

• 综述 •

女性阻塞性睡眠呼吸暂停的研究现状

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[摘要] 阻塞性睡眠呼吸暂停(obstructive sleep apnea, OSA)是一种有潜在致死性的睡眠呼吸疾病,可导致多种不良健康结局。女性OSA的患病率在不同生命阶段存在差异,特别是在妊娠期和绝经后显著上升。其病理生理机制涉及解剖、生理和激素变化,导致临床表现与男性不同。据此,文章针对女性OSA的研究现状,包括流行病学、病理生理机制、诊断与评估、治疗与管理等进行综述,希望为优化女性OSA的诊治提供新的思路。

[关键词] 阻塞性睡眠呼吸暂停;女性;病理生理机制;诊断;治疗

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Research status of obstructive sleep apnea in women

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[Abstract] Obstructive sleep apnea (OSA) is a potentially fatal sleep-related respiratory disease that can lead to serious health complications. The prevalence of OSA in women varies by life stages, especially increasing significantly during pregnancy and after menopause. Its pathophysiological mechanism involves anatomical, physiological and hormonal changes, resulting in different clinical manifestations from men. Accordingly, this article reviews the research status of female obstructive sleep apnea, including epidemiology, pathophysiological mechanisms, diagnosis and evaluation, treatment and management. This review aims to provide new ideas for optimizing the diagnosis and treatment of female OSA.

[Key words] obstructive sleep apnea; female; pathophysiology; diagnosis; treatment

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阻塞性睡眠呼吸暂停(obstructive sleep apnea, OSA)表现为睡眠中反复出现上气道塌陷和梗阻,引起呼吸暂停或低通气,导致间歇性缺氧、交感神经激活、血流动力学紊乱等生理异常^[1]。尽管OSA在男性中更为常见,但女性患者同样面临严重的健康风险,且其临床表现和病理生理机制存在性别差异^[2]。女性OSA的诊断和治疗面临着特定的挑战,这要求临床工作者对这一群体有更深入的理解和针对性

的干预措施。此外,女性在不同生命周期阶段的激素变化对OSA的影响也不容忽视^[3],这要求临床工作者在诊疗策略上应充分考虑性别差异性。文章将对女性OSA的诊治进展,包括流行病学、病理生理机制、诊断与评估、治疗选择以及特殊人群的管理进行综述。

1 流行病学

1.1 患病率

不同生命阶段的女性OSA患病率不同。在儿童和青少年中,OSA患病率和严重程度无明显性别差异^[4]。在青春期之后,女性OSA比例大大降低,男

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女OSA患者的比例在3:1~10:1^[5],激素可能是导致该现象的主要因素^[6]。而随着女性年龄的增长,尤其是进入更年期后,这种性别差异又会逐渐缩小^[7-8],但这时女性患病率急剧增加的原因存在争议,究竟是年龄还是激素的影响或者是多种因素作用的结果目前尚不明确。此外,妊娠期女性OSA的发病率也呈现上升趋势,这可能主要归因于孕期生理机能的调整以及激素水平的波动^[9]。

1.2 危险因素

在育龄期女性群体中,肥胖、多囊卵巢综合征、甲状腺功能减退症、肢端肥大症等疾病会增加OSA的患病风险^[10-13]。在我国,体重指数(body mass index, BMI)≥24.6 kg/m²被认为是女性OSA的主要危险因素之一^[14];而在OSA严重程度相似的情况下,女性的BMI值通常比男性更高^[15]。多囊卵巢综合征患者激素水平和脂肪分布的改变影响上气道的通畅程度,可导致OSA病情的恶化^[16]。甲状腺功能减退症、肢端肥大症与OSA之间相互作用的确切机制仍不清楚。

妊娠期女性OSA的危险因素主要包括肥胖、体液潴留、高血压、高龄、激素水平的变化^[17-18],尤其年龄>35岁和妊娠早期肥胖的女性更需提高警惕^[19]。不仅如此,妊娠期女性的上气道会发生动态变化,更易出现气道阻塞^[18]。此外,上气道结构异常、妊娠期高血压、妊娠期糖尿病、甲状腺疾病、OSA家族史等也是妊娠期OSA的危险因素^[20-21]。

绝经是女性睡眠障碍的独立危险因素^[8],绝经期女性由于雌、孕激素水平下降,对上气道的保护作用减弱^[22-23],且女性在性激素水平发生变化时易出现睡眠呼吸暂停、失眠、不宁腿综合征等睡眠障碍^[24],这可能是绝经前后OSA的发病机制之一。

