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孕期血红蛋白与早产的关联研究进展

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摘　要

早产已经成为严重威胁母体和胎儿健康的公共卫生问题。它是全球婴儿最常见的死因，且早产儿患有脑性麻痹、发育迟缓、听力与视力障碍等相关并发症的风险更高，但是早产原因尚不明确。而血红蛋白是评价妊娠期母体营养状况最常见的指标之一，其异常不仅由遗传、饮食和地理等因素综合外，还受母体血容量和子宫扩增、宫内感染、免疫代谢以及妊娠并发症等早产发生风险因素的影响。因此明确血红蛋白对早产发生的影响有助于识别高危孕妇。已有研究发现贫血和高浓度血红蛋白合并妊娠均可能会影响早产发生。本文综述了孕期血红蛋白早产发生的关联，并进一步讨论该关联发生的可能机制，为未来的研究提供研究线索。

关键词

孕期，血红蛋白，早产，妊娠结局

The Advance in the Associations between Hemoglobin and Preterm Delivery during Pregnancy

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Abstract

Preterm birth has become a public health problem that poses a serious threat to maternal and fet-

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al health. It is the most common cause of infant death worldwide, and preterm infants are at higher risk for complications related to cerebral palsy, developmental delays, hearing and visual impairment, but the causes of preterm birth are unknown. Hemoglobin is one of the most common indicators of maternal nutritional status during pregnancy, and its abnormalities are influenced not only by a combination of genetic, dietary, and geographic factors, but also by maternal blood volume and risk factors for preterm birth such as uterine dilation, intrauterine infection, immunometabolism, and pregnancy complications. Therefore, clarifying the effect of hemoglobin on the risk of preterm labor can help be a possible way to identify high-risk pregnancies. Both anemia and high hemoglobin levels in combined pregnancies have been found to affect the occurrence of preterm labor. This article reviews the progress of research on the effect of hemoglobin in pregnancy on the occurrence of preterm labor and further discusses the possible mechanisms by which this effect occurs, providing a research direction for future studies.

Keywords

Pregnancy, Hemoglobin, Preterm Birth, Pregnancy Outcome

1. 引言

近年来，早产或低出生体重已成为我国 5 岁以下儿童死亡的第 1 位死因[1]，也是影响婴儿其他疾病发病率的主要因素之一[2] [3]。新生早产儿发生体温不稳定、呼吸窘迫、呼吸暂停、低血糖、癫痫发作、黄疸、核黄疸、喂养困难、脑室周围白质软化和再住院的风险更高。远期来看，早产儿从儿童至青少年期的发育障碍、晚年的心血管和代谢紊乱的发生率也均高于足月儿[4] [5] [6] [7]。越来越多的证据显示孕期血红蛋白与早产、低出生体重、足月小样儿等不良妊娠结局关系密切[8] [9] [10]。本文综述了孕期血红蛋白与早产发生风险的关联。

2. 孕期贫血和高血红蛋白

健康妇女孕期血红蛋白浓度呈现规律性变化，表现为在孕早期逐渐下降至孕中期达到最低值，并在孕晚期呈上升趋势[11]。为适应母体营养和胎儿生长发育的需求，孕妇的血浆容量从约第 6 孕周增加，并在第 32~34 孕周达到高峰值[12] [13]。期间因红细胞增加程度相对血浆容量较小可引起血液稀释，导致血红蛋白值降低，即出现“生理性贫血”[14]。至孕晚期，因血浆容增量少于红细胞质量，血红蛋白浓度会随着红细胞比容增加而轻微上升[15]。Shen 等人 2010 年的一项研究[16]发现，孕早期血红蛋白均值为 122.0 g/L，中晚期平均水平分别为 113.0 g/L 和 115.0 g/L。孕期血红蛋白的生理性变化增加了贫血诊断的不确定性[17]。因此，常规检查难以区分孕期正常的血红蛋白值降低和贫血。目前对血红蛋白阈值的定义及贫血严重程度的划分仍有争议[18]。根据不同孕期，世界卫生组织(World Health Organization, WHO)和美国疾病控制和预防中心(Centers for Disease Control and Prevention, CDC)制定的贫血标准为[19] [20]，孕早期：<110 g/L；孕中期：<105 g/L；孕晚期：<110 g/L。由于实验室条件和流行病学方法相对落后，研究人群以欧洲和北美白人[21] [22] [23] [24]以及服用铁补充剂的妇女为主[25] [26] [27] [28] [29]，且血红蛋白界定值和胎儿发育(例如大脑发育)、妊娠结局的相关性暂不明确[30]-[35]等原因，其适用性仍然有限。除此之外，大部分贫血诊断标准均未考虑妊娠各时期的血液变化特征。

