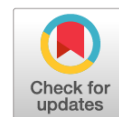


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子痫前期的病因病机及危险因素的现代认识研究

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2—8%的妊娠合并子痫前期。根据文献,子痫前期与产妇和围产期发病率和死亡率的增加有关,也预示着慢性疾病在遥远的未来的发展,这是一个重要的医学和社会问题。尤其值得关注的是子痫前期的发病机制和危险因素的分子机制,目前对其研究和认识尚不充分,这就要求对这一可怕的妊娠并发症进行进一步的研究。本文介绍子痫前期的病因、发病机制及危险因素的现代认识。

关键词: 子痫前期; 病原学; 发病机理; 风险因素

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Modern concepts of etiology, pathogenesis and risk factors for preeclampsia

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Preeclampsia is a serious complication of pregnancy and complicates its course in 2–8% of all cases. According to the literature, the disease is associated with an increase in maternal and perinatal morbidity and mortality, and is a predictor of the development of chronic diseases in the distant future, which is an important medical and social issue. Of particular interest is the study of the molecular mechanisms of etiopathogenesis and risk factors for preeclampsia, which, unfortunately, are currently poorly studied and understood, thus dictating the need for further study of this complication of pregnancy. This article discusses the current understanding of the etiology, pathogenesis and risk factors for preeclampsia.

Keywords: preeclampsia; etiology; pathogenesis; risk factors.

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Современные представления об этиологии, патогенезе и факторах риска преэклампсии

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Преэклампсия осложняет течение беременности в 2–8 % всех случаев. Преэклампсия, по данным литературы, ассоциирована с увеличением материнской и перинатальной заболеваемости и смертности, а также является предиктором развития хронических заболеваний в отдаленном будущем, что представляет собой важную медико-социальную проблему. Особый интерес вызывают молекулярные механизмы этиопатогенеза и факторы риска преэклампсии, которые, к сожалению, в настоящее время недостаточно изучены и понятны, что диктует необходимость дальнейшего исследования данного грозного осложнения беременности. В данной статье рассмотрены современные представления об этиологии, патогенезе и факторах риска преэклампсии.

Ключевые слова: преэклампсия; этиология; патогенез; факторы риска.

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现代概念认为,子痫前期(PE)临床表现为动脉高压($\geq 140/90$ mmHg),蛋白尿(≥ 0.3 g/天),并伴有水肿和各种器官和系统的破坏[1]。这些症状可能发生在怀孕期间(20周后)和产后期间(长达28天)。

2—8%的妊娠合并子痫前期,是全球孕产妇死亡的主要原因之一[2]。根据俄罗斯联邦卫生部卫生监测、分析和战略发展司2018年《统计汇编》公布的数据,俄罗斯中度子痫前期妇女发病率为27.4%,重度子痫前期妇女发病率为8.4%[3]。

早发子痫前期(妊娠34周前)对母亲和胎儿的预后都是最不利的。有子痫前期病史的女性在未来很可能发生慢性动脉血压、2型糖尿病、肾功能衰竭、冠心病、各种形式的心律失常等高危人群[4]。尽管现代医学取得了成就,治疗子痫前期的唯一有效方法是分娩,无论妊娠期如何,这对围产期发病率和死亡率结构有重要影响,其主要原因是早产、慢性缺氧和胎儿发育迟缓[5]。

子痫前期的形成机制在国内外得到了广泛的研究,关于该并发症的发生发展有30多种假说,其中胎盘障碍在其中起着关键作用[6]。目前,由Redman于1991年提出的子痫前期发展的两阶段模型已被普遍接受。在子痫前期的第一阶段,异常的胎盘在妊娠早期发生,导致播散性内皮功能障碍,并在第二阶段形成母体综合征[7]。一般认为早期和晚期子痫前期的形成机制不同。因此,88%的子痫前期的晚期发展主要是由于母亲的原因(代谢综合征、高血压、慢性肾脏疾病等),并伴有胎盘功能障碍。只有一小部分在怀孕34周后出现子痫前期的妇女有螺旋动脉不完全重塑的迹象[8]。在所有子痫前期病例中,有12%的病例出现早发,并与广泛的胎盘病变和母亲和胎儿发生并发症的高风险有关。子痫前期早期形成的一个触发因素是妊娠初期胎盘异常[9]。