2 病理生理机制

OSA的病理生理机制是多因素的,但主要包含解剖因素和非解剖因素两个方面。Eckert等^[25]提出了OSA的不同病理生理亚型,即PALM模型,包括上气道可塌陷性(P)、低觉醒阈值(A)、高环路增益(L)和上气道肌肉反应性(M)。在女性中,这些病理生理表型展现出独有的特征。

2.1 上气道可塌陷性

女性的上气道解剖结构与男性有所不同。女性的气道相对男性更窄、更短^[26],颈部脂肪增加的女性更容易产生OSA风险^[27]。临界闭合压(critical closing pressure, Pcrit)可以衡量气道的可塌陷性,OSA的严重程度与Pcrit呈正相关^[25]。但与男性相

反,衰老加重上气道的可塌陷性这一结论在女性中并不成立^[28],这表明其他因素在影响女性上气道可塌陷性上发挥了作用。在呼吸暂停低通气指数(apnea hypopnea index, AHI)相同的情况下,Pcrit不存在性别差异,但是匹配BMI后,女性的Pcrit更低^[29]。加之雌激素会改变上气道的肌肉张力和黏膜充血程度,对气道可塌陷性也会产生重要影响^[23]。

2.2 低觉醒阈值(arousal threshold, ArTH)

临床上低ArTH在OSA患者中普遍存在^[25]。低ArTH可导致更频繁的觉醒、睡眠片段化和睡眠不稳定,并引起呼吸中枢的不稳定^[30]。低ArTH的OSA患者病情相对较轻,女性和低BMI患者在其中的比例较高,且他们更频繁地经历睡眠紊乱症状^[28,31-32]。特别是在女性OSA患者中发现,呼吸暂停事件在快速眼动(rapid eye movement, REM)睡眠期间更为集中,ArTH也呈现更低的趋势^[33-34]。而且,可以在37岁以上的女性中观察到ArTH随着年龄的增长而降低的趋势^[28]。

2.3 高环路增益(loop gain, LG)

LG计算的是增加呼吸驱动力后带来的通气量,用于评估呼吸控制系统的稳定性^[25]。高LG可能加重OSA的严重程度,这与其诱发低碳酸血症和抑制上气道呼吸驱动力有关^[35]。有研究报道,女性表现出较低的LG,意味着女性的通气稳定性较强,但随着年龄的增长,这种优势会逐渐减弱^[28,36]。此外,雌激素可以增强通气反应^[23]。因此年龄及绝经期激素水平的改变可能是LG增加而导致OSA严重程度增加的潜在机制。

2.4 上气道肌肉反应性

上气道的通畅主要通过肌肉收缩和周围的软组织结构来维持,女性上气道肌肉的力量相对男性较弱,特别是颏舌肌力量比男性明显减低。在睡眠过程中,随着肌肉松弛,这种力量差异会导致女性上气道更容易塌陷。但也有研究发现,低雌激素水平可能会增加气道扩张肌的疲劳并改变其结构和功能^[37],且女性的气道扩张肌对于缺氧的刺激有更强的耐受力^[38],说明相同的缺氧条件下,女性在保持上气道通畅方面较男性具有明显的优势。同时,颏舌肌的功能也会随着衰老而下降,从而影响老年女性上气道的通畅性^[39]。

3 诊断与评估

3.1 临床特征

OSA患者存在不同的病理生理表型及对应的

临床亚型。Pataka等^[40]基于女性OSA患者的临床表现、睡眠监测结果和常见并发症分析了4种不同的临床特征(表1)。

基于女性患者临床特征分析, 肥胖更年期女性更易出现OSA; 且重症OSA女性患者合并症发生率较高, 可能与夜间低氧血症对女性造成的损伤更为

表1 女性OSA不同临床特征

Table 1 Different clinical characteristics of female OSA patients

Cluster	Age(years)	BMI(kg/m ²)	AHI(events/h)	ESS score	Sleep efficiency(%)	Incidence of comorbidities
Women with mild OSA and low comorbidities	46-60	26.9-33.5	6.9-10.4	5-13	75.6-92.1	Lowest rate of comorbidities
Elderly women with comorbidities	60-71	31.6-40.4	30.0-60.1	6-13	67.0-89.0	Highest rate of comorbidities
Sleepy obese women	42-55	37.6-48.9	32.0-80.5	8-16	70.6-90.1	Highest rate of psychiatric diseases and asthma
Women with ischemic heart disease	53-65	26.9-33.5	17.4-30.0	5-12	72.0-91.6	Highest rate of ischemic heart disease

AHI: apnea hypopnea index; BMI: body mass index; ESS: Epworth sleepiness scale.

