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Diagnostic and Management Approach to Common Sleep Disorders During Pregnancy

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Abstract

The significance for maternal and fetal health of gestational Obstructive Sleep Apnea, Primary Insomnia, Restless Legs Syndrome, & Narcolepsy are summarized. The pathophysiology, signs, symptoms, and basic Sleep Medicine concepts that assist the obstetrician in suspecting these four conditions are described. Where appropriate, initial management options are also outlined. Referral guidelines to a Sleep Medicine specialist are included when further diagnostic, severity assessment, and management suggestions are needed.

Introduction

Sleep Medicine is a recognized and maturing sub-specialty. The 2nd edition of the International Classification of Sleep Disorders (ICSD) describes over 50 specific disorders plus additional isolated symptoms, normal variants, and conditions occurring during sleep or in the differential diagnosis of sleep disorders [1]. Sleep Medicine Fellowships accredited by the Council on Graduate Medical Education are widely available and are a prerequisite to the standardized certification exam administered by different specialty boards. Accreditation of Sleep Centers by the American Academy of Sleep Medicine (AASM) is necessary for reimbursement in many states. Several journals are now devoted to either clinical Sleep Medicine or the fundamental biology of normal and abnormal sleep.

Establishing an effective referral relationship with a Sleep Medicine specialist is important for the Obstetrician because 1) the obstetrician must be comfortable with Sleep Medicine recommendations, especially pharmacological ones, before they are implemented, 2) delayed scheduling of Sleep Medicine consultation may increase the risk of permanent sequelae of maternal sleepiness-related accidents and of fetal exposure to adverse in-utero and postnatal environments, and 3) the sleep disorder severity may change relatively quickly as the pregnancy evolves and then ends.

Several Sleep Medicine concepts are generally true across the four diverse sleep disorders considered here. Chronic sleep disruption of any cause is a significant psychological and physiological stress that may impair pregnancy outcome [2]. The absence of recalled awakenings does not confidently predict good sleep quality. Either fatigue or sleepiness may be a clue to a sleep disorder. The driving safety risk of sleepiness is often under-estimated. A thorough and pertinent sleep history is best obtained by physicians experienced in Sleep Medicine with input from the bed partner. Such a careful history should always be a prerequisite to either home or sleep-laboratory recordings. Sleep recordings in the home or in the laboratory are rarely helpful by themselves. Consistent with the AASM sleep center

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accreditation standards, this author believes the best Sleep Medicine outcomes are achieved when the same provider takes the sleep history, negotiates and explains the sleep tests, and then negotiates and initiates the sleep management plan.

Obstructive Sleep Apnea Syndrome (OSAS)

Clinical Presentation

By definition, sleep apnea events (transient, repetitive diminution or cessation of lung ventilation for ≥ 10 -seconds) occur in sleep and thus are usually not recalled by the patient despite the severe degree of sleep disruption and daytime impairment that can result. Therefore, the transient, repetitive upper airway obstruction or narrowing of OSAS often comes to attention because of bed partner reports of labored, loud (e.g. “snoring”), and/or irregular (e.g. alternating breath-holding and gasping) breathing during sleep in the setting of daytime fatigue or sleepiness that were either ignored, unexplained, or falsely attributed to other causes. However, females in particular may have considerable respiratory-related sleep disruption with only minimal decrements in airflow, little or no oxygen desaturation, and little or no upper airway noise (the so-called “hypopneas” of Obstructive Sleep Apnea-Hypopnea Syndrome or the even more subtle Upper Airway Resistance Syndrome (UARS) [3]. Therefore, it is important to identify additional risk factors for OSAS or UARS including obesity, chronic non-gestational hypertension [4], recessed chin, Japanese or Chinese ethnicity with even minimal obesity [5], nasal or pharyngeal airway limitation, positive family history of OSAS, polycystic ovary syndrome [6], and possibly pregnancy itself [7].

