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· 综述 ·

## 孕妇牙周病与早产低出生体重儿的关系

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**【摘要】** 早产低出生体重儿在生长发育过程中容易发生发育迟缓、传染病等并发症,且病死率较健康新生儿高,属于高危儿。流行病学等资料表明孕妇牙周病与早产低出生体重儿具有一定相关性,孕妇牙周病是早产低出生体重儿等不良妊娠结局的危险因素之一,本文就孕妇牙周病与早产低出生体重儿的相关性、牙周治疗对早产低出生体重儿发生率的影响,以及孕妇牙周病引发早产低出生体重儿的相关机制作一综述。本文综述结果表明,目前的研究证实孕妇牙周病与早产低出生体重儿的相关性,但未完全阐明两者的因果关系以及具体的机制和途径,可能的机制为孕妇牙周致病菌通过胎盘屏障进而影响妊娠结局。因此,还需对其两者关系具体的机制、途径以及干预治疗等进行更深入的研究。

**【关键词】** 孕妇; 早产低出生体重儿; 牙周病; 牙周致病菌; 感染; 牙周治疗

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**【Abstract】** Preterm low birth weight newborns are prone to complications during growth and development, such as growth retardation and infectious diseases, and the mortality rate of high-risk infants is higher than that of healthy newborns. Epidemiological data show that periodontal disease in pregnant women is correlated with preterm low birth weight. Periodontal disease in pregnant women is one of the risk factors for adverse pregnancy outcomes, such as preterm low birth weight. This paper addresses the correlation between maternal periodontal disease and preterm low birth weight, the influence of periodontal treatment on the incidence of preterm low birth weight, and premature birth caused by maternal periodontal disease. The mechanism of infant weight is reviewed. The results of this review show that the current studies confirm the correlation between maternal periodontal disease and preterm low birth weight. However, the causal relationship between maternal periodontal disease and preterm low birth weight is not fully elucidated, and the specific mechanism and approach are not clear. A possible mechanism is that periodontal pathogens in pregnant women pass through the placental barrier to influence pregnancy outcomes. Therefore, more in-depth research is needed on the specific mechanism, approach, intervention and treatment based on the relationship between these two factors.

**【Key words】** pregnant women; preterm low birth weight; periodontal disease; periodontal pathogen; infection; periodontal treatment

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早产低出生体重儿(preterm low birth weight,

PLBW)是指妊娠时间不足37周,出生体重低于2.5 kg的新生儿<sup>[1]</sup>。牙周病(periodontal disease, PD)是一种高发的慢性感染性疾病,其作为PLBW潜在的、独立的危险因素之一<sup>[2-5]</sup>,已引起国内外学者的广泛关注。现就孕妇PD与PLBW的关系及其可能的机制进行综述,旨在为预防PLBW提供理

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论依据和研究方向。

## 1 牙周病与PLBW的关系

PLBW在生长发育过程中容易发生发育迟缓、传染病等并发症,是属于高死亡率的一种疾病。据de Onis等<sup>[6]</sup>报道,1995年全球共有2 050万低出生体重儿,其中发展中国家低出生体重儿的出生率已达16%。据世界卫生组织(World Health Organization, WHO)于2012年5月发布的《早产儿全球报告》,报道统计全球每年约有1 500万早产儿出生,超过全部新生儿的1/10,且同期有超过100万患儿死于早产儿相关并发症<sup>[7]</sup>。2010年美国在PLBW上的支出花费(包括防治、教育及生产力损失)总额高达260亿美元<sup>[8]</sup>。因此,PLBW不仅严重影响着人类生殖健康,而且给社会家庭带来了沉重的经济负担,俨然成为全球性公共卫生问题。我国早产儿人数居世界第二位,且随着试管婴儿技术的日益成熟、高龄孕妇的增多、环境污染的加重及药物广泛使用,我国早产儿的出生率呈逐年上升趋势,已由2005年的8.1%上升至2016年的9.9%<sup>[9]</sup>。而关于低出生体重儿的出生率,我国尚无统一的报告。

