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评 述 生殖健康专辑

女性代谢与生殖健康

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摘要 女性代谢与生殖健康关系紧密、互相调控. 女性的生殖活动特殊复杂, 代谢可通过多种机制在不同生命阶段调节生殖活动; 反之, 生殖活动的开展也会影响女性机体的代谢. 近年来, 女性代谢问题与生殖障碍日益突显, 深入了解女性代谢与生殖之间的相互作用, 揭示两者的内在调控关系, 对于理解和干预生殖代谢相关疾病至关重要. 本文主要围绕女性代谢与生殖健康, 从代谢对生殖的影响、生殖对代谢的影响以及生殖代谢常见疾病三方面进行综述, 旨在为进一步研究和生殖代谢疾病的干预提供有价值的参考.

关键词 生殖内分泌, 代谢, 下丘脑-垂体-卵巢轴, 妊娠, 子代健康

女性生殖健康与代谢密不可分, 二者相互协调、互相影响. 相较于男性而言, 女性群体拥有更为特殊的生殖功能, 包括周期性卵泡发育和排卵、妊娠、分娩和哺乳等, 女性生殖活动的正常开展需要机体代谢的支持, 代谢异常能够在全生命周期影响女性生殖功能, 甚至通过影响卵子发育和妊娠哺乳等过程影响子代健康[1,2]; 同时, 生殖功能的实现又会通过生殖相关激素、生殖过程等来协调代谢适应, 对女性的寿命和身心健康产生影响[3~5].

近年来随着物质生活水平的提高和生活方式转变, 女性面临着日趋加重的代谢问题与生殖障碍. 世界卫生组织指出自1980年以来, 全世界肥胖的发病率增加约两倍, 所有代谢疾病包括糖尿病、肥胖症、高脂血症、高血压、非酒精性脂肪性肝病等的患病率均显著上升[6], 发达国家中成年女性超重/肥胖的患病率近乎50%[7]. 与此同时, 生殖障碍性疾病的发病率也在逐年攀升: 自1990至2019年, 我国男性和女性不孕不育患病率均有上升[8], 不孕率已高达18%, 其中女性患病和疾病负担情况均高于男性. 例如, 我国多囊卵巢综合征(polycystic ovary syndrome, PCOS)患病率在过去十年内从5.6%上升至7.8%, 且表现出更加严重的肥胖、高雄和不孕症状, 患者人数已超2400万[9]. 代谢问题与生殖障碍的同向改变和严峻形式都在提醒人们: 女性代谢与生殖健康需要更多关注. 本文综述了女性代谢与生殖功能之间的关系及其内在分子机制, 并对几种典型的生殖代谢疾病进行了详细讨论, 旨在为女性生殖

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代谢障碍的干预提供理论基础.

1　代谢调控女性全生命周期的生殖活动

1.1　代谢调控女性生命早期原始卵泡池的形成

根据“健康与疾病的发育起源”理论(DOHaD Paradigm), 生命在发育过程早期(包括胎儿和婴幼儿时期)经历的不利因素, 会增加其成年后罹患慢性疾病的风险[10], 生殖系统也同样遵循这一规律[11,12]. 人类卵泡发生早在胚胎期就已启动, 原始生殖细胞经历减数第一次分裂后逐渐形成原始卵泡[13], 在出生后不久建立原始卵泡池[14]. 原始卵泡池形成历经生殖细胞巢破裂、部分卵母细胞凋亡、 前体颗粒细胞包绕这3个主要步骤, 是事关卵巢储备的关键环节, 女性一生中发育的所有卵泡均来自于此(图1). 原始卵泡不可再生, 上述任一过程的异常均会使得原始卵泡池形成受到影响, 继而影响女性的卵巢储备和生殖寿命.

生命早期代谢问题会通过影响原始卵泡池继而影响女性卵巢储备和生殖寿命. 荷兰大饥荒的队列研究发现, 出生前后的饥荒暴露均会引起女性绝经年龄提前, 出生后暴露尤为显著[15,16]; 动物实验证实, 营养不良会引起新生儿酮体缺乏, 不能有效抑制卵巢内活性氧(reactive oxygen species, ROS), 导致原始卵泡过度凋亡, 原始卵泡池受损, 生殖寿命缩短[17]. 出生后过度喂养同样会引起原始卵泡池受损, 过剩的营养素会通过瘦素依赖途径过度激活原始卵泡, 降低原始卵泡池储备, 引起卵巢衰老和生殖效率降低[18].

1.2　代谢调控女童的青春期启动

青春期是从儿童过渡到性成熟的重要阶段, 青春期启动预示着女性生殖功能开始成熟, 通常始于8~10岁, 历经乳房萌发、肾上腺功能初现、生长加速和月经初潮4个时期, 是内分泌、生殖、体格等逐渐发育成熟的过程, 最终获得生殖能力(图1).

下丘脑-垂体-卵巢轴(hypothalamic-pituitary-ovarian axis, HPO axis)的激活介导了青春期的启动. 下丘脑促性腺激素释放激素(gonadotropin-releasing hormone, GnRH)神经元由前期抑制状态转变为激活状态, 脉冲式分泌GnRH, 刺激垂体合成分泌卵泡刺激素(follicle-stimulating hormone, FSH)和黄体生成素(luteinizing hormone, LH), 促进卵泡发育、卵巢分泌性激素和第二性征出现[19].

代谢活动参与HPO轴的激活调控. 下丘脑GnRH神经元受到下丘脑KNDy(Kisspeptin/Neurokinin B/Dynorphin)神经元的激活调控[20], KNDy神经元能够分泌Kisspeptin, 主要位于下丘脑弓状核, 在该核团中还富集多种能量代谢神经元如AgRP-NPY(agouti-related protein/neuropeptide Y)、POMC(proopiomelanocortin)等神经元[21]. 机体代谢信号, 如瘦素和胰岛素能通过激活/抑制上述神经元, 进而激活相邻的KNDy神经元分泌Kisspeptin, 并通过其受体GPR45最终刺激GnRH神经元, 引起HPO轴的激活[22].

营养不良和营养过度引起的代谢问题均会影响青春期启动[23,24]. 已有临床数据证实, 身体质量指数(body mass index, BMI)与青春期启动年龄呈现反比例关系, 即青春期启动需要体重和脂肪储备达到一定阈值[25], 近30年来随着社会经济的发展和生活的富足, 国内外女性BMI增大, 月经初潮/青春期启动年龄明显减小[26], 青春期提前和性早熟的发生率显著升高, 对于孩子的身心发育造成不良影响, 还会增加青春期PCOS、成年后乳腺等雌激素敏感肿瘤的发生风险. 还有一部分女童因患慢性代谢性疾病如糖尿病、营养不良, 导致下丘脑-垂体功能障碍, HPO轴激活延迟或激活不足, 出现明显的青春期延后延长, 被归类为功能性低促性腺激素性性腺功能减退症[27].

