OBSTETRICS

Twin-to-twin transfusion syndrome: an antiangiogenic state?

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OBJECTIVE: An imbalanced chronic blood flow between the donor and recipient twin through placental vascular anastomoses is the accepted pathophysiology of twin-to-twin transfusion syndrome (TTTS). Vascular endothelial growth factor receptor-1 (VEGFR-1) mRNA is overexpressed only in the syncytiotrophoblast of the donor twin in some cases of TTTS. This study was conducted to determine maternal plasma concentrations of placental growth factor (PlGF), soluble VEGFR-1, and soluble endoglin (s-Eng) in monochorionic-diamniotic pregnancies with and without TTTS.

STUDY DESIGN: This case-control study included monochorionic-diamniotic pregnancies between 16-26 weeks with and without TTTS. Maternal plasma concentrations of PlGF, sVEGFR-1, and s-Eng were determined with ELISA. A P value $< .05$ was considered statistically significant.

RESULTS: Patients with TTTS had higher median plasma concentrations of s-Eng (14.8 ng/mL vs 7.8 ng/mL; $P < .001$) and sVEGFR-1 (6383.1 pg/mL vs 3220.1 pg/mL; $P < .001$]; and lower median plasma concentrations of PlGF (115.5 pg/mL vs 359.3 pg/mL; $P = .002$) than those without TTTS.

CONCLUSION: We propose that an antiangiogenic state may be present in some cases of TTTS.

Key words: angiogenesis, angiogenic factors, birthweight discordancy, endoglin, monochorionic, placental growth factor, PlGF, sFlt1, sVEGFR-1, TTTS, twin pregnancy.

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Chorionicity, rather than zygosity, is the main determinant of pregnancy outcome in twin gestation.[1-3] Indeed, monochorionic (MC) twins have a higher risk of miscarriage, fetal death, preterm delivery, intrauterine growth restriction, birthweight discordancy,[2,4-7] as well as a higher rate of cerebral palsy and neurologic morbidity[8,9] than dichorionic (DC) twins. These differences have been attributed to abnormalities in the placental angioarchitecture, including abnormal umbilical cord insertion,[10-12] unequal placental sharing,[13] and to the presence of placental vascular anatomoses that lead to the twin-to-twin transfusion syndrome (TTTS) and its consequences.[3,14]

★ EDITORS' CHOICE ★

The conventional view is that a chronic blood flow imbalance from the donor to the recipient twin due to a net unidirectional blood flow through placental vascular anastomoses[15-17] is responsible for the development of TTTS. However, the presence of vascular anastomosis is necessary but not sufficient to induce TTTS. Indeed, almost all monochorionic twin placentas have vascular anastomoses[16-18]; however, TTTS is present only in 5-15% of these pregnancies,[19-21] and no more than 25% of the MC twin pairs with TTTS have > 15% of hemoglobin discordance.[22] Thus, although placental vascular anastomoses are a sine qua non requirement for the development of TTTS, the pathophysiology of TTTS may not be explained only on the basis of placental vascular anastomoses.

Angiogenesis plays a central role in normal placental development,[23-25] and accumulating evidence indicates that angiogenic factors, such as vascular endothelial growth factor (VEGF) and pla-

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cental growth factor (PlGF), and antiangiogenic factors such as soluble VEGF receptor-1 (sVEGFR-1, also referred to as sFlt1) and the soluble form of Endoglin (s-Eng) are involved in the pathophysiology of preeclampsia,[26-54] small for gestational age (SGA),[31,54-59] placental abruption,[60] "mirror syndrome,"[61-63] preeclampsia with parvovirus-induced hydrops,[64] and unexplained fetal death.[65] Recently, it has been reported that VEGFR-1 mRNA is overexpressed in the syncytiotrophoblast of the donor but not in that of the recipient twin in some cases of TTTS,[66] suggesting that this antiangiogenic factor may play a role in TTTS. The objective of this study was to determine if there are changes in the maternal plasma concentrations of angiogenic (PlGF), and antiangiogenic factors (sVEGFR-1 and s-Eng) in monochorionic-diamniotic twin pregnancies with and without TTTS.

