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胎儿炎症反应综合征的产前诊断

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摘　要

胎儿炎症反应综合征(fetal inflammatory response syndrome, FIRS)是指在感染或缺氧等刺激下胎儿体内大量炎性因子释放的一种亚临床状态，与新生儿不良预后相关，靠脐血或胎盘组织检查可确诊。随着对FIRS对新生儿损伤影响及无创诊断方法的研究，使超声探查胎儿器官改变(如心脏、肾脏、肾上腺及胸腺)诊断FIRS成为可能。

关键词

胎儿炎症反应综合征，超声，无创诊断

Prenatal Diagnosis of Fetal Inflammatory Response Syndrome

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Abstract

Fetal inflammatory response syndrome (FIRS) is a sub-clinical state of a massive releasing of in-

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flammatory factors in the fetus under the infection or hypoxia. It is related to the adverse outcomes of neonates and is usually diagnosed by umbilical cord blood or placenta histological examination. With the recognition of the impact of FIRS on neonates and the development of non-invasive diagnostic methods, it is possible to diagnose FIRS by detecting fetal organ changes (heart, kidney, adrenal gland and thymus) on ultrasound.

Keywords

Fetal Inflammatory Response Syndrome, Ultrasound, Non-Invasive Diagnosis

1. 引言

胎儿炎症反应综合征(fetal inflammatory response syndrome, FIRS)是全身炎症反应综合征(systemic inflammatory response syndrome, SIRS)在胎儿期的特殊表现，常见于围产期有早产胎膜早破(preterm prelabor rupture of the membranes, PPROM)、绒毛膜羊膜炎(chorioamnionitis, CA)高危因素的新生儿。作为宫内感染的发展结局，FIRS 与胎儿多脏器损伤有关，也是早产及早产相关并发症的重要推动因素[1]。FIRS 诊断标准为胎儿脐血中 IL-6 > 11 pg/mL，和/或病理活检有脐带炎和(或)绒毛膜血管炎表现[2] [3]，目前多在产时诊断。若及时识别并诊断 FIRS，就能争取时间窗、采取针对性措施、改善新生儿预后。本文拟对产前诊断 FIRS 的必要性与可行性进行综述，以期为产前无创诊断 FIRS 提供思路。

2. FIRS 与新生儿疾病

SIRS 是指机体遭受各种刺激因素(严重感染、创伤、烧伤、胰腺炎、缺氧及再灌注损伤等)产生的失控性全身炎症反应[4]，FIRS 作为胎儿期的 SIRS，可由感染或非感染性刺激因素引发[5] [6]，常累及血液系统、肺、心脏、肾脏、肾上腺、胸腺及大脑等多器官，发生形态学变化，甚至功能障碍[7]。

宫内感染或慢性缺氧可诱发 FIRS，即胎儿体内促炎因子释放以抵御刺激，大量炎症因子释放，初期抗炎反应占主导，继而发展至炎症－抗炎交叉免疫阶段，出现胎儿组织、器官受损，机体处于免疫紊乱状态，易感性增加。胎儿体内促炎及抗炎因子产生，作用持续存在，FIRS 的影响可能不仅局限于胎儿期，不会随妊娠终止而停止，以致新生儿在生后一段时间也处于免疫抑制状态[8] [9]，导致易感性增加，罹患感染性疾病。

目前诸多研究表明，FIRS 是新生儿早产及早产相关不良预后的危险因素，主要包括新生儿早发型败血症、坏死性小肠结肠炎、脑室内出血、脑白质损伤、支气管肺发育不良，除此以外还有心肌损害、早产儿视网膜病变等[10] [11] [12]，可见其作用范围广、影响深远，若不及时干预，可能对新生儿造成难以恢复的损伤，影响生存质量，增加家庭及社会的负担。

3. FIRS 的诊断方法

美国胸科医师学会和重症监护医学会在 1992 年提出 SIRS 的定义，诊断标准涵盖体温、心率、呼吸频率和白细胞水平等多项指标[4]，而胎儿除胎心率外的其它生命体征及血常规都难以获取，用此标准评估胎儿是否处于 FIRS 状态，临床实施较困难，可行性欠佳。目前诊断 FIRS 需取脐带血或胎盘组织进行

检验，而脐带血穿刺或羊膜腔穿刺等侵袭性操作，增加宫内感染、流产或早产的风险，所以临床罕见为产前诊断 FIRS 而行有创操作，绝大多数 FIRS 都在产时诊断。但 FIRS 是影响新生儿预后的独立危险因素，产生的影响常由胎儿时期延续到分娩，若能在胎儿期诊断，可能预测早产的发生，争取干预时间窗、采取相应措施，达到延长孕期、改善预后的目的。产前诊断 FIRS 对新生儿预后的重要意义与诊断操作有创性相互矛盾，使得研究者们不断探索产前微无创诊断 FIRS 的手段。因 FIRS 可能引起胎儿血流动力学改变，组织、器官功能及形态变化，所以超声检查成为孕期诊断 FIRS 潜在的工具，即通过超声探测胎儿胸腺、心脏、脾脏、肾上腺或肾脏血流变化，预测 FIRS。