在妊娠的生理过程中,着床时,合体滋养细胞被引入子宫内膜,为胚胎提供组织营养,直到血液营养类型建立。然后,血管内滋养细胞逆行侵入子宫血管,取代血管内皮内皮[10]。这些变化导致螺旋动脉肌壁的凋亡,从而形成低血管内压力的血管床,这有助于在整个妊娠期间维持足够的胎盘灌注。在子痫前期,这些过程是异常的,最终导致滋养层侵袭不完全和子宫胎盘血流量的形成异常[11]。

胚胎和胎盘的早期发育是在生理氧含量低(1—2%)的条件下发生的,这可能是防止胎儿氧化损伤和正常的滋养细胞功能所必需的[12]。

低氧水平刺激缺氧诱导因子(HIF-1 α 和HIF-2 α)和转化生长因子 β (TGF- β)的表达增加,这也抑制了滋养细胞向侵袭型的转变。子宫胎盘血流量的加强从妊娠第10周开始,伴随着氧分压显著升高,HIF-1 α /HIF-2 α 和TGF- β 表达降低,滋养细胞由增殖型向侵袭型的重组,保证了子宫血管的正常转化。妊娠10周后持续缺氧,滋养层分化过程异常,导致螺旋动脉浸润不够深,不典型转化[13]。缺氧介导的HIF-1 α /HIF-2 α 和TGF- β 持续过表达是化解侵袭过程的机制之一。R.E. Albers等人(2019)发现HIF-1 α 的延长表达导致小鼠的高血压、伴有蛋白尿的肾脏肾小球内皮病变和胎儿生长受限[14]。HIF-2 α /HIF-3 α 作为血管内皮生长因子(VEGF)和胎盘生长因子(PlGF)的抑制剂,通过激活可溶性fms样酪氨酸激酶-1(sFlt-1)的信号通路,也对胎盘的形​​成产生负面影响[15]。

其致病作用不仅在于缺氧,而且还在于系统地反复发生缺血和再灌注,而缺血和再灌注伴随着活性氧的增加,从而为氧化应激的发展创造了一个良好的环境[16]。胎盘的氧化损伤诱导细胞凋亡,释放各种抗血管生成因子,促炎细胞因子和血管活性化合物到母亲的血液中,导致内皮细胞大量全身性功能障碍,并伴有炎症和血管收缩[17]。氧化应激也可增强线粒体功能障碍。V.R. Vaka等人(2018)研究了子痫前期线粒体功能障碍及其与内皮功能障碍、全身血管痉挛、炎症和氧化应激的关系。他们得出的结论是,在子痫前期,线粒体代谢加速,伴随着钙离子含量的增加,磷酸化过程的破坏和活性氧形成的增加,其在DNA和RNA损伤、细胞死亡和内皮功能障碍的发生中起重要作用[18]。自由基激活脂质过氧化和花生四烯酸代谢环加氧酶途径产物的合成过程。因此,T.N. Pogorelova等人(2019年)发现,在子痫前期女性中,胎盘组织中的血栓烷B₂和花生四烯酸含量比对照组女性增加了30%以上,而血管扩张剂前列环素的浓度下降了20%[19]。花生四烯酸代谢产物参与炎症过程的发展,也影响血小板的粘附和聚集,从而导致血管内凝血病、血栓形成、胎盘梗死和功能不充分的子宫胎盘血流量更大的功能恶化[20]。此外,氧化应激通过刺激促炎细胞因子(如肿瘤坏死因子 α 和白细胞介素(IL)-6)的产生,以及减少抗炎细胞因子(IL-10)的合成来增强炎症反应,从而导致细胞损伤[21]。同时,随着氧化应激的发展,胎盘抗氧化机制的工作受到抑制,表现为子痫前期中超氧

化物歧化酶、过氧化氢酶和谷胱甘肽过氧化物酶的表达减少[22]。

内皮功能障碍是母体综合征子痫前期发病机制中的一个中心环节。内皮细胞的异常是血管活性介质失衡发展的基础, 这将导致血管收缩剂产量的增加[23, 24]。循环血管生成因子失衡间接影响内皮功能障碍的形成和子痫前期的临床表现, 形成恶性循环。可溶性fms样酪氨酸激酶1(sFlt 1)是一种内源性抗血管生成因子(内皮抑素), 是一种有效的VEGF拮抗剂, 在子痫前期显著升高。VEGF不仅在血管生成中起重要作用, 而且在维持内皮细胞的正常功能和控制内皮窗(肾小球内皮细胞的特征)的形成方面起重要作用[25]。sFlt 1(体外)的表达增加诱导肾小球内皮增生伴小窗消失, 组织学上类似于子痫前期的肾脏损害。更严重的子痫前期, 包括HELLP综合征, 也与sFlt 1和可溶性内毒素(也是一种抗血管生成因子)水平的同时升高有关[26]。

