

Placenta Share Discordance and Umbilical Artery Doppler Change After Antenatal Betamethasone Administration in Monochorionic Twins With Selective Intrauterine Growth Restriction: Is There a Link?

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This study was designed to evaluate the degree of placenta share discordance in relation to the betamethasone-induced return of positive end-diastolic flow in monochorionic twin pregnancies with selective intrauterine growth restriction (sIUGR) and abnormal umbilical artery Doppler. Monochorionic twins with sIUGR was defined as one twin having an estimated fetal weight below the 10th percentile combined with an estimated fetal weight discordance >25%. The umbilical artery Doppler directly prior to (D0) and 24 hours (D1) and 48 hours (D2) after the first dose of betamethasone administration was recorded. The estimated individual placental weight in monochorionic twins was obtained by cutting the placenta along the vascular equator into two territories; the placenta share discordance was calculated as [(estimated individual placental weight of appropriated for gestational age twin- estimated individual placental weight of growth restricted twin)/estimated individual placental weight of appropriated for gestational age twin] × 100%. Six (23.1%) of the 26 included cases achieved betamethasone-induced return of positive umbilical artery end-diastolic flow. The difference of placenta share discordance and birth weight discordance were not significantly different between twins with and without betamethasone-induced return of positive umbilical artery end-diastolic flow. Thus, according to our study results, it was proposed that although the placenta share discordance correlated with the abnormal umbilical artery Doppler in the IUGR fetus in monochorionic twin, the betamethasone-induced return of positive umbilical artery end-diastolic flow, however, did not reveal the similar relationship with the severity of placenta share discordance.

■ **Keywords:** monochorionic twin pregnancy, intrauterine growth restriction, fetal Doppler, betamethasone, placenta share

In singleton pregnancies with an absence of end-diastolic flow (AEDF) in the umbilical artery (UA) Doppler, betamethasone administration had been reported as associated with a transient return of positive UA end-diastolic flow in 63% (Robertson et al., 2009) and 81.8% of cases (Thuring et al., 2011). But the etiology of betamethasone-induced return of positive end-diastolic UA flow is unclear (Robertson et al., 2009). Selective intrauterine growth restriction (sIUGR) occurs in about 12% of monochorionic twin (MC) pregnancies (Gaziano et al., 2000; Gratacos et al., 2004; Sebire et al., 1997); MC twins have a higher incidence of respiratory and neurological complications than their dichorionic counterparts (Acosta-Rojas et al., 2007;

Fick et al., 2006; Gonzalez-Quintero et al., 2003). Antenatal corticosteroids are often administered to enhance fetal lung maturity due to the frequent need for delivery earlier than 34 weeks of gestation in order to avoid the intrauterine fetal demise of the sIUGR twin, which could subsequently lead to

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brain injury of the co-twin arising from agonal transfusion (Russell et al., 2007).

As revealed in our previous studies, MC pregnancies with sIUGR and UA-AEDF saw more severe placenta share discordance than those where the sIUGR twin showed normal UA Doppler (Chang et al., 2009). So, the etiology of UA-AEDF in sIUGR twin could be partly attributed to severe placenta share discordance (Chang et al., 2009). However, would a similar relationship also exist between the betamethasone-induced return of positive UA end-diastolic flow and the placental share discordance in MC pregnancy with sIUGR and UA-AEDF? The purpose of this study was aimed at addressing this issue.

Materials and Method

Data were collected prospectively between March 2006 and July 2011 from women who gave birth at Chang Gung Memorial Hospital to MC twins with sIUGR and UA-AEDF. MC was diagnosed by ultrasound as having a single placenta, a thin dividing membrane and lacking a twin peak sign, and was confirmed by postpartum placenta examination.

An MC pregnancy with sIUGR was defined as a combination of the co-twin with an estimated fetal weight below the 10th percentile and fetal weight discordance between the twin pair >25% (Acosta-Rojas et al., 2007; Ananth et al., 1998). Intermittent UA-AEDF is not recognized as abnormal Doppler in this study. Pregnancies with signs of twin-twin transfusion syndrome (TTTS), presenting at the time of betamethasone administration, were not included in this study. The study was approved by the local institutional ethics committee.

