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HYPOGLOSSAL NERVE STIMULATION
A NEW FRONTIER FOR SLEEP APNEA MANAGEMENT

COMBINATION THERAPY OAT AND CPAP

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HSAT INNOVATION

The Interplay Between Obstructive Sleep Apnea and Polycystic Ovary Syndrome

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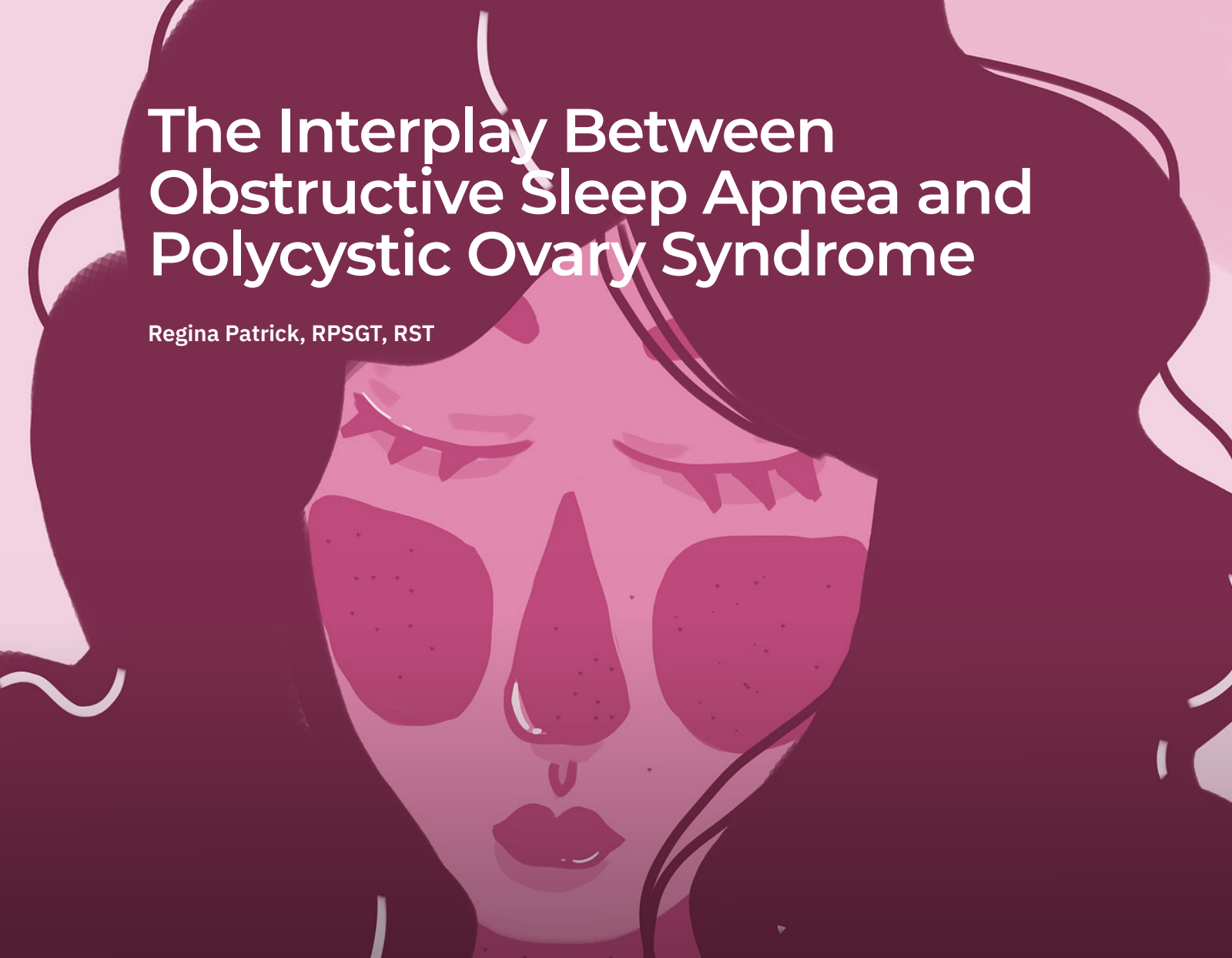

