·综述·

母体系统性疾病对新生儿唇腭裂发生的影响

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【摘要】 唇腭裂是最常见的先天性缺陷之一,其病因复杂,目前被认为是遗传和环境因素共同作用的结果。唇腭裂会导致颌面发育、牙齿发育、语言、饮食和听力等方面的问题,不仅给患儿带来生理和社会心理上的影响,同时增加家庭经济负担。已有大量研究明确母体患系统性疾病与后代患唇腭裂的风险密切相关。本文将从糖尿病、高血压、肥胖和系统性红斑狼疮4种系统性疾病及与系统性疾病密切相关的牙周炎入手,综述其与唇腭裂发生的关系及其影响机制的研究进展,为孕期预防和减少唇腭裂的发生提供系统性疾病角度的临床参考依据,避免或尽量减少后代出现先天性唇腭裂的风险。

【关键词】 唇裂; 腭裂; 糖尿病; 高血压; 肥胖症; 红斑狼疮,系统性; 牙周炎

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The impact of maternal systemic diseases on the incidence of cleft lip and palate in newborns

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【**Abstract**】 Cleft lip and palate are among the most common congenital anomalies, with aetiology that is complex and currently considered to be the result of both genetic and environmental factors. This condition can lead to issues in facial and dental development, speech, nutrition, and hearing, which not only impact the physiological and socio-psychological well-being of the child but also increase the financial burden on the family. Numerous studies have established a clear association between maternal systemic diseases and the risk of offspring developing cleft lip and palate. This article reviewed the relationship and mechanisms of action between four systemic diseases—diabetes, hypertension, obesity, and systemic lupus erythematosus—as well as periodontitis, which are closely related to systemic diseases, and their association with the occurrence of cleft lip and palate. It aimed to provide a clinical reference for the prevention and reduction of the incidence of cleft lip and palate during pregnancy from the perspective of systemic diseases, thereby avoiding or minimizing the risk of congenital cleft lip and palate in offspring.

【**Key words**】 Cleft lip; Cleft palate; Diabetes mellitus; Hypertension; Obesity; Lupus erythematosus, systemic; Periodontitis

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唇腭裂是一种常见的颌面部先天性缺陷疾病,是人类最常见的颅颌面畸形,全球新生儿平均患病率为1/700[1],其特征是嘴唇或上腭有异常的开口或间隙。根据涉及的部位,可分为单纯唇裂、单纯腭裂和唇腭裂3种类型[1]。唇腭裂可单独发生(更为多见),称为非综合征型[2];也可以与其他先天性疾病合并发生,称为综合征型唇腭裂,其中合并先天性心脏病最为常见[3]。从胚胎发育角度来看,正常胚胎发育的第6周,随着球状突与两侧的上颌突融合形成上唇,在这个过程中,球状突往口腔侧生长形成前腭突于第7周末由上颌突发展而来的侧腭突融合,形成上腭[4-5];在胚胎的球状突和上腭融合阶段出现障碍,可能导致唇裂、腭裂或者唇腭裂的发生。唇腭裂不仅影响美观和口腔功能,还会出现一些相关的合并症,如进食困难、言语问题、牙列缺陷、牙错𬌗畸形、面

部生长异常、中耳感染和心理障碍等[6],并可能经历终生的社会心理问题,对患儿的心理健康造成极大的创伤[7]。

唇腭裂的病因尚不完全清楚,目前认为是遗传和环境因素共同作用的结果[8]。基因突变或变异、父母的生活方式和生存环境,如孕妇在怀孕期间大量接触酒精、吸烟,维生素或矿物质的补充不足,以及不良用药(如止痛药、抗生素和抗高血压药物)等,都会增加新生儿患唇腭裂的发生率[9]。同时,父母的血缘关系、文化程度及健康状况也可能与患儿唇腭裂的发生有关[1,8,10-13]。

近年来,越来越多的学者开始专注于研究母体的健康状况与新生儿唇腭裂之间的关系。母体患有某些全身系统性疾病可能会对妊娠结局产生不良影响,如心血管疾病(高血压、动脉粥样硬化)、糖尿病、肥胖和自身免疫性疾病[系统性红斑狼疮(systemic lupus erythematosus,SLE)]等,均已被证实可增加妊娠期间并发症的发生风险[14-19]。妊娠期代谢性疾病也可增加不良结局的风险,并显著影响胎儿发育,包括口面形成和融合[20-21]。因此,在胎儿发育的过程中,母体患全身系统性疾病可能也与新生儿发生唇腭裂息息相关。有研究表明,母体的牙周炎、心血管疾病、肥胖、SLE、糖尿病和感染等均会增加新生儿发生唇腭裂的风险[22-23]。