1) 胸腺：为了减少母胎排斥反应，最初胎儿体内免疫处于相对抑制状态，这种状态会随着生理需求的转变而变化，胸腺退化可能与机体应激和促炎因子的作用有关[13]。应激时，下丘脑－垂体－肾上腺轴激活，糖皮质激素促进胸腺细胞表达类固醇受体，诱发胸腺皮质细胞凋亡；在感染因素作用下时，促炎因子(如 IL-1β、IL-6 等)和活化的巨噬细胞也能激活调节轴，使得单核细胞、淋巴细胞增殖活化并向靶器官迁移，造成胸腺细胞凋亡、皮质－髓质比值下降[14]。研究表明，因宫内感染自然流产的胎儿和因败血症死亡的新生儿会出现胸腺退化[15]。

Claudio 等[16]以 X 线中胸腺－胸廓比(Cardiothymic to thoracic ratio, CT/T)为判断标准，发现孕期有组织学 CA (histological chorioamnionitis, HCA)的新生儿 CT/T 值较对照组患儿小(0.21 *vs* 0.34, $P < 0.001$)，提示生后胸腺体积减小与宫内炎症反应相关。Edoardo 等[17]进行了一项前瞻性研究，孕期由同一医生行 3 次以上超声检查评估胎儿胸腺大小，以产时病理活检示脐带炎为 FIRS 诊断标准，在 FIRS、HCA 及无感染征象的胎儿中，小于同胎龄儿平均胸腺体积的比例分别为 100%、71.4%和 12.5%，发现 FIRS 组患儿胸腺体积均小于同胎龄儿第 5 百分位水平，与对照组组间差异有统计学意义($P < 0.01$)。El-Haieg 等[18]的研究也认为，胎儿胸腺减小可作为 FIRS 的可靠超声征象。

2) 脾脏：在胎儿期，脾脏是免疫器官及造血器官。Toti 等[19]实验证明，有 HCA 病史及诊断败血症的新生儿脾脏细胞数明显减少，包括 B 淋巴细胞和 T 淋巴细胞，同时有脾脏细胞功能及形态改变。Mari 等[20]发现，96%的健康孕妇中，胎儿脾静脉血流模式是连续的。大鼠实验显示，炎症时体内代谢产物的堆积，使血管压力改变、脾门小静脉持续收缩、液体外渗且在脾门周围组织间隙重新分布，脾血管系统和周围结缔组织的改变使脾静脉顺应性降低，导致脾静脉血流速度改变[21] [22] [23]。因此，Musilova 等[24]假设发生 FIRS 时胎儿脾静脉血流模式改变，设计了一项前瞻性队列研究，孕妇在 PROM 后至分娩前由 2 名超声科医生行超声探查胎儿肾脏及肾血管血流情况，在一个心动周期内肾静脉血流速度不变是为连续的血流模式，而搏动的血流模式表现为与胎儿心脏搏动同步的反相模式，发现 HCA 和 FIRS (以病理活检发现脐带炎为诊断标准)与脾静脉血流模式相关($P < 0.0001$)；2 年后，该团队进行了一项回顾性研究，讨论了以 IL-6 升高为诊断标准的 FIRS 与脾静脉血流模式改变的相关性，发现 FIRS 胎儿中脾静脉血流是搏动式而非连续的，差异具有显著性($P < 0.0001$)，脾静脉血流图预测 FIRS 敏感度为 47%，准确度为 96%，阳性预测值 96%，阴性预测值 50% [25]，提示超声检测脾静脉流速模式，可作为产前识别 FIRS 的无创检查方法。

3) 肾上腺：胎儿肾上腺分为永恒区、移行区和中央区，而中央区又称胎儿区，约占肾上腺体积的 85% [26]。下丘脑－垂体－肾上腺轴激活、各种胎盘和胎儿之间内分泌信号通路的表达，在正常的分娩启动过程中起重要作用[27]，为了解胎儿皮质醇和硫酸去氢表雄酮(dehydroepiandrosterone sulfate, DHEA-S)与早产启动是否相关，Yoon 等[28]对比发生 PROM7 天内及 7 天后娩出的新生儿脐血皮质醇浓度，发现前者较高，差异有统计学意义($P < 0.0001$)，而 DHEA-S 表达无显著差异($P > 0.05$)；同时，还发现脐血皮质醇浓度与 IL-6 浓度有关，认为其可作为 PROM 后妊娠启动的预测因子。宫颈弹性成像可用于预测早产，宫颈长度缩短时早产已临近且难以避免，对临床决策效益有限，Agarwal 等[29]研究发现，胎儿肾上腺体积 ≥405 mm^3 诊断 FIRS 的敏感度 92.6%、特异度 95.8%，因此，其预测早产指标，与宫颈长度变化作为指标

相比，更灵敏，可争取临床干预时间窗。Turan 等[30]研究中，胎儿区体积增大超过 49.5%时，7 天内分娩发生率为 100%，所以，超声测量肾上腺胎儿区体积用于预测早产优于宫颈长度，是早产的最佳预测指标(敏感度 100%，特异度 89%)。