基质金属蛋白酶(MMP)在子痫前期内皮功能障碍的形成中具有重要作用。MMP-2、MMP-9、MMP-3、MMP-13与血管着床、滋养层浸润和重塑过程直接相关。它们参与内皮素和肾上腺髓质素的降解, 这有助于螺旋动脉的血管扩张[27]。各种MMP组表达的降低, 结合内源性MMP抑制剂合成的增加, 诱导内皮损伤, 增加血管反应性, 从而导致明显的血管收缩[28]。

有关肾素-血管紧张素-醛固酮系统参与子痫前期发病机制的数据已经获得[29]。F. Herse等人(2013)发现内皮功能障碍、内皮素-1产生增加和血管紧张素II型1受体自身抗体(AT2R1)表达的激活之间存在联系。与生理上的妊娠相反, 内皮细胞对血管紧张素II的敏感性较低, 子痫前期孕妇对血管紧张素II的敏感性增加, 这是由遗传、免疫或外源性因子介导的[30]。子痫前期妇女对血管紧张素II敏感性增加的潜在机制之一是AT2R1自身抗体的表达, 这是对胎盘缺血和全身炎症反应的反应。AT2R1自身抗体刺激胎盘抗血管生成因子(sFlt 1和sENG)的产生, 诱导滋养细胞中纤溶酶原激活物抑制剂PAI-1的合成, 间接影响凝血止血的激活[31]。

母亲身体的免疫不适应也有助于子痫前期的发展。胎儿是一种半异基因移植物(因为50%的父系抗原在胎盘和胎儿组织中表达), 由于妊娠过程中整个免疫机制的复杂作用而没有排斥反应, 其中天然细胞毒性细胞(NK细胞)发挥了关键作用[32]。

在妊娠早期, 子宫内膜70%以上的中性粒细胞是CD56hi和CD57lo(UNK)表型的子宫NK细胞, 确保囊胚的成功着床, 以后它们通过分泌细胞因子和血管生成介质参与血管重塑, 其数量在妊娠晚期显著减少[33]。以滋养层细胞表面为代表的HLA-G与uNK细胞的KIR受体(抑制剂)相互作用, 降低天然杀伤细胞的细胞毒性, 限制其在胎盘的迁移, 保护胎儿免受来自母亲身体的不良免疫反应。因此, 胎盘中HLA-G和KIR受体表达的缺陷可能与妊娠并发症的风险增加有关, 这是基于子宫胎盘循环的异常[34]。根据S.A. Robertson等人(2018), T淋巴细胞占妊娠早期蜕膜免疫细胞的10—20%, 在着床和胎盘过程中发挥重要作用[35]。调节T淋巴细胞占(Treg)和效应T淋巴细胞占(Teff)之间的不平衡(偏向Teff)也可能是子痫前期发生的潜在免疫机制之一[36]。Teff通过释放促炎细胞因子和激活滋养细胞的抗原依赖性细胞毒性对胎盘发育产生负面影响。蜕膜Treg分泌IL-10和TGF- β , 表达CD25和PD-L1, 它们是效应T淋巴细胞的抑制剂并中和其作用, 还具有强大的抗炎、免疫和血管调节特性[37]。

子痫前期发病机制的一个组成部分是补体系统的失调, 这通常与控制补体激活调节因子生物合成的基因突变有关: H因子、膜辅因子(MCP)、I因子、组分C3等。补体系统的溶解导致组织结构、内皮细胞、血细胞和血小板的内源性损伤, 随后形成微血栓, 内皮功能障碍的发展和对胎儿耐受的系统性异常[38]。

子痫前期动脉性高血压的病理生理学的主要组成部分是内皮细胞产生的参与血管张力调节的生物活性物质的不平衡。胎盘缺血刺激释放引起全身血管内皮增生的介质, 从而导致血管扩张剂[前列环素, 一氧化氮(NO), 内皮依赖性超极化因子]合成的减少。同时内皮素-1和血栓素A₂的产生增加, 具有强大的血管收缩作用。异常导致外周血管阻力增加, 血压相应升高[39]。子痫前期女性对血管紧张素II和去甲肾上腺素的敏感性增加, 这可以通过AT2R1的激活来解释。胎盘缺血诱导AT2R1和缓激肽B₂受体的异源二聚体化和AT2R1受体自身抗体的产生也导致血管紧张素II的升压作用增加[40]。免疫机制也有助于子痫前期高血压的发展。CD4⁺T淋巴细胞(Th1/Th2)、Tregs和Teff两个亚群之间的不平衡和IL-17的过度分泌导致AT2R1受体的血管活性介质和自身抗体的产生增加, 从而加重内皮功能障碍, 这也会导致子痫前期血压升高[41]。