1.3　代谢对生育期女性月经周期及妊娠的影响

女性性成熟期又称生育期, 指的是卵巢功能成熟并有周期性性激素分泌及排卵的时期, 月经周期性出现是该阶段重要标志; 在这一时期女性生殖功能最为旺盛, 能够完成受精和妊娠过程、生育子代, 而这些生殖活动均受到代谢的支持和调控(图1).

(1) 月经周期. 月经周期能够大致反映卵巢周期性排卵和子宫内膜周期性变化, 是评估卵巢功能和生育能力的便捷指标. 一个完整且规律的月经周期需要HPO轴及子宫内膜的协调变化才能得以完成: 月经周期始于下丘脑释放GnRH, 通过神经途径刺激垂体分泌促性腺激素; FSH进入血液循环后到达卵巢, 刺激卵泡发育和雌激素合成分泌; 雌激素一方面刺激子宫内膜增厚, 为受精卵提供适宜的着床环境, 另一方面高水平的雌激素还会诱发LH峰引起卵泡破裂, 使成熟的卵子从卵巢释放进入输卵管, 等待受精; 排卵后的卵泡

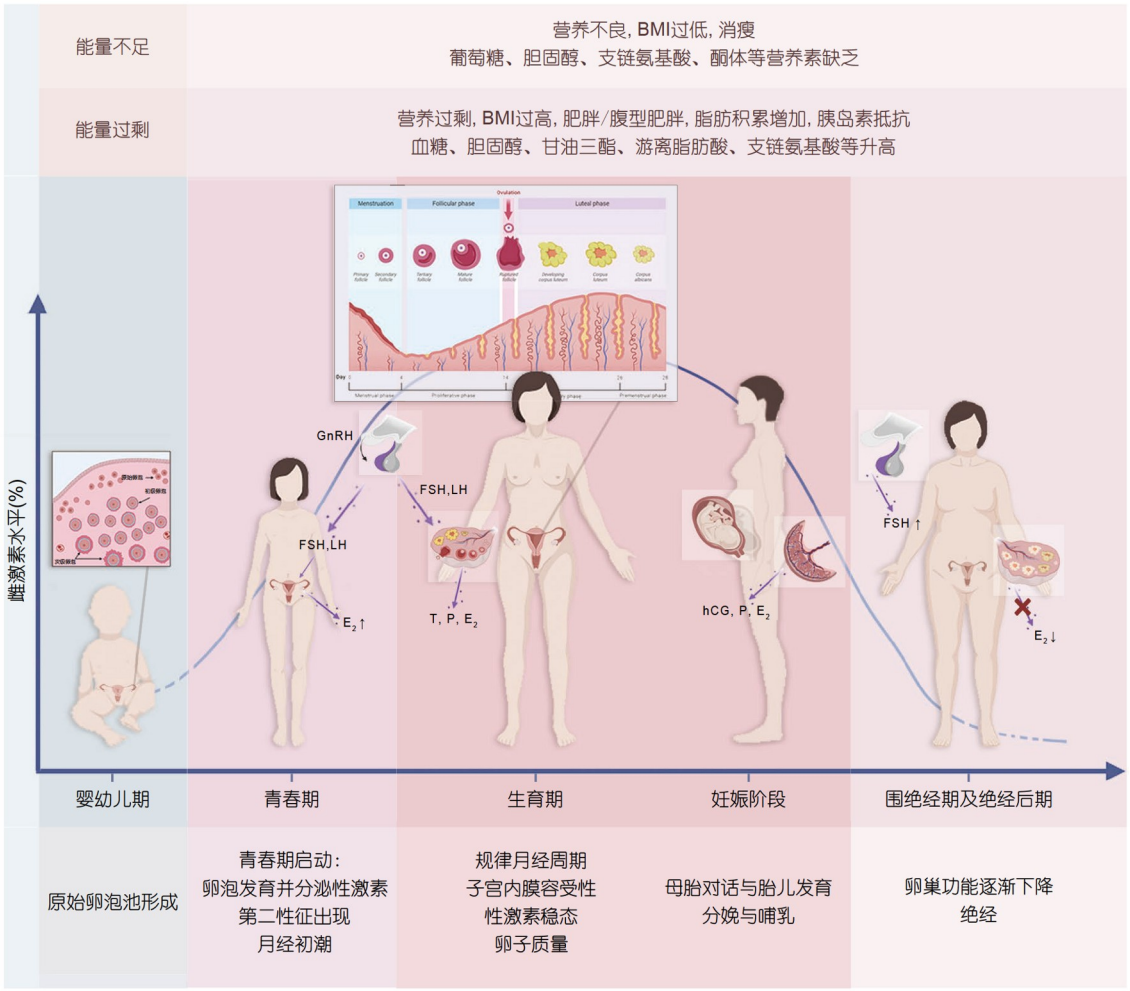

图 1 代谢影响女性全生命周期的生殖活动. 代谢风险因素对女性全生命周期不同阶段中生殖功能的影响. 本图由BioRender.com生成

Figure 1 Metabolism influences the reproductive activities throughout the entire lifespan of women. The impact of metabolic risk factors on reproductive function during different stages of a woman's lifespan. The figure was created with BioRender.com

转变为黄体, 开始产生孕激素, 在孕激素的作用下, 子宫内膜进一步增厚, 准备受精卵的着床; 如果没有受精, 黄体会逐渐萎缩, 孕激素水平下降, 导致子宫内膜脱落, 形成经血[28]. 月经的出现象征着上一个周期结束, 新一个月经期的开始. 机体的代谢能通过下丘脑-垂体-卵巢三个层面参与调控HPO轴和子宫内膜协调变化.

代谢调控下丘脑和垂体功能影响月经周期的起始. 与青春期阶段一致, 下丘脑能量代谢神经元接受并整合机体代谢信号传递给同区域KNDy神经元, 调控GnRH神经元释放GnRH[20,29], 给予卵巢周期最高等级信号调控. 有研究发现, 高胰岛素能够刺激垂体细胞释放促性腺激素, 而循环中游离脂肪酸增多和垂体周围脂肪沉积则会引起细胞脂毒性, 通过内质网应激等分子机制影响垂体功能, 降低循环中FSH和LH水平[30~32].

