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专论与综述

奶牛产后感染性子宫疾病对子宫和卵巢的影响研究进展

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摘　要：微生物入侵是引起奶牛产后子宫疾病的主要因素，产后子宫能检出丰富的微生物种群，主要包括公认的致病菌如大肠杆菌、隐秘脓杆菌、坏死梭杆菌等，机会病原菌如产气荚膜梭菌、肺炎克雷伯菌、微球菌等和潜在致病菌如消化链球菌、金黄色葡萄球菌等。近年来，运用分子微生态技术发现子宫中的微生物属于变形菌门、梭杆菌门、厚壁菌门、拟杆菌门和软壁菌门 5 个已知的门和一类未被培养的种群，其中拟杆菌属、梭菌属等种群与子宫疾病密切相关。细菌侵入子宫后，以大肠杆菌为代表的革兰氏阴性菌和以化脓隐秘杆菌为代表的革兰氏阳性菌可被子宫内膜细胞上的 Toll 样受体识别引起炎症反应，改变子宫前列腺素分泌类型，影响卵泡发育、黄体大小，降低血清中雌激素和孕激素浓度，造成奶牛不发情、不排卵，导致产犊间隔延长、产奶量和产犊数量下降，严重影响奶业经济效益。本文从产后奶牛子宫内主要病原菌的种类及其与子宫健康状态的关系、子宫内膜对病原菌的识别与先天免疫、子宫疾病对子宫和卵巢功能的影响等方面对国内外研究进展进行了综述。

关键词：奶牛，产后，子宫疾病，微生物，免疫，卵巢

Advances of the effects of infectious uterine disease on uterus and ovary in postpartum dairy cow

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Abstract: Infectious uterine diseases are mainly caused by bacteria invasion following parturition in dairy cows. A wide range of bacteria population were revealed in the postpartum uterus of cattle, including recognized uterine pathogens such as *Escherichia coli*, *Arcanobacterium pyogenes*, *Fusobacterium necrophorum*; potential pathogens such as *Clostridium perfringens*, *Klebsiella pneumoniae*, *Micro Streptococcus*; opportunist pathogens such as *Peptostreptococcus*, *Staphylococcus aureus*. Recently, phyla of Proteobacteria, Fusobacteria, Firmicutes, Bacteroidetes, Tenericutes and a group of uncultured bacteria were observed in the uteri using molecular biology techniques. A positive correlation were found between *Bacteroides*, *Fusobacterium* and uterine diseases. G^- bacteria, *E. coli* as representative, and G^+ bacteria, *A. pyogenes* as representative can be detected by Toll like receptors

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in the endometrial cell membrane and subsequently resulted in inflammation responses, such as changes in prostaglandins type, small size of follicle and corpus luteum, reduction in serum concentration of estrogen and progesterone. Finally, this led to anestrus and anovulation, prolonged calving interval, lowing milk yield and the number of calves, which largely reduced economic profit. This review outlines the dominant microbial community in uterus after calving, correlations between bacterial species and the uterus status, recognitions of pathogen in endometrium and innate immunity, effects of uterine diseases on ovary and uterus function.

Keywords: Dairy cows, Postpartum, Uterine disease, Microbiota, Immunity, Ovary

奶牛分娩前子宫是无菌的，分娩时子宫颈口开张，大量细菌入侵导致约90%的奶牛产后两周发生细菌感染，其中36%−50%有明显的临床表现(临床子宫炎)[1]，15%−20%奶牛产后3周仍持续表现临床子宫内膜炎，30%的奶牛虽无明显临床症状但子宫内部长期处于发炎状态(亚临床子宫内膜炎或隐性子宫内膜炎)[2-4]，其结果是近50%的奶牛产后出现延迟发情、不发情、不排卵或黄体期延长，导致患过子宫疾病的奶牛受胎率比正常奶牛低20%，产犊至受胎间隔延长约30 d，3%的奶牛因无法受胎而被淘汰，养殖和治疗成本急剧增加[4-5]，严重影响奶牛业的生产效益和可持续性发展。因此，本文从产后奶牛子宫黏液中微生物种类、微生物与黏液性状、子宫健康状态的关系、主要致病菌引起奶牛产后子宫疾病的机理及产后奶牛子宫感染对子宫和卵巢生物学功能的影响等方面进行综述，以期为临床子宫内膜炎的预防和治疗提供理论参考。