目前已经进行了大量的研究,其中包含了约130个可能的子痫前期危险因素的信息,涵盖了大量的伴随疾病、生物标志物、环境因素和遗传决定因素[42,43]。因此,在S. Rana等人(2019)将研究的子痫前期发生的危险因素按相对风险(RR)的大小进行排序,并分为以下几类:高危因素(RR>2.5)主要包括子痫前期病史,如糖尿病、多胎妊娠、孕前体重指数(BMI)>30 kg/cm²、抗磷脂综合征;第二组危险因素(RR 1.8—2.5)包括系统性红斑狼疮、死胎、不孕症和胎盘早剥史、辅助生殖技术的使用、慢性肾脏疾病、母亲妊娠年龄>35岁、候选基因(*FLT1*基因rs4769613、*PLEKHG1*基因rs9478812等)多态性;最后一组不太显著的危险因素(RR<1.8)包括子痫前期家族史和胎儿13对染色体三体(Patau综合征)[44]。

根据现代数据,慢性动脉血压在所有孕妇中占1—5%,其中先兆子痫的发生率可达75%。A. Syngelaki等人(2018)发现,妊娠前慢性动脉高血压与子痫前期高风险相关(RR 5.76; 95% CI 4.93—6.73),死产(RR 2.38; 95% CI 1.51—3.75)、胎龄婴儿出生(RR 2.06; 95% CI 1.79—2.39)[45]。此外,D. Nzelu等人(2018)指出,在患有慢性动脉血压的孕妇中,尽管从妊娠前三个月开始通过药物纠正了高血压,并且血压控制数字保持在140/90 mmHg以下,患子痫前期和出生发育延迟2倍以上的儿童的风险仍然存在。这与进行性内皮功能障碍、小动脉重塑和肌壁增厚、血管收缩和对血管扩张剂敏感性降低有关[46]。

子痫前期最常见的可改变危险因素是超重(BMI≥25 kg/m²)超过10%的孕妇为肥胖。在X.J. He等人进行的19项队列研究的荟萃分析中发现,肥胖和超重与子痫前期风险增加有关(RR 2.48; 95% CI 2.05—2.90)[47]。体重指数每增加1 kg/m²,患子痫前期的风险在统计学上显著增加15%。超重妇女在怀孕时,发生这种妊娠并发症的可能性增加30%[48]。O.B. Kalinina等人(2012)表明BMI增加与子痫前期早发相关:体重正常的患者,临床表现为子痫前期30.25±0.38周,妊娠26.00±2.35周BMI≥35 kg/m²(*p*<0.001)。BMI与血压(收缩压、舒张压、平均、脉搏)也有直接相关性[49]。

遗传性血栓形成可导致胎盘血管血栓形成,这与胎盘相关妊娠并发症的风险增加有关[50]。G. Mello等人(2005)发现

FV Leiden、MTHFR C677T、*Pt* G20210A等至少一种突变的存在与更严重的子痫前期病程相关(RR 4.9; 95% CI 3.5—6.9)[51]。MTHFR基因突变(15—40%)、纤溶酶原激活物抑制剂1型(5—8%)、Leiden突变(3—6%)和凝血酶原II(1—4%)认为子痫前期止血成分发展中最重要先天性缺陷。发现当高同型半胱氨酸血症和FV Leiden突变结合时,血栓并发症的风险增加10—20倍[52]。文献资料显示亚甲基四氢叶酸还原酶C677T基因突变是妊娠期高血压和子痫前期的独立危险因素[53]。