牙周病是最为常见的两大口腔疾病之一,可引起牙龈红肿、口臭、牙齿松动、牙周溢脓等,是成年人牙齿丧失的最主要原因<sup>[10]</sup>。而对于女性患者而言,相比于月经周期,妊娠期体内黄体酮及雌激素水平分别会升高10倍和30倍,而牙龈作为雌激素靶器官,会造成牙龈毛细血管扩张充血,血管的通透性就会增高,渗出相对增多,细胞再生、上皮角化能力减弱,降低了屏障功能,因此对局部炎症的刺激反应增高,导致牙龈的炎症加重<sup>[11]</sup>。据2018年刘萍等<sup>[12]</sup>调查报道,约有38.9%孕妇患有牙周病。

Miller<sup>[13]</sup>在1891年首次提出“口腔病灶感染”假设理论,该理论主要认为口腔中的微生物及其产物可通过血液循环进入机体各个部位,从而导致一系列系统性疾病,如关节炎、细菌性心内膜炎等。随后,口腔疾病和系统疾病之间的相关性开始引起国内外学者的广泛关注。牙周病作为口腔的感染病灶之一,不仅可以引起颌骨骨髓炎,还可以引起远隔脏器的病损如脑膜炎、虹膜睫状体炎、慢性肾炎等。同时,牙周病与糖尿病、心血管疾病、骨质疏松等疾病密切相关。1994年,Collins等<sup>[14]</sup>首次发现孕妇的牙周状况与早产呈现显著相关性,且牙周病的严重程度和早产存在“剂量一反

应”关系,提出牙周病是早产的危险因素之一。随后,越来越多的证据表明<sup>[15-16]</sup>牙周病可能是不良妊娠结局(尤其是PLBW)的危险因素之一。

## 2 牙周病导致PLBW的可能机制

关于孕妇牙周病引发早产低出生体重儿的机制目前仍无统一定论,研究显示孕妇牙周病引发早产低出生体重儿可能的机制和途径有以下3种<sup>[17-19]</sup>:①牙周致病菌通过血液循环直接侵入胎盘组织,引发单核细胞的炎症前细胞因子反应,合成并释放前列腺素催生因子,导致早产;②由G-厌氧菌代谢产生的内毒素、外毒素和脂多糖,可通过血流作用于胎膜,刺激前列腺素、炎症性细胞因子分泌,造成早产;③由口腔微生物诱发的免疫应答反应可能改变胎盘的结构,引发早产甚至流产。

目前大多数学者<sup>[20]</sup>认为牙周致病菌,如牙龈卟啉单胞菌(*Porphyromonas gingivalis*, Pg)、伴放线聚集杆菌(*Actinobacillus actinomycetemcomitans*, Aa)、中间普氏菌(*Prevotella intermedia*, Pi)等,与阴道炎致病菌相类似<sup>[21]</sup>,牙周局部微生物与产道病原微生物呈正相关,引发早产。原因可能是牙周致病菌及其代谢毒素侵入牙周上皮组织,造成牙周组织破坏,细菌及代谢产物经血流形成全身播散,激发单核、巨噬细胞释放多种炎症因子,如白细胞介素1(interleukin-1, IL-1)、白细胞介素6(interleukin-6, IL-6)和肿瘤坏死因子 $\alpha$ (tumor necrosis factor alpha, TNF- $\alpha$ )等,释放前列腺素尤其是前列腺素E2(prostaglandin E2, PGE2)和基质金属蛋白酶(matrix metalloproteinase, MMP)等,甚至传播至胎盘和宫腔,造成感染物质和炎症因子的大量聚集。而这些炎症因子如PGE2、IL-1等,可直接刺激子宫平滑肌的收缩导致早产<sup>[22]</sup>。

