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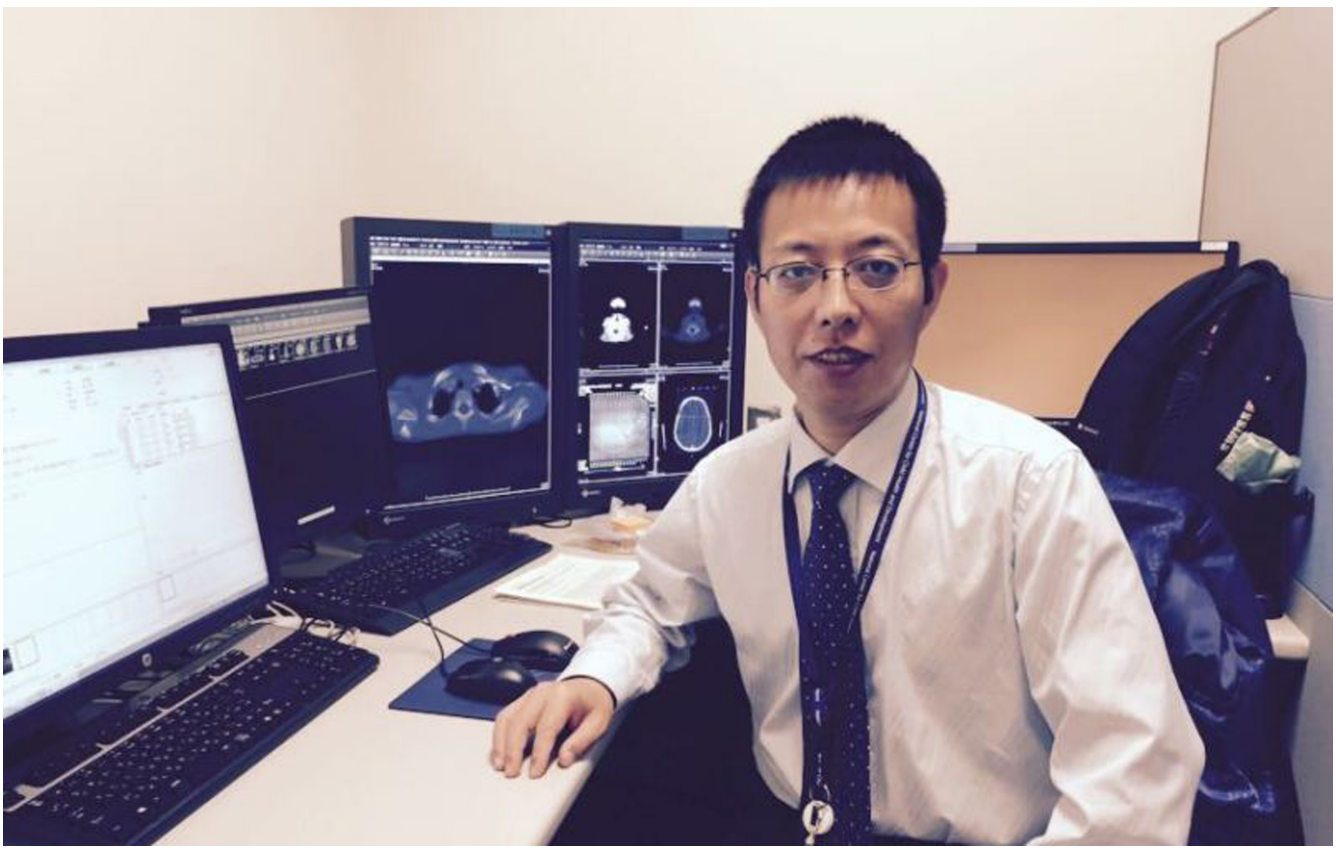

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文献综述 REVIEW

妊娠期急性胰腺炎研究进展

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Progress in research of acute pancreatitis in pregnancy

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Abstract

Acute pancreatitis in pregnancy (APIP) is a rare and severe complication of pregnancy, which is characterized by rapid onset, rapid progression, many complications, and high mortality. According to previous studies, the incidence of APIP is about 1/10000-1/1000 and increases with gestational age. Due to the differences in genetic background and dietary habits between Asian and European populations, the incidence of APIP in China is as high as 1.14‰-2.27‰, significantly higher than that in Western countries. The lack of specific clinical symptoms of APIP often leads to misdiagnosis or missed diagnosis, which greatly increases the difficulty of diagnosis and treatment. Despite the deepening of the research on APIP, its pathogenesis is still unclear. This paper will give a systematical review of APIP.