代谢调控卵巢中卵泡发育和排卵. 卵泡发育和排卵均需要大量能耗和代谢物[33], 卵泡细胞需要大量摄取能量物质, 如葡萄糖或脂肪酸用以实现卵泡发育和排卵, 同时还需要从循环中摄取胆固醇用以满足性激素的合成需要. 营养素缺乏的卵泡不能正常发育, 已有研究证实, 卵泡发育期间缺乏葡萄糖会明显降低卵泡颗粒细胞的增殖扩张, 导致卵泡成熟度不足[34]; 敲除小鼠*Ldlr*基因会降低卵巢中胆固醇含量, 引起小鼠

发情周期减少，且每个周期的发育期卵泡数目、雌激素水平和排卵数目明显下降[35]；缺少支链氨基酸会造成小鼠闭锁卵泡数目增加[36]．同样营养素过多也会对卵泡发育动力学和排卵形成不良影响．饮食及遗传因素引起的肥胖均可影响卵泡颗粒细胞FSH敏感性及类固醇激素转化功能，从而造成卵泡发育动力学改变[37]．例如，循环中葡萄糖过多会明显阻碍卵泡发育；游离脂肪酸增多会引起卵巢炎性反应增强、闭锁卵泡数目增加，发育中的卵泡也会出现颗粒细胞凋亡、颗粒细胞-黄体细胞转变障碍、雌孕激素合成降低等一系列问题[38]；支链氨基酸水平异常升高会引发育龄期雌鼠睾酮水平上升、发情周期紊乱、卵巢体积增大及卵泡发育异常[39]；胆固醇水平升高则会阻碍卵泡发育和抑制排卵，降低生育力，这已经在胆固醇关键分子ABCA1A和SR-BI敲除小鼠中得到证实，也更加强调了胆固醇平衡在卵巢中的重要性[40~42]．此外，许多循环代谢因子例如胰岛素样生长因子-1(insulin-like growth factor 1, IGF-1)、瘦素、胰岛素、脂联素等可以直接结合卵泡细胞中相应受体，通过下游信号通路直接参与卵泡发育[43,44]．

代谢调控子宫内膜的周期性改变和容受性．在女性的每个月经周期中，与卵巢周期同步，子宫内膜周而复始地为胚胎着床做准备：卵巢产生的雌孕激素与内膜紧密协同，引导子宫内膜在月经周期中从增殖期向分泌期的有序转变，逐渐建立适合胚胎植入的容受性．子宫内膜容受性建立过程需要大量能量代谢以适应内膜形态改变、调节内膜环境与功能，为胚胎植入做准备[45,46]．然而，能量代谢紊乱会造成子宫内膜容受性下降．实验发现，高血糖暴露的糖尿病小鼠子宫内膜容受性明显降低，子宫内膜的血流量明显受到抑制，给予胰岛素降低血糖后子宫内膜状况有所恢复[47~49]；通过饲喂高脂饮食诱导的肥胖小鼠血脂和血胰岛素明显升高，这导致其子宫内膜功能障碍和容受性下降，胚胎植入点显著减少[50~52]．

机体作为一个整体，异常的代谢可能会通过作用于HPO轴和子宫内膜的某个或多个环节来调控周期性排卵，并最终在月经周期这一临床最易观察的指标上体现．临床研究发现，女性机体需要一个合适的BMI水平来支持月经周期，BMI过高或者过低均会引起月经周期的异常[53]：肥胖女性月经周期紊乱的发生率比正常者高3倍，经期普遍超过36天[54]；而当机体处于负能量状态，例如在过度减重、营养不良、神经性厌食等人群中，发生月经周期延长、月经量减少甚至闭经的比例显著升高[55]．

(2) 性激素稳态．女性性成熟后，体内主要的性激素包括雌激素、孕激素和雄激素三类．雌激素包括雌酮、雌二醇和雌三醇，以雌二醇活性最高，雄激素包括睾酮和少部分的双氢睾酮．在育龄期女性体内，三种性激素呈动态平衡，有助于第二性征的维持和生殖功能的正常发挥．

性激素的稳态依赖于激素合成、作用和灭活三个过程之间的互相协调．性激素合成的前体物质为胆固醇，需要多种酶参与催化反应；女性体内雄激素合成的主要位置包括肾上腺髓质及卵泡膜细胞，雌激素的主要合成器官或组织是卵巢，其次是脂肪，孕激素则主要在非孕期妇女卵巢黄体细胞中合成．性激素在循环中以游离态和结合态两种方式存在，当与性激素结合球蛋白(sex hormone-binding globulin, SHBG)呈结合状态时[56]，不能发挥激素生物活性[57]；女性体内SHBG主要由肝脏合成，负责转运性激素及调节性激素作用活性．性激素在靶器官发挥作用后，主要在肝脏中灭活，例如，雌激素在肝内与葡萄糖醛酸结合失去活性，雄激素在肝内与硫酸结合失去活性．

代谢通过影响性激素的合成、作用及灭活参与调控性激素稳态．性激素的合成受到能量代谢信号调控和胆固醇原料的制约，机体处于负能量状态的女性表现出循环胆固醇减少和性激素水平降低[58]．过度的代谢信号也会影响激素合成，例如，高胰岛素会增强垂体LH释放、促进卵泡膜细胞合成雄激素，高浓度的胰岛素还会在促进IGF-1生成的同时抑制肝脏IGF结合球蛋白合成，增强IGF-1在卵巢的生物利用度，进一步增强卵泡膜细胞合成雄激素；脂肪组织具有一定合成雌激素功能，脂肪的积聚会明显上调女性体内雌激素水平．雌雄激素生物活性的发挥受到SHBG水平的调控，高胰岛素/胰岛素抵抗人群中肝脏SHBG的合成减少，具有生物活性的游离激素增加，而SHBG主要与睾酮结合，与睾酮的亲和力是雌激素的3倍，因此该人群中高雄的体征更为明显，运动减重或热量限制等措施可以提高胰岛素敏感性进而促进SHBG合成，纠正性激素稳态[59]．由于肝脏在性激素灭活中的不可替代作用，严重的代谢性肝病，如非酒精性脂肪肝病(non-alcoholic fatty liver disease, NAFLD)、非酒精性脂肪肝

炎等患者易出现高雌激素体征.

(3) 卵子质量和胚胎发育潜能. 卵母细胞提供了胚胎发育初期所需的、包括线粒体在内的几乎所有细胞组分, 因而对于妊娠的成功与否起着关键作用. 高质量的卵母细胞通常具有更高的胚胎发育和着床潜力, 能够增加妊娠概率.

卵母细胞正常发育具有特殊的代谢特征, 需要能量和多种代谢物的支持. 有研究表明, 卵母细胞在成熟过程中至少需要2 pmol的腺苷三磷酸(adenosine triphosphate, ATP)以维持正常生理活动[60], 且能量需求在之后的受精和胚胎发育事件中不断递增[27]. 由于卵母细胞缺乏一些代谢关键酶, 其成熟所消耗的部分能量代谢底物来源于卵丘颗粒细胞, 两者通过缝隙连接实现代谢物的胞间传递, 从而满足卵子发育过程中的能量和代谢需求[61]. 卵母细胞通常以糖脂代谢供能为主, 通过利用卵丘颗粒细胞供给的丙酮酸、乳酸和脂肪酸等实现氧化供能, 体外卵母细胞成熟过程中丙酮酸更是不可或缺的营养物质. 近期几项研究还发现, 颗粒细胞中柠檬酸和甲羟戊酸等代谢物减少会明显降低卵子质量, 增加卵子减数分裂缺陷和非整倍体的形成[62,63]; 此外, 谷氨酰胺也被认为是支持卵母细胞发育的有效能量底物[64].