UA Doppler examinations directly prior to (D0) and after 24 hours (D1) and 48 hours (D2) after administration of the first dose of the treatment cycle (including two doses of 12 mg betamethasone, injected 24 hours apart) were recorded. Pulsed and color Doppler was detected by a multifrequency sector array transabdominal transducer (Voluson 730 Pro, GE Medical Systems, Milwaukee, WI, USA). The system operated at output intensities of <100 mW/cm spatial peak temporal average in both imaging and Doppler modes, and the high-pass filter was set at 100 Hz. The sample volume was positioned about 3 cm from the placental insertion of the umbilical cord. All recordings were taken during episodes of fetal inactivity. If positive end-diastolic flow was detected after betamethasone administration, then the Doppler examination was performed on a daily basis in order to record the duration of betamethasone-induced positive end-diastolic UA flow.

Because of the risk of fetal demise in the sIUGR twin with abnormal UA Doppler, all MC pregnancies with sIUGR and UA-AEDF would be suggested to deliver no later than 34 gestational weeks in our institution. Therefore, the indications of betamethasone administration for studying cases

included the following situations: (1) deterioration of fetal condition such as reverse of end-diastolic flow of UA Doppler, (2) threatening preterm delivery before gestational age of 34 weeks, (3) two days before planned delivery. For clinical purposes, final decisions regarding delivery were made depending on clinical fetal condition or obstetric situation at that time.

The placenta was examined carefully after delivery. Following draining of the blood from the umbilical cord vessels, the placenta was washed to remove all the clots to ensure the completeness of cotyledons and membranes. Then, after removal of the umbilical cord and membranes, the placenta was freshly cut along the vascular equator into two territories between both cord insertions. The vascular equator was defined as a border drawn in the middle of the avascular zone on the chorionic fetal surface where there were no intertwining vascular anastomoses, or on the anastomosis points where twin-twin communicating vessels met. Each placental portion was weighed separately, which yielded an estimated individual placental mass (eIPM). The placenta share discordance was calculated as the difference between the eIPM of the appropriated for gestational age (AGA) and the sIUGR twin divided by the eIPM of the larger twin, the equation expressed as $[(\text{eIPM of AGA} - \text{eIPM of sIUGR})/\text{eIPM of AGA}] \times 100$. Birth weight discordance was calculated in a similar fashion.

Statistical analysis was conducted with SPSS software (version 11.0 for Windows; SPSS Inc, Chicago, IL, USA). Two-sample Student *t* test or Mann-Whitney U test was used to compare between groups for the continuous variables. Qualitative data were compared by means of χ^2 test. A probability value of less than 0.05 was considered statistically significant.

Results

There were 26 MC pregnancies with sIUGR and UA-AEDF who received antenatal betamethasone for accelerating fetal lung maturation and the D0, D1, and D2 UA Doppler examination data were obtained during the study period. Part of the data on fetal UA Doppler have been published before (Chang et al., 2011). The characteristics of those MC pregnancies are listed in Table 1. Six cases (23.1%) saw the sIUGR twin UA Doppler returning to positive end-diastolic flow after maternal betamethasone administration, all happening at D1 examination. Three of them had their positive end-diastolic UA flows last for 7 days, 5 days, and 1 day, respectively, and then became AEDF again; the other three cases whose flow was still detectable after 48 hours needed delivery due to either preterm labor or scheduled cesarean section, so the exact duration of return of UA positive end-diastolic flow could not be determined. In the remaining 20 patients with persistent UA-AEDF after betamethasone administration, there were seven neonatal deaths: two twin pairs losing both fetuses due to extreme prematurity and the

TABLE 1

Characteristics of Monochorionic Twins With Selective Intrauterine Growth Restriction With Abnormal Umbilical Artery Doppler That Received Antenatal Betamethasone for Accelerating Fetal Lung Maturation

