

异常子宫出血与内分泌疾病

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收稿日期: 2023年1月9日; 录用日期: 2023年2月6日; 发布日期: 2023年2月13日

摘要

异常子宫出血是女性最常见的妇科疾病之一, 内分泌腺(垂体、甲状腺、胰腺、肾上腺和卵巢)在月经周期的内分泌调节中具有功能性作用。异常子宫出血是多囊卵巢综合征、甲状腺功能亢进症、糖尿病等多种慢性内分泌疾病的临床表现, 部分内分泌疾病的首发表现可能是异常子宫出血。因此, 本文就多种内分泌疾病导致的异常子宫出血进行综述, 以期为临床诊治提供新思路。

关键词

异常子宫出血, 月经周期, 多囊卵巢综合征, 甲状腺功能亢进症

Abnormal Uterine Bleeding and Endocrine Diseases

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Received: Jan. 9th, 2023; accepted: Feb. 6th, 2023; published: Feb. 13th, 2023

Abstract

Abnormal uterine bleeding is one of the most common gynecological diseases in women, and the endocrine glands such as pituitary, thyroid, pancreas, adrenal gland and ovary play a functional role in the endocrine regulation of the menstrual cycle. Abnormal uterine bleeding is the clinical manifestation of polycystic ovarian syndrome, hyperthyroidism, diabetes and other chronic endocrine diseases. The first manifestation of some endocrine diseases may be abnormal uterine bleeding. Therefore, the article reviews abnormal uterine bleeding caused by various endocrine

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diseases, in order to provide new ideas for clinical diagnosis and treatment.

Keywords

Abnormal Uterine Bleeding, Menstrual Cycle, Polycystic Ovary Syndrome, Hyperthyroidism

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1. 引言

异常子宫出血(abnormal uterine bleeding, AUB)是妇科常见的症状和体征,指与正常月经的周期频率、规律性、经期长度、经期出血量中的任何1项不符、源自子宫腔的异常出血,包括月经频发、月经稀发、闭经、月经过多、经期延长等表现。正常的月经功能取决于下丘脑-垂体-卵巢轴和内源性激素之间复杂的相互作用[1],在各种疾病中,内分泌疾病通过几种激素途径影响月经周期,部分内分泌疾病的首发表现可能是异常子宫出血。常见的引起异常子宫出血的内分泌疾病包括:多囊卵巢综合征、糖尿病、甲状腺功能亢进症、甲状腺功能减退症、库欣综合征、高泌乳素血症。因此,正确认识内分泌疾病的异常子宫出血表现,有利于提高临床诊疗水平。

2. 多囊卵巢综合征

多囊卵巢综合征(polycystic ovarian syndrome, PCOS)是影响育龄期女性的最常见的慢性生殖和内分泌代谢疾病,全球患病率估计为4%~21% [2] [3],其特征表现为月经不规则、慢性无排卵、多毛症、雄激素性脱发和痤疮。Strowitzki等[4]对118名德国PCOS女性的研究表明,月经周期不规则程度作为一种简单的临床参数,可作为评价内分泌代谢紊乱程度的一种有价值的手段。PCOS患者通常会出现月经稀发、继发性闭经等异常子宫出血表现,约85%~90%的月经稀发女性和30%~40%的闭经女性患有PCOS [5]。Balen等[6]研究调查了1741名PCOS女性,其中约30%的女性月经周期规律,近50%表现为月经稀发,近20%为闭经。翟军等[7]对1834例PCOS患者进行的辅助生殖结局的研究中,214例月经规律(11.6%),1402例月经稀发(76.4%),218例闭经(11.8%)。石玉华等[8]对140例中国PCOS患者的临床特征研究分析中,月经稀发率达62.6%,闭经率为19.71%。Sarwat Anjum等[9]研究分析了153例PCOS患者的临床表现,其中61例(39.8%)报告月经稀发,44例(28.7%)报告闭经。由此可见,PCOS女性最常见的异常子宫出血表现是与无排卵相关的月经稀发及闭经。

然而PCOS诱发无排卵的机制仍不确切,有证据表明窦卵泡发育停滞与内分泌异常有关,特别是胰岛素和促黄体生成素(LH)对颗粒细胞分化的相互作用[10]。

PCOS的治疗策略主要取决于预期目标和临床获益,目前的管理方式仍包括生活方式干预、药物治疗(联合口服避孕药、抗雄激素药物、二甲双胍等)、手术治疗。生活方式干预仍然是超重患者的一线治疗选择,Oberg等[11]在一项68名肥胖PCOS女性的随机对照研究中的数据表明,行为干预可以改善PCOS女性的月经状况。一项Meta分析结果显示,口服避孕药在改善月经模式方面的效果优于二甲双胍[12]。