虽然临床和公共卫生关注的重点是孕期贫血，但是妊娠期妇女也存在因孕期高血红蛋白而出现不良后果的情况。高血红蛋白的诊断暂未有明确共识。非孕女性高血红蛋白浓度的规范定义可参考平均值加上两倍标准差，即正常上限为 155~160 g/L，轻度高血红蛋白为 160~170 g/L，超过 170 g/L 可视为中度高血红蛋白。孕期由于妊娠期血红蛋白浓度的生理变化，定义高血红蛋白的上限将低于非孕女性[25]。孕期高血红蛋白发生的原因一般可归结为两种机制：第一种为孕期血浆容量扩增不足损害血氧承载能力，为了满足氧需求，机体代偿性增加红细胞或收缩血浆体积导致血红蛋白浓度上升。这种机制在较高海拔、环境氧浓度较低地区居民以及烟民等群体最为常见；第二种则不受组织氧影响，是由于机体产生有缺陷的红细胞而导致真性红细胞增多症[36]。这种情况具有一个基本特征，即当红细胞增加时，总血量随之增加或保持正常水平；当红细胞不增加时，血浆体积就会收缩导致血红蛋白浓度上升或血液浓缩[37]。如果血红蛋白浓度上升超过 180 g/L，血液粘度就会达到损害微循环的水平，产生类似于严重贫血而导致组织输送氧量不足的情况[38]。

3. 早产

早产是指从孕妇末次月经周期首日算起，妊娠时间 < 37 周或 259 d 的分娩。然而，对于低胎龄的界限，或用于区分早产和自然流产的界限，其标准在不同国家存在差异。我国定义早产的分娩孕周的下限为孕 28 周或新生儿出生体质量 ≥ 1000 g 者，而发达国家定义的低胎龄界限为孕 20~26 周[39]。早产儿占围产期死亡婴儿死亡总数的 75%，占儿童期发病人群的一半以上[40]。早产的病因尚未明确[41] [42]，它可能代表正常分娩过程的早期特发性激活或病理损伤的结果，已有学者提出胎儿在分娩孕周方面的作用[43]，但未有定论。明确早产的风险因素是开展有效干预措施的关键。尽管流行病学研究报告了多种早产风险因素，但在临床上却很少得到明确的验证，临床上比较认可的危险因素主要为早产史和明显的妊娠风险因素，如多胎妊娠和出血[44]。一项针对五个高收入国家 410 万单胎分娩的个体参与者数据分析结果表明，大约 65%的早产没有表现出 21 个预先设定的风险因素[45]。在针对这些危险因素开展的干预研究发现，二级和三级预防措施存在临床效果差，开展困难等问题，只能减轻早产相关的疾病负担，对早产发生率影响不明显[46] [47] [48] [49] [50]。因此，一级预防干预措施的开展可能是减少早产发生关键。当前，针对早产的一级预防措施主要包括孕前的生育间隔、围孕期叶酸摄入、控制室内空气污染；孕期的戒烟计划、各类补充剂(均衡蛋白质和能量、多种微量营养素、铁和叶酸、锌、硫酸镁、钙、长链不饱和脂肪酸)、各类监测(心电图、多普勒和晚期超声)等。在这些措施中，绝大多数仍缺乏足够的研究证据[51]。因此，进一步明确影响早产的危险因素，并开展针对性的一级预防措施显得尤为重要。

4. 孕期血红蛋白与早产发生风险

已有大量关于孕期血红蛋白异常与早产发生风险的研究，但结果并不一致[8] [52] [53] [54] [55] [56]。较多研究表明孕早期和中期贫血会增加早产发生风险，但孕晚期血红蛋白浓度以及孕期高血红蛋白与早产发生风险的关联仍不明确。2013 年 Haider BA 等在 BMJ 上发表了 92 项研究(包括 48 项随机试验和 44 项队列研究，共 1,869,475 名女性)的 meta 分析提示，孕早期或者孕中期贫血(<110 g/L)增加早产发生风险(OR = 1.2, 95% CI: 1.13~1.30)，而孕晚期或分娩前的血红蛋白浓度与早产发生风险无关[57]，这提示孕晚期血红蛋白浓度可能与早产发生无关联。但是，2013 年 Sukrat 发表的系统综述结果却显示孕早期贫血虽增加早产发生风险(OR = 1.10, 95% CI: 1.02~1.19)，但孕晚期除轻度贫血(100~110 g/L)无影响外，血红蛋白浓度分别低于 90 g/L (OR = 3.41, 95% CI: 1.38~8.42)和 100 g/L (OR = 2.64, 95% CI: 1.19~5.86))也增加早产风险和，而孕晚期高 Hb 水平(≥140 g/L)对早产具有保护性作用(OR = 0.50, 95% CI: 0.26~0.97)，但可能受到发表偏倚的影响[58]。