Maternal age of delivery (years)	30.9 ± 3.2
Mean gestational age of delivery (weeks)	31.6 ± 2.6
Gestational age of betamethasone given (weeks)	29.7 ± 2.5
Interval of complete betamethasone given until delivery (days)	13.2 (0~43)
sIUGR twin UA Doppler returned to positive end-diastolic velocity	23% (6/26)
Mean birth weight of AGA twin (gm)	1642 ± 509
Mean birth weight of sIUGR twin (gm)	1016 ± 359
Birth weight discordance	38%

Note: sIUGR = selective intrauterine growth restriction; UA = umbilical artery; AGA = appropriate for gestational age.

other three experiencing a single neonatal death. One case that turned into TTTS one week after betamethasone administration (the reason of betamethasone administration is preterm labor) received amnioreduction and was delivered at gestational age of 33 weeks. So with respect to the neonatal death rate, seven (17.5%) of the 40 fetuses without betamethasone-induced return of positive end-diastolic flow died, whereas no death was observed in the 12 babies with return of UA positive end-diastolic velocity; the difference, however, was not statistically significant ($p = .18$).

The characteristics of MC pregnancies with sIUGR, based on with or without betamethasone-induced return of UA positive end-diastolic flow were listed in Table 2. Placental share discordance and birth weight discordance were not statistically different between return of positive UA end-diastolic flow group ($n = 6$) and persistent UA-AEDF group ($n = 20$): 63.3% versus 62.5% and 39.0% versus 38.3%, respectively. Their gestational age of betamethasone administration and gestational age at delivery, were also comparable in comparison between these two groups of MC pregnancies.

Discussion

Our previous study found that MC pregnancies with a sIUGR twin exhibiting UA-AEDF would have more severe

unequal placenta share than those with a sIUGR twin demonstrating positive end-diastolic UA Doppler (Chang et al., 2009). Owing to the fact that these MC pregnancies with one sIUGR often require maternal corticosteroid injection because of the pressing need for early delivery, we are interested to know if the severity of placenta share discordance will have an effect on UA Doppler change after antenatal betamethasone administration. From our study results shown in Table 2, we discovered that both the discordances of placenta share and birth weight did not correlate with the betamethasone-induced return of sIUGR twin UA positive end-diastolic flow.

The incidence of betamethasone-induced return of positive UA end-diastolic velocity in MC with sIUGR and UA-AEDF found by our present study was 23.1% (6/26). It has elsewhere been reported as 63% (58/92) (Robertson et al., 2009) and 81.8% (9/11) (Thuring et al., 2011) in singleton pregnancies with UA-AEDF. So the incidence of betamethasone-induced return of positive end-diastolic flow in singleton pregnancies is higher than those reported for multiple pregnancies. There are two theories explaining the etiology of the betamethasone-induced return of UA positive end-diastolic flow in the IUGR fetuses: one is that exogenous steroid increases fetal blood pressure (Derks et al., 1997); the other is corticosteroid reducing placental resistance by altering the placental tone (Clifton et al., 2002; Korebrits et al., 1998). Due to the fact that the current dose of betamethasone administration for twin pregnancy is suggested as the same for the singleton pregnancy and studies have shown that maternal and umbilical cord blood serum betamethasone concentrations after antenatal betamethasone administration are not different between twin and singleton pregnancy (Ballabh et al., 2002; Gyamfi et al., 2010). So the impact of betamethasone-induced increasing fetal blood pressure is not sufficient enough to explain the different incidence of betamethasone-induced return of UA positive end-diastolic flow between singleton and multiple pregnancies. Thus, we favor the second theory that different degree of betamethasone-induced placenta vascular dilatation may be responsible for the different incidence of betamethasone-induced

TABLE 2

The Characteristics of Monochorionic Twins With sIUGR With and Without Betamethasone Induced Return of the UA Doppler End-Diastolic Velocity