显著有关^[41]。在女性OSA患者中, 失眠、睡眠质量差、情绪障碍、疲倦、晨起头痛、噩梦等非典型症状更为常见, 而典型的打鼾、呼吸暂停、日间嗜睡等OSA临床症状则相对少见^[42-44]。女性OSA与嗜睡无相关性或相关性并不高, 但目前的诊断标准中^[45], 中重度OSA患者需满足嗜睡这一要求, 表明许多女性OSA患者的严重程度可能被低估。

上气道的解剖结构、脂肪分布、激素水平的改变以及不同的病理生理类型是导致女性OSA临床特征不同的原因。随着女性年龄的增长, LG明显增加, 通气稳定性减弱, 上气道肌肉反应性降低, 这是老年女性OSA风险显著上升的常见原因^[28, 39]。肥胖女性常伴更严重的OSA, 其潜在机制可能与肥胖本身、LG升高及上气道不稳定相关^[27, 46]。而且, 肥胖女性OSA患者的上气道阻力增加, 可引起胸腔内负压波动, 导致血流动力学变化, 增加心血管疾病风险^[27, 47]。不仅如此, 在37岁以上女性中普遍观察到的低ArTH可导致睡眠碎片化和反复的觉醒, 激活交感神经系统, 进一步加重心脏缺血^[28, 47]。由睡眠中断和肥胖引发的全身炎症也会促进OSA及其合并症的进展, 而这在女性OSA中更为显著^[48-49]。在OSA与失眠共病患者中, 老年女性占比更高^[50], 有研究报道这可能与激素水平波动、大脑退化以及心理因素相关^[51-53]。此外, 焦虑、抑郁等情绪障碍在女性OSA患者中也比较明显, 且患有情绪障碍的女性同样具有较高的OSA风险^[54], 这可能与情绪相关脑区的灌注减少并出现显著萎缩有关^[55-56]。值得注意的是, 情绪障碍的治疗会增加低ArTH的几率, 睡眠片段化会更严重, 可能导致情绪认知功能障碍陷入

恶性循环^[56-58]。

女性OSA的临床特征可以为识别潜在的OSA患者和管理现有患者提供更有效的方法, 并且在确定预后因素和指导治疗方面也具有重要意义。

3.2 评估工具

目前的临床指南在很大程度上是基于以男性为研究主体的临床特征数据^[45], 由于女性OSA的病情程度较轻且症状不典型, 临床上常不能有效识别女性OSA, 这可能会导致女性OSA的诊断不足。在一项大型研究中, 纳入更宽松的氧去饱和标准后有更多的女性OSA得到诊断^[36]。由此可见, 过于严格的氧去饱和标准也会导致对女性OSA的低估。目前针对女性OSA群体, 临床常用的评估诊断工具包括多导睡眠监测(polysomnography, PSG)、筛查模型、NoSAS评分等。

3.2.1 PSG

目前睡眠呼吸障碍的金标准仍是PSG, 多个指南及专家共识明确女性(包括高危妊娠期妇女)PSG或家庭睡眠呼吸暂停监测发现AHI \geq 5次/h即可诊断OSA^[20, 59-60]。但不同性别的PSG结果存在显著差异。与男性相比, 女性拥有更多的慢波睡眠时间, 在此期间呼吸事件显著减少, AHI更低^[15, 61-62]。女性OSA患者, 特别是年轻女性, 表现出较短的呼吸事件持续时间, 这与ArTH降低、LG增加和Perit较低有关^[63]。此外, 女性OSA低通气频率也较高, 尤其是在绝经期女性中^[64], 这可能与高LG或低ArTH有关。意外的是, 尽管低ArTH可导致更频繁的觉醒, 但女性患者的觉醒指数也比男性低^[15], 可能是雌激素减少了频繁醒来的风险^[51]。因此, 在诊断女性