本综述将从糖尿病、高血压、肥胖、SLE和牙周炎5种疾病入手,探讨母体系统性疾病与患儿先天性唇腭裂发生之间的关系,为通过母体健康管理与孕期干预以预防新生儿唇腭裂发生的基础及临床研究提供参考。

一、全身系统性疾病

全身系统性疾病累及全身多个组织、器官,在系统性疾病的发生、发展过程中,炎症反应是其重要的影响因素[24],其特点是对机体或外源的核酸或其他细胞内成分反应过强,引起固有免疫系统失调,导致血管炎症和内皮功能障碍等问题[25]。研究表明,固有免疫系统失调将导致全身炎症反应[26-27]。除了固有免疫细胞相关的全身炎症反应外,氧化应激也是值得注意的,氧化应激是由活性氧产生和抗氧化防御系统之间的不平衡引起的,活性氧(reactive oxygen species,ROS)是氧气不完全还原时形成的化学产物[28],它会造成细胞损伤并引起全身炎症反应[29]。已有研究证明,ROS可能影响神经嵴的发育从而影响胎儿口颌面的发育[30]。

二、糖尿病

妊娠期糖尿病是最常见的妊娠并发症,其定义为妊娠期间首次发生或发现的高血糖[31]。研究表明,先天性唇腭裂的发生与妊娠期糖尿病正相关[15,32]。除了妊娠期糖尿病,母体既有的糖尿病(1型或2型)也可能会增加妊娠并发症的风险[33]。长期的糖尿病患者所生后代的先天性异常风险高达80%,是非糖尿病母亲后代的3~4倍[34-36]。动物实验也表明,患有高血糖的怀孕小鼠产生的后代比正常怀孕小鼠更易发生腭裂[37]。在一项随机对照研究中,患有糖尿病的母亲其胎儿患唇腭裂风险较高[38],而妊娠前已患有糖尿病的母亲生产唇腭裂胎儿的发生率更大[39],说明与妊娠期糖尿病相比,母体糖尿病更容易导致先天性畸形[40]。

有证据表明,糖尿病母体的子代胚胎发生缺陷的发病机制与微环境氧化应激状态相关,母体糖尿病导致胎儿在子宫内暴露于母体高血糖和(或)高胰岛素状况[41]。过量的葡萄糖代谢消耗更多的氧气,加剧了缺氧状态,诱导胚胎氧化应激[30],这种高血糖引起的缺氧会导致先天性异常。例如,发育中的胎儿缺氧会改变配对盒基因3(Paired box gene 3,*Pax3*)的DNA甲基化状态,*Pax3*基因在神经嵴发育中起关键作用,并可能对神经管闭合和颅面发育产生不利影响[30,42];而在非糖尿病妊娠中,高氧并没有增加氧化状态相关标志物或抑制*Pax3*基因的表达[30]。先天性唇腭裂与孕前糖尿病高度相关,强调了孕前检查的必要性,通过早期诊断、管理和评估毛细血管血糖水平,筛查异常葡萄糖耐量,有望预防新生儿口面裂[43]。

三、高血压

高血压相关疾病包括先前存在的高血压、妊娠期高血压、轻度/严重子痫前期、子痫和子痫前期叠加先前存在的高血压,在所有妊娠疾病中占5%~10%[44]。先兆子痫被定义为一种起源于胎盘的全身性综合征,表现为妊娠期高血压和蛋白尿[45]。妊娠期慢性高血压会增加新生儿肾脏、肢体和唇腭裂先天性畸形的风险,如叠加子痫进一步增加新生儿患病风险[46]。相关研究表明,患有子痫前期的女性在怀孕前可能有较高的血压,孕前血压与妊娠患高血压和子痫前期均正相关[47],妊娠期高血压疾病母体的子代唇腭裂的发生率高于血压正常的母体[23,44,48]。

Arias Urueña等[49]发现,产妇高血压与唇腭裂之间的潜在机制可能包括参与血管生成和相关的必要基因突变。另一项针对美国孕妇高血压患者队列的研究发现,妊娠期血压异常与影响胎儿发育异常相关,而胎盘DNA甲基化可能是母体血压影响胎儿发育结果的调控途径[50]。妊娠期发生高血压的妇女通常其妊娠前或妊娠早期胎盘中存在缺氧和滋养细胞侵袭不足,宫内高压环境和高血糖环境一样可引起氧化应激,加剧了缺氧状态[30],增加胎儿发生先天性异常的风险[51]。