3. 甲状腺疾病

甲状腺疾病是育龄期女性第二常见的内分泌疾病,发病率在全球范围内存在差异,女性发病率高于

男性。甲状腺激素参与调控月经周期, 通过卵母细胞上特定的三碘甲状腺原氨酸(T₃)位点影响促卵泡生成素(FSH)和促黄体生成素(LH)对类固醇生物合成的作用[13], 甲状腺功能亢进和甲状腺功能减退会导致性激素结合球蛋白(SHBG)、催乳素、促性腺激素释放激素和类固醇激素水平发生变化[14]。

据报道, 继发性闭经、月经量少是已观察到的与甲状腺功能亢进症相关的异常子宫出血表现, 并且重度甲状腺功能亢进症患者继发性闭经(2.5%)和月经量少(3.7%)的发生率更高[15]。

在育龄期女性中, 甲状腺功能减退会导致周期长度和出血量的变化, 继发性闭经、月经稀发、月经过多为其主要的异常子宫出血表现, 重度甲状腺功能减退症患者的异常子宫出血发生率(34.8%)明显高于轻中度患者(10.2%) [15]。

4. 糖尿病

国际糖尿病联合会最新发布的糖尿病地图集显示 2021 年全球 20~79 岁人群的糖尿病患病率估计为 10.5% (5.366 亿人), 女性为 10.2% [16]。有研究表明, 1 型糖尿病女性的异常子宫出血比正常女性更常见, 闭经、月经过少、周期延长是最常见的表现。一项评估患有和未患 1 型糖尿病的青少年月经周期的前瞻性研究表明, 患有 1 型糖尿病的女性月经不规律的风险是没有患 1 型糖尿病的女性的 6 倍, 而且随着 HbA_{1c} 的升高, 这种风险会更高[17], HbA_{1c} 每增加 1.0, 月经周期延长 5 天[18]。相关研究指出, 胰岛素刺激下丘脑促性腺激素释放激素(GnRH)的分泌, 因此胰岛素的绝对缺乏导致中枢性性腺功能减退, 进一步引发异常子宫出血表现。

在一项针对 190 名初诊为 2 型糖尿病的少女的多中心研究中, 21%有月经不规律, 这与 BMI 升高和类固醇激素(睾酮、雌激素)、性激素结合球蛋白(SHBG)浓度的改变有关, 与胰岛素敏感性或 β 细胞功能的改变无关, 并且在 2 年的降糖治疗后月经状况没有改善[19], 这一结果表明在 2 型糖尿病女性患者中, BMI 升高可能与排卵功能障碍、月经周期异常的关系更加密切。在一项针对青少年女性的研究中, 肥胖女孩的月经不规律(定义为每年少于 9 次月经)占比为 46% [20], 高于普通人群, 提示肥胖本身可通过抑制促性腺激素导致异常子宫出血[21]。

5. 高催乳素血症

高催乳素血症是较常见的内分泌疾病, 与异常子宫出血密切相关, 在女性患者中常见的症状为月经改变和溢乳。排除药物影响, 催乳素瘤是高催乳素血症的最常见原因, 催乳素瘤的患病率为 50/10 万, 年发病率为 2~5/10 万[22], 女性比男性高 3 倍。在催乳素瘤女性患者中, 85%~90%都有月经稀发或闭经症状, 而在继发性闭经或月经过少的女性中, 近 15%被发现为高催乳素血症[23]。高催乳素血症是促性腺激素减退性无排卵引起闭经的最常见原因。证据表明, 高催乳素血症诱导的垂体促性腺激素缺乏是间接的, 催乳素通过 kisspeptin 神经元影响促性腺激素释放激素(GnRH)神经元, 从而抑制下丘脑促性腺激素释放激素(GnRH)释放, 导致垂体促性腺激素缺乏[24]。

多巴胺受体激动剂(卡麦角林、溴隐亭)是高催乳素血症初始治疗的主要选择, 在某些情况下, 手术也是一种合适的选择。多巴胺受体激动剂的单一疗法通常可以成功地控制催乳素水平和肿瘤大小, 但对于耐药性或侵袭性催乳素瘤可能需要辅助治疗。在大多数患者(约 80%)中, 多巴胺受体激动剂可以诱导正常的月经周期并排卵, 并且已经证明卡麦角林在减少持续性高催乳素血症、闭经、月经稀发和溢乳方面比溴隐亭更有效[25]。一项纳入了 14 项催乳素瘤手术治疗观察性研究的系统综述表明, 经蝶鞍手术治疗后闭经发生率从 96%降低为 40%, 提示手术可以改善催乳素瘤女性的月经周期及生育能力[26]。