Key Words: Acute pancreatitis in pregnancy; Diagnosis; Treatment

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摘要

妊娠期急性胰腺炎(acute pancreatitis in pregnancy, APIP)是妊娠期较少见却病情凶险的妊娠合并症, 具

有起病快、进展急、并发症多、病死率高等特点. 据相关研究报道, APIP发病率约为1/10000-1/1000, 且随胎龄的增加而升高. 由于亚洲人群与欧美人群基因背景以及饮食生活习惯的差异, 我国APIP的发病率高达1.14‰-2.27‰, 显著高于西方国家. APIP的临床症状缺乏特异性, 容易导致误诊或漏诊, 极大增加了诊疗的难度. 尽管对APIP的研究不断深入, 然而其发病机制仍不明确. 本文将对APIP的综合现状进行综述.

关键词: 妊娠期急性胰腺炎; 诊断; 治疗

核心提要: 妊娠期急性胰腺炎(acute pancreatitis in pregnancy, APIP)是急性胰腺炎(acute pancreatitis, AP)的特殊类型, 是一种罕见但病情凶险, 严重威胁孕产妇及胎儿生命安全的妊娠合并症. 由于APIP临床特征缺乏特异性, 极易导致误诊或漏诊, 增加了临床诊治的难度. 本篇结合近些年APIP的病因、发病机制及诊疗等方面的研究现状进行系统性综述, 概括了当前APIP的认识, 强调了多学科团队(MDT)诊疗模式对APIP诊治的重要性. 期望本综述可以对APIP的临床实践及基础研究提供一定的参考.

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0 引言

妊娠期急性胰腺炎(acute pancreatitis in pregnancy, APIP), 是发生在妊娠期及产后3月内的急性胰腺炎(acute pancreatitis, AP)[1]. 其发病急, 病情凶险, 是妊娠期严重的合并症[2]. 以急性上腹痛、恶心、呕吐等为主要临床特点. 因其发病时无特异性症状, 易与其他妊娠期疾病混淆, 贻误治疗时机[3].

APIP对胎儿结局有不良影响, 但其患病率与AP严重程度或损害程度的关系尚不清楚[4]. 妊娠期急性胰腺炎按病因主要分为胆源性、高脂性和酒精性等方面, 不同病因导致的胰酶激活进而诱发胰腺组织自身消化是目前公认的发病机制[5]. 急性胰腺炎状态下大量炎症因子释放[6,7], 进展加重可引起胰腺水肿坏死和胰腺(周)组织坏死, 甚至多器官功能障碍综合征(multiple organ dysfunction syndrome, MODS)[2,8]. 文献报道中APIP的结局差异较大, 可能产妇和胎儿有较高的死亡率. 有报道称APIP所致的孕产妇病死率及围生儿病死率分别为3.3%-5.3%和11.6%-31.6%[9,10]. APIP具有不同于其他类型AP的临床特点,到目前为止仍然缺乏APIP足够的临床研究证据, 本篇将结合现有研究基础对APIP发病及临床诊疗情况进行综述.

1 流行病学

APIP是妊娠期少见的急腹症, 其发生与种族、年龄、地域、饮食习惯等因素相关. 欧美国家的发生率总体较低, 约为1/10000-1/1000[2,11,12]. 目前国内报道多为单中心、小样本研究. 国内报道APIP的发生率约为1.14‰-2.27‰[13]. 随着出生率的提高, APIP的发病率亦逐年上升[14].

2 APIP病因及发病机制

APIP的病因以胆石和高甘油三酯血症为主, 其他如特发性、酒精、甲状旁腺功能亢进、外伤等病因在国内并不多见[15].