OSAS may also co-exist with non-upper airway obstructive breathing pathologies such as so-called “central” apneas especially as elevation increases to even moderate altitudes ($> 3,000$ ft). Mixed central-obstructive sleep apnea syndrome can be very difficult to treat. Moderate altitudes are common throughout the American west but the author’s PubMed search for maternal central sleep apnea syndrome in pregnancy produced no relevant citations. Non-obstructive sleep-related hypoventilation may also co-occur with OSAS especially in the setting of morbid obesity, sedative hypnotic and opioid drugs, pulmonary or neuromuscular disease, and central-congenital hypoventilation syndrome. Overnight home pulse oximetry recordings, though inexpensive, are not sufficiently standardized or sensitive to be recommended and are very difficult to interpret without significant ancillary information plus Sleep Medicine expertise. At this time protocols to screen for OSAS specifically in pregnancy [4] should first be considered in consultation with a Sleep Medicine specialist. Sleep Medicine consultation including laboratory polysomnography and/or home sleep testing provides the most specific diagnostic information but the Obstetrician must insist on follow-up consultation when potentially sleep-related signs, symptoms, and risk factors persist or change for two reasons: 1) sleep apnea severity may worsen or abate with progression of the pregnancy or delivery, 2) the variation in OSAS severity from night-to-night is large enough that the false-negative rate of one night of polysomnography is clinically significant. The prevalence of OSAS in pregnancy is uncertain but is probably greater than the estimated 2% prevalence in the general female population.

OSAS Pathophysiology

Complete occlusion (apnea) or various degrees of airway stenosis (hypopneas or upper airway resistance events) during episodes of OSAS occur in the (extra-thoracic) upper airway between the glottis and the soft palate. The tongue is the largest single upper airway dilator muscle that relaxes with the onset of sleep but the soft palate can also contribute to upper airway stenosis. When ribcage and diaphragmatic inspiratory effort are greater than

upper airway dilator muscle tone then the pharyngeal airway narrows or collapses. The resulting compensatory increase in inspiratory effort to sustain tidal volume causes further collapse of the upper airway which eventually triggers brain arousal to a lighter stage of sleep or a brief (but usually unremembered) awakening that terminates the event by restoring wakeful upper airway dilator muscle tone. One common metric of OSAS severity is the frequency of these events per hour of sleep, the so-called apnea-hypopnea index (AHI). The AHI cannot by itself predict the consequences of OSAS: it does not summarize hypoxia or the UARS, and does not account for unique patient (mother and fetus) co-morbidities and vulnerabilities. Therefore, ideally, the Obstetrician and the Sleep Medicine specialist communicate sufficiently to integrate their clinical impressions and laboratory tests and thus arrive at a management and surveillance plan.

OSAS pathophysiology suggests specific risk factors that the Obstetrician can quickly document in the clinic: 1) anatomic or congestion-related nasal/nasopharyngeal airway stenosis promotes mouth-breathing in sleep which retro-positions the tongue via a more posteriorly-rotated mandible, 2) habitual supine sleeping position (admittedly less common in later pregnancy) adds an airway-collapsing, posteriorly-directed gravitational force on the tongue and mandible, 3) higher Mallampati scores or, more simply, difficulty visualizing the posterior pharyngeal wall in the sitting position with the jaw wide open and the tongue relaxed suggests some oro-pharyngeal airway stenosis even before sleep-onset, 4) a neck circumference > 42 cm in females suggests increased fat in the upper airway, and 5) even minimal obesity (BMI $\geq$ 25) in Japanese or Chinese women [5], perhaps because they are already predisposed to OSAS by their cranio-facial proportions.

OSAS Significance in Pregnancy

OSAS may mediate some of the poor maternal and fetal pregnancy outcome associated with maternal obesity [7]. The associations between maternal OSAS and poor fetal outcome have been interpreted as weakly demonstrated and the mechanisms unproven though suspicion falls on fetal oxygen dependence and gestational hypertension. Recent data from a large Taiwanese study add strength to the association but will need to be replicated in other ethnic groups [8]. OSAS could exacerbate the partial sleep deprivation of later pregnancy and thereby increase maternal irritability and apathy perhaps with greater risk of post-partum depression and impaired mother-infant interactions. OSAS patients are thought to be at elevated risk of hypoxia, hypercapnia, cardiac arrhythmias, and sudden death after general anesthesia including obstetrical procedures such as cesarean section [9].