IUGR twin UA Doppler status after betamethasone administration	UA Doppler return to positive end-diastolic velocity (N = 6)	UA Doppler persisting AEDF (N = 20)	p-Value
Neonatal death (N)	0	7	0.18
Progression to TTTS (N)	0	1	0.80
Mean GA of delivery (weeks)	33.0 ± 1.6	31.0 ± 2.8	0.11
Mean GA (weeks) of betamethasone administration (range)	29.4 (25.4~33.7)	29.8 (25.6~33.4)	0.82
Placenta share discordance	63.3%	62.5%	0.90
Birth weight discordance	39.0%	38.3%	0.87

Note: N = case number; sIUGR = selective intrauterine growth restriction; UA = umbilical artery; TTTS = twin-twin transfusion syndrome; GA = gestational age; AGA = appropriate for gestational age.

return of UA positive end-diastolic flow between these two groups.

Recent studies have revealed that the current standard dose or interval for antenatal corticosteroid administration in singleton pregnancy, whether it be single or multiple courses, has not helped much in reducing respiratory distress in twins (Choi et al., 2009). And also the effect of antenatal corticosteroids decreases with increasing plurality (Blickstein et al., 2005). So, combining our finding of a lower rate of betamethasone-induced return of UA positive end-diastolic flow in twin pregnancies than in singleton pregnancy, the optimal dose and interval of antenatal corticosteroid to enhance the fetal lung maturation in multiple pregnancies may need further studies to evaluate.

In conclusion, although more severe unequal placenta share correlates with the sIUGR twin abnormal UA Doppler in MC twins, the severity of placenta share discordance was not different between MC twins with and without return of positive sIUGR twin UA end-diastolic flow after betamethasone administration.