2.1 胆源性APIP 胆源性因素是APIP的主要病因[9-11,16,17], 可能与妊娠期女性激素水平相关. 妊娠期雌激素水平升高, 促进相关代谢酶类的合成, 进一步导致胆汁中胆固醇、胆汁酸盐比例失衡, 造成结晶风险. 此外妊娠期孕激素水平升高引起胆囊平滑肌松弛, 导致胆道排空延长, 发生结石风险增加[5]; 妊娠晚期, 子宫压迫胆道系统, 导致胆汁淤积, 结石风险同样增加.

2.2 高甘油三酯血症性APIP 目前高甘油三酯血症所致的APIP发病机制尚不完全明确. 一般认为肥胖、高脂饮食、运动量少、激素改变等因素导致HTG进而诱发APIP的发生[18,19]. 正常妊娠状态, 血清甘油三酯(triglycerides, TG)水平较孕前增加, 最高可达2-3倍(最高TG水平均值为4.25 mmol/L, 正常TG<1.7 mmol/L), 并在孕晚期达到高峰[20].

高脂血症时脂蛋白(triglyceride-rich lipoproteins, TRLs)水解并释放高浓度的游离脂肪酸(free fatty acid, FFA)[21]. 过量的FFA引发细胞毒性, 激活胰酶, 最终造成高甘油三酯血症性急性胰腺炎[22]. 研究表明重度高脂血症通常与基因突变相关, 脂代谢相关基因突变可导致妊娠期TG水平异常增高, 诱发急性胰腺炎[23].

2.3 酒精性APIP 酒精性APIP是国外主要的病因来源. 国内怀孕期间饮酒极为少见, 故酒精性APIP的发生率很低[9,24,25]. 酒精能够刺激胰液分泌增加, 亦可导致Oddi括约肌痉挛, 进而导致胰管梗阻; 同时酒精的相关代谢产物可激活胰酶, 诱发胰腺炎[26].

2.4 其他 妊娠期合并甲状旁腺功能亢进、高血压、糖尿病、肥胖等都可诱发APIP[24, 27-30]. 妊娠期间服用激素、利尿剂、非甾体类抗炎等药物也可诱发胰腺炎[5,26].

3 APIP诊断

目前APIP没有统一的诊断标准, 根据我国的急性胰腺炎

诊治指南(2021)及亚特兰大标准[31,32], APIP的诊断需要同时满足以下3个特点中的2项: 腹痛(上腹部为主)、血清淀粉酶或脂肪酶升高≥正常值上限3倍以及具有急性胰腺炎特征性的影像学征象(胰腺水肿渗出、出血坏死等).

3.1 临床表现 APIP与非妊娠期急性胰腺炎临床表现相似, 仍以腹痛、恶心、呕吐为主. 但需注意, 由于孕产妇出现腹痛不适等症状较为常见, 一般认为与妊娠相关而就诊于妇产科, 极易误诊延误病情[16]. 当APIP患者病情进展加重时或可伴随局部或全身并发症, 危及生命[2].

3.2 实验室检查 结合非孕期急性胰腺炎的诊断标准, 血淀粉酶水平≥正常上限值的3倍时, 即可诊断为急性胰腺炎. 妊娠期激素水平变化对淀粉酶的影响较大, 因此单纯淀粉酶检测对APIP诊断效果有限[33,34]. 另外, 有研究表明血脂肪酶对APIP有较高的诊断价值[35].

其他实验室指标如: 血钙<1.5 mmol/L, 往往提示急性胰腺炎预后不良[36]. TG>1000 mg/dL(11.3 mmol/L)或>500 mg/dL(5.65 mmol/L)且排除其他病因, 是高甘油三酯血症性急性胰腺炎的诊断标准[37].

3.3 影像学检查 影像学检查是明确诊断的主要手段, 但妊娠期患者的影像学检查具有一定特殊性.