1 引起产后子宫疾病的主要病原菌

微生物体外培养发现，奶牛分娩后子宫能检出丰富的微生物菌群，其中大肠杆菌、化脓隐秘杆菌等在产后患病奶牛子宫中检出率最高[6-7]，大肠杆菌、化脓隐秘杆菌与坏死梭杆菌等菌群互作引起重度子宫感染；普雷沃氏菌属、拟杆菌属、链球菌属、葡萄球菌属、绿脓杆菌属等不会引起严重组织损伤但可引起子宫持续性感染，诱发子宫疾病[7-8]。根据微生物的致病性可将致病菌分为3类，即公认病原菌(Recognised bacteria)、潜在病原菌(Potential pathogen)和条件病原菌(Opportunist pathogen)。公认病原菌是指能造成子宫内膜损伤的细菌，如大肠杆菌、化脓隐秘杆菌、坏死梭杆菌、普雷沃氏菌和变形杆菌，这些细菌通常与严重子宫内膜炎有关；潜在病原菌常存在于患临床子宫内膜炎奶牛子宫中，但不引起内膜损伤，如地衣芽孢杆菌、粪肠球菌、非溶血性链球菌等；条件病原菌常分离自无明显临床症状的奶牛子宫中，如产气荚膜梭菌、肺炎克雷伯菌、α溶血性链球菌等[9]。生殖道流出的黏液是诊断炎症的主要指标之一，研究表明，菌群种类、密度与黏液特征存在密切关系，Williams等发现化脓隐秘杆菌、变形杆菌和坏死梭杆菌等菌群生长密度可导致黏液脓性增加，非溶血性链球菌、大肠杆菌等生长密度导致黏液产生恶臭气味[6]；彭宇等发现志贺氏菌、产气荚膜梭菌等菌群与奶牛脓血黏液有关[10]。

虽然传统微生物培养方法帮助人们初步认识了子宫内的微生物，但培养环境和选择性培养基的局限，只有约1%的微生物得到了认识[11]，2011年世界首篇利用变性梯度凝胶电泳技术和克隆文库方法研究产后奶牛子宫内微生物菌群的报道发现，产后奶牛子宫内微生物种类远比人们认识的复杂，微生物菌群主要包括变形菌门、梭杆菌门、厚壁菌门、拟杆菌门和软壁菌门5个已知菌群和1个未知菌群，首次发现*Hemophilus somnus*、*Peptostreptococcus anaerobius*和*Veillonella parvula*等引起人和动物呼吸道疾病的病原菌也能存活于牛子宫内[11]。Peng等[7]报道，产后奶牛子宫内菌群种类和数量随产后时间呈动态变化，产后10 d以拟杆菌门、厚壁菌门和梭杆菌门类菌为主，产后40 d以拟杆菌门、厚壁菌门、软壁菌门和变形杆菌门为主；子宫状态与菌

群种类和数量也有关，如软壁菌门细菌只发现于健康牛，变形杆菌门细菌只发现于患病牛。最新研究表明，奶牛分娩当天健康牛与患病牛均会发生细菌感染，分娩后2 d最先侵入的变形菌门丰度下降，拟杆菌门、梭菌门等菌群数量上升，发生子宫炎症。*Helcococcus*、*Filifactor*、*Porphyromonas*、*Peptoniphilus*、*Peptostreptococcus*、*Campylobacter*、*Prevotella*与梭菌、拟杆菌互作，导致炎症程度加深，患病牛伴有恶臭红褐色、水样黏液排出并出现发烧症状。研究也发现，拟杆菌、梭菌等菌群与子宫黏液性状存在显著相关，拟杆菌属、梭菌属等菌群数量增加，子宫黏液脓性加重[12]。新的技术手段为人们深入研究子宫疾病的发病机理、预防和治疗提供了新的视野。