过量的营养和代谢物会降低卵母细胞质量和胚胎发育潜能. 高血糖会引起小鼠卵母细胞的游离葡萄糖水平升高[65], 卵母细胞线粒体的结构和空间改变, 并伴有卵母细胞中的ATP和三羧酸循环代谢物(包括柠檬酸、苹果酸和天冬氨酸)水平降低等代谢异常[66,67]. 不仅如此, 糖尿病小鼠的卵母细胞在减数分裂中表现出更高频率的纺锤体缺陷和染色体错位, 导致排卵后卵母细胞的非整倍体率增加[66~69]. 临床患者和动物实验均证明, 暴露于高血糖的卵子在受精后胚胎发育潜能下降, 囊胚形成率明显降低[70,71]. 高血脂患者及小鼠也面临同样的卵子质量下降问题[72~74]: 高脂饮食的肥胖小鼠排卵前卵母细胞内的脂质水平明显高于正常饮食小鼠[75], 且细胞中ROS生成增加[76]; 饲喂富含长链n-3多不饱和脂肪酸(polyunsaturated fatty acids, PUFA)的饲料会导致小鼠卵母细胞线粒体功能障碍和ROS水平升高, 从而降低受精和囊胚形成能力[76]. 这些数据表明, 女性营养过剩可能不利于卵母细胞的线粒体状态, 会破坏卵母细胞代谢, 同时对减数分裂和纺锤体形成产生不良影响, 明显降低卵母细胞质量.

代谢对卵母细胞表观遗传的重编程可能会引起异常表型的代际/跨代遗传. 卵母细胞中携带的表观遗传信息受机体代谢的影响会发生改变, 其中一部分能够抵抗受精后表观遗传信息擦除和重建, 将卵子中获得的异常表观修饰保留至子代体细胞甚至是子代配子中, 造成后代发育异常[77,78]. 小鼠实验已经证实, 肥胖雌鼠的卵母细胞可以介导肥胖相关代谢损伤的跨代遗传[79]; 高血糖暴露的雌鼠卵子中去甲基化酶TET3表达缺陷, 胚胎中与胰岛素分泌相关基因呈现高甲基化直至小鼠成年, 期间这些基因的表达不足导致子代胰岛素分泌缺陷, 增加糖尿病易感性[80].

(4) 妊娠与分娩. 胚胎着床后, 需要在母体内生长至38周才能健康分娩, 在这期间, 母胎之间时刻存在着信息和代谢交流, 母体为胚胎/胎儿发育提供所需的全部营养. 由子宫内膜与胚胎滋养外胚层互作形成的胎盘进一步提高了母胎交流的效率. 母体异常代谢会通过母胎对话影响胎儿发育, 并增加妊娠并发症的风险.

母体-胎盘-胎儿间高效的代谢交流支持妊娠的完成[81]. 母体的营养物质经胎盘转运至胎儿, 供给其生长发育: 人类胎儿自身葡萄糖生产效率极低, 几乎完全依赖胎盘供应的母体葡萄糖, 胎儿的血糖水平比母亲低15%~20%, 因此总的葡萄糖流量受母体-胎儿葡萄糖浓度梯度和血流驱动, 几乎不受胎盘形态的影响[82,83]. 脂肪酸是胎儿脂肪增长的关键脂质, 大约一半的胎儿体内脂肪来自母体, 不同脂质通过胎盘的方法不同, 对于大多数脂肪酸来说, 存在母体-胎儿浓度梯度, 游离脂肪酸通过简单扩散穿过胎盘, 然而, 复杂的脂质类型如甘油三酯、磷脂等需要在胎盘中经过酶的水解才能通过[82].

母体代谢异常介导妊娠并发症和胎儿发育异常. 正常妊娠过程中, 母体通常需要体重增加和一定的代谢适应: 经统计测算不同人种怀孕的平均总能量成本约为55000千卡[84], 期间母体还表现出高胰岛素血症、胰岛素抵抗、血浆脂质增加和更有效的血浆氨基酸转运等代谢适应性变化以支持妊娠[83,85]. 母体妊娠期间能量摄入不足、代谢适应性变化不足、蛋白摄入不足等情况均会引起胎儿生长受限及出生后追赶生长[86,87]. 孕前或者孕期营养过度也会对妊娠造成不良影响: 研究证实, 孕前BMI、孕期BMI及孕期体重增量过大与多种妊娠并发症有关, 能显著增加妊娠糖尿病、妊娠高血压的发病风险[88]; 妊娠初期

高血糖暴露会降低胚胎发育潜能、增加胎儿发育异常概率，妊娠后期高血糖暴露会引起经胎盘转运至胎儿的葡萄糖明显增多，胎儿血糖升高引起胰岛素分泌过多，巨大儿风险增加[41,89]；妊娠初期母体高甘油三酯血症与高胰岛素作用与胎儿β细胞功能受损密切相关[90]，妊娠后期母体血浆中的甘油三酯和非酯化脂肪酸与胎儿的脂质、胎儿生长和脂肪量均明显相关[91,92].

1.4　代谢对女性围绝经期及绝经后期影响

绝经期是女性生殖周期的最后一个阶段，它标志着生殖寿命和卵泡活动的结束，随着人们平均寿命的延长，目前绝经期已经占据女性人生近乎三分之一时长. 绝经后卵巢的卵泡减少，雌二醇和抑制素B产生下降，排卵和月经不再发生；由于卵巢对FSH和LH敏感性的丧失，GnRH，FSH和LH的产生和释放增加. 绝经期的到来并不是一蹴而就，从卵巢功能开始衰退直至绝经后一年内的时期，称之为围绝经期，这期间由于卵巢功能渐进式下降，雌激素水平波动不稳定，可能导致下丘脑-垂体-卵巢轴的失衡(图1).

目前糖脂代谢对绝经年龄的影响并无统一定论. 多项临床研究发现，一型糖尿病(type 1 diabetes mellitus，T1DM)女性比正常女性绝经的年龄更早，20岁前发生T1DM与早绝经有相关关系；但同时也有多项人群队列研究分析无论何时发病，T1DM人群绝经年龄与普通人群并无差别. 二型糖尿病(type 2 diabetes mellitus, T2DM)患者中情况类似, 部分研究发现, T2DM人群绝经年龄提前, 但也有很多研究并不支持该观点[93]. 有关肥胖是否影响女性绝经年龄的研究中，目前也尚未有足够证据证明肥胖人群的绝经年龄较正常人群有一致性改变[94].