6. 库欣综合征

库欣综合征(cushing syndrome, CS)是一种罕见的内分泌疾病, 估计年发病率为每百万人 1.2 至 2.4 例,

儿童约为成人的 5% [27]。库欣综合征的症状和体征通常是非特异性的：向心性肥胖、蛋白质消耗表现、高血压、多毛症、异常子宫出血(闭经、月经过少)等。异常子宫出血是库欣综合征女性的常见主诉，在一项 45 名新诊断的垂体依赖型库欣综合征女性患者研究中[28]，14 人出现月经稀发(31.1%)，15 人出现闭经(33.3%)，4 人出现月经频发(8.8%)，3 人周期不规律(6.6%)，异常子宫出血比例高达 80%，这与高皮质醇对下丘脑促性腺激素释放激素(GnRH)的抑制相关，而不是与雄激素水平有关。在欧洲库欣综合征登记处的 1564 名患者临床数据中，59%女性患者有异常子宫出血，其中垂体依赖型库欣综合征相较肾上腺依赖型库欣综合征更容易出现月经不规则表现[29]。

库欣综合征的治疗选择需在多学科团队中进行、强调个体化，目前针对病因的手术切除治疗仍是一线治疗方法，二线治疗包括各种药物治疗、双侧肾上腺切除术和促肾上腺皮质激素肿瘤的放射治疗。一项对手术治愈后症状和合并症随访的研究显示[30]，15 名(75%)女性患者在诊断库欣综合征时出现月经稀发或闭经，其中 11 例患者在术后早期评估(中位 12 个月)时月经周期恢复正常，4 例(20%)仍处于月经稀发或闭经状态，术后晚期评估(中位 58 个月)时有 7 例(35%)仍表现为异常子宫出血。

7. 其他内分泌疾病

肢端肥大症总患病率为 2.8~13.7/10 万，年发病率为 0.2~1.1/10 万[31]。由于垂体肿瘤压迫导致促性腺激素分泌减少，50%以上的女性患者表现出性腺功能减退的闭经、月经稀发等异常子宫出血症状。

非典型型先天性肾上腺皮质增生症(non-classic congenital adrenal hyperplasia, NCCAH)也是一种可以影响月经周期的单基因遗传病，患者最常见的异常子宫出血表现为原发性或继发性闭经和月经稀发[32]。

腺垂体功能减退症是以一种或多种垂体激素分泌不足为特征的疾病[33]，临床表现因激素缺乏的数量和严重程度而异，由于性腺功能减退而导致闭经症状。治疗主要是针对激素缺乏的生理替代。

8. 结论

异常子宫出血与多种内分泌代谢疾病相关，月经稀发、闭经是内分泌疾病中最常见的异常子宫出血表现，复杂而精细的内分泌通路在女性正常月经周期的维持中起着重要的作用，更多的机制及相关性还有待进一步研究、探讨。

参考文献

- [1] Hahn, K.A., Wise, L.A., Riis, A.H., *et al.* (2013) Correlates of Menstrual Cycle Characteristics among Nulliparous Danish Women. *Clinical Epidemiology*, **5**, 311-319. <https://doi.org/10.2147/CLEP.S46712>
- [2] Lizneva, D., Suturina, L., Walker, W., *et al.* (2016) Criteria, Prevalence, and Phenotypes of Polycystic Ovary Syndrome. *Fertility and Sterility*, **106**, 6-15. <https://doi.org/10.1016/j.fertnstert.2016.05.003>
- [3] Belenkaia, L.V., Lazareva, L.M., Walker, W., *et al.* (2019) Criteria, Phenotypes and Prevalence of Polycystic Ovary Syndrome. *Minerva Ginecologica*, **71**, 211-223. <https://doi.org/10.23736/S0026-4784.19.04404-6>
- [4] Strowitzki, T., Capp, E. and Von Eye Corleta, H. (2010) The Degree of Cycle Irregularity Correlates with the Grade of Endocrine and Metabolic Disorders in PCOS Patients. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, **149**, 178-181. <https://doi.org/10.1016/j.ejogrb.2009.12.024>
- [5] Meier, R.K. (2018) Polycystic Ovary Syndrome. *The Nursing Clinics of North America*, **53**, 407-420. <https://doi.org/10.1016/j.cnur.2018.04.008>
- [6] Balen, A.H., Conway, G.S., Kaltsas, G., *et al.* (1995) Polycystic Ovary Syndrome: The Spectrum of the Disorder in 1741 Patients. *Human Reproduction (Oxford, England)*, **10**, 2107-2111. <https://doi.org/10.1093/oxfordjournals.humrep.a136243>
- [7] Yu, T., Wu, D., Cao, Y., *et al.* (2021) Association between Menstrual Patterns and Adverse Pregnancy Outcomes in Patients with Polycystic Ovary Syndrome. *Frontiers in Endocrinology (Lausanne)*, **12**, Article ID: 740377. <https://doi.org/10.3389/fendo.2021.740377>
- [8] Shi, Y., Guo, M., Yan, J., *et al.* (2007) Analysis of Clinical Characteristics in Large-Scale Chinese Women with Poly-

