



改善子宫内膜血流状态提高体外受精-胚胎移植成功率 的中医研究与思考

郭佳¹, 王丽娜², 李东¹
1. 北京大学第三医院中医针灸科, 北京 100191
2. 北京大学生殖医学中心, 北京 100191

摘要:子宫内膜的血流状况直接关系到子宫内膜的容受性,进而影响体外受精-胚胎移植(*in vitro* fertilization and embryo transfer, IVF-ET)的结局。近年来,临床研究和动物实验均表明以补肾、活血中药为基础组成的方剂可通过调控多种血管生成因子来促进子宫内膜血管生成,并通过调节一氧化氮水平抑制子宫血管平滑肌收缩来改善内膜的血流状态,促进胚胎着床。但多数研究没有体现中医辨证论治的特点,我们认为有必要进一步摸索子宫内膜血流障碍的中医辨证规律,将辨病与辨证相结合。不仅补肾活血药物,疏肝理气养血药、健脾益气补血药等都可能具有改善子宫内膜血流的作用。未来临床研究可通过对子宫内膜血流的动态观察,确定针对不同证型患者进行治疗的各类中药的配伍比例、量效关系等,改变仅凭经验来定的现状,提高临床疗效,促进临床推广应用。在 IVF-ET 过程中采用针刺进行辅助治疗已有十余年历史,电针通过抑制交感神经兴奋来扩张子宫动脉影响子宫血供的机制已经基本明确,但针灸对决定内膜血流状态的细小动脉的调节作用还有待进一步观察和研究。中医治疗可能是改善子宫内膜血流状态,提高 IVF-ET 孕育率的一个有价值的方法。临床中可以采取中西药配合、药物与针灸结合的方法,发挥各自的优势,获得更大的临床效益。

关键词:子宫内膜血流; 体外受精胚胎移植; 中药; 补肾; 活血; 针灸疗法

1988 年 Goswamy 等^[1]借助彩色多普勒超声检测不孕患者子宫动脉血流状态后发现,子宫动脉血流存在异常,并提出子宫血流灌注损伤有可能是导致女性不孕的一个重要原因。子宫体血供主要来自子宫动脉,因此,子宫动脉血流参数曾被当作是判断子宫内膜容受性的较为可靠的预测指标之一^[2]。但

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<p>DOI: 10.3736/jcim20111204 http://www.jcimjournal.com</p> <p>郭佳, 王丽娜, 李东. 改善子宫内膜血流状态提高体外受精-胚胎移植成功率的中医研究与思考. 中西医结合学报. 2011; 9(12): 1301-1306.</p> <p>Guo J, Wang LN, Li D. Exploring the effects of Chinese medicine in improving uterine endometrial blood flow for increasing the successful rate of <i>in vitro</i> fertilization and embryo transfer. <i>J Chin Integr Med</i>. 2011; 9(12): 1301-1306.</p> <p>Received June 21, 2011; accepted July 31, 2011; published online December 15, 2011.</p> <p>Full-text LinkOut at PubMed. Journal title in PubMed: <i>Zhong Xi Yi Jie He Xue Bao</i>.</p> <p>Correspondence: Jia Guo, Associate Professor; Tel: 010-82265821; E-mail: guojia65@163.com</p>	<p><i>Journal of Chinese Integrative Medicine (JCIM)</i> or <i>Zhong Xi Yi Jie He Xue Bao</i> is an international, peer-reviewed, open access journal for the study of complementary and alternative medicine or integrative medicine from all regions of the world. <i>JCIM</i> is indexed in PubMed and Directory of Open Access Journals (DOAJ). <i>JCIM</i> is a member journal of CrossRef. Articles published in <i>JCIM</i> have maximum exposure to the international scholarly community.</p> <p>Submit your manuscript here: http://mc03.manuscriptcentral.com/jcim-en (for manuscripts written in English) http://mc03.manuscriptcentral.com/jcim-cn (for manuscripts written in Chinese)</p> <ul style="list-style-type: none">• No submission and page charges for manuscripts written in English• Quick decision and rapid publication <p>Send your postal address by e-mail to jcim@163.com, we will send you a complimentary print issue upon receipt.</p> <p>ISSN 1672-1977. Published by JCIM Press, Shanghai, China.</p>

