBC and fetal respiratory outcomes between twin and singleton pregnancies are shown in Table 2. The rate of RDS/TTN in infants was significantly higher and the LBCs significantly lower in singleton pregnancies than in twin pregnancies ($P < 0.001$). After analyzing these relationships by chorionicity, the rate of RDS/TTN in infants was significantly higher in singleton pregnancies than in dichorionic twins ($P < 0.001$), but not in monochorionic twins.

3.3. Logistic regression analyses regarding the risk for neonatal RDS/TTN between singletons and twins

The results of univariate and multivariate logistic regression analyses regarding the risk of fetal respiratory outcomes between singleton and twin pregnancies are shown in Table 3. Twin pregnancies (odds ratio [OR], 0.34; 95% CI, 0.22–0.55) and gestational age at delivery (OR, 0.56; 95% CI, 0.5–0.63) were significant preventive factors for neonatal RDS/TTN. The only positive factor for neonatal RDS/TTN was male infant gender (OR, 1.97; 95% CI, 1.31–2.96). After analyzing the factors of chorionicity, both DCT (OR, 0.34; 95% CI, 0.2–0.58) and MCT (OR, 0.35; 95% CI, 0.20–0.60) were found to be significant preventive factors for neonatal RDS/TTN (Table 4).