“胎盘标志物对单绒双羊双胎妊娠合并双胎输血综合征的预测:深部动静脉吻合的形态学分析”点评

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1 原文摘要

Objectives The aim of this study was to perform a detailed prospective morphometric analysis of a large consecutive series of monochorionic twin placentas in order to determine the frequency of candidate placental markers in TTTS placentas and, in particular, to determine the potential role of unbalanced deep AV anastomoses.

Design A cohort of 284 consecutive monochorionic placentas was examined between 2001 and 2008. Triplet and quadruplet placentas, monochorionic-monoamniotic placentas, placentas of gestations complicated by twin reversed arterial perfusion (TRAP) sequenceand placentas with remote (>48 h prior to delivery) fetal demise of one twinwere excluded. Of the remaining 253 diamniotic-monochorionic twin placentas, 53 were complicated by TTTS, based on clinical and ultrasound evidence. Of the 53 TTTS cases, 29 were treated by laser coagulation of communicating vessels. These laser-coagulated TTTS placentas were excluded from this study. Thus 24 TTTS placentas were compared with 200 placentas of non-TTTS diamniotic-monochorionic twin gestations.

Results

1) clinical data

The gestational age at delivery and the birth weights of the TTTS twins were lower than those of non-TTTS twins (Table 1).

2) General placental anatomy

The placental weights of TTTS twins were significantly lower than those of non-TTTS control twins. The placental markers, including velamentous insertion, frequency of marginal cord insertion, magistral or mixed magistral/disperse vascular distribution patterns, >25% difference in placental territory between twins and a single umbilical artery, were compared between non-TTTS control placentas and TTTS placentas (Table 2).

3) Choriovascular anatomy: superficial anastomoses (AA and VV)

The total number of anastomoses visualized in the chorionic plate varied widely between cases and reached a maximum of 23 in both TTTS and non-TTTS control groups. Superficial AA anastomoses were significantly more frequent in non-TTTS placentas than in TTTS. None of the TTTS placentas had more than one AA anastomosis. Among the non-TTTS cases, two placentas had 2 and one had 3 AA anastomoses. The diameter of AA anastomoses ranged from 0.05 to 0.4 cm in TTTS placentasand from 0.05 to 0.6 cm in non-TTTS controls.

VV anastomoses were more than twice as frequent in TTTS placentas as in non-TTTS controls. None of the TTTS placentas had more than one VV anastomosis, whereas six non-TTTS

control placentas had 2 VV anastomoses. The maximal diameter of VV anastomoseswas 0.6 cm in TTTS placentas and 0.4 cm in non-TTTS controls.

4) Choriovascular anatomy: deep AV anastomoses

AV anastomoses were seen in95% TTTS placentas and 96% of non-TTTS placentas. The median net number of AV anastomoses was 2 in both groups, with values ranging from 0 to 7 in TTTS and from 0 to 15 in non-TTTS placentas (Table 2). The NCSA was significantly smaller in TTTS placentas than in non-TTTS controls. Sensitivity and specificity of key placental markers as post-hoc predictors of TTTS are shown in Table 3. None of the individual candidate placental variables, however are reliable post-hoc predictors of TTTS.

2 论文核心内容及点评

该文发表在《Placenta》2010 年第 31 卷 269-276 页上。该文对双胎输血综合征(TTTS)病因的传统观点作一深入的直接的研究和分析。主要内容如下:

传统观点认为双胎间存在动静脉(AV)吻合,而 AV 吻合中的血流是单向的,因此正是 AV 吻合中的单向血流造成双胎间血液分配不平衡,进而发生 TTTS。尽管认为 AV 吻合是 TTTS 的主要病因,但以往的研究大多集中在胎盘表面的动动脉(AA)和静静脉(VV)吻合,对 AV 吻合的直接研究很少。因此可以说 AV 吻合是 TTTS 的主要病因还只是 1 种观察实验的推测。并无直接实验验证。这可能与 AV 吻合在胎盘深部,无法直接观察,且研究费时有关。