OSAS Management Considerations

Weight loss is a difficult and very prolonged treatment path for OSAS. Sleep-position training to the lateral position or raising the head of the bed in early pregnancy is usually only helpful in mild cases. Even if otherwise indicated as a secondary treatment option, upper airway (tongue base, soft palate, nasal, or mandibular) surgery would generally be avoided due to the unpredictable benefit, uncertain risks of general anesthesia to the fetus, and the potential for short-term exacerbation of upper airway swelling in the mother. Continuous positive airway pressure (CPAP) via nasal (see Figure 1), oral, or nasal-oral masks to stent the upper airway open in sleep is usually the most benign and effective treatment, if tolerated.

Primary (Psychophysiological) Insomnia (PI)

Clinical presentation

The physical discomforts of pregnancy including difficulty finding a comfortable position, back pain, and nocturia are commonly presumed to cause sleep disruption particularly after

the first trimester. Pregnancy-related psychological stresses may promote insomnia. OSAS and Restless Legs Syndrome can be associated with pregnancy and usually cause fragmented sleep. Behaviors that impair sleep (poor “Sleep Hygiene”) are common in the general population. However, PI is the most common chronic insomnia in the general adult population, is particularly prevalent among females, and is often misdiagnosed as psychopathology (indeed, the affect is often dysphoric with depressive and anxious features) or due entirely to stress factors. Therefore, PI may easily be missed as a significant additional but treatable factor contributing to the sleep disruption of pregnancy.

The presenting complaint is typically worded as “not sleeping,” “unable to sleep,” or “can’t sleep” associated with daytime cognitive, emotional, and/or physical fatigue that are attributed by the patient to the poor sleep. Simultaneously, patients describe continuous (day and night) cognitive and emotional hyper-arousal including a perfectionistic style of daytime accomplishment despite the fatigue, and “racing” thoughts in bed before sleep. Concern about falling asleep and staying asleep worsens as bedtime approaches often to the point of self-fulfilling sleep-performance anxiety with a complaint of “dread the bed.” A physiological hyper-arousal has also been quantified by measurements of oxygen consumption and sympathetic nervous system activity. A seemingly paradoxical but diagnostically and pathophysiologically important feature of chronic cognitive-behavioral hyper-arousal is the absence of daytime sleepiness despite the chronic tiredness and claim of sleep deprivation. Observers often believe the patient is asleep at night but, consistent with cognitive arousal, the patient reports continued or frequent awareness of herself and her surroundings including the sounds of various people, appliances, machines, animals, or meteorological events throughout the night.

Pathophysiology

Predisposing characteristics, a precipitating event, and perpetuating behaviors and cognitions (the PPP of PI) are an important clue to the diagnosis, an explanation for the patient, and a guide to treatment. A childhood history of light or intermittent poor sleep (e.g. the night before birthdays, holidays, or social events) should be sought as a predisposing feature. Usually, the patient can clearly identify a precipitating event associated with acute sleep loss even if the associated affect was generally positive (e.g. a daughter’s marriage). Perpetuating behaviors and factors include counter-productive learned sleep onset associations (e.g. “dread the bed”).

The neurobiology of PI appears to include a fascinating combination of simultaneous chronic partial sleep deprivation (particularly in the pre-frontal cortical areas tasked with executive functions) and chronic brain hyper-arousal. Presumably, the former explains much of the fatigue and sense of being cognitively and emotionally overwhelmed. The expected electroencephalographic (EEG) and metabolic correlates of brain hyper-arousal during sleep have been reported in sleep EEG and sleep Positron Emission Tomography studies of PI and in EEG studies of a rat model of chronic insomnia.