4) 心脏：心脏是机体炎症反应的靶器官之一，感染、炎症时常有心脏顺应性改变、心律失常或心功能不全等表现[31]。在一项灵长类动物实验中，羊膜内注射内毒素会导致胎儿心脏功能异常和调节心脏发育的基因调控网络的改变[32]，有学者认为，宫内胎儿心脏的炎症性损伤可能导致生后心功能不全的发生[33]。超声在胎儿心功能评估的应用受到限制(胎儿心脏体积小，无法经胎儿胸壁直接测量，胎儿运动及体位影响等)，医疗成像技术的发展使得超声直接胎儿心脏室壁动度、定量测量组织变形的程度、变形组织发生的比率成为可能。

目前，常用于评估胎儿心功能的参数：① E/A：E 波波峰与 A 波波峰的比值，反映心脏舒张功能；② 速度时间积分(velocity time integral, VTI)：E 波与 A 波下面积，可评估容量状态；③ 心肌做功指数(Tei index)：是等容收缩期与等容舒张期之和与心室射血时间的比值，用于评估总体心功能；④ 心肌组织应变率成像：可用于测量心室壁运动速度和应变率(strain rate, SR)，是评价节段心肌功能的量化指标[34] [35] [36] [37]。有 PPROM 的早产儿右室 ΔE/A 升高，左室 ΔE/A 及 VTI 升高，SR 峰值更高，在炎症反应时，当胎儿心输出量不能维持机体需要时，这些改变可以避免重要脏器缺血。PPROM 组胎儿 Tei 指数明显升高，表明左心功能受损。而在确诊宫内感染中上述变化更显著[38]。Edoardo 等[39]研究发现在确诊宫内感染的早产儿中，胎儿心脏收缩及舒张功能均受到影响，表现为 E/A 升高、舒张早期 SR 升高，收缩应变峰值和 SR 等于零或相反。

5) 风险评分：胎盘是母体与胎儿物质交换的场所，母体感染常常导致胎儿也处于宫内感染的亚临床状态，胎盘炎症性病变主要表现绒毛膜羊膜炎、脐带炎和绒毛膜血管炎，分别代表母体及胎儿的炎症反应[40]。CA 又分为 HCA 和临床 CA (clinical chorioamnionitis, CCA)。CCA 诊断标准[41]为产妇产时发热并出现一下 1 种及以上表现：产妇白细胞增多、阴道分泌物异味、母体外周血白细胞 $\geq 15 \times 10^9$/L、子宫激惹状态、宫体有压痛、母体心动过速(≥100 次/分)或胎儿心动过速(≥160 次/分)；HCA 诊断标准为胎盘活检见绒毛膜、羊膜炎症细胞浸润。有 HCA 的患儿 FIRS 发生率更高[40]，但这同样需行侵入性操作，那么 CCA 的表现是否可作为 FIRS 的信号灯呢？

Mariko 等[42]进行了一项纳入 PPROM 早产儿的回顾性研究，根据生后脐血 IL-6 水平分为 $FIRS^+$与 $FIRS^-$组，通过二元 logistic 回归分析研究孕期各指标预测 FIRS 的能力，创建 FIRS 风险评估模型，包括预产期、C 反应蛋白、白细胞计数、PROM 发生时间，因为使用糖皮质激素可能会增加白细胞计数，因此增加了产前糖皮质激素的使用这一因素(表 1)，曲线分析结果：曲线下面积 0.82，截断值 7.5，敏感性 89%，特异性 63%，阳性预测值 63%，阴性预测值 89%。根据此模型，0~7 分时 FIRS 发生概率为 11%，8~15 分为 50%，16~22 分为 88%。

Table 1. The risk score mode of FIRS [42]
表 1. FIRS 评分系统[42]

妊娠相关因素	值	得分
预产期	≤30 周	6
血清 C 反应蛋白	≥1.2 mg/dL	7
血清白细胞计数	≥13,000/μL	3
使用糖皮质激素	无	1
PROM 发生时间	≥3 天	5

虽然此研究为回顾性研究，还缺乏多中心环境的验证，但为产前诊断 FIRS 提供了新思路，为确定 PROM 孕妇终止妊娠的时间提供依据。

4. 总结

综上所述，FIRS 是影响新生儿预后的独立危险因素，目前主要在产时诊断，产前常常需要侵入性操作。随着对 FIRS 在胎儿及新生儿损伤中所起作用认识的深入、超声技术的发展，产前超声诊断 FIRS 成为可能，通过超声探查胎儿器官改变，如胸腺、肾上腺大小，肾脏血流模式，心功能相关指标(E/A 指数、Tei 指数)等的变化预测 FIRS 是可行的。FIRS 风险评分模型的提出，也为产前无创诊断 FIRS 提供了新思路。若能通过无创手段产前尽早诊断 FIRS，可达到争取干预时间窗、改善新生儿预后的目的。

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