## 3 牙周病与PLBW关系的研究进展

### 3.1 动物研究

1994年,Collins等<sup>[14]</sup>在受孕的仓鼠身上进行病灶感染发生的模拟实验,发现孕妇牙周致病菌与炎症因子可随着血液系统转移,通过胎盘屏障进而引发多种并发症,发现母体的牙周状况与早产呈现显著的相关性。Newnham等<sup>[23]</sup>将3种牙周致病菌Aa、Pg、具核梭杆菌(*Fusobacterium nucleatum*, Fn)的脂多糖注射到孕羊羊膜内,结果导致较高的胎羊致死率,认为牙周致病菌可穿过胎盘屏障感染胎羊。但是,关于牙周致病菌穿过胎盘屏

障的机制和途径尚未明确。

### 3.2 微生物学研究

Carrillo-de-Albornoz等<sup>[24]</sup>发现患有牙周病的孕妇在其妊娠中晚期时, Pg会广泛存在于牙周组织破坏部位, 且Pg存在位点的牙龈炎症程度和牙周组织破坏程度明显高于无Pg存在的位点, 提示Pg可能影响孕妇牙龈炎症程度。Han<sup>[25]</sup>认为, Fn在胎盘中转变为引起PLBW的主要致病菌。相反, Abusleme等<sup>[26]</sup>研究显示牙周病患者口腔内可能检测不到这些特定种类的致病菌或者这些细菌在口腔中的分布和健康的人群无明显差异。因此, 笔者认为口腔生态群的破坏, 可能导致口腔致病菌的转移, 导致早产。

### 3.3 流行病学研究

Offenbacher等<sup>[27]</sup>对1 020名妊娠妇女进行前瞻性研究, 在排除其它危险因素后分别对孕妇进行产前和产后的牙周检查, 发现牙周组织健康的孕妇发生早产的几率为11.2%, 患有中重度牙周病的孕妇为28.6%, 产前患有中重度牙周病的孕妇自发性早产的几率较高, 且牙周病的严重程度和早产存在“剂量—反应”关系, 进而提出牙周病是早产的危险因素之一。同时, 影响孕妇牙周病发生发展的流行病学因素还包括社会人口因素、口腔保健行为、饮食情况、吸烟、口腔健康相关的知识和态度等<sup>[28]</sup>。为证实两种疾病的关系仍需要更大的样本量。

### 3.4 临床实验

Naorungroj等<sup>[29]</sup>研究报道称, 18.2%早产低出生体重儿可能是由牙周病引起。Offenbacher等<sup>[30]</sup>报道, 患有严重牙周病的产妇发生早产低体重的风险要比牙周健康的产妇高7.5倍。Mobeen等<sup>[31]</sup>调查显示巴基斯坦妊娠期女性的围产期死亡率比发达国家高出10倍; 发现产生不良妊娠结局的妇女在孕期均患有中度到重度的牙周病, 总结出围产期死亡率随妇女牙周病的加重而增加。

Weidlich等<sup>[32]</sup>研究发现, 对患有牙周病的孕妇在妊娠中期进行牙周治疗包括龈上洁治、龈下刮治和根面平整、牙周翻瓣术等可提高孕妇的牙周健康指数, 减轻牙周症状, 但是这些孕期进行的牙周治疗并不能降低早产低体重儿的出生率。这与Pirie等<sup>[33]</sup>人的研究结果相一致。因此, 孕期牙周病的治疗对于妊娠结局已无明显意义, 牙周疾病的孕前筛查以及预防性检查和治疗对于孕妇和新生儿来说意义重大, 需着手于牙周病的预防, 将牙

周检查纳入孕前筛查中, 最终才能改善妊娠结局。

因现有的研究还存在一些不足, 比如牙周病的诊断标准的不统一, 样本量的大小; 动物模型与人体情况可能不一致等因素; 且流行病学只能说明两者的相关性并不能代表因果关系, 孕妇牙周病与PLBW的关系尚未明确。因此, 对其两者关系具体的机制、途径、预测指标以及干预治疗的效果等仍需更深入的研究和更大样本的流行病学调查加以证实。

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