近年的研究发现,子宫动脉血流参数并不能完全反映子宫内膜的血流状态^[3],因为营养子宫内膜的主要血管是子宫动脉的终末分支螺旋动脉,只有螺旋动脉的血流参数才能作为评估子宫内膜容受性的有效指标^[4,5]。王丽娜等^[6]研究发现,不孕患者子宫内膜内的血流分布与胚胎能否在宫内种植及此后的持续发育密切相关,子宫内膜内存在血流者较无血流者显示出更高的妊娠率和胚胎种植率,进一步提出了子宫内膜血流存在状态及血流参数关系到体外受精-胚胎移植(*in vitro* fertilization and embryo transfer, IVF-ET)结局的观点。对子宫内膜血流状况不佳的患者尝试应用药物改善内膜血流,能够提高 IVF-ET 的妊娠率和着床率^[7]。

引起子宫内膜血流状态异常的原因和病理机制目前尚不十分明确,可改善子宫内膜血流的药物和治疗方法也十分有限。临床研究显示,口服或阴道内使用枸橼酸西地那非(sildenafil,商品名“万艾可”)能够改善子宫内膜的血流状态,促进子宫内膜生长,提高内膜容受性^[8-10]。万艾可是一氧化氮(nitric oxide, NO)样药物,目前主要用于治疗男性勃起功能障碍,可使阴茎海绵体平滑肌和阴茎小动脉平滑肌松弛,增加组织局部血流。由于女性的子宫也是由平滑肌组成的肌性器官,有子宫动脉和丰富的血管分支,故用万艾可可能调节子宫血流治疗子宫内膜生长不良^[11]。小剂量阿斯匹林则可能通过抑制环氧合酶活性发挥抑制血小板活性的作用,预防微血栓形成,降低子宫动脉血流阻力,改善子宫内膜的血流灌注来促进子宫内膜的生长^[12]。

近年来中药、针灸介入辅助生殖技术提高成功率成为国内外研究热点,已有相当多的研究显示中药和针灸对子宫内膜血流状态能够起到良好的调整作用。本文就该方面的研究进展进行评述,并就今后研究的方向进行探讨。

1 中药对子宫内膜血流的影响

《素问·上古天真论》曰:“二七肾气盛,任脉通,太冲脉盛,月事以时下,故能有子……七七任脉虚,太冲脉衰少,天癸竭,地道不通,故形坏而无子。”冲为血海,任主胞胎,若肾气不足,肾精不能化生气血,使冲任二脉无法充盛,也就不能为胚胎着床和发育提供物质基础。同时肾气虚弱无力推动血行,造成胞脉瘀阻,也会导致胞宫失养。因此女性不孕症的一个重要病理机制是“肾虚血瘀”^[13]。补肾活血成为现代临床治疗不孕症最常用的指导原则之一。

1.1 以补肾填精的中药为主,兼以养血活血 陈秋梅等^[14]的研究表明,以补肾填精中药组成的“调经孕育方”(菟丝子、熟地黄、覆盆子、山茱萸、肉苁蓉、枸杞子、当归、黄芪、淮山药、白术、鸡血藤、香附等)在促进内膜生长的同时,也显示出对子宫动脉和子宫内膜血流的促进作用。李秀然等^[15]采用助孕增膜方(菟丝子、淫羊藿、何首乌、熟地黄、当归、川芎、赤芍、黄芪、丹参、鸡血藤、香附等)治疗排卵障碍性不孕患者,观察到患者子宫内膜螺旋动脉变粗,螺旋动脉的搏动指数和阻力指数下降。配伍类似的方药二至天葵颗粒^[16](二至丸、四物汤加菟丝子、枸杞子、香附等)可改善注射人绒毛膜促性腺激素(human chorionic gonadotropin, HCG)患者的子宫动脉血流动力学参数。

1.2 以活血化瘀通络药为主 张鸿慧等^[17]将丹莪妇康煎膏(紫丹参、莪术、竹叶柴胡、三七、赤芍、当归、三棱、香附、延胡索、甘草等)用于治疗 103 例反复自然流产的患者,观察到治疗组子宫内膜螺旋动脉的搏动指数和阻力指数值较未治疗组显著下降($P < 0.05$)。孟海萍等^[18]用七厘失笑棱莪汤灌肠治疗子宫内膜异位症后,患者黄体中期的子宫动脉阻力指数显著降低。复方丹参滴丸是治疗心血管疾病



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的常用药,耿彩平等^[19]对超促排卵阶段子宫内膜过薄的患者予以复方丹参滴丸治疗,注射 HCG 时患者子宫动脉搏动指数和阻力指数显著低于用药前的周期($P<0.01$)。张明敏等^[20]在控制性超排卵前,给予患者服用 2 个月经周期的银杏叶制剂后,内膜血液灌注指标有改善的趋势。