References

- Acosta-Rojas, R., Becker, J., Munoz-Abellana, B., Ruiz, C., Carreras, E., & Gratacos, E. (2007). Twin chorionicity and the risk of adverse perinatal outcome. *International Journal of Gynaecology and Obstetrics*, *96*, 98–102.
- Ananth, C. V., Vintzileos, A. M., Shen-Schwarz, S., Smulian, J. C., & Lai, Y. L. (1998). Standards of birth weight in twin gestations stratified by placental chorionicity. *Obstetrics and Gynecology*, *91*, 917–924.
- Ballabh, P., Lo, E. S., Kumari, J., Cooper, T. B., Zervoudakis, I., Auld, P. A., & Krauss, A. N. (2002). Pharmacokinetics of betamethasone in twin and singleton pregnancy. *Clinical Pharmacology and Therapeutics*, *71*, 39–45.
- Blickstein, I., Shinwell, E. S., Lusk, A., & Reichman, B. (2005). Plurality-dependent risk of respiratory distress syndrome among very-low-birth-weight infants and antepartum corticosteroid treatment. *American Journal of Obstetrics and Gynecology*, *192*, 360–364.
- Chang, Y. L., Chang, S. D., Chao, A. S., Hsieh, P. C., Wang, C. N., & Wang, T. H. (2009). Clinical outcome and placental territory ratio of monochorionic twin pregnancies and selective intrauterine growth restriction with different types of umbilical artery Doppler. *Prenatal Diagnosis*, *29*, 253–256.
- Chang, Y. L., Chang, S. D., Chao, A. S., Hsieh, P. C., Wang, C. N., & Wang, T. H. (2011). Fetal hemodynamic changes following maternal betamethasone administration in monochorionic twin pregnancies featuring one twin with selective growth restriction and abnormal umbilical artery Doppler. *Journal of Obstetric and Gynaecological Research*, *37*, 1671–1676.
- Choi, S. J., Song, S. E., Seo, E. S., Oh, S. Y., Kim, J. H., & Roh, C. R. (2009). The effect of single or multiple courses of antenatal corticosteroid therapy on neonatal respiratory distress syndrome in singleton versus twin pregnancies. *Australia and New Zealand Journal of Obstetrics and Gynaecology*, *49*, 173–179.
- Clifton, V. L., Wallace, E. M., & Smith, R. (2002). Short-term effects of glucocorticoids in the human fetal-placental circulation in vitro. *Journal Clinical Endocrinology and Metabolism*, *87*, 2838–2842.
- Derks, J. B., Giussani, D. A., Jenkins, S. L., Wentworth, R. A., Visser, G. H., Padbury, J. F., & Nathanielsz, P. W. (1997). A comparative study of cardiovascular, endocrine and behavioural effects of betamethasone and dexamethasone administration to fetal sheep. *Journal of Physiology*, *499*, 217–226.
- Fick, A. L., Feldstein, V. A., Norton, M. E., Wassel Fyr, C., Caughey, A. B., & Machin, G. A. (2006). Unequal placental sharing and birth weight discordance in monochorionic diamniotic twins. *American Journal of Obstetrics and Gynecology*, *195*, 178–183.
- Gaziano, E. P., De Lia, J. E., & Kuhlmann, R. S. (2000). Diamniotic monochorionic twin gestations: an overview. *Journal of Maternal Fetal Medicine*, *9*, 89–96.
- Gonzalez-Quintero, V. H., Luke, B., O'Sullivan, M. J., Misiunas, R., Anderson, E., Nugent, C., Witter, F., Mauldin, J., Newman, R., D'alton, M., Grainger, D., Saade, G., Hankins, G., & Macones, G. (2003). Antenatal factors associated with significant birth weight discordancy in twin gestations. *American Journal of Obstetrics and Gynecology*, *189*, 813–817.
- Gratacos, E., Carreras, E., Becker, J., Lewi, L., Enriquez, G., Perapoch, J., Higuera, T., Cabero, L., & Deprest, J. (2004). Prevalence of neurological damage in monochorionic twins with selective intrauterine growth restriction and intermittent absent or reversed end-diastolic umbilical artery flow. *Ultrasound in Obstetrics and Gynecology*, *24*, 159–163.
- Gyamfi, C., Mele, L., Wapner, R. J., Spong, C. Y., Peaceman, A., Sorokin, Y., Dudley, D. J., Johnson, F., Leveno, K. J., Caritis, S. N., Mercer, B. M., Thorp, J. M., Jr., O'Sullivan, M. J., Ramin, S. M., Carpenter, M., Rouse, D. J., Miodovnik, M., Sibai, B., & Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. (2010). The effect of plurality and obesity on betamethasone concentrations in women at risk for preterm delivery. *American Journal of Obstetrics and Gynecology*, *203*, 219.e1–5.
- Korebrits, C., Yu, D. H., Ramirez, M. M., Marinoni, E., Bocking, A. D., & Challis, J. R. (1998). Antenatal glucocorticoid administration increases corticotrophin-releasing hormone in maternal plasma. *British Journal of Obstetrics and Gynaecology*, *105*, 556–561.
- Robertson, M. C., Murila, F., Tong, S., Baker, L. S., Yu, V. Y., & Wallace, E. M. (2009). Predicting perinatal outcome through changes in umbilical artery Doppler studies after antenatal corticosteroids in the growth-restricted fetus. *Obstetrics and Gynecology*, *113*, 636–640.

Russell, Z., Quintero, R. A., & Kontopoulos, E. V. (2007). Intrauterine growth restriction in monochorionic twins. *Seminars in Fetal and Neonatal Medicine*, *12*, 439–449.

Sebire, N. J., Snijders, R. J., Hughes, K., Sepulveda, W., & Nicolaides, K. H. (1997). The hidden mortality of mono-

chorionic twin pregnancies. *British Journal of Obstetrics and Gynaecology*, *104*, 1203–1207.

Thuring, A., Malcus, P., & Marsal, K. (2011). Effect of maternal betamethasone on fetal and uteroplacental blood flow velocity waveforms. *Ultrasound in Obstetrics and Gynecology*, *37*, 668–672.