代谢影响女性围绝经期症状和绝经后健康. 虽然肥胖对于绝经年龄的影响尚无定论，但是已有足够证据证明，过度肥胖是影响围绝经期妇女生活质量的主要因素：肥胖女性通常面临更长的围绝经期和更高的血管舒缩症状患病率，这与机体过高的血糖血脂对HPO轴的破坏有关，而脂肪组织产生的促炎性环境对中枢神经系统的体温调节活动也有着负面影响[94]. 绝经后女性孕激素水平极低，在此阶段肥胖带来的高雌激素持续作用于靶器官而无孕激素拮抗，发生乳腺癌和子宫内膜癌的风险都明显升高[95].

2　生殖激素和生殖活动影响代谢

2.1　性激素/促性腺激素调控代谢

生殖相关激素不仅在性腺发育及生殖功能调节方面发挥着重要的生理作用，还作为机体不可或缺的内分泌激素广泛作用于全身靶器官，参与众多生理功能的调节. 青春期后，生殖相关激素活动是继遗传学因素后引起雌雄两性差异的最主要因素[96]，尤其在代谢功能调节过程中，女性生殖相关激素对多器官代谢功能产生影响, 并贯穿全生命周期.

(1) 雌激素对女性代谢影响. 雌激素在维护女性身体的新陈代谢和能量代谢中起着极其重要的作用, 可以增加机体对营养物质利用, 从而增强代谢功能. 循环中的雌激素主要通过其受体(estrogen receptor，ER)发挥功能，ER包括核受体(ERα和ERβ)及膜受体，分别具有不同的组织分布特征及功能，赋予了雌激素在不同靶器官中特殊的能量代谢调节角色[97].

雌激素作用于中枢神经系统下丘脑，发挥控制食物摄入，促进能量消耗及体重平衡等多种功能[98]. 啮齿类动物下丘脑的腹内侧核、弓状核、内侧视前区和室旁核中均有大量的ER表达[99]. 不同下丘脑神经元的ER缺失会对机体能量代谢产生多种效应：在下丘脑大部分脑区中进行ER敲除会通过增加摄食、减少活动、降低能量代谢引起雌性小鼠腹型肥胖；类固醇生成因子1(steroidogenic factor, SF-1)神经元中的ER缺失则仅造成能量代谢水平降低和肥胖，并不影响其摄食功能；与之相反，POMC神经元中的ERα缺乏会直接导致暴饮暴食, 但不直接影响能量消耗或脂肪分布; 同时从SF-1和POMC神经元中删除ERα会引起能量代谢减低、暴饮暴食和内脏脂肪积累[100]. 此外，雌激素还通过增加POMC神经元内瘦素敏感性来调节能量稳态，从而发挥瘦素样厌食作用抵抗肥胖[101,102].

外周组织中，雌激素通过不同受体参与糖脂代谢功能的调控. 雌激素可以保护胰岛β细胞、促进胰岛素合成[103]，并提高葡萄糖刺激下的胰岛素分泌能力[104,105]；在肝脏、骨骼肌、脂肪等胰岛素敏感组织中，雌激素和ER可以通过不同方式促进外周胰岛素敏感性[104,106,107]. 临床研究和动物实验均证实，ERα和ERβ是胰岛素敏感组织中葡萄糖转运蛋白GLUT4的正调控因子, 能够促进葡萄糖的组织摄取, 雌激素降低或者ER缺失会直接造成胰岛素抵抗的发生[108~110]. 雌激

素在糖代谢过程中总体上发挥着增加胰岛素敏感性, 减少糖异生, 增加肝糖原合成和储存, 降低循环葡萄糖水平的作用[107,111,112]. 而在脂代谢方面, 雌激素可以影响脂肪分布, 减少游离脂肪酸的摄取和新生脂肪的形成[112], 并通过影响各种载脂蛋白功能促进脂质氧化及分解[113]: 高水平的雌激素与女性皮下脂肪尤其是臀部及大腿的脂肪存储相关[114], 绝经期后女性内脏脂肪积累也与雌激素水平下降直接相关[115]; 脂肪组织中, ERα通过调控线粒体DNA聚合酶γ亚基Polg1的表达来调节线粒体功能, 从而促进代谢和脂肪分解[116]; 雌激素还能抑制异位脂质蓄积, 减少肝脏、肌肉等组织中的脂肪酸摄取, 促进脂质氧化[117~119]. 此外, 雌激素对胆固醇代谢也起着重要的调节作用[120], 临床研究发现, 雌激素可以降低血液中的低密度脂蛋白胆固醇水平, 增加高密度脂蛋白胆固醇水平[121].

(2) 雄激素对女性代谢影响. 雄激素在代谢调节过程中展现出显著的性别差异, 不同于在男性体内的代谢保护作用, 女性体内高水平的雄激素会直接促进代谢综合征的发生[122~124]. 育龄期女性体内, 雄激素主要来源于卵巢和肾上腺, 主要通过与雄激素受体(androgen receptor, AR)结合发挥功能, 女性脂肪、肝、骨骼肌和大脑等组织中都有AR分布[125].

雄激素具有强烈的促同化作用, 可以促进摄食、能量吸收和储存. 研究证实, 哺乳动物早期发育过程中雄激素暴露可通过AR作用于下丘脑POMC神经元, 抑制雌性小鼠BAT产热、降低能量消耗[126]. 雄激素参与腹部内脏脂肪积累, 高雄激素水平将造成女性向心性肥胖的发生. 临床研究发现, 在慢性雄激素过量的女性中, 血浆睾酮水平与腰围呈正相关[127]. 过量雄激素可以引起雌性白色脂肪组织重塑, 脂肪细胞肥大及局部脂代谢紊乱, 进而造成脂肪在肝脏等组织的异位积累[128,129]. 已有临床研究证实, 高雄是造成女性NAFLD发生的独立危险因素[130], 啮齿类动物模型的研究中也发现, 产前雄激素暴露可以通过影响过氧化物酶体增殖物激活受体PPARα和PPARγ改变雌性子代肝脏脂质代谢功能[131].

雄激素也与女性胰岛素抵抗和T2DM风险升高强烈相关[132~137]. 患有高雄激素血症的女性基础胰岛素分泌率显著升高, 餐后胰岛素分泌反应减弱[138]. 游离睾酮增多直接引起女性胰岛β细胞功能障碍[139], 过量雄激素引起的AR过度激活可造成雌性小鼠全身氧化应激水平增加、β细胞过度分泌进而衰竭[140]. 高雄激素与高胰岛素相互促进, 共同造成女性外周组织中(包括肝脏、骨骼肌、脂肪等)胰岛素抵抗的发生[125,135,141,142].