Significance in Pregnancy

Cognitive, emotional, and physical fatigue with dysphoric mood and anxiousness plus the possible stress of physiological hyper-arousal may all be counter-productive to maternal and fetal well-being. Sleep disturbance early in pregnancy has been reported to predict increased depressive symptomatology later in pregnancy [10]. In non-pregnant people the combination of depression and insomnia is a significant risk factor for suicide in both sexes [11].

Management Considerations

Most sedative-hypnotic drugs commonly used for insomnia are Pregnancy Category C, D, or X. Significant hazard ratios for death or cancer, including a dose-response effect, from these drugs have been reported from several large health care plans [12, 13]. A nation-wide (Taiwanese) population-based study found elevated adjusted odds ratios for adverse pregnancy outcomes in mothers prescribed zolpidem [14]. Therefore, certified Behavioral Sleep Medicine specialist assessment and treatment with Cognitive Behavioral Therapy for Insomnia (CBTI) may be safer than medication. In the non-pregnant population, CBTI is usually as effective, and more durable than, sedative hypnotics. Theoretically, CBTI should satisfy and promote an internal locus of control. Early epidemiologic studies suggest that CBTI is more cost-effective at a population level than drugs. Unfortunately, CBTI is often confused with a simple list of sleep hygiene techniques.

Properly done, CBTI: 1) substitutes sleep-promoting cognitions for counter-productive ones and directly confronts unfounded or exaggerated fears of insufficient sleep; 2) extinguishes learned counterproductive behaviors, (controllable) substance use, and sleep-onset associations; 3) optimizes bedtime relative to internal circadian time; 4) more effectively utilizes sleep deprivation sleepiness; 5) trains the relaxation response; and 6) helps identify other contributing sleep disorders. Accredited Sleep Centers are required to have an insomnia program and should be encouraged to hire a Behavioral Psychologist certified and experienced in CBTI if they do not have one. Unfortunately, the author is unaware of any original research on the effectiveness of CBTI in pregnancy or on nuances and considerations for the application of CBTI specifically to the pregnant population.

Restless Legs Syndrome (RLS)

Clinical presentation

RLS is a sensory-motor syndrome and a clinical diagnosis based on four major defining features: 1) an urge to move the legs that is often irresistible and accompanied by other disagreeable sensations, especially in the legs, that are difficult to describe, 2) the urge to move and associated sensations are worse at rest, 3) the symptoms are temporarily relieved by leg movement, and 4) the severity is worse in the evening and often gone or greatly ameliorated by morning [1]. It is important to rule out itch, pain, and cramp in part by noting that the RLS patient has great difficulty localizing and describing the paresthesias. Along with these symptoms, the expected complaints of sleep-onset and sleep maintenance insomnia plus daytime fatigue, sleepiness, and mood disturbance are in fact the usual complaints. Because RLS symptoms are under circadian influence patients sometimes present with a change in sleep schedule toward a compensatory later wake-up time or longer mid-afternoon nap when the symptoms are in abeyance.

RLS is more prevalent in women and the prevalence increases further later in pregnancy [15], up to 30% in one study. RLS in pregnancy was associated with anemia in a Taiwanese population but a greater prevalence in pregnancy, a greater persistence of RLS after delivery, no association with anemia, no association with parity, and a positive association with snoring was found in a Scandinavian population suggesting significant ethnic differences. By comparison, a recent review in the general adult population found the prevalence of RLS to be 5–15% with risk factors of female gender, pregnancy, low iron levels, lower socioeconomic status, poor health, positive family history of RLS, and a comorbidity with psychiatric disorders [16]. A prospective cohort study found that women with RLS were at increased risk of depression six years later. Some studies report executive-type cognitive deficits in RLS. So-called “secondary RLS” may be diagnosed in the presence of neuropathy or iron-deficiency anemia.

