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血清肿瘤坏死因子与妊娠相关疾病的研究

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摘　要

妊娠过程受环境、代谢及遗传等异常因素影响时，机体会发生一系列生理病理改变，进而导致子痫前期、妊娠期糖尿病、胎儿宫内生长受限等妊娠相关疾病，给胎儿和孕妇健康带来严重威胁。近年来，随着疾病机制研究的不断深入，研究人员发现TNF-α与妊娠相关疾病之间也存在关联。

关键词

血清肿瘤坏死因子(TNF-α)，不良妊娠结局

Study on Serum Tumor Necrosis Factor and Pregnancy-Related Diseases

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Abstract

When the pregnancy process is affected by abnormal factors such as environment, metabolism and genetics, a series of physiological and pathological changes will occur in the body, which will lead to pregnancy-related diseases such as preeclampsia, gestational diabetes, and fetal growth restriction, posing a serious threat to the health of the fetus and pregnant women. In recent years, with the deepening of the study of the disease mechanism, researchers have found that there is also an association between TNF-α and pregnancy-related diseases.

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Keywords

Serum Tumor Necrosis Factor (TNF-α), Adverse Pregnancy Outcomes

1. 引言

尽管世界人口已增加到 30 多亿，但妊娠仍然是一个成功率较低、灵活性低的过程。着床失败、自然流产(SM)、妊娠期高血压、妊娠期糖尿病、死产(SB)等的高发生率表明不良妊娠结局普遍存在，导致30%~60%的新生儿存活失败[1] [2]。不良妊娠结局的发病机制至今尚不清楚，预防这些结局的有效治疗策略仍然难以捉摸。为了更好地预测和改善妊娠结局，确定新的敏感、可靠的生物标志物并开发新的靶向治疗至关重要。怀孕和分娩期间的生理过程是紧密而特殊的。特别是，宫腔创造了一个局部环境来保护胚胎免受排斥并调节胎儿的生长和发育。分娩是一个独特的生理过程，其中炎症性免疫环境将免疫反应从免疫耐受状态转变为激活状态，导致肌层激活[3] [4] [5]。因此，胎儿和母体免疫耐受之间的良好平衡在维持正常妊娠中起着重要作用。在最近的观察性研究中，不良妊娠结果可能是由母体免疫耐受失衡或过早或过度炎症的直接刺激引起的[6]。异常细胞因子，如肿瘤坏死因子(TNF-α)与围产期不良结局的风险有关，例如 SM、PTB 和胎儿宫内生长受限[7]。

肿瘤坏死因子(TNF-α)是由激活的巨噬细胞、肥大细胞和内皮细胞产生的一种促炎的 Th1 细胞因子[8]，也是最重要的炎性细胞因子之一。在生理条件下，肿瘤坏死因子参与免疫监视和防御，细胞稳态，防止某些神经损伤以及控制细胞存活、增殖、迁移和分化[9]。而在女性妊娠期间，TNF-α 具有双重作用，生理浓度的 TNF-α 有利于早期胚胎发育和黄体维持。而高于生理浓度的 TNF-α 对精子活力、精子穿透卵细胞、精卵结合及早期胚胎发育具有不良作用，甚至可导致妊娠不良结局。因此，在导致不良妊娠结局相关的研究领域中，肿瘤坏死因子逐渐成为热点。

2. TNF-α 与妊娠相关疾病

妊娠过程受环境、代谢及遗传等异常因素影响时，机体会发生一系列生理病理改变，进而导致子痫前期、妊娠期糖尿病、胎儿宫内生长受限等妊娠相关疾病，给胎儿和孕妇健康带来严重威胁。近年来，随着疾病机制研究的不断深入，研究人员发现 TNF-α 与妊娠相关疾病之间也存在关联。鉴于此，本文对 TNF-α 在不同妊娠相关疾病中的研究进展综述如下，以期为妊娠相关疾病的诊治提供新的方向。

2.1. TNF-α 与子痫前期

子痫前期是妊娠期高血压疾病较为严重的一种，妊娠 20 周后以水肿、蛋白尿、高血压为主要临床表现，严重影响妊娠结局、身心健康、生活质量[10]。根据相关流行病学研究，子痫前期是一种影响全球3%~5%孕妇的疾病[11]，而中国的患病率约为 10% [12]。子痫前期的发病机制尚不完全清楚，认为内皮损伤、无菌性全身炎症和胎盘“浅表胎盘”在子痫前期(PE)的发病机制中起作用[13]。肿瘤坏死因子-α (TNF-α)作为一种促炎细胞因子，能够在亚细胞水平上刺激一系列级联反应，诱导包括 TNF-α 在内的各种促炎因子的表达，介导母体血管内皮的广泛损伤并引起 PE 的典型症状。此外，TNF-α 作用于血管内皮细