(3) 卵泡刺激素FSH对女性代谢影响. FSH由垂体分泌, 通过G蛋白偶联受体FSHR发挥生物功能, 主要作用是促进卵泡成熟、刺激雌激素的合成与分泌[143]. 近年来关于FSH的认识不仅仅局限于生殖功能的调节, 研究发现, 多种性腺外组织, 如脂肪组织、肝脏、骨组织等中均有FSHR的表达, 并在相关疾病发病中发挥一定作用[144~147]. 在女性围绝经期, 体内FSH的水平随着卵巢功能衰竭而升高, 雌激素水平降低及FSH水平升高共同参与了女性绝经相关代谢性疾病的发生[148~150]. 多中心多种族队列研究显示, FSH与女性绝经期间骨质疏松直接相关, 绝经期女性骨转换标志物和骨密度的变化与与FSH水平的变化呈负相关[151]. 脂肪组织中, FSH通过FSHR作用引起成脂基因表达上调、诱导脂质生物合成[144], 阻断FSH作用可以诱导棕色脂肪组织产热并减少脂质积累[152]. 此外, FSH可以通过调控肝脏胆固醇合成增加血清胆固醇水平[153], 抑制低密度脂蛋白受体基因*Ldlr*的表达, 从而导致血清低密度脂蛋白胆固醇水平的升高[154]. 在糖代谢过程中, FSH还能通过AMPK-GRK2增强肝脏糖异生功能[146]. 最新研究发现, 人和小鼠胰岛β细胞中同样表达FSHR, 且对不同浓度的FSH反应性不同: 低浓度FSH(<10 IU/L)可以促进葡萄糖刺激下的胰岛素分泌, 参与糖稳态调控; 而当机体FSH水平异常升高(如临床围绝经及绝经女性), 则会直接引起胰岛素分泌不足及糖耐量损伤, 代谢综合征风险进一步升高[155].

(4) 催乳素对女性代谢影响. 催乳素(prolactin, PRL)是一种由垂体前叶分泌的蛋白质激素, 因其在哺乳期促进乳汁分泌中的作用而得名, 其受体(PRLRs)存在于大多数组织和细胞类型中, 因此也发挥多种生物学作用, 如生长发育、免疫功能、大脑和行为、血管生成、内分泌和代谢等[156]. 妊娠期间, 女性循环催乳素水平显著增加, 能够促进下丘脑发生瘦素抵抗、刺激食物摄入及体重增加, 与妊娠期间其他代谢改变, 如胰岛素抵抗等相协调, 以促进后代发育和生存的营养吸收[157~159]. 大量基础与临床研究均认为, PRL参与机体代谢稳态调节, 并在下丘脑、胰岛β细胞、脂肪及肝脏等组织中发挥代谢保护作用, 促进各组织胰岛素

敏感性, 调节脂质存储与代谢过程, 并抑制肥胖相关的代谢紊乱的发生[160~165]. 队列研究证实, 低PRL水平与代谢性疾病相关, 是T2DM的危险因素[166]. 然而在某些病理状态下(如催乳素瘤等), PRL水平升高至200 μg/L以上, 将对代谢功能造成严重的不利影响, 如食欲亢进、体重和脂肪量升高、肝脂肪变性、葡萄糖耐受不良和胰岛素抵抗[167~169].

2.2　生殖活动影响代谢

青春期是女性生命周期中的第一个关键时期, 青春期的启动标志着生长发育和生殖功能的开启. 这一时期, 快速生长发育的需求及激素水平的改变也会使得女性代谢率显著上升, 食欲增加[170]. 月经初潮后, 性激素水平显著上升对女性的骨骼、肌肉和脂肪等的发育至关重要. 青春期是女性骨峰值质量形成的关键时期, 雌激素在骨骼的形成和保持中起到重要作用[171]. 同时, 由于雌激素水平的显著升高, 女性脂肪分布发生显著改变, 皮下脂肪积累增加, 并集中于乳房、臀部和大腿等部位, 这些脂肪储备对随后的女性健康及生殖功能维持至关重要[114].

妊娠期是女性生命周期中最为特殊的阶段, 涉及到许多生理功能的大幅改变. 这一时期女性体内的激素水平发生显著的变化, 以适应胎儿的生长和发育[172]. 首先, 由于胎儿的生长发育需要额外的能量和营养, 女性在妊娠过程中的代谢率也会随之增加, 进食量及脂肪储备增加[173]. 妊娠早期, 母体雌孕激素增加引起血糖下降伴随胰岛素敏感性增强; 而在妊娠中晚期, 随着胎盘内分泌功能上升, 分泌胎盘催乳素、皮质醇和胎盘胰岛素酶等因子拮抗胰岛素功能, 引起明显的胰岛素抵抗, 这一时期母体的胰岛素敏感性、β细胞功能及肝脏糖异生功能的协调变化, 可以促进葡萄糖和营养物质向胎儿分流[174]. 多数妊娠期女性可以适应这一生理变化, 但胰岛素分泌受限的孕妇, 由于机体无法代偿引起血糖升高, 发生妊娠期糖尿病(gestational diabetes mellitus, GDM)[89]. 生产后的哺乳期, 女性体内的激素水平和代谢功能继续调整, 催产素与催乳素分泌增加, 以支持乳腺的产生和分泌乳汁. 同时, 代谢率的增加也提供了额外的能量来满足母亲的营养需求和乳汁的产生[175].

女性卵泡发育和排卵在进入围绝经期后缓慢下降直至结束, 在这个过程中, 女性的卵巢功能开始逐渐减退, 雌、孕激素水平骤然下降, 刺激中枢FSH水平显著上调, 而雄激素下降速度较慢, 这些激素变化导致了一系列围绝经期症状[93,149]. 大量临床研究表明, 围绝经期与女性代谢性疾病风险升高密切相关[176~179]. 雌激素缺乏导致骨钙大量丢失, 因此绝经后女性是骨质疏松的高危人群[180]. 此外, 女性糖脂代谢异常也往往发生在绝经之后[148]. 雌激素及其他生殖激素参与调节葡萄糖和脂质代谢的各个方面, 围绝经期这些代谢信号的紊乱导脂质谱变化、动脉硬化、体重增加(腹部脂肪量增加和瘦体重减少)、胰岛素抵抗增加, 患代谢综合征、糖尿病以及动脉粥样硬化的风险增加[181]. 研究发现, 围绝经期女性激素替代治疗可以在缓解绝经相关症状的同时预防慢性代谢性疾病发生[182], 但在激素补充同时还应注意子宫内膜癌、乳腺癌等恶性肿瘤发病风险[183,184].