Pathophysiology

The precise pathophysiology of RLS is unknown but considerable evidence suggests brain alterations in iron-handling as well as in dopaminergic and opioid systems. Coincidentally, the main positive therapeutic options are iron supplementation, dopamine agonists, and, with great caution in selected refractory cases, opioid medications. Thus, attention to RLS in the gravid outpatient often turns to iron status, avoidance of exacerbating substances, and behavioral interventions.

Significance in Pregnancy

New onset RLS in pregnancy may increase the risk of both RLS independent of pregnancy several years later and RLS during the next pregnancy [15]. Increased daytime sleepiness with risk of motor vehicle accident, fatigue, and more irritability and apathy would seem to be logical concerns but sleep is usually sufficiently disrupted by normal pregnancy that it is currently difficult to say with certainty how much additional adverse impact on mother and child might be specifically attributed to RLS [15]. In any case, RLS is very unpleasant and deserves treatment for that reason alone.

Management Considerations

A wide array of treatment options exist for RLS in the general population but currently there is insufficient evidence to recommend any specific treatment for RLS in pregnancy [17]. A quick screen for peripheral neuropathy affecting the legs is reasonable to decrease the likelihood of secondary RLS (see accompanying article on Peripheral Neuropathy in this issue of COG). Antidepressant drugs usually exacerbate RLS and should be avoided if clinically possible. Bupropion's dopaminergic property makes it a possible exception, but like most antidepressants, it is in pregnancy category C. Antihistamines (including over-the-counter) and caffeine (even many hours before bedtime) reliably worsen RLS. Alcohol can also exacerbate RLS in some people providing justification for confirming the alcohol history.

Dopamine agonists such as pramipexole and ropinirole are standard first-line RLS treatments in the general population. The smallest effective starting dose (one tenth of a Parkinson Disease dose or ~ 0.125–0.25 mg pramipexole-equivalent) is used to delay the rebound of restlessness earlier in the day and the augmentation of RLS severity that occurs eventually in many people on dopamine agonists. Very little is known about the teratogenic risk of these dopamine agonists and in the USA they are listed as pregnancy category C. As of 2008 in Canada, dopamine agonists were not recommended in pregnancy [18]. Combinations of L-DOPA with carbidopa are generally contraindicated in RLS whether the patient is pregnant or not because they carry an even higher risk of rebound and augmentation.

Brain iron stores are known to be low in idiopathic RLS even in the absence of obvious systemic iron deficiency. Thus, iron supplementation, regardless of normal hemoglobin level or hematocrit, is often considered in RLS when more subtle indications (ferritin < ~ 40–50 ng/ml or transferrin saturation < ~ 20%, depending on local laboratory reference ranges) of iron insufficiency are found. Low or borderline low iron reserve is not at all unusual even in non-pregnant women. An unusually high Total Iron Binding Capacity in this context may also prompt consideration of iron supplementation. However, current AASM guidelines rate this intervention only as an "Option" rather than a Guideline or Standard [17]. Again, one should not wait for iron-deficiency anemia before considering iron supplements for RLS. However, it is not known how to identify those individual patients who will respond symptomatically for prolonged periods of time to iron supplementation and published reviews provide little support for this intervention. The placebo response in RLS is also

known to be significant. Proprietary, over-the-counter formulations of slow-release iron are sometimes better tolerated than standard iron-gulconate or iron-sulfate tablets. Absorption is thought to be promoted by ingesting the iron on an empty stomach with an acidifying agent such as vitamin C. Enteral iron supplementation is safer but slower than intravenous infusion. Consideration of the latter should be done in consultation with a Sleep Medicine specialist. It is difficult to justify parenteral iron in the absence of iron-deficiency anemia though anecdotal reports of improvement in RLS within days to one week following intravenous infusions are not uncommon. More research on iron supplementation in RLS during pregnancy is clearly warranted given the paucity of safe and effective alternatives.