在众多子宫病原菌中，部分病原菌与炎症的关系得到了相对较深的认识。研究发现，公认病原菌中革兰氏阴性菌如大肠杆菌、坏死梭杆菌在产后奶牛子宫早期(1−2周)检出率很高，坏死梭杆菌主要与急性炎症有关，化脓隐秘杆菌通常较晚出现在子宫内，与慢性子宫炎症有关[7,9]，而大肠杆菌作为产后奶牛子宫的先期入侵者，主要产生内毒素(LPS)，它的先期入侵可增强子宫内膜对化脓隐秘杆菌、坏死梭杆菌和普雷沃氏菌等严重致病菌的敏感性；当化脓隐秘杆菌、坏死梭杆菌和普雷沃氏菌共同存在时，易发生严重子宫炎症。深入研究发现，坏死梭杆菌产生白细胞毒素，普雷沃氏菌产生抑制吞噬细胞吞噬细菌的物质，而化脓隐秘杆菌又能产生一种促进坏死梭杆菌生长的物质，因此当这3种病原菌共同存在时菌群互作导致炎症加重[4]。虽然相关新技术的应用加深了对子宫内微生物菌群的认识，但微生物菌群与子宫环境、子宫健康状态及繁殖功能的关系尚有待深入研究。

2 子宫内膜对病原菌的识别与先天免疫

子宫抵御微生物入侵主要依赖于先天性免疫对侵入细菌的识别，这种识别作用与子宫内膜细胞上含有可识别病原菌相关模式分子(Pathogen associated molecular patterns，PAMPs)的Toll样受体(Toll-like receptors，TLRs)密切相关。子宫内膜能表达TLRs1–10，其中TLRs4主要识别大肠杆菌等革兰氏阴性菌的脂多糖LPS，TLR1、TLR2和TLR6以二聚体形式结合后主要识别化脓隐秘杆菌等革兰氏阳性菌的脂磷壁酸或肽聚糖。当TLRs受体信号系统被激活，促炎细胞因子和趋化因子被合成释放，激活免疫细胞，促使免疫细胞流向炎症部位发挥作用。然而，许多奶牛分娩后免疫细胞功能减弱，导致子宫疾病的发生[7]。拟杆菌侵入后也可以通过产生短链脂肪酸抑制中性粒细胞噬菌作用，降低子宫防御功能。Cronin等报道，当用LPS刺激体外培养的子宫内膜细胞时，TLR4通路下游信号分子IκB降解，丝裂原蛋白激酶MAPK3/1(ERK1/2)和MAPK14(p38)快速磷酸化，核转录因子NF-κB移位，细胞因子IL1β、IL-6和趋化因子IL-8的mRNA和蛋白表达上调；当TLR4的表达受到阻抑时，IL1β、IL-6和IL-8的mRNA表达和蛋白分泌均降低[13]。此外，大肠杆菌的LPS还能促进子宫分泌前列腺素E_2 (PGE_2)而不是前列腺素$F_{2\alpha}$ ($PGF_{2\alpha}$)，致使血液PGE_2浓度上升(图1B)[14]，PGE_2浓度上升可抑制外周淋巴细胞的母细胞化，降低子宫免疫球蛋白浓度，影响子宫复旧，而$PGF_{2\alpha}$可促进嗜中性粒细胞到达子宫清除病原菌。

化脓隐秘杆菌和溶血性链球菌等革兰氏阳性菌可以通过其细胞壁上的肽聚糖等刺激TLR2受体激活NF-κB通路引起IL-8和IL-6的上升[15-16]，产生炎症。也有研究发现，这些革兰氏阳性菌因带有致病基因*plo*而表现出比大肠杆菌更严重的致病性[17]。基因*plo*主要编码依赖胆固醇的细胞毒素Pyolysin (PLO)，当PLO结合在细胞膜上可与胆固醇通过物理聚集的方式形成管孔，导致细胞渗透死亡[17]。体外培养牛子宫细胞发现，PLO可引起子宫上皮细胞和基质细胞死亡，由于子宫基质细胞胆固醇含量比上皮细胞高，使得子宫基质细胞比上皮细胞更易受到PLO的侵染而溶解[18]。研究还发现，PLO主要通过诱导MAPK通路中p38、ERK和JNK磷酸化以及引发细胞自噬发挥毒素作用[19]。