Materials and Methods

Study design and population

A case-control study was designed to examine the maternal plasma concentration of angiogenic and antiangiogenic factors in monochorionic twins with and without TTTS. We searched our clinical database, bank of biological samples, and digital library of ultrasound images to identify patients with monochorionic-diamniotic twin pregnancies between 16 and 26 weeks of gestation with and without TTTS. Patients with the diagnosis of preeclampsia at the time of venipuncture or fetal congenital anomalies were excluded.

Definitions

Monochorionic placentation was diagnosed by ultrasonography before 20 weeks of gestation based on the presence of a single placental mass, same fetal gender, absence of the twin-peak sign, and dividing membrane thickness < 2 mm,[67-70] confirmed with placental histopathology. TTTS was defined as oligohydramnios (maximum vertical pocket [MVP] of amniotic fluid < 2 cm) in the donor twin and polyhydramnios (MVP > 8 cm) in the recipient twin. Preterm delivery was defined as delivery before 37 completed weeks of gestation. Preeclampsia was diagnosed in the presence of systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg on at least 2 occasions 4 hours to 1 week apart, after the 20th week of gestation, and proteinuria > 300 mg in a 24-hour urine collection, or 2 random urine specimens obtained 4 hours to 1 week apart containing $\geq 1+$ protein by dipstick[71,72] or 1 dipstick measurement $\geq 2+$ protein.[73] Fetal death was considered to have occurred in the absence of fetal heart activity after 20 weeks of gestation. Intrauterine growth restriction was defined as a birthweight below the 10th percentile.[74,75]

All patients provided written informed consent before participating in the study. The collection and utilization of samples, and the use of clinical and ultrasound data for research purposes was approved by the Institutional Review Boards of the Sotero del Rio Hospital (a major affiliate of the Catholic University, Santiago, Chile), Wayne State University, and the National Institute of Child Health and Human Development (NICHD/NIH/DHHS).

TABLE

Demographic and clinical characteristics of patients with monochorionic-diamniotic twin pregnancies between 16 and 26 weeks of gestation

	No TTTS (n = 53)	TTTS (n = 16)	*P*
Maternal age (y)	27 (22–34)	28.5 (23–33)	NS
Primigravida	39.6 (21/53)	12.5 (2/16)	.04
Height (cm)	155 (152–160)	155.5 (152–162)	NS
Weight (kg)	58 (55–68)	59.5 (53–68)	NS
Prepregnancy BMI (kg/m^2)	24.0 (21.9–27)	23.8 (22.5–28.9)	NS
Smoking	9.4 (5/53)	12.5 (2/16)	NS
Gestational age at blood draw (wk)	21.7 (19.8–23.3)	21.3 (19.5–23.5)	NS
SBP (mmHg)[a]	110 (104–125)	110 (110–120)	NS
DBP (mmHg)[a]	70 (65–80)	70 (60–72)	NS
Preeclampsia	11.8 (6/45)	0 (0/15)	NS
Gestational age at delivery (wk)	35.6 (31.9–37.5)	31 (22.7–34.2)	.009
Preterm delivery (wk)			
< 37	64.2 (34/53)	84.6 (11/13)	NS
< 34	30.2 (16/53)	69.2 (9/13)	.009
< 32	24.5 (13/53)	61.5 (8/13)	.01
IUGR	39.6 (21/53)	60 (6/10)	NS
Fetal death[b]	7.5 (8/106)	10 (3/30)	NS
Sample storage time (y)	4.1 (2.4–6)	2.7 (1.3–5.8)	NS

Values are expressed as percentage (number) or median (interquartile range).
BMI, body mass index; *DBP*, diastolic blood pressure; *IUGR*, intrauterine growth restriction; *NS*, not significant; *SBP*, systolic blood pressure; *TTTS*, twin-to-twin transfusion syndrome.

[a] Systolic and diastolic blood pressures at the time of blood draw.

[b] Values are expressed as percentage (number/total number of fetuses).

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Sample collection and human PlGF, sVEGFR-1, and s-Eng immunoassays

Samples of peripheral blood were obtained by venipuncture and collected in tubes containing EDTA. The samples were centrifugated at 4°C for 10 minutes and stored at −70°C until assay. Maternal plasma concentrations of sVEGFR-1,