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生殖医学

·专题报道·

剖宫产子宫瘢痕缺损对采用辅助生殖技术孕妇妊娠结局的影响及对策

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［摘　要］ 近二十年中国的剖宫产率持续上升，导致继发性不孕的剖宫产瘢痕缺损（CSD）患者增加，需要通过辅助生殖技术（ART）解决再生育问题。CSD可显著降低ART活产率、临床妊娠率和胚胎植入率，这与患者子宫内膜容受性下降、瘢痕局部发生腺肌病及子宫内膜异位症、宫腔微环境紊乱、ART操作难度及妊娠并发症增加有关。除了使用促性腺激素释放激素类似物可能改善妊娠结局，宫腔镜手术、腹腔镜手术和经阴道手术是治疗CSD的有效方法，可提高妊娠率。本文通过文献回顾，分析CSD对采用ART孕妇妊娠结局的影响及相应的治疗方法，以期为CSD患者管理及改善ART妊娠结局提供新思路。

［关键词］ 剖宫产；剖宫产瘢痕缺损；辅助生殖技术；妊娠结局；综述
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Impact of cesarean scar defect on reproductive outcomes after assisted reproductive technology

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［**Abstract**］ In the last twenty years, the cesarean section rate has been rising in

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China, leading to an increased prevalence of cesarean scar defect (CSD) and secondary infertility. CSD decreases receptivity of endometrium, induces adenomyosis and endometriosis, disrupts uterine micro-environment and causes difficulties in embryo transplant operation as well as has further pregnancy complications. For women undergoing assisted reproductive technology (ART), CSD significantly reduces live birth rate, clinical pregnancy rate and embryo implantation rate. CSD can be effectively treated by hysteroscopic surgery, laparoscopic surgery and transvaginal surgery to increase the pregnancy rate. This article reviews the research progress on the impact of CSD on the reproductive outcomes of ART, the potential factors and related treatments, and provides a reference for the management of CSD patients undergoing ART.

[**Key words**] Cesarean section; Cesarean scar defect; Assisted reproductive technology; Pregnancy outcome; Review

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[**缩略语**] 剖宫产瘢痕缺损(cesarean scar defect,CSD);辅助生殖技术(assisted reproductive technology,ART);体外受精(*in vitro* fertilization,IVF);卵胞质内单精子注射(intracytoplasmic sperm injection,ICSI);人绒毛膜促性腺激素(human chorionic gonadotrophin,hCG);子宫内膜异位症(endometriosis,EMT);胰岛素生长因子结合蛋白(insulin-like growth factor binding protein,IGFBP);胰岛素样生长因子(insulin like growth factor,IGF);残留子宫肌层厚度(residual myometrial thickness,RMT);促性腺激素释放激素类似物(gona-dotropin-releasing hormone analogue,GnRHa)

近二十年,全球范围剖宫产率持续上升,从2000年的12%增长到2015年的21%,2015年全球约2970万人通过剖宫产分娩[1-2]。中国妇幼健康统计数据显示,2008年我国剖宫产率为28.8%,2018年达到36.7%[3]。CSD是指剖宫产术后子宫切口愈合不良、瘢痕处肌层变薄导致的与宫腔相通的凹陷或腔隙,是剖宫产常见的并发症之一[4]。2018年,欧洲专家认为大于2 mm的宫腔肌层缺损可诊断为CSD[5],在经历0、1、2和3次剖宫产女性中,CSD的发生率分别为35%、63%、76%和88%[6],可导致继发性不孕[7-8]。ART是治疗不孕的有效方法之一,包括采用IVF/卵胞质内单精子注射–胚胎移植。当前,许多CSD伴继发性不孕患者拟通过ART满足再生育需求。然而,CSD对ART妊娠结局的影响尚无定论。本文回顾文献,综述了CSD对ART妊娠结局的影响及其潜在的影响因素,探讨了CSD患者辅助生殖的对策,以期加强CSD患者的管理,为改善CSD患者ART妊娠结局提供证据和思路。