不良妊娠结局的风险与孕期母体血红蛋白浓度之间往往呈U型曲线，贫血和高血红蛋白的妇女娩出低出生体重儿和早产儿的风险较高[59] [60] [61] [62]。Deway, K.G.等的综述发现孕期血红蛋白与不良妊娠结局呈U型关系，但这种关系在不同孕期中存在较大差异，表现为孕早期贫血与早产相关，孕中期与其关联性变弱至无，孕晚期贫血和不同孕期高血红蛋白水平与早产相关的证据存在混杂[31]。Jung 等也报道了孕期血红蛋白水平与早产的非线性关系，并比较其在不同收入国家中的差异，结果表明，在中低和高收入国家存在非线性趋势，但中高和低收入国家中则没有[63]。其可能原因为，不同经济水平国家的孕妇血红蛋白异常的主要原因并不一致，比如铁剂的服用水平和传染病的患病率等[64] [65]。在2019年，Young 等纳入95项研究进行meta分析得出，在整个孕期中，低血红蛋白浓度都与早产风险增加有关，OR值分别为：孕早期1.28 (95% CI: 1.17~1.40)，孕中期1.37 (95% CI: 1.15~1.63)，孕晚期1.45 (95% CI: 1.23~1.71)，但高血红蛋白浓度与早产相关性不显著，这也许与包含评估高血红蛋白浓度的研究数目较少有关[66]。

既往关于孕期血红蛋白与早产关联研究的异质性主要来源于血红蛋白测量的孕周不一致。随着孕期进展，由于妊娠期血液系统的生理性变化，孕早期血红蛋白水平出现生理性降低，在孕中期降至最低值而孕晚期呈升高趋势[11]。因此，不同孕期血红蛋白浓度与早产的关系存在差异，可归结为部分研究未具体说明测量血红蛋白时所处孕周或未对孕周进行分组。其次，研究人群、血红蛋白异常的病因、血红蛋白阈值的异质性也是导致研究结果不一致的原因。

5. 孕期血红蛋白对早产的影响机制

主要机制可能是来自缺铁/缺铁性贫血和缺氧对母婴的影响。缺铁/缺铁性贫血或其他因素导致的缺氧使得母胎循环含氧量降低，去甲肾上腺素分泌增加[67]，而去甲肾上腺素是释放肾上腺皮质激素和皮质醇的强烈刺激物，可促进胎儿皮质醇分泌增加，激活孕妇和胎儿的应激反应，引起胎儿早产。另外，缺铁性贫血会造成免疫功能低下，比如影响B淋巴细胞和T淋巴细胞的增殖、降低吞噬细胞和中性粒细胞的杀伤力，以及杀菌和自然杀伤细胞的活性。因此，可能引发母体多种症状和体征(如头痛，疲劳，心动过速，呼吸急促)使感染易感性增加，从而间接影响妊娠状况导致早产。如果母体血红蛋白浓度下降至70 g/L以下，孕妇发生高输出性心力衰竭的风险较高，包括心肌在内的组织氧合减少，也可能引起早产[68] [69]。

高血红蛋白和早产之间关联的病理生理学很难解释，但最有可能与血液的高粘度性有关。血液粘稠度增高会危害组织的氧气输送以及引起脑血管并发症[70]。已有流行病学研究还发现，现有证据并不表明高血红蛋白浓度与早产发生风险间的关联存在因果关系，两者之间的联系受到妊娠期高血压疾病和子痫前期的影响[71] [72] [73]，因此也较难明确高血红蛋白浓度是否为引起妊娠高血压疾病、围产期并发症增加的原因[74]。孕期这些病理情况下可产生较高的血红蛋白浓度，因为正常的血浆膨胀减少，并且由于胎盘－胎儿灌注减少而导致胎儿应激。因此，高血红蛋白浓度应被视为可能的妊娠并发症的指标，而不一定是铁营养充足的标志，因为铁的补充并不能使血红蛋白增加到超过氧气输送所需的最佳浓度[75]。其次，母体铁过量导致的氧化应激也是重要的原因。如果母婴已经处于应激和感染，铁过量会直接加重氧化应激和感染程度，且不利于营养物质的输送。母体导致的胎儿高血红蛋白浓度会反过来影响母体循环，进一步损害胎盘而影响妊娠结局[76]。

6. 总结与展望

综上所述，孕期血红蛋白异常可能与早产有重要关联，或可有助于识别早产高风险群体。尽管研究中血红蛋白异常对早产发生的影响并不一致，但不能否认血红蛋白浓度对提示早产发生风险的潜在价值。已有研究支持[15] [77] [78] [79]，应在围产期尽快诊断和治疗贫血，以避免其触发早产发生病理生理过程。

孕前贫血很可能会影响胎儿发育和随后的妊娠结局。最大的影响发生在胚胎发育期，通常是在妇女第一次在产科门诊建档或者进行产前检查时，甚至在知道自己怀孕之前[80]。母体血红蛋白异常对大多数新生儿在胚胎发育早期的损害甚至远期健康的风险已经形成，如不加强管理母婴将失去孕期干预和改善妊娠结局的机会[68] [81]。因此未来研究可探索评估孕期血红蛋白水平和早产之间的关联，并可通过管理血红蛋白水平来识别和改变影响早产的生物医学、行为和社会等各种风险因素。

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