2 针刺对子宫血流状态的调整作用

1996 年瑞典学者 Stener-Victorin 等^[21]对 10 例子宫高血流阻力的不孕妇女在使用激素治疗期间,采用电针进行治疗。他们依据内脏的神经节段性支配规律,选取与子宫和卵巢在同一神经节段内的主要穴位肾俞(BL23)、膀胱俞(BL28)、三阴交(SP6)、承山(BL57)等进行电针刺激。研究发现,子宫动脉搏动指数较治疗前显著降低($P<0.0001$),患者前额的皮肤温度明显上升,证明电针可能通过抑制交感神经活动来降低子宫动脉搏动指数。Ho 等^[22]发现,虽然电针刺激使接受 IVF-ET 患者的子宫动脉搏动指数较治疗前明显下降($P<0.01$),但临床妊娠率却没有显著提高。任蓉等^[23]采用电针治疗原发性痛经时观察到电针能够改善子宫动脉的血流动力学参数。针刺在不同内脏器官上都显示出对局部血流的调节作用^[24]。虽然电针能够调节子宫动脉的血流参数,但目前尚不能肯定针刺是否可以影响螺旋动脉的血流参数。

3 中药改善子宫内膜血流状态的作用机制

3.1 通过调控子宫内膜血管生成影响子宫内膜的血供状态 女性生殖系统的功能与其血管生成表现直接相关,受血管生成因子及其受体的精细调控。子宫内膜丰富的血液供应离不开内膜血管生成增多、重建和血管通透性增强的周期性变化。因此,若能提高子宫内膜的血管生成,改善内膜的血流灌注,可提高 IVF-ET 的成功率。

张树成等^[25,26]研究证实,以补肾为基础的方剂具有促进子宫组织血管生成的作用,补肾中药能够通过调控多种血管生成因子如血管内皮生长因子(vascular endothelial growth factor, VEGF)的表达,促进子宫内膜血管的增殖、重建,改变血管渗透性,并在此基础上提出“补肾生脉”理论^[27]。齐宁等^[28]的动物实验证实,具有温补肝肾、益气活血作用的“健胎液”通过上调胚泡着床障碍大鼠子宫内膜环氧酶 2(cyclooxygenase-2, COX-2)、VEGF 及 6-酮-前列腺素 F1 α 表达的水平,促进子宫内膜血管增殖,改善子宫内膜的发育,利于胚泡着床。有研究发现,补肾活血方若拆分为补肾方和活血方,则无法产生原有的围着床期促进 VEGF 表达的作用^[29]。

3.2 通过调节 NO 水平来改善子宫血流灌注 既往研究显示,NO 能够通过增加子宫内膜的血管通透性、内膜的蜕膜化以及胚胎的发育来促进小鼠胚胎着床^[30]。由丹参、黄芪、川芎、当归、桑寄生等组成的补肾益气活血方能够增强胎盘组织中 NO 的合成与分泌,从而改善胎盘微循环障碍^[31]。耿彩平等^[19]认为,复方丹参滴丸有可能通过调节血管内皮细胞内皮素 1(endothelin-1, ET-1)mRNA 的表达水平提高血中 NO 的浓度,从而降低子宫动脉血流阻力,增加子宫动脉的血流量,增加子宫内膜的容受性。张明敏等^[20]指出,银杏叶制剂可能参与了 NO、前列腺素、血栓素等调节血管活性物质的合成和释放,对子宫及卵巢周围的血液循环及微环境起到调整作用。

3.3 通过调节血液流变学指标对子宫内膜血供产生影响 血液流变学指标异常,如血液黏稠度增高,可使血管内血液流动的阻力增大,造成局部微循环障碍,直接造成子宫、输卵管以及卵巢等生殖器官的血供不良^[16]。血液黏稠度增高与不孕存在一定相关性^[32],具有补肾填精、养血活血作用的调经孕育方药对血液流变学指标有明显的改善作用^[14]。

4 针灸影响子宫血流灌注的作用机制

王少军等^[33]认为,针刺对生殖内分泌系统的作用机制可能存在“针刺-中枢电兴奋-植物神经系统-内脏”以及“神经冲动又继发神经组织内的肽类物质释放和内分泌免疫系统的活动”两个主要的方面。Stener-Victorin 等^[21]提出,电针改善子宫动脉的血流参数有可能是通过刺激相应脊髓节段的交感神经传出支来抑制交感神经兴奋,使血管扩张;也可能是通过释放 P 物质和降钙素基因相关肽作用于周围神经末梢产生逆行的神经冲动而实现;同时,低频的脉冲电刺激使脑脊液中的 β 内啡肽增加,也能够降低交感神经的兴奋性。