Enhanced External Counter Pulsation (EECP) has been reported to be effective for 6–12 months in small studies and would seem to be benign, but the 2012 AASM guidelines found insufficient evidence to recommend it [17]. ECCP is occasionally considered in heart failure and coronary syndromes and is thus not familiar to most Obstetricians or Sleep Medicine specialists. The device provides ~ 40 cm H₂O sequential pneumatic compression to the calves, then lower thigh, then upper thigh during diastole to enhance venous return to the heart. Studies reporting benefit for RLS typically employed EECP one-hour per day for about one month. The tolerability, low risk, and short latency to benefit of EECP justify further research in pregnancy.

Reduction of RLS symptom scores after daily 1-hour lower leg exposure to monochromatic near infrared light has been reported by only one author. The proposed mechanism includes vasodilatation via increased nitric oxide synthesis. The device is not yet commercially available. However, the biochemistry may overlap with the very extensive and compelling literature on photobiomodulation. Therefore, the plausibility of benefit and the safety of near-infrared light seem to justify clinical trials in pregnancy.

Narcolepsy

Clinical presentation

Narcolepsy onset in women is usually between age 15 and 25 and evolves in severity and manifestations over a period of several months. Though antecedent influenza vaccinations and streptococcal infections have been epidemiologically associated with narcolepsy, the patient typically denies any obvious precipitating factor. There is no clinically-significant predominance of female sex in the narcoleptic population despite the presumed autoimmune pathogenesis. Genetic risk factors have been identified but the reported family history is almost always negative (however, see the Pathogenesis section below). Though uncommon, narcolepsy is not rare with an estimated prevalence of about 1 in 3,000. Though academic performance and driving safety are impaired, the predominant symptom of excessive daytime sleepiness is often dismissed as just a common correlate of adolescence, perhaps because narcoleptics appear to be physically and neurologically normal. Tragically, the parents and/or the patient herself may falsely assume that the drop in grade point average or job performance is primarily due to Chronic Fatigue Syndrome, depression, or lack of discipline. Though not uncommon in narcolepsy (even without co-morbidities), fatigue (as opposed to sleepiness) is neither universal in narcolepsy nor necessary for the diagnosis. Dysphoric helplessness in the face of chronic irresistible sleepiness and cataplectic attacks may, in many cases, be more accurately viewed as a secondary consequence of narcoleptic symptoms rather than as a primary and explanatory diagnosis of affective disease. In contrast to Chronic Fatigue Syndrome, a directed history typically reveals frequent short and refreshing naps during the day (often with dream recall) and short awakenings at night consistent with the underlying pathophysiology of high REM sleep pressure plus difficulty consolidating both wakefulness in the day and sleep at night. Carefully-measured total 24-hour sleep time is thus normal. The weight gain that often accompanies narcolepsy onset

(see below under Pathophysiology) could falsely suggest a diagnosis of stress and depression-related hyperphagia or weight-related sleep apnea.

It is also not always appreciated that Narcolepsy can occur without cataplexy. Cataplectic spells can usually be distinguished from faints or seizures by the retention of consciousness throughout the episode (unless it is prolonged enough to result in sleep) and by the immediately preceding provocative emotion (most commonly laughter or excited anticipation). The loss of voluntary muscle tone in cataplexy is conceptualized as an intrusion of REM sleep muscle atonia. Thus, the atonia is always bilateral but can be focal (e.g. only in the eye lids or facial muscles). If the legs are not involved, then a fall is unlikely. If only the face is involved then only transient dysarthria with facial droop may result. Embarrassment in social situations leads some narcoleptics to preempt cataplexy by habitually blunting their emotions. Cataplexy usually only lasts from seconds to minutes but can cause injuries and is of great concern for driving safety. Other manifestations of high REM sleep pressure in narcolepsy include dream-like images (hypnagogic hallucinations) and/or frightening generalized immobility at sleep-onset (sleep paralysis).