(1)腹部B超能较好的显示胰腺肿胀及胰周渗出[38]. 但易受胃肠积气等因素的干扰, 难以准确评估APIP严重程度, 诊断价值有限; (2)CT检查能准确反映病情严重程度, 是当前诊断急性胰腺炎的主要影像学检查. 但存在辐射的影响, 因此妊娠期CT检查受到限制[15,39]; (3)核磁共振成像(magnetic resonance imaging, MRI)检查具有无创、无辐射等优点, 对于评估胰胆管及胰周渗出方面具有优势[40]. 此外, 核磁共振胰胆管成像(magnetic resonance cholangiopancreatography, MRCP)技术对胰胆管系统显影具有独特优势. 相反有学者指出在妊娠早期行MRI检查可能给胎儿带来热损伤风险, 孕早期MRI检查亦慎重[41]; (4)经内镜逆行性胰胆管造影术(endoscopic retrograde cholangiopancreatography, ERCP)可在明确胆管内结石情况的同时, 行取石治疗. 但其存在辐射暴露、出血等风险, 不推荐将ERCP作为APIP的常规检查方法[42]; (5)超声内镜(endoscopic ultrasonography, EUS)检查可以准确地探查胆道情况, 尤其当腹部B超或生化检查高度怀疑胆总管结石时, 半侵入性EUS检查能准确有效的评估胆总管结石, 但EUS在妊娠期患者中的应用尚缺乏足够依据[43,44].

3.4 鉴别诊断 APIP应与妊娠合并急性胆囊炎、急性阑尾炎、胃十二指肠溃疡等急腹症和产科相关急症如流产、早产、临产、胎盘早剥等相鉴别.

4 APIP治疗

目前, APIP治疗尚无明确的临床指南或共识. 临床推荐由普通外科、消化内科、妇产科、重症医学科等相关专业人员组成的多学科诊疗团队(multiple disciplinary team, MDT)进行规范化诊疗. 去除病因是APIP良性转归和避免复发的关键. 根据患者病因、病程和疾病严重程度采取个体化治疗. 孕早、中期APIP患者应重点进行病因治疗, 其次考虑胎儿因素; 而对于孕晚期APIP, 需同时考虑胎儿因素, 必要时则应进行手术干预或及时终止妊娠.

4.1 一般治疗 主要包括加强孕产妇及胎儿生命体征的监测、禁食水、胃肠减压、抑酸抑酶、抗感染、早期液体复苏、维持水电解质酸碱平衡、镇痛, 营养支持等方面.

4.2 营养支持 营养支持是治疗APIP患者的重要组成部分. 早期肠内营养有助于恢复胃肠道蠕动, 有效防止胃肠道菌群失调, 促进胰周和腹膜后坏死组织局限并吸收, 保护胃肠道功能屏障[45]. 但当患者出现肠内营养不耐受, 胃肠道功能受损时, 可行短期肠外营养以确保母体及胎儿营养需求. 肠内营养较肠外营养在急性胰腺炎治疗中更具优势[46,47]. 近期由笔者所在团队牵头, 在中国118家重症监护病房(intensive care unit, ICU)开展的关于危重病人循证喂养流程的临床研究结果显示, 循证喂养流程的成功实施减少了危重症患者开始使用肠内营养(enteral nutrition, EN)和总体肠外营养(parenteral nutrition, PN)的时间, 该研究也为APIP患者的营养支持策略选择提供了有力的参考依据[48]. 同时, 探索更加精准的APIP营养支持模式将使患者获益.

4.3 药物治疗

4.3.1 抑酸药: 质子泵抑制剂与H2受体阻断剂通过适当抑制胃酸分泌, 间接减少胰液的分泌, 但因其可进入乳汁, 故产褥期哺乳的APIP患者, 应尽量避免使用.

4.3.2 生长抑素: 生长抑素可抑制胰液分泌或降低胰酶活性, 但目前关于其对胎儿和孕产妇的影响未知, 故应谨慎使用.