1 剖宫产瘢痕缺损会影响辅助生殖技术妊娠结局

剖宫产对ART妊娠结局的不利影响已有较多临床及循证医学证据:在接受ART治疗的患者中,有剖宫产史的女性更易出现流产,且活产率、临床妊娠率、hCG阳性率和胚胎植入率较正常人群低[9-11]。然而,CSD对ART妊娠结局影响的研究报道较少。本文对已发表的文献进行回顾总结,共检索到11项研究,均为回顾性分析[12-22],其中8项研究来自中国(附表1)。除Lawrenz等[13]的研究,其余10项研究均观察到CSD患者活产率和/或临床妊娠率下降[12, 14-22];有10项研究报道了流产率,其中流产率下降1项[17],流产率升高9项[12-16, 18-20, 22]。也有研究提示CSD患者植入率、hCG阳性率显著下降[14, 19]。多项研究均发现CSD组相比剖宫产无瘢痕缺损组活产率及临床妊娠率下降、流产率升高,表明CSD对ART的妊娠结局能产生更显著的负面影响[12, 15, 18-19]。Wang等[16]

进一步分析了CSD大小对妊娠结局的影响，发现CSD越大，活产率、临床妊娠率、hCG阳性率越低。

CSD可导致月经和液体积聚形成病理性宫腔积液[23]。多项研究比较了CSD伴宫腔积液对ART的影响。如Huang等[15]证实在接受IVF患者中，CSD伴宫腔积液患者相比CSD无宫腔积液患者活产率（分别为11.22%和32.22%）和临床妊娠率（分别为20%和40%）均显著降低。Diao等[14]指出CSD伴宫腔积液患者活产率、临床妊娠率、hCG阳性率和胚胎植入率下降，但差异无统计学意义。上述两项研究结果的差异可能与病例纳入较少有关，因此，仍需要进一步的大样本研究来证实宫腔积液对ART妊娠结局的影响。

CSD对接受ART治疗患者妊娠结局的影响与胚胎移植数量也存在一定的相关性。Zhang等[17]评估了CSD对单胚胎移植和双胚胎移植妊娠结局的影响：在双胚胎移植中，CSD患者的临床妊娠率和活产率显著降低；但在单胚胎移植中差异无统计学意义。瘢痕憩室妊娠的发病率虽然较低，但其妊娠风险极高，如子宫破裂、产后出血、胎盘植入、前置胎盘或胎盘增生，甚至危及产妇和胎儿的生命；当CSD合并多胎妊娠时，上述风险显著增加[24]。因此，2018年我国专家一致推荐CSD患者进行选择性单胚胎移植[25]。

综上所述，CSD会降低ART妊娠的活产率和临床妊娠率，当CSD伴有宫腔积液时会进一步影响活产率和临床妊娠率，易导致患者早期流产，且在双胚胎移植中影响更为显著。为避免剖宫产瘢痕妊娠的不良妊娠结局，CSD患者应考虑进行选择性单胚胎移植。然而，以上证据大部分来自回顾性队列研究，缺少高质量、大样本、多中心、前瞻性的临床研究及循证医学证据。

2　剖宫产瘢痕缺损影响辅助生殖技术妊娠结局的机制

CSD对ART妊娠结局影响的机制可概括为以下四个方面：①影响子宫内膜容受性；②瘢痕局部发生腺肌病和EMT；③影响宫腔微环境；④影响ART操作及增加妊娠并发症。

2.1　影响子宫内膜容受性

CSD通常伴有子宫内膜厚度减低、周围组织粘连、子宫内膜容受性下降，同时肌肉顺应性及正常收缩功能下降，易导致子宫不规则收缩，进而影响胚胎植入，甚至引起早期流产[26]。Abdullgaffar等[27]回顾了22例CSD伴继发性不孕患者宫腔镜术后病理学检查结果发现，所有患者CSD边缘组织都存在不同程度的纤维化。另有研究显示，瘢痕表面的正常子宫内膜组织及肌纤维密度显著降低[28]。因此，CSD可能通过降低子宫内膜容受性，影响肌层收缩功能，导致胚胎移植失败或不良妊娠结局。