总的来说, 女性生殖活动的起始、发展和衰减均会对女性的代谢产生重要影响. 从青春期开始到绝经期前后, 女性激素水平的变化会引起机体代谢的调整, 以适应不同生殖阶段的生理需求, 理解这些变化有助于人们更好地认识女性不同时期的健康风险, 并加以干预, 促进生殖及代谢健康.

3　经典生殖代谢互作疾病

3.1　肥胖症和代谢综合征

超重和肥胖目前已经被世界卫生组织定义为一种慢性疾病, 身体脂肪增多常带来血糖升高、甘油三酯升高、高密度脂蛋白胆固醇降低、血压升高等健康问题, 根据国际糖尿病联盟诊断标准, 肥胖合并以上两项或更多改变, 可诊断为代谢综合征. 正如开篇所述, 肥胖在全球的发病率逐年上升, 对女性生殖健康影响逐渐加重[185].

肥胖和代谢综合征女性通常伴有不同程度的生殖功能紊乱: 超重/肥胖的青春期女孩多表现为青春期提前, 月经初潮年龄小, 这是青春期PCOS的风险因素[186]; 育龄期女性肥胖则会促使机体处于持续高雌激素、胰岛素抵抗及慢性炎症状态, 对整个HPO轴均有损伤, 干扰正常的卵巢激素分泌和排卵, 临床多表现为月经周期延长、异常子宫出血、甚至闭经, 因此这部分女性通常面临着不孕问题, 对辅助生殖技术的需求增大, 但即使部分女性通过人工辅助生殖技术(as-

sisted reproductive technology, ART)助孕, 也因为卵子质量差、胚胎发育潜能低、子宫内膜容受性下降[187,188]等问题, 导致更高的妊娠丢失率和更差的助孕结局; 妊娠期间肥胖女性发生妊娠糖尿病和妊娠高血压等妊娠并发症的概率也一并增加, 由于母胎代谢互作的异常, 巨大儿比例和剖宫产需求均升高, 子代也常因为来自卵胚的表观异常修饰和不良的宫腔内暴露表现为肥胖和代谢损伤[189]; 肥胖女性还通常面临着更为严重和持久的围绝经期综合征、子宫内膜癌症和乳腺癌的发病风险也明显增加.

3.2 多囊卵巢综合征

PCOS自1935年首次报道至今, 是女性无排卵性不孕的主要原因, 也是最典型的生殖代谢互作疾病, 根据2003年鹿特丹诊断标准, 符合月经稀发、高雄激素和卵巢多囊样改变中两条即可诊断[190]. 目前育龄期女性PCOS的患病率高达10%~13%, 且有不断增高趋势[191]. PCOS患者不仅仅表现出生殖损害, 同时高度合并肥胖、胰岛素抵抗和代谢综合征等[192,193].

肥胖、高胰岛素和高雄激素三者互相促进、循环加重是PCOS发病的核心(图2). PCOS的起病目前尚不明确, 但孟德尔随机化分析发现, 肥胖、胰岛素抵抗和雄激素均为PCOS的致病因素[194], 动物实验也证实, 以上任一因素的单独暴露均可以引起大小鼠PCOS样表型[195,196], 从而进一步明确了PCOS生殖代谢互作疾病的本质. PCOS体内高雄激素会促进内脏脂肪的蓄积和胰岛素高分泌, 促进腹型肥胖、高胰岛素血症和胰岛素抵抗的发生; 肥胖的患者由于脂肪增多、游离脂肪酸升高, 进一步促进胰岛素的分泌并降低胰岛素敏感性; 胰岛素升高能够刺激卵泡膜细胞分泌更多的雄激素, 降低肝脏中SHBG的合成, 增强循环中雄激素的水平和活性, 进一步加剧肥胖和胰岛素抵抗[197]. 在这样的恶性循环机制下, PCOS患者表现出卵泡发育异常、月经和排卵稀发等生殖问题, 并且容易合并T2DM, 非酒精性脂肪肝病等代谢问题[191].

PCOS患者的卵子质量、子宫内膜容受性、妊娠过程和子代健康均受到PCOS特殊生殖内分泌代谢状况的影响[187,188,197~199]. 在ART助孕过程中, PCOS卵子往往有更低的受精率和优质胚胎率, 移植后的胚胎着床率、临床妊娠率也偏低而流产率升高[200]; 此外, PCOS是妊娠糖尿病和高血压的独立危险因素[201], 妊娠并发症合并宫内高雄激素、高抗苗勒管激素(anti-Müllerian hormone, AMH)等异常暴露, 对胎儿的发育有着不良编程效应: PCOS的子代患生殖、代谢和心理疾病的风险更高[202,203], 女儿被诊断出PCOS的可能性是正常人群的5倍[204]. 小鼠实验则发现, 宫内雄激素或AMH暴露可以将PCOS样生殖和代谢特征会传递给第三代雌性小鼠后代, 实现PCOS跨代遗传[204,205].

PCOS面临着更严重的绝经期代谢问题, 但卵巢储备较同龄女性更好. 随着年龄的增长, PCOS女性生殖表型例如雄激素水平会有所改善, 但是代谢问题更加严重[206], 患T2DM的风险明显升高[207]; 而因为育龄期排卵稀发, PCOS妇女的卵巢储备较同龄健康女性要好, 预期绝经年龄延后, 生殖寿命延长[208].

3.3 糖尿病

糖尿病患者最显著的特征是血循环中葡萄糖水平的升高, 伴或不伴胰岛素抵抗. 虽然以代谢功能异常起病, 但糖尿病患者往往伴随着明显的生殖功能损伤, 并且具体生殖功能的损害程度和类型根据糖尿病分型而有所不同.

T1DM患者胰岛素注射前后有不同的生殖表现. T1DM是由于胰岛β细胞破坏、胰岛素分泌缺乏所致, 特征是胰岛功能差, 终身需要依赖胰岛素治疗. 一型糖尿病患者通常发病较早, 发病年龄高峰在10~14岁[209], 因而对女性生殖的影响往往是从青春期开始. 由于胰岛素分泌不足, T1DM女孩出现生长和青春期发育迟缓, 皮下脂肪含量少, 月经初潮年龄推迟, 下丘脑和垂体分泌的GnRH, FSH及LH水平降低, 卵巢呈幼稚型[210,211]; 在应用胰岛素治疗后, 患者代谢器官及HPO轴的胰岛素信号均明显激活, 脂肪合成明显增多, 下丘脑和垂体分泌恢复, 发育中的卵泡明显增多, 一部分女性会出现雄激素升高、卵巢多囊样改变, 甚至在成年后发展为PCOS[212,213].