因此在 2001～2008 年之间,该研究以 200 例未合并 TTTS 的单绒双羊双胎妊娠和 24 例合并 TTTS 的单绒双羊双胎妊娠为样本,采用分娩后胎盘灌注技术,对两者的胎盘进行了分析比较。为了对 2 组胎盘进行尽可能准确的比较,该研究应用净 AV 吻合数、净 AV 吻合横截面积,即考虑到 AV 吻合内血流既有供血儿流向受血儿也有受血儿流向供血儿,因此可相互抵消,最终转化为实际的 AV 吻合数和 AV 吻合面积。

该研究结果显示:首先,non-TTTS 胎盘 AV 吻合(96%)较 TTTS 胎盘 AV 吻合(95%)更常见,non-TTTS 胎盘无论净 AV 吻合数还是 AV 吻合净横截面积都较 TTTS 多。而且 non-TTTS 极值情况更易见。甚至在本研究中有 1 例 TTTS 胎盘并无 AV 吻合(表 1 和表 2)。因此传统观点认为 AV 吻合是 TTTS 的病因可能不合理。其次,该研究通过分娩后胎盘灌注比较后,对 TTTS 胎盘特征进行了总结并深入分析了这些胎盘特征预测 TTTS 的特异性和敏感性。研究发现 TTTS 胎盘特征包括胎盘不均衡分配(双胎间胎盘面积差异>25%)、缺乏 AA 吻合、VV 吻合较多、脐带帆状附着等。各胎盘特征的特异性和敏感性见下(表 3)。最后,该研究还发现 AV 吻合内血流方向与供血儿—受血儿的鉴别并无肯定的联系。因为 AV 吻合中的血流既可以从"供血儿"流向"受血儿",亦可从受血儿"流向"供血儿"。

表 1 胎盘数据

	TTTS 双胎 (24)	非 TTTS 双胎(200)	*P*
孕龄(周)	27.3±3.8 (20～33)	34.5±3.8 (21～42)	<0.01
较大出生体重 (g)	1149±525 (250～1935)	2271±697 (579～3845)	<0.01
较低出生体重(g)	904±449 (190～1527)	2008±676 (520～3523)	<0.01
出生体重差异 (%)	24.0±14.0 (3～67)	12.0±8.8 (0～18)	<0.01
出生体重异常≥20%	12/24 (50%)	30/200 (15%)	<0.001
发生胎死宫内	8/24 (33%)	4/200 (2%)	<0.001
双胎胎死宫内	6/24 (25%)	2/200 (1%)	<0.001
单胎胎死宫内	2/24 (8%)	2/200 (1%)	0.08

数据结果表示采用:均值± SD或 所占样本的百分比(%)

表 2a 胎盘

大体解剖	TTTS 胎盘(24)	非 TTTS 胎盘(200)	*P*
胎盘重量(g)	471± 161	708± 210	<0.01
AGA 胎盘	17/24(71%)	172/200(86%)	0.06
LGA 胎盘	4/24(17%)	11/200(6%)	0.06
SGA 胎盘	3/24(13%)	14/200(7%)	NS
脐带帆状附着[a]	14/42(33%)	41/394(10%)	<0.0001
脐带边缘附着[a]	8/42(19%)	82/394(21%)	NS
脐带帆状或边缘附着[a]	22/42(52%)	123/394(31%)	<0.01
单支或混合型血管分布	18/21(86%)	118/197(60%)	<0.02
双胎所占胎盘面积相差>25%	11/21(52%)	50/197(25%)	<0.01
单脐动脉	3/48(6.3%)	10/394(2.5%)	NS

表 2b 绒毛膜血管吻合

绒毛膜血管吻合	TTTS 胎盘(21)	TTTS 胎盘 (197)	*P*
血管吻合总数	6(2-23)	7(0-23)	NS
动动脉吻合	12/21(57%)	175/197(89%)	<0.001
静静脉吻合数	8/21(38%)	28/197(15%)	<0.02
深部动静脉吻合总数	5(0-22)	6(0-22)	NS
净深部动静脉吻合数	2(0-7)	2(0-15)	NS
NCSA(mm^2)	0.39(0-6.67)	0.98 (0-42.78)	<0.05
NCSA>1mm^2 部分(%)	7/21(33%)	91/197(46%)	NS
NCSA>5mm^2 部分(%)	1/21(5%)	26/197(13%)	NS

数据结果表示采用:均值 ± SD 所占样本的百分比(%)
AGA: 与孕龄相符; LGA:大于孕龄; SGA: 小于孕龄 NCSA: 动静脉吻合血管净横截面积
a:胎儿脐带附着形式.