胞，从而增加毛细血管通透性，诱发血栓形成，导致局部组织缺血缺氧。研究表明[14]临床子痫前期患者血清中 TNF-α 水平高于正常孕妇，而胎盘组织中 TNF-α 表达也随着病情的进一步升高而升高，提示 TNF-α 在先兆子痫的病理发展中发挥作用。洪[15]等报道，先兆子痫患者的血清中含有大量由白细胞激活的炎症介质，并且子痫前期与生物体中炎症反应的存在之间存在实质性关联。在这项研究中，我们发现，相对于健康对照组，早发性和晚发性患者中外周血中的 TNF-α 水平升高，这表明子痫前期患者的免疫炎症机制已经受到干扰，并且早发患者的 TNF-α 水平高于晚期患者。这被认为是由于怀孕期间滋养层细胞的相对缺氧，这增加了促炎细胞因子 TNF-α 的表达。由于 TNF-α 作用于胎盘区域的血管内皮细胞和滋养层细胞，导致内皮细胞受损，毛细血管通透性增加，刺激血栓形成，导致局部组织缺血缺氧、浅表胎盘着床和子痫前期[16]。

2.2. TNF-α 与 GDM

妊娠期糖尿病(gestational diabetes mellitus, GDM)是在怀孕期间发病或首次发现的任何程度的糖耐量异常[17]，是妊娠期常见的代谢并发症之一，不仅在短期内而且在长期内，都会增加母亲及其后代的不良妊娠结局风险[18]。随着经济水平的提高，人们的饮食结构和生活习惯发生改变，全球 GDM 发生率随之升高。据统计，全球 GDM 发病率为 13.2% [19]，中国为 14.8% [20]。GDM 是一种慢性炎性疾病，炎症因子可能通过抑制胰岛素信号转导引起胰岛素抵抗(insulin resistance, IR)，参与 GDM 的发病[21]。有相关研究表明，GDM 女性中母体炎性细胞因子(TNF-α)水平较正常妊娠孕妇高，但其参与 GDM 病理过程的机制尚不清楚。Teng 等[22]研究发现，硫化氢(hydrogen sulfide, H2S)可抑制胰岛素释放和胰岛 β 细胞的活性，当血糖升高时 H2S 下降，同时伴随 TNF-α 的升高，这可能是 GDM 炎症机制的一环。值得注意的是，随着母体 TNF-α 水平的升高，孕早期胎盘分泌的粒细胞－巨噬细胞集落刺激因子、趋化因子配体 5 和白细胞介素(interleukin, IL)-10 增多，而 IL-6 和 IL-8 水平无明显变化，表明在炎症初期体内可能存在抑制炎症状态的保护机制[23]。可见，TNF-α 通过调节炎症因子影响 GDM 病理过程的因素众多，且机制复杂，有待进一步研究。促炎因子 TNF-α 已被证实对于 GDM 的发生具有较好的预测价值，但是 GDM 的病理过程涉及的炎症介质众多且彼此影响，炎症机制十分复杂，未来需要大量研究进一步探讨。

2.3. TNF-α 与胎膜早破

胎膜早破(PPROM)是指胎膜在临产前发生自发性破裂，又称临产前胎膜自然破裂，可分为足月胎膜早破和未足月胎膜早破。PPROM 使约 3%的妊娠复杂化，并导致约三分之一的早产。胎膜早破的原因尚不清楚，但最近，新的理论认识到 PPROM 可能是由复杂和多方面的途径引起的，通过改变胶原蛋白网络和/或激活由细菌产物或促炎细胞因子(TNF-α)触发的基质金属蛋白酶，导致膜形态减弱[24]。有研究表明[25]，与正常足月分娩者相比，胎膜早破患者胎膜、血清以及羊水中的 TNF-α 表达更高，表明胎膜早破后孕妇体内发生炎性反应导致大量细胞因子释放，使胎膜早破孕妇细胞因子总体水平高。研究还表明，母血中 TNF-α 水平与破膜时间有明显关系，及破膜时间越长，机体越有充足的时间对细菌及其产物产生应答，TNF-α 产生越多[26]。可能原因是，TNF-α 参与了机体的炎症反应过程，触发胎膜组织中 CasDase 基因表达，诱导胎膜细胞凋亡，从而导致胎膜早破。