5 中药、针灸改善内膜血流,提高 IVF-ET 成功率的未来研究思路

5.1 辨病与辨证相结合,研究应用中药、针灸改善内膜血流的规律 子宫内膜血供是否优良主要取决于营养内膜的血管生成数量和血流的参数等。虽然已经证实补肾、活血药可通过促进子宫组织的血管生长和调节子宫内膜血流参数来改善子宫内膜的血流状态,但目前的研究尚未充分体现中医辨证论治的特点,应辨病与辨证相结合,要进一步研究子宫内膜血流障碍的辨证规律。补肾活血药物、疏肝理气养血药物和健脾益气生血药物等可能都具有改善子

宫内膜血流的作用。可以通过对内膜血流的动态观察,摸索出不同证型的各类中药的配伍比例、量效关系等,改变仅凭经验决定用药的现状。

5.2 从研究针灸对子宫内膜血流状态影响的角度进一步探明针灸治疗不孕症的机制 针灸在辅助生殖技术中的应用价值一直备受海内外学者的关注,尽管已经证实电针能够改善子宫动脉的血流参数,但仍不能确定其对螺旋动脉的作用。今后需借助三维超声及其衍生技术对针灸的作用环节进行深入研究,如针灸是直接作用于内膜血管来改善内膜血流状态,还是通过消除影响内膜血流的客观因素来发挥作用的。

5.3 中西医治疗相互配合提高临床疗效 万艾可对子宫的血流灌注有一定调节作用,但存在个体差异,对子宫血流量基线水平较高者的作用明显。目前临床采用万艾可改善内膜血流的治疗方法仍处于观察阶段,尚无公认的指导意见。有些患者服用万艾可后出现难以忍耐的副作用而停止治疗。我们认为今后临床可以尝试通过中医辨证分型的方法去分析预测万艾可的临床效果和应用价值。此外,还可进一步研究能否将万艾可与中药、针灸结合使用,发挥各自的长处,获得更大的临床疗效。

6 利益冲突

本文无任何利益冲突。

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Exploring the effects of Chinese medicine in improving uterine endometrial blood flow for increasing the successful rate of *in vitro* fertilization and embryo transfer

Jia Guo¹, Li-na Wang², Dong Li¹

1. Department of Traditional Chinese Medicine and Acupuncture, Peking University Third Hospital, Beijing 100191, China
2. Reproductive Medicine Center, Peking University Third Hospital, Beijing 100191, China

Abstract: Endometrial blood flow is directly related to endometrial receptivity thereby affecting *in vitro* fertilization and embryo transfer (IVF-ET) outcomes. In recent years a growing number of studies have shown that traditional Chinese medicine (TCM) can play a role to improve endometrial blood flow and embryo transfer. Studies have confirmed that formulas based on reinforcing kidney and activating blood can promote the formation of uterine endometrial blood vessels by adjusting expressions of a variety of vessel growth factors, and regulating nitric oxide level for inhibition of vascular smooth muscle contraction of the uterus. Treatments based on differentiation of syndromes are key to the theory of TCM. Differentiation of syndromes should be combined with biomedical disease diagnosis. It is also necessary to further clarify other endometrial blood flow disorders using TCM diagnostic methods. In these cases, drugs for reinforcing kidney and activating blood are relevant, but other medicines for smoothing liver qi and nourishing blood, as well as tonifying the spleen and generating blood may also be effective. Future clinical studies should focus on the observation of different types of TCM syndromes and the research on compatibility ratio and dose-dependent relationship of Chinese medicines. Acupuncture has been used during IVF-ET for more than 10 years. Electro-acupuncture can control the expansion of the uterine arteries by inhibiting the sympathetic nerves. However, acupuncture has not been proved to regulate endometrial arteries. To sum up, TCM can be applied to improve endometrial blood flow so as to increase birth rates in IVF-ET. The combination of Chinese and Western medicines and acupuncture application will increase their combined effect, thereby obtaining greater clinical benefits.

Keywords: endometrial blood flow; *in vitro* fertilization and embryo transfer; drugs, Chinese herbal; reinforcing kidney; activating blood; acupuncture-moxibustion