OSA患者时应充分考虑Perit、LG、ArTH和激素水平等因素的影响。同时,理解这些差异有助于开发更个性化的治疗方案。

3.2.2 女性OSA的筛查模型

研究人员在纳入女性危险因素和相关症状后建立了新的筛查工具。卜梦滢等^[14]通过对女性OSA的危险因素及打鼾情况进行调查与分析,建立了女性打鼾人群OSA筛查模型,该模型综合了包括女性激素水平、上气道解剖结构、肥胖及OSA常见症状等多种危险因素,对于OSA患者,尤其是中重度OSA患者有较强的识别作用,但存在对鼾症人群过度抽样的不足。Facco等^[65]开发了妊娠期女性OSA特异性筛查工具,包含打鼾、高血压、BMI、年龄4个变量,但有研究表明该模型在肥胖的女性中敏感性和特异性较差^[66]。Louis等^[67]开发的预测模型可以预测妊娠早期和中期的睡眠障碍,频繁打鼾(每周>3次)被认为可预测OSA状态。Balsarak等^[68]将睡眠呼吸暂停症状评分和其他患者特征(即年龄、BMI、目睹的打鼾和呼吸暂停)组合的新工具显示出较高的敏感性和特异性,在临床实践中可能对预测孕妇OSA具有更大的效用。

这些筛查模型涵盖了女性的多种危险因素、常见症状及不同妊娠时期等多种综合性因素,可以帮助医务工作者识别女性OSA患者。虽然以上预测模型在筛查女性OSA方面均有一定的价值,但这些风险预测工具因为样本有限,尚未在大型队列或多中心人群中得到前瞻性验证,外推性不佳。

3.2.3 NoSAS评分

Marti-Soler等^[69]利用HypnoLaus队列的数据基

于5个项目(颈围、肥胖、打鼾、年龄和性别)构建了NoSAS评分,并证明其效果明显优于睡眠呼吸暂停初筛量表(STOP-Bang questionnaire, SBQ)和柏林问卷(Berlin questionnaire, BQ)。2018年卿思敏等^[70]将其引入、汉化,并证实其诊断OSA的准确性高于Epworth嗜睡量表(Epworth sleepiness scale, ESS)、SBQ和BQ。黄兰等^[71]首次在女性群体中验证NoSAS评分的筛查效果,并将其与女性打鼾人群OSA筛查模型对比,发现二者都对中重度女性OSA患者有较强的识别作用,但都放大了筛查效果。后续有研究也证明了NoSAS评分在预测女性OSA,尤其是非老年女性时效果优于同类评分^[72]。NoSAS评分简单、高效且易于实施,它将主观变量的数量限制为打鼾。虽然研究表明NoSAS评分对女性OSA具有较好的预测效果,但这些研究中女性占比较低,敏感性也较差,可能未能筛出部分OSA患者。通过调整相关阈值,有望提高其在女性人群中的应用效果。

3.2.4 其他评估工具

因为未充分考虑女性因素、女性症状的不典型以及妊娠期其他因素的干扰,在女性患者中,中国社区OSA筛查问卷(Chinese community questionnaire for OSA, CNCQ OSA)、SBQ、BQ几个量表在筛查女性OAS时敏感性或特异性不足(表2)。而由于药物诱导睡眠内窥镜(drug-induced sleep endoscopy, DISE)可以直接识别气道阻塞,故而更有临床价值。但对于其他因素所致的OSA可能缺乏识别能力,且由于DISE的药物选择、程序和分类存在固有的偏倚,需要对一般OSA人群进行大规模研究才可以消除偏倚。

表2 其他评估工具

Table 2 Other evaluation tools

Evaluation tool	Clinical significance
CNCQ OSA	A total score ≥ 13.5 was defined as high risk of OSA, with lower weights for women than for men ^[73]
SBQ	① The screening performance was improved after modifying BMI and neck circumference thresholds ^[74] ; ② A lower score can predict more severe female OSA ^[75] ; ③ It cannot effectively screen for OSA during pregnancy ^[66]
BQ	① The specificity and negative predictive value were improved after gender division, but the overall validity was insufficient ^[76] ; ② It cannot effectively screen for OSA during pregnancy ^[66]
DISE	① Identify the collapse of the upper airway during sleep ^[77] ; ② Post-menopausal female patients showed a tendency with a more severe airway obstruction for all obstruction sites, and patients showed more concentric palatal collapse in higher BMI group and retrolingual collapse in lower BMI group ^[78]

4 治疗

4.1 一般治疗

目前中国《女性阻塞性睡眠呼吸暂停诊治专家共识》^[20]主要建议女性OSA患者进行减重、饮食控制、运动。吸烟、饮酒、咖啡因摄入及镇静催眠药物的不当应用会增加OSA的患病风险^[79-81],故患者在日常生活中也需要注意戒烟、减少乙醇和咖啡因摄入、慎用镇静催眠药物。除此之外,也需要及时评估和治疗女性OSA相关合并症及并发症,并特别关注女性生理周期和激素变化对睡眠的影响。