4.3.3 抗生素: 对APIP患者预防性抗生素应用尚无定论, 有研究指出急性胰腺炎合并胰腺坏死时预防性使用抗生素并无益处[49]. 患者出现感染加重时, 需要及时、合理应用抗生素. 原则上应根据血培养及药敏试验结果及时调整用药方案[50]. 当怀疑有脓毒症或感染时, 应进行细菌培养和胸部放射学检查. 如有需要, 可行CT引导下胰腺坏死区的细针穿刺进行细菌和真菌培养, 以指导使用合适的抗生素[51,52]. 如果培养结果为阴性, 患者出现脓毒症、器官衰竭或至少30%的胰腺

坏死, 则应继续使用抗生素治疗. 对于感染性胰腺坏死, 抗生素的选择受培养的指导[53].

4.4 降脂治疗 (1)目前并没有专门针对孕产妇安全有效的降脂药物. 贝特类和他汀类药物存在潜在的致畸作用, 因此在妊娠期不建议使用[54,55]. 高甘油三酯血症性APIP患者饮食、运动等方式效果不佳时, 应使用Omega-3脂肪酸降低甘油三酯水平[56]. 此外, 胰岛素可增强脂蛋白脂肪酶的活性, 低分子量肝素可刺激脂蛋白脂酶的释放, 且两者合用可加快乳糜微粒分解, 降低血脂水平[57]; (2)血液净化主要包括血液透析、血液滤过、血液灌流、血浆置换和免疫吸附等[58]. 连续血液净化能迅速降低高脂血症型APIP患者的甘油三酯水平, 有效清除炎性介质, 进而改善临床和预后[59].

4.5 菌群调理 有研究表明益生菌对AP的治疗有一定作用[60], 可能的机制包括: 通过与致病菌群竞争, 调节肠道菌群平衡; 促进谷胱甘肽合成, 改善肠黏膜屏障功能障碍; 影响免疫细胞的功能等[61]. 但也有报道显示益生菌并不能降低SAP患者的坏死率和病死率, 甚至可能提高病死率[62].

4.6 中医治疗 中医疗法如清胰承气汤、柴胡汤以及针灸等方法可明显减轻胰腺炎患者症状及改善预后[63]. 中医疗法具有操作简单, 毒副作用小等优势. 但中医治疗AP仍需要大样本研究, 进一步评估其治疗急性胰腺炎的临床效果.

4.7 手术治疗 APIP患者应谨慎选择手术治疗途径. 通常包括开腹手术、腹腔镜手术以及ERCP. 孕早期的APIP患者尽可能进行保守治疗; 而孕中期胎儿已基本发育成熟, 必要时可选择手术干预; 孕晚期APIP患者若保守治疗无效, 则应及时进行手术并终止妊娠, 确保母婴生命安全[64].

4.8 产科治疗 应加强对胎儿的监护, 适时的终止妊娠可有效改善妊娠结局[65]. 有早产征象者及时予以硫酸镁抑制宫缩, 并尽可能维持到足月; 孕6 mo内患者一旦发现死胎应及时引产. 妊娠28 wk以上, 为防止早产儿发生呼吸窘迫综合征, 在应用足量使用抗生素的情况下, 可适当使用地塞米松促进胎儿肺成熟. 对妊娠中晚期患者(胎龄≥37 wk), 胎儿发育已基本成熟, 可适时行剖宫产术终止妊娠. 若出现严重胎儿宫内窘迫或明显早产征象, 以及病情已进展为重症APIP等状况时, 应尽快终止妊娠, 降低孕妇及围产儿死亡率.

4.9 心理干预 APIP患者情绪易波动, 合理的心理干预能够缓解患者焦虑状态, 对降低孕产妇及胎儿死亡率以及改善妊娠结局具有一定价值[66].

5 结论

综上所述, 妊娠期急性胰腺炎发病急、并发症多, 严重威胁着母婴健康. 目前其发病机制尚不完全清楚. 快速诊断、明确病因是诊疗的关键. APIP一旦确诊, 应立即启动多学科团队(MDT)诊疗模式, 积极进行临床干预. 治疗过程中, 严密监测孕产妇及胎儿情况, 结合病情严重程度、孕周、疗效等情况, 谨慎把握终止妊娠的时机及方式, 保证母婴生命安全. 为寻求更加安全、有效的治疗方案, 并提高APIP患者治愈率、降低不良妊娠结局的发生, 仍需更加深入的研究.

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