2.4. TNF-α 与早产

根据世界卫生组织的定义，早产被定义为终止妊娠少于 37 整周[27]，是五岁以下儿童死亡的主要原因。一般来说，早产对早产儿的健康有负面影响，给早产儿家庭和社会造成负担。早产与遗传因素、炎症和免疫力有关[28]。一方面，胎膜早破(PROM)是早产的原因之一。在小鼠模型中，胎盘组织中 TNF-α

和 IL-6 上调导致 PROM [29]。王等证明 TNF-α 引起的胎儿膜细胞凋亡增加与 PROM 有关，进一步导致早产[30]。另一方面，子宫收缩力异常也会导致早产。许多研究表明，TNF-α 与子宫肌层的收缩力有一定的相关性，主要是通过影响黄体酮(PG)和基质金属蛋白肽酶 9 (MMP9)的表达。子宫肌层中 PG 和 MMP9 的表达和敏感性的增加将导致子宫收缩和分娩[31] [32]。具体而言，据报道 TNF-α 会降低滋养层细胞中 NAD + 依赖性 15-羟基前列腺素脱氢酶(PGDH)的活性和表达，导致母体 PE 和早产[33]。最近的进展表明，TNF 家族可能调节导致早产的巨噬细胞功能障碍，但具体的分子机制需要进一步研究。

2.5. TNF-α 与胎儿生长受限

胎儿生长受限(IUGR)被定义为胎儿预期生长潜力的损害，估计胎儿体重小于胎龄小 10%。母体营养、胎盘运输和胎儿遗传潜力的异常可能导致胎儿的异常生长发育。Azizieh 和 Raghupathy 等人发现 IUGR 患者外周血单核细胞中 TNF-α 的表达高于正常孕妇，说明了 TNF-α 在 IUGR 发生中的潜在作用[34]。然而，IUGR 中 TNF-α 免疫学研究的具体机制是有限的。胎儿血管疾病是 IUGR 的致病机制。TNF-α 直接损害内皮细胞，损害滋养层细胞的侵袭和融合[35] [36]，并损害螺旋动脉的重塑。此外，TNF-α 还可以干扰血液凝固系统，导致胎盘血栓形成和加重胎盘灌注不足[37] [38]。因此，这些表明 TNF-α 与 IUGR 和骨骼迟缓密切相关。埃尔法约米等。证明 IUGR 血清中抗苗勒管激素(AMH)、IL-6 和 TNF-α 高于正常妊娠，可作为 IUGR 的有用生化标志物。然而，关于 IUGR 调查的报告很少[39]。值得注意的是，需要更多的临床研究来确定它们是 IUGR 生物标志物的诊断，治疗和预防。在小鼠中，阻断 TNF-α 可以改善螺旋动脉重塑和妊娠结局[40]。因此，TNF-α 为 IUGR 的治疗和预防提供了新的选择。目前，关于 IUGR 中 TNF 家族的研究屈指可数，TNF 在 IUGR 发病机制中的作用需要进一步研究。

2.6. TNF-α 与其他不良妊娠结局

据兰等报道，TNF-α 和 Th1/Th2 比率水平升高与胚胎停滞率呈阳性[41]。李等首先发现 TNF-α 基因多态性与复发流产风险增加有关[42]。随后，其他研究小组进一步证明了 TNF-α 在蜕膜组织和复发性流产外周血中的高表达[43]。丰塞卡等发现 TNF-α 在流产的蜕膜组织中的高表达可以抑制胚胎干细胞的分化并损害蜕膜化，从而干扰囊胚植入和/或妊娠维持[44]。杨等人的最新研究。结果表明，dNK 细胞在自发流产组织中高度表达 TNF-α，TNF-α 诱导 dNK 细胞中芳烃受体表达上调，从而增强蜕膜自然杀伤细胞(dNK 细胞)的细胞毒性，使 dNK 细胞对胎儿产生免疫反应，导致流产。

3. 总结

总之，成功妊娠需要蜕膜免疫细胞和炎性细胞因子之间的胎儿－母体免疫串扰。TNF-α 失调可能导致不良妊娠结局。在妊娠过程中，高 TNF-α 浓度不仅增加 NK 细胞的细胞毒性并刺激 B 细胞，而且破坏了 Th1/Th2 和 Th17/Treg 细胞的平衡，增加了滋养层的死亡，损害了其侵袭和融合，损害了内皮细胞，影响了蜕膜化。因此，上述机制诱发妊娠并发症，即 PE，IUGR，SA 和早产。尽管如此，TNF-α 的特殊机制仍需进一步研究。

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