2.2　瘢痕局部发生腺肌病和EMT

CSD常伴有瘢痕局部的腺肌病和EMT。Morris[29]研究了51例CSD患者子宫切除术后组织标本的病理改变，发现瘢痕周围子宫内膜充血、息肉形成、淋巴细胞浸润、毛细血管扩张，伴有子宫腺肌病。Piriyev等[30]对28例有生育需求的CSD患者行腹腔镜术后病理检查，发现其中19例伴子宫腺肌病。Nobuta等[31]通过腹腔镜发现70%的CSD患者合并EMT。Gulz等[32]认为CSD与盆腔腹膜EMT（瘢痕局部EMT除外）相关。腺肌病和EMT可导致子宫和盆腔解剖结构异常，干扰胚胎植入；EMT还可通过产生细胞因子、免疫因子及前列腺素等增加对子宫蜕膜和滋养层的负面影响，从而导致不良妊娠结局[33-34]。

2.3　影响宫腔微环境

CSD与慢性子宫内膜炎密切相关，而慢性子宫内膜炎是导致ART胚胎植入失败的重要原因[35]。Wei等[36]对331例CSD患者和170名健康女性的临床研究证实，CSD患者慢性子宫内膜炎的患病率较健康女性升高。同时，相比剖宫产无瘢痕缺损伴继发性不孕患者，CSD伴继发性不孕患者慢性子宫内膜炎发生率也显著升高[31]。免疫组织化学分析也证实CSD患者常伴慢性子宫内膜炎，即肿瘤坏死因子-α、IL-1β、CD138水平显著升高[37]。慢性子宫内膜炎会导致内膜上皮–间质转化[38]，进而影响胚胎植入，而且子宫内膜基质细胞在蜕膜化过程中分泌IGFBP1，IGFBP1表达增加和IGF1表达减少不利于胚胎植入和胚胎发育[39]。

CSD还可能伴有活动性出血。通过组织病理学检测可观察到CSD表面异常增生的血管[27]，这些新生毛细血管容易破裂且不能及时止血，可积聚形成宫腔积液。此外，ART治疗过程会增加CSD患者宫腔积液的风险。Lawrenz等[13]研究显示，40%的CSD患者在IVF过程中因卵巢刺激而出现宫腔积液。积聚的宫腔积液流入子宫对着

床造成物理障碍[40]。宫腔积液还能促进微生物生长,进一步导致慢性炎症状态,其中存在的微生物、内毒素、炎症因子、氧化应激产物会影响胚胎植入及胚胎发育潜能[41-42]。

综上,CSD可伴有子宫内膜炎和活动性出血,产生的宫腔积液进一步影响宫腔微环境,导致ART成功率下降。

2.4 影响ART操作及增加妊娠并发症发生

CSD增加了ART的操作难度。为避免瘢痕妊娠,操作者需要将胚胎放置在远离瘢痕憩室的部位。当CSD较大时,宫腔形态发生改变,需要更多的操作以确定胚胎植入部位,这一过程会刺激子宫并最终影响胚胎植入。而且CSD患者常伴有周围组织粘连,这会增加宫颈暴露和胚胎移植的难度[24]。有研究显示,与阴道分娩组比较,剖宫产无瘢痕缺损组的胚胎移植平均时间增加30 s,导管出血发生率升高两倍,黏液发生率升高一倍[43]。研究还发现,CSD患者在IVF手术中需要更多的工具进行胚胎移植,导管转移深度超过7 cm的人数也增多[44]。此外,CSD患者妊娠并发症(包括瘢痕妊娠、瘢痕子宫破裂、胎盘异常等)可危及产妇和胎儿的生命[45],在一定程度上影响ART的最终活产率。