3 子宫疾病对卵巢和子宫功能的影响

产后子宫疾病可引起奶牛不发情、不排卵和黄体期延长[20]。Williams等[21]报道，当子宫化脓隐秘杆菌或大肠杆菌数量较高时，卵泡生长缓慢，血液雌二醇浓度较低，卵泡优势化不足，不排卵动物比例增高，即使排卵，排卵后5−7 d血浆中孕酮浓度也较低(<2 μg/L)[22-23]。通常健康奶牛卵泡液检测不到LPS，但临床发病奶牛卵泡液LPS高达0.8 mg/L，亚临床型病牛产后60 d卵泡液LPS仍能达到0.4 mg/L[23]。Bromfield等[24]体外培养人卵巢颗粒细胞发现，LPS能促进TLR4的表达，p38和ERK的磷酸化以及IL-6和IL-8的分泌(图1A)，当TLR4被抑制时，IL-6和IL-8分泌减少，卵丘-卵母细胞复合体扩张、卵母细胞减数分裂和生发泡裂解都受到影响，卵母细胞成熟率下降。体外培养牛颗粒细胞和内膜细胞发现，LPS不影响细胞存活，胆固醇转化为雄烯二酮，但下调卵泡芳香化酶基因表达，影响雄烯二酮转化为雌激素，降低雌激素分泌，影响卵泡生

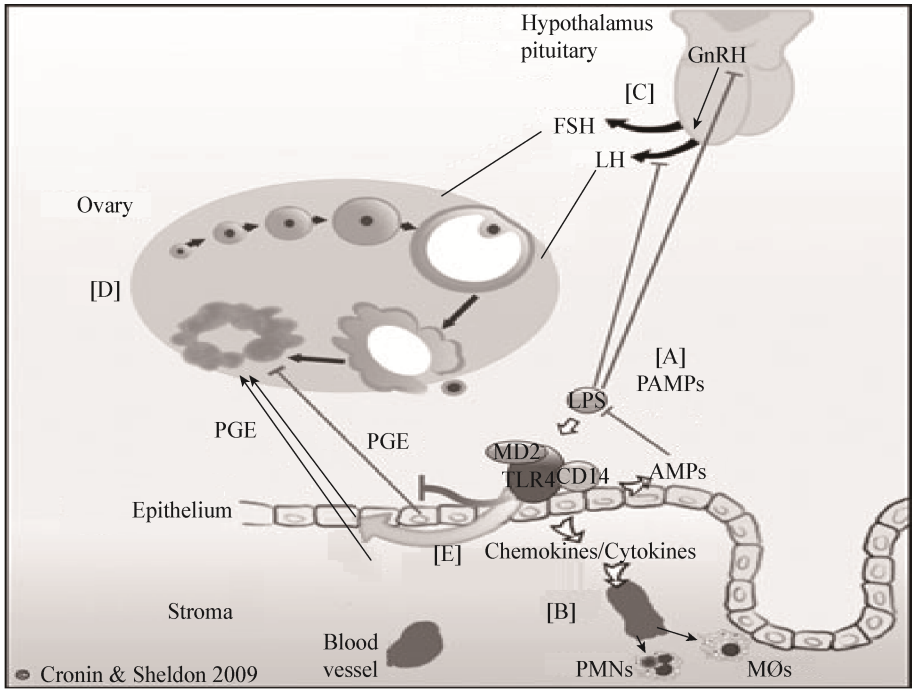

图1 子宫疾病影响繁殖性能的机理[32]

Figure 1 The mechanisms underlying infertility associated with uterine disease[32]

注：A：大肠杆菌和化脓隐秘杆菌引起的子宫内膜组织损伤，TLRs通过识别细菌PAMPs (LPS、脂肽或脂磷壁酸)引起子宫内膜细胞分泌细胞因子、趋化因子和抗菌肽(AMPs)；B：细胞因子和趋化因子介导的免疫反应. 趋化因子吸引中性粒细胞(PMNs)和巨噬细胞(MØs)到达炎症部位清除细菌；C：卵泡刺激素(FSH)不受子宫疾病影响，因此分娩后第一周仍出现卵泡波. 然而，LPS通过抑制促性腺激素释放激素(GnRH)和促黄体生成激素(LH)的合成与释放，抑制卵泡的优势化；D：子宫内膜炎动物卵泡液中含有LPS时，颗粒细胞表达TLR4复合物，优势卵泡芳香化酶的表达和雌二醇分泌减少，卵泡生长缓慢，排卵减少；E：子宫内膜炎奶牛即使排卵，但外周血孕激素浓度仍低于正常动物，且黄体期延长，与细胞因子抑制孕激素合成、促进子宫PGE_2分泌有关.