T2DM患者的生殖损伤与肥胖及PCOS患者类似. T2DM是糖尿病患者中最主要的群体, 其主要发病原因是胰岛素抵抗及胰岛素分泌相对不足, 通常发病年龄较大、体型偏胖并伴有代谢紊乱. 近年来T2DM的发病年龄逐渐年轻化, 因而生殖功能的损害越来越受到重视[209]. T2DM的发病机制与肥胖和PCOS有很强的一致性, 临床上T2DM女性合并PCOS的概率达21%, 合并肥胖的比例更是高达67%, 其生殖损伤与肥胖及

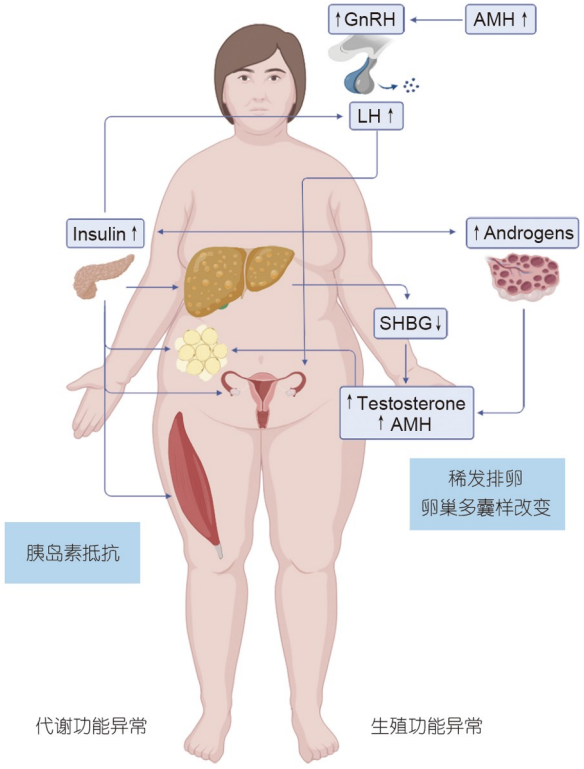

图 2　生殖与代谢在多囊卵巢综合征中的互作关系. PCOS患者中存在生殖异常与代谢异常交互影响, 共同参与PCOS发病. 本图由BioRender.com生成

Figure 2　The interaction between reproduction and metabolism in PCOS. There is a mutual interaction between reproductive abnormalities and metabolic disturbances in patients with PCOS, both of which contribute to the development of PCOS. The figure was created with BioRender.com

PCOS患者相似, 总体上生育概率下降了约36%[213,214].

3.4　功能性下丘脑闭经

功能性下丘脑闭经(functional hypothalamic anovulation, FHA)是指排除器质性病变, 由于下丘脑-垂体-卵巢轴的功能异常而引起的闭经现象, 多发生于青少年和年轻女性, 病人表现出青春期延迟、闭经、不孕以及低雌激素相关改变[55].

GnRH分泌或动力学异常是FHA的核心特征, 严重营养不良、节食减肥、过度运动引起的能量负平衡是功能性下丘脑闭经重要致病原因. 当体内脂肪存储量不足或者短期内能量摄入明显减少, 外周代谢组织可以明显感知, 患者通常会有皮质醇和饥饿素升高, 瘦素分泌降低等改变[215~217], 通过神经/体液的作用传递给下丘脑, 改变下丘脑反馈灵敏度并降低GnRH神经元的脉冲性分泌, 造成GnRH驱动的垂体功能不足, LH和FSH水平不足以维持卵泡发育和排卵性卵巢功能. 值得注意的是, FHA是功能性下丘脑性腺功能减退的最严重类型, 其他轻型包括无排卵性正常月经和伴有黄体期缺陷的正常月经, 也与不孕有关.

纠正能量平衡可以改善FHA妇女的月经和生殖结局. 在FHA患者中, 出现月经失调的严重程度与能量减少的指标是相称的[218], 而当体重接近正常或运动强度降低时, 闭经可能会发生逆转[23,219]; 因自发排卵困难, FHA女性往往需要药物诱导排卵助孕, 但其流产、小于胎龄儿、早产和因体重极轻而剖腹产分娩的风险明显增加, 因此临床上建议仅应在BMI至少为18.5 kg/m^{2}的FHA妇女中诱导排卵, 且应在纠正能量正平衡后进行[55].

4　总结与展望

生殖功能是物种赖以存续的基础, 代谢功能则是个体存活的保证, 两者存在能量权衡. 生殖是一个耗费巨大能量的过程, 生物体会增加摄食并调动能量储

备用以支持生殖活动，然而分配给生殖的能量将无法用于其他维持生命的过程，生殖占用引起的能量储备枯竭被认为会损害生物体细胞维持和生存的能力．能量的“生殖成本”提示人们：生殖和机体代谢之间似乎存在一种不可避免的能量权衡，并有可能影响生物寿命；事实上，在大多数动物中也的确是这样，繁殖减少与多种生物体的脂肪储存增加和寿命延长有关，反之亦然[5].

现代生活中，能量短缺已经不是人类存活和繁衍的首要问题，相反过于富足的营养造成的肥胖和心血管代谢疾病会损害健康、缩短寿命，且对女性生殖功能也有不良影响．因此，新的生活方式要求女性生殖与代谢之间新的平衡，用以满足女性长生命周期中更健康的身体素质和更优的生育需求．本文所述文献提供了有关生殖内分泌代谢状况与女性生殖健康之间相互关系的宝贵见解，但当前研究也存在一定的局限性：大多数临床研究样本量较小且随访时间较短，缺乏高质量的纵向研究，难以连续性观察生殖代谢在女性全生命周期的关系及对子代健康的长期影响，且研究本身容易受到混杂因素的影响，因果关系难以界定；此外，生殖生理和代谢之间相互作用的复杂性也造成了一定程度的研究局限，生殖过程和能量调节涉及到众多激素和代谢途径的复杂网络，人们对其了解仍然不完全．未来的研究应致力于解决这些局限性，进一步推进人们对女性生殖和代谢之间复杂关系的理解．对女性生殖与代谢的研究，事关女性自身和子代健康，对于保障女性健康、促进优生优育、提高人口素质均具有重要意义.

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Metabolism and reproduction in females

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Metabolism and reproduction are closely intertwined and mutually regulated in females. Female reproductive activities are complex, and metabolism could regulate reproductive functions at different stages of life through various mechanisms. Conversely, reproductive activities could also impact female metabolism. Recently, the significance of female metabolic issues in relation to reproductive disorders has become increasingly apparent. Gaining a deeper understanding of the interplay between metabolism and reproduction, as well as unraveling their intrinsic regulatory relationship, is crucial for comprehending and intervening in reproductive metabolic diseases. This article provides a literature review focusing on metabolism and reproduction in females, including the impact of metabolism on reproduction, the influence of reproduction on metabolism, and typical reproductive metabolic disorders. The review aims to offer valuable references for further research and intervention in reproductive metabolic diseases.

reproductive endocrinology, metabolism, hypothalamic-pituitary-ovarian axis, pregnancy, offspring health

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