3 剖宫产瘢痕缺损患者辅助生殖的对策

临床医师首先应更清晰地告知孕妇剖宫产的适应证和并发症,并对剖宫产进行严格限制,以降低CSD的发生率;其次应重视CSD的早期评估,包括其大小、位置、RMT、宫腔积液情况。对于无明显伴随症状的CSD患者可考虑药物治疗及ART助孕,但对于症状明显或经历过两次以上高质量胚胎植入仍失败的患者,建议进一步行手术治疗[13]。若有宫腔积液,在胚胎移植前消除积液有助于提高妊娠率[23]。

3.1 药物治疗

基于CSD组织病理为局部子宫腺肌病和EMT,专家建议患者在胚胎移植周期前三个月服用GnRHa,从而有利于提高妊娠率[30, 46]。GnRHa可能有利于控制CSD患者的异常出血并抑制局部炎症反应,提高胚胎着床的成功率[47]。CSD患者接受GnRHa超长方案促排卵后,移植周期活产率为33.3%,临床妊娠率为40.7%[48]。因此,使用GnRHa可能改善妊娠结局。

3.2 手术治疗

宫腔镜手术、腹腔镜手术、经阴道手术可显著改善CSD相关症状。一般建议患者术后避孕两年,若子宫完整性没有破坏,术后6个月可酌情计划妊娠[49]。三种手术方式优劣总结见表1。

宫腔镜手术对于CSD伴一定厚度RMT的患者是安全、有效的治疗方式。Al Mutairi等[58]一项纳入18项研究共1165例CSD患者的meta分析结果显示,宫腔镜手术治疗后CSD患者的总妊娠率为69.77%。Iskakov等[59]对29例CSD伴继发性不孕患者进行宫腔镜手术,后续40个IVF周期中,45%的患者实现了临床妊娠,其临床妊娠率与非CSD患者相似。但是,对于宫腔镜手术RMT尚无定论。Harjee等[60]认为宫腔镜手术对RMT大于2.5 mm的CSD伴继发性不孕患者有效。也有研究

表1 三种CSD手术治疗优劣比较

Table 1 Comparison of the advantages and disadvantages of three surgeries of CSD

手术名称	手术方式	优 势	劣 势	参考文献
宫腔镜手术	宫腔镜引导下暴露CSD部位,剪切CSD周围的瘢痕瓣,进行缝合	①手术视野清晰,可精准定位;②术中阴道出血量较少,术后阴道出血时间短;③手术及住院时间短、费用低	①无法修复解剖异常;②要求一定残留子宫肌层厚度,否则子宫破裂、憩室妊娠风险较高	[49-53]
腹腔镜手术	腹腔镜下打开膀胱腹膜反折,下推膀胱,暴露CSD部位,进行切除和缝合	①手术视野广,可探查盆腹腔环境、分离粘连;②可修复瘢痕肌层	①难以精准定位及切除CSD,有时需结合宫腔镜手术;②住院时间长、费用高,手术并发症风险增加	[50,52-55]
经阴道手术	窥阴器暴露宫颈后,切开阴道黏膜,钝性分离宫颈、膀胱间隙,上推膀胱,剪开膀胱腹膜反折,触诊或探针定位CSD部位,切除瘢痕组织,进行缝合	①无腹壁切口;②术后阴道出血时间短;③手术及住院时间短、费用低,患者接受程度高	①手术视野较窄,难以精准定位;②术中出血量相对多;③易损伤膀胱	[49,53,55-57]

CSD:剖宫产瘢痕缺损.

人员认为RMT大于2.2 mm的CSD伴继发性不孕患者首选宫腔镜手术；对RMT小于2.2 mm的患者，腹腔镜手术是首选[61]。2019年我国《剖宫产术后子宫瘢痕憩室诊治专家共识》推荐RMT大于3 mm有再生育要求的患者选择宫腔镜手术，但应充分告知患者再次妊娠时存在子宫破裂风险[49]。