- cystic Ovary Syndrome. *Neuro Endocrinology Letters*, **28**, 807-810.
- [9] Anjum, S., Askari, S., Riaz, M., *et al.* (2020) Clinical Presentation and Frequency of Metabolic Syndrome in Women with Polycystic Ovary Syndrome: An Experience from a Tertiary Care Hospital in Pakistan. *Cureus*, **12**, e11860. <https://doi.org/10.7759/cureus.11860>
 - [10] Gorry, A., White, D.M. and Franks, S. (2006) Infertility in Polycystic Ovary Syndrome: Focus on Low-Dose Gonadotropin Treatment. *Endocrine*, **30**, 27-33. <https://doi.org/10.1385/ENDO:30:1:27>
 - [11] Oberg, E., Gidlöf, S., Jakson, I., *et al.* (2019) Improved Menstrual Function in Obese Women with Polycystic Ovary Syndrome after Behavioural Modification Intervention—A Randomized Controlled Trial. *Clinical Endocrinology (Oxford)*, **90**, 468-478. <https://doi.org/10.1111/cen.13919>
 - [12] Fraison, E., Kostova, E., Moran, L.J., *et al.* (2020) Metformin versus the Combined Oral Contraceptive Pill for Hirsutism, Acne, and Menstrual Pattern in Polycystic Ovary Syndrome. *The Cochrane Database of Systematic Reviews*, **8**, Cd005552. <https://doi.org/10.1002/14651858.CD005552.pub3>
 - [13] Medenica, S., Nedeljkovic, O., Radojevic, N., *et al.* (2015) Thyroid Dysfunction and Thyroid Autoimmunity in Euthyroid Women in Achieving Fertility. *European Review for Medical and Pharmacological Sciences*, **19**, 977-987.
 - [14] Dittrich, R., Beckmann, M.W., Oppelt, P.G., *et al.* (2011) Thyroid Hormone Receptors and Reproduction. *Journal of Reproductive Immunology*, **90**, 58-66. <https://doi.org/10.1016/j.jri.2011.02.009>
 - [15] Kakuno, Y., Amino, N., Kanoh, M., *et al.* (2010) Menstrual Disturbances in Various Thyroid Diseases. *Endocrine Journal*, **57**, 1017-1022. <https://doi.org/10.1507/endocrj.K10E-216>
 - [16] Sun, H., Saeedi, P., Karuranga, S., *et al.* (2022) IDF Diabetes Atlas: Global, Regional and Country-Level Diabetes Prevalence Estimates for 2021 and Projections for 2045. *Diabetes Research and Clinical Practice*, **183**, 109-119. <https://doi.org/10.1016/j.diabres.2021.109119>
 - [17] Schroeder, B., Hertweck, S.P., Sanfilippo, J.S., *et al.* (2000) Correlation between Glycemic Control and Menstruation in Diabetic Adolescents. *The Journal of Reproductive Medicine*, **45**, 1-5.
 - [18] Gaete, X., Vivanco, M., Eyzaguirre, F.C., *et al.* (2010) Menstrual Cycle Irregularities and Their Relationship with HbA1c and Insulin Dose in Adolescents with Type 1 Diabetes Mellitus. *Fertility and Sterility*, **94**, 1822-1826. <https://doi.org/10.1016/j.fertnstert.2009.08.039>
 - [19] Kelsey, M.M., Braffett, B.H., Geffner, M.E., *et al.* (2018) Menstrual Dysfunction in Girls from the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) Study. *The Journal of Clinical Endocrinology and Metabolism*, **103**, 2309-2318. <https://doi.org/10.1210/jc.2018-00132>
 - [20] Rieder, J., Santoro, N., Cohen, H.W., *et al.* (2008) Body Shape and Size and Insulin Resistance as Early Clinical Predictors of Hyperandrogenic Anovulation in Ethnic Minority Adolescent Girls. *The Journal of Adolescent Health: Official Publication of the Society for Adolescent Medicine*, **43**, 115-124. <https://doi.org/10.1016/j.jadohealth.2008.02.003>