表 3 胎盘检查确诊 TTTS 的准确性

	检出率(敏感性)	特异性	假阳性率(1-特异性)
脐带帆状或边缘附着	86%	47%	53%
单支或混合型血管分布	86%	40%	60%
所占胎盘面积差异>25%	52%	75%	25%
单脐动脉	6%	97%	3%
缺乏动动脉吻合	43%	89%	11%
有静静脉吻合	38%	86%	14%
动静脉吻合不均衡	33%	54%	46%
脐带帆状或边缘附着+缺乏动动脉吻合	43%	92%	8%
脐带帆状或边缘附着+所占胎盘面积差异>25%	43%	88%	12%
脐带帆状或边缘附着+有静静脉吻合	29%	92%	8%
缺乏动动脉吻合+所占胎盘面积差异>25%	10%	96%	4%
缺乏动动脉吻合+动静脉吻合不均衡	14%	99%	1%

血液在血管中的流动受许多因素的影响包括:血管直径、血液压力、血液黏度、血管活性因子及各种感受器等。而以往研究(包括该研究),主要针对血管形态学。因此以往从形态学研究得出的结论最

终又被形态学研究否定。但这也提示 TTTS 病因可能并非形态学异常,而是各种非形态学因素。现在已经有一些研究证实这一观点。Bajoria R 等和 Sooranna SR 等分别发现 TTTS 供血儿体内胰岛素样生长因子-II 及瘦素水平较受血儿低,这与胎盘的生长紊乱有关,而与血流无关。Bajoria R、Galea P、Mahieu-Caputo D 等还发现血管活性因子脑钠钛(BNP)、内皮素-1 及肾素-血管紧张素(RAS)系统异常可能是导致、维持并促使 TTTS 恶化的原因。

该研究发现双胎间胎盘面积差异>25%及胎盘血管单支分布是 TTTS 特异性较高的标志。可做如下推论,假设双胎所占胎盘面积分别为 A 和 B。若发生 TTTS 的风险较小(考虑胎盘共享)应满足:A+B>100%且 A-B<25%。可以得出 B>37.5%。据上述推论单绒双羊双胎时,每个胎儿所占胎盘面积可能应大于 37.5%。TTTS 胎盘标志为胎盘不均衡分配(双胎间胎盘面积差异>25%)、缺乏 AA 吻合、脐带帆状附着、血管单支分布等似乎都与胎盘面积有关。这也提示在对于 MCDA 的双胎胎盘的病理学检查中,要将以上几个指标纳入常规的病理解剖报告中。

胎盘是胎儿-母体进行物质交换的场所。TTTS 实质是胎盘异常,包括胎盘血管的构建和功能异常。而正常胎盘的形成需要细胞增殖与新生血管形成两者之间密切协调。而且有多种细胞(如巨噬细胞)和细胞因子(如有血管内皮生长因子(VEGF)、酸性碱性成纤维细胞生长因子(FGF)、转化生长因子(TGF)、血小板源生长因子(PDGF)、胎盘生长因子(PIGF)、肿瘤坏死因子(TNF)、血管生成素(angiopoietins)等共同参与胎盘血管形成的调节。而且胎盘形成是动态变化的过程,不同孕周胎盘血管生成的形态及调节因素是不同的。因此 TTTS 胎盘异常应该包括形态学异常和非形态学异常。甚至非形态学的异常,包括各种细胞因子和血管活性因子,在 TTTS 发生发展中可能起决定作用。TTTS 胎盘特征也提示 TTTS 胎盘中可能存在着抗血管生成的因素。

近 9%~15%的单绒双羊双胎妊娠并发 TTTS,胎儿发病率和死亡率高达 70%以上。而至今尚无预测 TTTS 的理想指标和方法。综合这几年文献,各种血管活性因子和促进血管形成的细胞因子可能是 TTTS 病因和预测进一步的研究方向。