由于CSD患者常伴有盆腔EMT，而腹腔镜手术视野广，可探查盆腹腔环境，因此有学者推荐CSD伴继发性不孕患者行腹腔镜手术以改善盆腔内环境[61]。Donnez等[62]也证实，腹腔镜手术可显著降低患者EMT范围，同时可以显著增加RMT并改善CSD症状，术后妊娠率为44%。腹腔镜手术安全性较好。但是，腹腔镜手术存在对CSD定位不精准的缺陷，因此推荐采用联合宫腔镜的手术方式以弥补腹腔镜手术的不足[61]。

经阴道手术对改善CSD临床症状也有较好的疗效，而且手术创面小、所需设备简单、患者恢复快。Zhou等[63]报道CSD患者经阴道手术后妊娠率为50.98%；Deng等[56]报道CSD患者在经阴道手术后妊娠率为66.94%。但目前尚未有研究报道经阴道手术对ART妊娠结局的影响。

4　结　语

CSD可降低ART患者的活产率、临床妊娠率、胚胎植入率、hCG阳性率，更易出现流产，且CSD伴宫腔积液也会对ART产生不利影响。这与CSD降低内膜容受性从而影响肌层收缩功能、瘢痕局部发生腺肌病和EMT、改变子宫微环境（慢性子宫内膜炎、活动性出血、宫腔积液）、增加胚胎移植难度以及增加妊娠并发症发生等相关。GnRHa可提高胚胎着床的成功率，宫腔镜手术、腹腔镜手术、经阴道手术可显著提高CSD妊娠率。目前，评估CSD术后ART妊娠结局的研究尚较少，仍需要高质量的前瞻性临床研究及循证医学研究来证明CSD的手术治疗对ART妊娠结局的影响。此外，CSD影响ART妊娠结局的机制研究也较少。本文就CSD对ART妊娠结局的影响及对策进行了综述，以期为临床上ART诊治CSD伴继发性不孕患者提供参考。

本文附表见电子版。

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Conflict of Interests　The authors declare that there is no conflict of interests

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· 学术动态 ·

朱永群教授团队合作成果揭示病原菌新型磷酰基腺苷酸化酶致病因子家族及其独特的作用机制

2024年5月22日,浙江大学生命科学研究院/动物科学学院朱永群教授与浙江大学生命科学学院周艳研究员、北京大学基础医学院刘小云研究员联合在《自然》(*Nature*)上发表了最新研究论文"*Legionella* effector LnaB is a phosphoryl-AMPylase that impairs phosphosignalling"(DOI:10.1038/s41586-024-07573-z)。研究发现了一类广泛存在于病原菌中新型的LnaB家族磷酰基单磷酸腺苷酸化酶致病因子家族,揭示了全新的磷酰基腺苷酸化修饰和调节磷酸化信号转导的方式,突破了磷酸化是终端化的、在细胞内不可被进一步共价修饰的传统观念。该研究还阐释了病原菌通过同一效应蛋白既保护宿主经典泛素通路,又抑制宿主免疫防御反应,达到与宿主细胞短期共存的目的,实现"绵里藏针"的致病策略。

嗜肺军团菌是导致人类军团病的致病菌,其感染肺巨噬细胞,在宿主细胞内通过形成独特的膜泡结构,而达到生存和繁殖的目的。该研究发现其致病因子LnaB是一个以ATP作为配体、宿主肌动蛋白(actin)作为激活剂的独特腺苷单磷酸化酶,能对非经典泛素化过程中产生的PR^{R42}-Ub上磷酰基进行腺苷单磷酸化修饰,并与另一个致病因子MavL形成级联催化反应,实现了对非经典泛素化过程的逆转。在感染过程中,LnaB还对宿主关键信号分子Src家族激酶进行磷酰基腺苷单磷酸化,产生特殊的腺苷二磷酸化修饰,从而抑制了其介导的免疫信号通路。LnaB同源蛋白广泛分布于20多个不同菌属中,构成一类新型的磷酰基腺苷单磷酸化酶家族。

王婷博士研究生、宋晓楠硕士研究生和谭加兴博士为论文第一作者。研究获得了国家自然科学基金、国家重点研发计划、中组部青年拔尖人才支持计划等资助。