糖尿病和胰岛素抵抗对子痫前期形成的作用是不可否认的。根据文献资料,25—40%的1型糖尿病孕妇和20—24%的2型糖尿病孕妇诊断为子痫前期[54]。S. Lisenkova等人(2013)发现,妊娠前发生的糖尿病是子痫前期两种早期表现的一个危险因素(长达34周,RR 1.87; 95% CI 1.60—2.81)和晚期发展(RR 2.46; 95% CI 2.32—2.61)。这与全身性糖尿病血管病变的发展和糖尿病与既存的慢性动脉高血压的频繁结合有关[55]。在K. Bramham(2017)指出,与未患糖尿病肾病的孕妇(9—17%)相比,患有糖尿病肾病的孕妇(35—66%)发生子痫前期的风险更高[56]。此外,胰岛素抵抗常与子痫前期的其他危险因素(肥胖、慢性动脉血压、代谢综合征等)相关,与子痫前期的发生发展有共同的机制,这可以通过不同的生物标志物(PAI-1、瘦素、细胞间黏附分子等)在这两种病理条件中相同的表达违反得到证实[57]。

负担过重的产科和妇科先兆子痫病史是发展这种妊娠并发症的最重要的危险因素。在M. Lewandowski等人(2020)揭示,有子痫前期病史的女性在妊娠期间发生高血压疾病的风险显著增加(RR 27.54; 95% CI 5.8—130.8; 子痫前期*p*<0.001, RR 22.90; 95% CI 7.3—72.4; 妊娠期高血压*p*<0.001)[48]。子痫前期的临床症状在以前和现在怀孕的同一时期的表现之间已经建立了直接的关系。早期发病的子痫前期患者发生相应形式子痫前期的风险增加25.2倍(95% CI 21.8—29.1),因此,34周后出现这种病理症状的患者发生晚期子痫前期的风险增加10.3倍(95% CI 9.85—10.9)。作者认为这是由于遗传因素对早期子痫前期的发展具有主要影响,而环境因素对晚期子痫前期的形成具有最重要的作用[58]。

现有文献提供了民族和种族与流行病学和子痫前期病程的关系数据。因此,A.B. Caughey等人(2005)发现,与白人女性相比,非裔美国

女性患子痫前期的风险明显更高 (RR 1.41; 95% CI 1.25—1.62), 在亚洲人群中更低 (RR 0.79; 95% CI 0.72—0.88) [59]。此外, 与欧洲人相比, 黑人妇女因子痫前期并发症而导致的产妇死亡率明显更高 (每10万例分娩121.8例, 95% CI 69.7—212.9和24.1例, 95% CI 14.6—39.8, $p < 0.01$) [60]。父亲的种族也会影响患子痫前期的风险, 与同种族的父母相比, 不同种族的夫妇患这种妊娠并发症的风险显著增加 (RR 1.13; 95% CI 1.02—1.26) [61]。

遗传易感性在子痫前期的形成中起重要作用。根据各种资料显示, 有一级亲属 (母亲、姐妹) 家族史的女性在妊娠期间出现高血压病, 并伴有蛋白尿, 会使子痫前期风险增加24—163% [62]。N.C. Serrano等人 (2020) 进行的一项研究表明, 近亲有子痫前期病史的女性发生妊娠并发症的风险显著增加 [姐妹子痫前期的风险增加2.43倍 (95% CI 2.02—2.93), 母亲为3.38倍 (95% CI 2.89—3.96), 母亲和姐妹为4.17倍 (95% CI 2.60—6.69)] [63]。母亲 (RR 1.41, 95% CI 1.04—1.90)、姐妹 (RR 2.48, 95% CI 1.31—4.69) 或所有女性亲属 (RR 3.65, 95% CI 1.65—8.09) 有慢性动脉高血压病史者,

子痫前期风险增加2倍以上 [64], 如果有两名家族成员有心血管疾病 (包括脑梗死) 或以上家族史, 则发生该并发症的几率会增加3倍以上 (RR 3.2, 95% CI 1.4—7.7) [65]。

因此, 通过对国内外文献的研究, 我们可以得出以下结论: 第一, 尽管有大量的研究, 但对子痫前期发病的分子机制尚未达成共识。其次, 胎盘障碍、母亲身体的免疫适应不良、内皮功能障碍、血管生成失衡等是妊娠并发症发展的关键因素, 但它们在早期和晚期子痫前期形成中的意义有显著差异。第三, 已有130多种不同的子痫前期发展危险因素 (子痫前期家族史、糖尿病、慢性动脉高血压、遗传性血栓形成等), 但现有数据往往不明确, 且根据研究人群的不同而不同。因此, 现有的矛盾和缺乏共识的参与某些生物学过程的发展子痫前期, 要求进一步研究这一妊娠并发症。

附加信息

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所有作者都对文章的研究和准备做出了重大贡献, 在发表前阅读并批准了最终版本。

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