四、肥胖

孕妇肥胖与妊娠并发症密切相关,如孕妇糖尿病、先兆子痫、妊娠早期流产,以及死产和先天性异常[19]。产妇肥胖会显著增加子代神经管缺陷,心血管、口面和肢体异常的发生率[16,52]。已有Meta分析表明,体质量指数(body mass index,BMI)超过30的母亲与婴儿单纯腭裂和唇腭裂风险增加显著相关,但与单纯唇裂无关[53]。有趣的是,新生儿的低出生体质量(新生儿体质量<2 500 g)为围产期死亡的主要原因[54-55],以新生儿体质量2 500~3 999 g作为正常体质量,新生儿体质量4 000 g或以上可能对唇腭裂具有保护作用,而体质量低于2 500 g是唇腭裂的一个危险因素[38],这一结论与母亲的体质量关系相反。肥胖导致相关唇腭裂的确切机制尚不清楚,母亲肥胖可能改变唇腭裂相关基因的DNA和组蛋白甲基化,导致对口面部发育至关重要的信号基因活性改变[56]。肥胖被认为是一个可改变的危险因素,故应

鼓励孕前咨询和建立与超重和肥胖相关的健康风险意识[57]。

五、系统性红斑狼疮

SLE是一种慢性自身免疫性疾病,其最常见的表现为口腔溃疡、唾液分泌不足、色素沉着、舌痛、唇裂、口唇炎、关节炎和继发性舍格伦综合征等[17]。Scott等[58-59]研究发现,患有自身免疫病的母亲血清中含有抗SSA抗体及抗SSB抗体,这两种自身抗体可通过血循环透过胎盘损伤正常发育的胎儿。既往研究结果显示,SLE本身并不影响女性生育,但妊娠期生理变化会加重SLE病情发展,从而增加孕产妇不良妊娠结局风险[60]。美国一项大样本资料显示,妊娠合并SLE发生不良妊娠结局的发生率约为非SLE者的3倍,严重者会危及母体和婴儿的生命安全[61-62]。

另外,在一项动物实验中,发现用于治疗SLE的免疫抑制剂霉酚酸酯与子代唇腭裂密切相关,当用霉酚酸酯治疗时,大鼠和家兔的后代畸形发生率增加[63]。此药物可能对人类也有致畸作用,患有SLE母体在怀孕早期常接受了高剂量的免疫抑制剂霉酚酸酯治疗,其子代可能出现面部发育不良、口面裂和耳畸形[63]。另一种常用的治疗SLE药物羟氯喹也被发现在妊娠早期中使用会增加胎儿畸形的风险,严重先天性畸形的发生率高达5.48%,其中唇裂常见[64],所以应注意妊娠期用药的指征。

六、牙周病

牙周病是一种局部炎症性疾病,主要与革兰氏阴性细菌、厌氧菌和嗜微氧细菌密切相关,这些细菌定植在牙龈下区域引起牙周组织炎症[65]。这种口腔局部炎症与全身系统性疾病的发生密切相关[66-67],且循环系统是可能的传递途径之一。牙周病患者在其血管中可发现牙周病原体[68],其全身炎症标志物如C反应蛋白和前列腺素E2(prostaglandin E2,PGE2)增加[69-70]。此外,细菌成分进入循环系统中可能引起自身免疫反应[71],细菌本身也可能通过循环系统传播至全身各处[72]。宫内感染可能由来自全身不同区域的细菌发展而来,其中之一就是口腔[73]。

牙周病的严重程度与不良妊娠结局的发生率呈正相关[74],这种关联可能是由龈沟微生物通过母体菌血症和经胎盘通道引起的,其循环系统中白细胞介素1(IL-1)、肿瘤坏死因子α(TNF-α)、IL-6和PGE2等细胞因子和基质金属蛋白酶显著升高并通过胎盘影响胎儿,也可能通过诱导高血压和继发性子宫血管改变干扰胎儿生长从而导致不良的妊娠结局[75-76]。

此外,产妇牙周病可能会触发新生儿的多基因易感性,怀孕期间母体牙周病与子代发生孤立性口面裂的高风险有强关联,其中发生唇腭裂和单纯腭裂的风险较高[18,77]。四环素是治疗牙周炎的常用药物,虽然四环素被列在人体致畸药物清单上,但已有研究发现用于治疗牙周病的四环素药物似乎没有并无增加对子代唇腭裂发生率[78]。