 - [21] Rosenfield, R.L. and Bordini, B. (2010) Evidence That Obesity and Androgens Have Independent and Opposing Effects on Gonadotropin Production from Puberty to Maturity. *Brain Research*, **1364**, 186-197. <https://doi.org/10.1016/j.brainres.2010.08.088>
 - [22] Chanson, P. and Maiter, D. (2019) The Epidemiology, Diagnosis and Treatment of Prolactinomas: The Old and the New. *Best Practice & Research Clinical Endocrinology & Metabolism*, **33**, Article ID: 101290. <https://doi.org/10.1016/j.beem.2019.101290>
 - [23] Lee, D.Y., Oh, Y.K., Yoon, B.K., *et al.* (2012) Prevalence of Hyperprolactinemia in Adolescents and Young Women with Menstruation-Related Problems. *American Journal of Obstetrics and Gynecology*, **206**, 213.e1-5. <https://doi.org/10.1016/j.ajog.2011.12.010>
 - [24] Bernard, V., Young, J. and Binart, N. (2019) Prolactin—A Pleiotropic Factor in Health and Disease. *Nature Reviews Endocrinology*, **15**, 356-365. <https://doi.org/10.1038/s41574-019-0194-6>
 - [25] Wang, A.T., Mullan, R.J., Lane, M.A., *et al.* (2012) Treatment of Hyperprolactinemia: A Systematic Review and Meta-Analysis. *Systematic Reviews*, **1**, 33. <https://doi.org/10.1186/2046-4053-1-33>
 - [26] Lamba, N., Noormohamed, N., Simjian, T., *et al.* (2019) Fertility after Transsphenoidal Surgery in Patients with Prolactinomas: A Meta-Analysis. *Clinical Neurology and Neurosurgery*, **176**, 53-60. <https://doi.org/10.1016/j.clineuro.2018.11.024>
 - [27] Ragnarsson, O., Olsson, D.S., Chantzichristos, D., *et al.* (2019) The Incidence of Cushing's Disease: A Nationwide Swedish Study. *Pituitary*, **22**, 179-186. <https://doi.org/10.1007/s11102-019-00951-1>
 - [28] Lado-Abeal, J., Rodriguez-Arno, J., Newell-Price, J.D., *et al.* (1998) Menstrual Abnormalities in Women with Cushing's Disease Are Correlated with Hypercortisolemia Rather than Raised Circulating Androgen Levels. *The Journal of Clinical Endocrinology and Metabolism*, **83**, 3083-3088. <https://doi.org/10.1210/jc.83.9.3083>
 - [29] Valassi, E. (2022) Clinical Presentation and Etiology of Cushing's Syndrome: Data from ERCUSYN. *Journal of Neu-*

- roendocrinology*, **34**, e13114. <https://doi.org/10.1111/jne.13114>
- [30] Espinosa-de-Los-Monteros, A.L., Sosa, E., Martinez, N., *et al.* (2013) Persistence of Cushing's Disease Symptoms and Comorbidities after Surgical Cure: A Long-Term, Integral Evaluation. *Endocrine Practice: Official Journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists*, **19**, 252-258. <https://doi.org/10.4158/EP12247.OR>
- [31] Lavrentaki, A., Paluzzi, A., Wass, J.A., *et al.* (2017) Epidemiology of Acromegaly: Review of Population Studies. *Pituitary*, **20**, 4-9. <https://doi.org/10.1007/s11102-016-0754-x>
- [32] Livadas, S. and Bothou, C. (2019) Management of the Female with Non-Classical Congenital Adrenal Hyperplasia (NCCAH): A Patient-Oriented Approach. *Frontiers in Endocrinology (Lausanne)*, **10**, 366. <https://doi.org/10.3389/fendo.2019.00366>
- [33] Yeliosof, O. and Gangat, M. (2019) Diagnosis and Management of Hypopituitarism. *Current Opinion in Pediatrics*, **31**, 531-536. <https://doi.org/10.1097/MOP.0000000000000779>