Note: A: Uterine infection with *Escherichia coli* and *Arcanobacterium pyogenes* causes endometrial tissue damage. The endometrial cells secrete cytokines, chemokines and antimicrobial peptides (AMPs) by Toll-like receptors (TLRs) detecting PAMPs; B: Cytokines and chemokines direct the immune response. Chemokines attract neutrophils (PMNs) and macrophages (MØs) to eliminate the bacteria; C: Follicle stimulating hormone (FSH) concentrations are unaffected by uterine disease and so waves of ovarian follicles emerge in the first weeks after parturition. However, the release of GnRH and luteinizing hormone (LH) can be suppressed by LPS-reducing the ability to ovulate a dominant follicle; D: Follicular fluid contains LPS in animals with endometritis, granulosa cells express the TLR4 complex required to detect LPS and LPS reduces oestradiol secretion from granulosa cells by reducing aromatase expression; E: If cows with endometritis ovulate, they form a corpus luteum but peripheral plasma concentrations of progesterone are lower than that in normal fertile animals and luteal phases are often extended. The reason is that bacteria switch the endometrial epithelial secretion of prostaglandins from the F to the E series.

长，减少排卵(图1D)[23]。子宫疾病对卵巢功能的影响可能也与LPS或免疫因子影响下丘脑-垂体功能有关，子宫灌注LPS的绵羊和奶牛，促性腺激素释放激素(GnRH)和促黄体生成激素(LH)分泌减少，抑制卵泡优势化(图1C)[25-26]。细胞因子IL-6和TNF-α可抑制雌激素和孕酮分泌[27]，对小卵泡的影响大于优势卵泡，增加了临床奶牛持久不孕发生的概率。

关于奶牛产后子宫疾病对子宫功能影响的研究较少。但有学者以小鼠为模型研究发现，子宫功能障碍可能与白血病抑制因子(LIF)[28]、同源框基因Hoxa10[29]等着床相关基因的异常表达有关，LIF和Hoxa10表达降低或不表达将导致胚胎着床失败。子宫疾病对奶牛子宫影响的研究主要集中在激素内分泌方面。Herath等[30]体外培养奶牛子宫组织块，培养液不含LPS时$PGE_2/PGF_{2\alpha}$值为0.45，添加LPS后$PGE_2/PGF_{2\alpha}$值上升至2.75。在奶牛，$PGF_{2\alpha}$主要溶解黄体，而PGE_2主要维持黄体[31]，PGE_2分泌增加使得黄体持久存在(图1E)，奶牛表现乏情。

4 小结与展望

综上所述，奶牛产后子宫发生感染是一种普遍现象，病原菌及其代谢产物不仅影响机体内分泌系统，还进一步影响子宫和卵巢的生物学功能，而先天免疫在阻止病原菌入侵、维持子宫内环境稳态方面显示出极为重要的作用。奶牛分娩后，通过注射催产素促进奶牛子宫的收缩，排出子宫内病理性内容物，减少子宫内细菌增生；或者注射前列腺素 2α 等促进黄体溶解，促进子宫清除感染；随着技术的发展，也可以利用 LPS、中性粒细胞提取物、微生态制剂等生物制剂干预，刺激机体活化自身免疫，尤其是先天免疫，清除病原菌；或者利用炎症信号通路阻断剂或某些衔接分子抑制剂阻止炎症发生，促进子宫收缩与复旧，达到预防或治疗子宫内膜炎的目的。此外，还需要更加深入地研究子宫感染后奶牛胚胎着床是否受阻及其机制，从而通过人为干预方式提高繁殖率，降低生产成本，提高动物福利。

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