七、结论

唇腭裂是相对常见的出生缺陷,不同人群的患病率各不相同[1]。唇裂和腭裂对个体的影响可能因病情的严重程度而异,通过影响患儿的外貌、喂养、发音、牙齿、听力和社会心理等,从而影响他们的整体生活质量和情绪健康。唇腭裂的治疗通常涉及多学科方法,唇腭裂患者需要在合适的时间和年龄进行序列治疗,包括唇裂、腭裂和唇腭裂手术、术后正畸、正颌治疗,还需进行相应的心理治疗以达到生理和心理的健康[8]。但母体健康对唇腭裂发生的影响还需更加深入地探索。

本文综述了母体孕期患糖尿病、高血压、肥胖和系统性

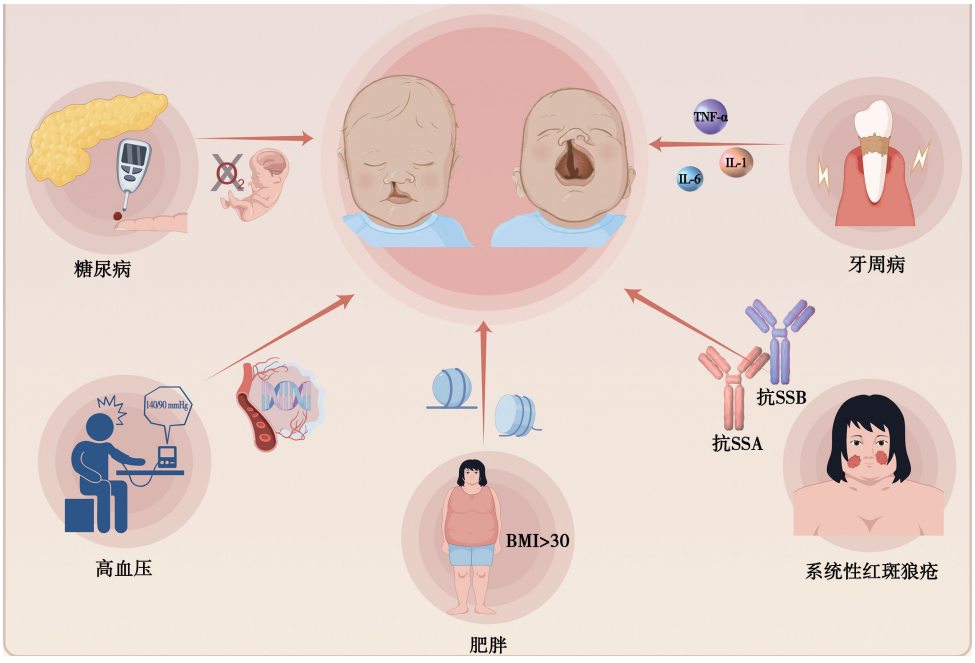

图1 母体系统性疾病与新生儿唇腭裂的关系 母体糖尿病、高血压、肥胖、系统性红斑狼疮和牙周病都可能导致新生儿患有唇腭裂的风险增加(本图使用Figdraw绘制)。

红斑狼疮4种系统性疾病及与系统性疾病密切相关的牙周炎与子代唇腭裂发生的关系,不管是产前已患有这些疾病或是孕期中才发现,都可能增加胎儿出生缺陷的风险,且不同疾病中还可能存在协同关系。这提示母体在备孕和怀孕过程中应当注意自己的身体状况,并进行相应的干预措施,尽可能地预防并降低唇腭裂的发生。但是,目前确切的证据仍不足够,还需要更多的实验以及数据进一步支撑。除了以上所描述的5种疾病之外,还有很多危险因素也会增加新生儿患有唇腭裂的风险,如怀孕期间母亲大量接触酒精、吸烟、孕期压力以及使用辅助生殖技术都与生下唇腭裂孩子之间存在显著关联[38-39,48,79]。

通过了解唇腭裂造成的危害并采取预防措施,可以潜在地降低这种情况的发生率并提高受影响个体的生活质量[80-81],定期进行产前检查和及早发现潜在问题有助于管理和规划唇腭裂的治疗[82]。因此,建议对患有全身性疾病的妇女,强调妊娠早期随访的必要性,在怀孕期间接受适当的医疗护理和密切监测,控制已确定的危险因素和接受相应的保护措施[81],以减少新生儿发生唇腭裂发生率,确保母亲和婴儿的最佳妊娠结局。

利益冲突 所有作者均声明不存在利益冲突

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