Narcolepsy could be confused with Attention Deficit Hyperactivity Disorder (ADHD) because both present with intermittent lapses of attention in class, poor overall school or job performance, and improvement on stimulant drugs. However, idiopathic ADHD is not associated with disabling sleepiness, cataplexy, or hypnagogic phenomena. Adolescent and young adult OSAS does exist and can produce pathological daytime sleepiness resembling narcoleptic somnolence. Furthermore, females are more likely than men to have OSAS only in REM sleep with resulting REM-deprivation and “pressure” to enter REM sleep. As described above (see OSAS), UARS as a cause of daytime sleepiness is also more common in females and more likely than frank OSAS to be missed by the family or bed partner. The positive diagnosis of narcoleptic sleepiness and REM sleep pressure without other confounding sources of sleep disruption requires an experienced Sleep Medicine clinician to review the history, the exam, and the Sleep Laboratory EEG recordings of nighttime sleep and daytime naps. For these reasons, formal Sleep Medicine consultation is mandatory in suspected narcolepsy. The HLA antigen DQB1*0602 is found in > 90% of narcolepsy with cataplexy cases but is not diagnostically useful because about one quarter of the Caucasian population also carries this allele. Cerebrospinal fluid hypocretin concentrations are currently only done on a research basis.

Pathophysiology

Variable degrees of wake-stimulating hypothalamic hypocretinergeric neuronal loss associated with variable decrements in spinal fluid hypocretin level and clinical severity have been demonstrated in narcolepsy. Hypocretin stabilizes the “sleep-wake switch” and suppresses REM sleep which could explain the poor consolidation of sleep/wake states and the exuberant expression of REM sleep phenomena respectively. Hypocretin also suppresses appetite for food, which could explain weight gain at narcolepsy onset. The mechanism of hypocretin loss may be an autoimmune attack, triggered by upper airway infections, that specifically targets hypocretinergeric neurons. Thus, the pathophysiology of narcolepsy is currently summarized as a genetic predilection plus an environmental exposure. This is consistent with a concordance rate in monozygotic twins of only about 20–35%.

Significance in Pregnancy

Cataplexy per se is concerning antepartum as it could result in a fall or other accident. The intermittent and sometimes unpredictable sleepiness during pregnancy is not per se dangerous to mother and fetus but could secondarily cause a motor vehicle or other accident that in turn is damaging or fatal. Moreover, the uncontrollable aspect of both sleepiness and

cataplexy are stressful, sometimes including anticipatory maternal concern that postpartum child care will be inadequate (e.g. not tending to the child during narcoleptic naps or dropping their infant during cataplexy). Additional stress may ensue from parental concern that their child will inherit narcolepsy. The prevalence of narcolepsy by strict objective criteria in first degree relatives may be as high as 12% in China and 5% in Europe but increased sleepiness not quite meeting narcolepsy criteria was also measured in additional relatives from the Chinese study. Therefore, until more data are available from more ethnic groups, reassuring advice of low heritability should be avoided.

Management Considerations

The current mainstays of managing sleepiness in narcolepsy outside of pregnancy and lactation include disease education, good sleep hygiene, and symptomatic pharmacologic treatments that promote consolidated sleep at night and alertness in the day. However, prescription modafinil, methylphenidate, dextroamphetamine, and methamphetamine are Pregnancy Category C based primarily on animal studies suggesting embryo-toxicity, adverse effects on murine brain development in utero, and/or neuro-degenerative effects even in postnatal mice. These phenylethylamine-based stimulants also have potential for maternal abuse and newborn withdrawal. Therefore, use of these medications in pregnancy and during breast-feeding is problematic at best. Even the literature on caffeine in pregnancy is concerning [19]. There is also considerable recent controversy surrounding the risk of common sedative hypnotic medications in pregnancy (see Primary Insomnia / Management Considerations above). Therefore, Sleep Medicine consultation with a confident diagnosis of narcolepsy and exclusion of other causes of sleepiness is paramount. If cataplexy is significant, some authors would consider sodium oxybate (also known as gamma-hydroxy butyrate) at bedtime in pregnancy given its category B rating, sleep-consolidating effects, and anti-cataplectic actions [20]. Unfortunately, sodium oxybate is much less helpful for narcoleptic sleepiness and has a narrow therapeutic window for respiratory suppression.