4.2 无创正压通气(non-invasive positive pressure ventilation, NPPV)

迄今为止,无创正压通气仍是中重度OSA的首选治疗手段,无论男女。无创正压通气可解除上气道梗阻,改善睡眠期间的低氧,纠正睡眠结构紊乱,提高睡眠质量^[82]。考虑到性别差异可能会影响治疗效果,出现了专为女性OSA患者设计的自动滴定算法,新算法对气流受限的敏感性更高,气流受限引起的压力上升较慢,气流受限得到有效改善^[83]。Su等^[84]发现,REM期患者需要的平均治疗压力更低,因此对于REM期呼吸事件多发的女性患者,在治疗压力的选择上还需要考虑睡眠时期的影响。

NPPV的依从性受人口学特征、疾病严重程度等诸多因素的影响^[85]。就性别因素而言,女性OSA患者的依从性更好^[86]。与此结论相反的是,在女性占比更高的REM期OSA中,患者在使用NPPV时更易中途退出^[87]。但也有研究显示NPPV的依从性与性别无关^[88]。

4.3 激素替代治疗(hormone replacement therapy, HRT)

雌、孕激素可调节女性的通气功能^[89],并且可激活颞舌肌等维持上气道扩张的肌肉,对抗气道塌陷^[22-23],从而起到保护作用。此外,雌激素还可以减轻与间歇性缺氧相关合并症的不利影响^[90-91]。雌、孕激素水平下降可能导致OSA及相关合并症的发病风险增加。

目前对于HRT作为绝经后妇女OSA的可能干预措施存在争议。在一项小型研究中,HRT被认为是有效的,尤其是REM期可观察到AHI值的下降^[92]。在之后的一项大型研究中也发现了同样的效果^[93]。但也有学者发现HRT对OSA无显著影响^[94]。此外,外源激素的使用可能引起阴道出血、恶心、呕吐等不良反应,HRT还可能增加心脑血管

疾病和癌症的风险^[95]。因此,OSA患者的HRT需要个体化,且治疗方案需与专科医生共同商议。

4.4 其他治疗方式

其他女性OSA的治疗方式还有应用口腔矫治器、上气道手术、舌下神经刺激、药物治疗等。对于不耐受NPPV治疗的女性OSA患者,使用定制的下颌复位装置可以达到不错的疗效^[96]。目前关于舌下神经刺激治疗研究中的大多数受试者都是男性,尚未发现明显性别差异。关于OSA药物治疗,关键靶点主要聚焦于与OSA病理生理学相关的呼吸控制系统的结构组织,治疗效果未发现有明显的性别差异且需要更加详尽的验证^[97]。

4.5 妊娠期女性OSA的管理

妊娠期OSA是一个需要高度重视的健康问题,早期识别和治疗对于改善母婴预后至关重要。参考《妊娠期阻塞性睡眠呼吸暂停低通气综合征临床诊治专家共识(草案)》^[60]以及《女性阻塞性睡眠呼吸暂停诊治专家共识》^[20],对于妊娠期OSA的管理需要考虑以下几个方面:加强体重管理、体位治疗、NPPV治疗、应用口腔矫治器、母婴合并症管理等。此外,建议在妊娠24周左右,重新对患者的病情进行评估和调整治疗方案,产后应再次进行睡眠监测,评估产后是否需要继续NPPV等治疗。

5 总结与展望

女性OSA的患病率在不同生命阶段存在显著差异,与男性相比,在育龄期较低,而在妊娠期和绝经后显著上升。女性OSA的病理生理机制涉及解剖结构、生理功能、激素水平变化等多个方面。由于女性OSA具有独特的病理生理学特征,故可表现出女性OSA打鼾、失眠及情绪影响等有别于男性的多种临床表现。女性OSA的诊断和评估包括临床症状的识别、PSG检查等,而新的检测工具和模型的应用为OSA的筛查和诊断提供了新思路。女性OSA首选NPPV治疗,但其他的治疗方式也有不可忽视的作用。妊娠期女性OSA威胁着母婴健康,需要特别的关注和适当的筛查与管理。

综上所述,女性OSA患者相对男性在病理生理、解剖结构及临床表现有其自身的特点,其研究涉及流行病学、病理生理、诊断评估、治疗管理等多个方面。未来的研究应进一步探索优化新的个性化诊断工具及治疗方案,并提高公众和医疗专业人员对女性OSA的认识。

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