Behavioral interventions with at least face-value to decrease the risk of physical trauma resulting from sleepiness or cataplexy include restrictions on driving, taking stairs, swimming, and social situations that trigger cataplexy. Brief prophylactic naps can be very effective if their timing is scheduled for optimal benefit by the patient herself. These interventions require a flexible schedule of social and/or personal obligations. Some patients may need to be given permission, or empowered by physician and spouse/partner, to take control of their daily schedule for this purpose for the sake of the pregnancy. Such flexibility is difficult in the work environment and requires a safe, socially-acceptable napping place but is also a “reasonable accommodation” for a medical condition that can be requested of the employer in writing by the physician. The nighttime sleep environment must also be optimized including as free of threats and environmental disturbances as possible. As in many disorders, patient-perceived symptom severity in narcolepsy may increase when patient-perceived stress increases. Behavioral stress-management interventions tailored to the individual patient, including Behavioral Psychology consultation, should be considered as needed. As a group, tricyclic (e.g. protriptyline) and serotonergic (e.g. fluoxetine) antidepressant medications might be considered here because they are also anti-cataplectic. On the other hand, these drugs reliably worsen RLS and are Pregnancy Category C. The possibility of labor-induced cataplexy prompts some authors to recommend consideration of elective cesarean delivery.

Summary and Future Directions

The diagnosis and management of sleep disorders specifically during pregnancy have not been well-studied and some aspects have not been studied at all. Larger and more detailed studies of: 1) obstructive, central, and complex (mixed) central-obstructive sleep apnea

syndromes, and 2) their treatment in different populations of pregnant women, are urgently needed to clarify the type, magnitude, and true costs of any resulting adverse pregnancy outcomes. Clinical research to customize CBTI for pregnant women, and to evaluate its efficacy in early pregnancy to ameliorate depression in later pregnancy and the postpartum, may bring long-term benefits for mother and child. Clinical trials of RLS treatments for pregnant women might emphasize: 1) different selection criteria for intravenous iron supplementation, 2) near infrared light, and 3) EECp. Animal studies of dopamine agonists in pregnancy could help prioritize clinical research on RLS during pregnancy. More basic research on the neuro-immunology of narcolepsy and greater community awareness would seem to be pre-requisites for autoimmune treatment trials in new-onset adolescent and young-adult narcoleptics before they become pregnant. To the extent that adverse pregnancy outcomes have the potential to incur long-term (in some cases life-long) societal costs of physical and neuro-behavioral disorders, all of the above clinical research holds great promise for improving health care system cost-effectiveness.

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Figure 1. Example of intranasal CPAP mask

It can also decrease nocturnal acid reflux. If CPAP is not tolerated after a few adaptation nights then follow-up with experienced physician-supervised Sleep Technicians to personalize and optimize mask fit, humidity, and air pressure profile may be necessary. Even in some moderate-to-severe cases, a dental appliance for mandibular advancement in sleep (Figure 2), preferably adjusted by a titration protocol, can be effective and better tolerated than CPAP. As seen in the Figure, the impression of the lower teeth is advanced anteriorly relative to the upper mold so as to advance the mandible and tongue and thus open the retro-glossal pharyngeal airway.

Figure 2. Example of dental appliance

In some mild cases, especially in habitual nose-breathers, so-called “nasal valves” worn in the nares during sleep can generate enough positive expiratory pressure to maintain adequate upper airway patency. There are no viable pharmacological options. Long-term follow-up is necessary after a diagnosis of OSAS, which may or may not resolve post-partum. A protocol for perioperative management has been developed for pregnant OSAS patients [9] including type of medical facility and unit, continued use of any CPAP or other home OSAS therapy after admission, close respiratory monitoring, early placement of regional anesthesia when operative management (e.g. cesarean section) seems likely, and avoidance of opioid medications. Such protocols will likely be refined and evolve over time.