Polycystic ovary syndrome (PCOS) is a disorder in which many small fluid-filled sacs (i.e., cysts) develop on a woman's ovaries and the ovaries produce high levels of male sex hormones (i.e., androgens). PCOS is also associated with insulin resistance, glucose intolerance, and other features of metabolic syndrome (e.g., hypertension, excess body fat accumulation around the waist, and abnormal cholesterol or triglyceride levels) and nonalcoholic fatty liver disease (NAFLD, a condition in which the liver has an excess amount of fat but liver disease is not present). However, an overlooked feature of PCOS is the sleep disorder, obstructive sleep apnea (OSA). To understand the interplay between PCOS and OSA, differences in ovarian function between women without PCOS and women with PCOS need to be discussed first.

Normal Menstrual Physiology

The normal ovary undergoes three phases during the menstrual cycle (lasting approximately 28 days): the follicular, ovulatory, and luteal phases. The following events occur in each phase:

At the beginning of the follicular phase (day 1 [first day of bleeding] to day 13), the pituitary gland releases follicle-stimulating hormone (FSH), which causes several ovarian follicles (i.e., small fluid-filled sacs, each of which contains an immature egg) to form. As this phase progresses, the levels of FSH decrease, and usually, only one follicle continues to mature fully. The mature follicle attaches to the inner wall of the ovary and releases estrogen.

During the ovulatory phase (days 13–15), the pituitary gland releases a surge of luteinizing hormone (LH) and FSH. The increased LH level causes the follicle to rupture and release its egg (i.e., ovulation). The egg passes outside of the ovary. Fringe-like projections (i.e., fimbriae) on the end of the fallopian tubes draw the egg into the fallopian tube. The egg travels through the fallopian tube and enters the uterus. As the ovulatory phase progresses, the estrogen level decreases and the progesterone level starts to increase.

During the luteal phase (days 15–28), LH and FSH levels decrease and the ruptured ovarian follicle forms a cyst, called the corpus luteum, on the surface of the ovary. The corpus luteum produces progesterone to prepare the uterus for a possible pregnancy. If no pregnancy occurs, the corpus luteum degenerates, the levels of progesterone and estrogen level decrease, menstruation occurs, and the ovaries go through the follicular phase again.

Impact of PCOS on the Menstrual Cycle

In women with PCOS, multiple follicular cysts develop on the ovary and contain an immature egg, but they fail to mature and release the egg. The levels of LH remain high (i.e., a surge does not occur), which stimulates the excessive production of androgens. As a consequence,

a lower-than-normal number of periods in a year (i.e., oligomenorrhea) or no periods (i.e., amenorrhea) may occur.

Menstrual dysfunction is a major feature of PCOS. However, it can have metabolic consequences such as the development of diabetes, high insulin levels due to insulin resistance (which can stimulate the LH-induced production of androgens), enlarged ovaries, hirsutism (i.e., excessive hair growth in a male-like pattern such as on the face, chest, and back), hypertension, infertility, metabolic syndrome (i.e., hypertension, excess body fat around the waist, and abnormal cholesterol or triglyceride levels), obesity, and virilization (i.e., the development of male physical characteristics such as increased muscle bulk, body hair, and deep voice).[1-3]

PCOS has four subtypes:

- Asymptomatic: A woman has only polycystic ovaries but not the other associated symptoms (e.g., hyperandrogenism)
- Mild: A woman has polycystic ovaries and anovulation
- Classic: A woman has hyperandrogenism and ovarian dysfunction (i.e., anovulation and/or polycystic ovaries)
- Metabolic: A woman has mild or classic forms of PCOS combined with obesity (e.g., abdominal obesity and increased waist-hip ratio) and/or insulin resistance

NIH Criteria

In 1990, a consensus workshop sponsored by the National Institutes of Health/National Institute of Child Health and Human Development (NIH/NICHD) proposed that a woman has PCOS if she has all of the following symptoms:[4]

- Oligo-ovulation
- Clinical or biochemical signs of androgen excess
- Symptoms are not caused by other disorders that can result in menstrual irregularity and hyperandrogenism.

These criteria well fit women with the classic form of PCOS, but not if they have other forms of PCOS. In the past 30 years or so, this condition is better understood; thus, other criteria have since been proposed that better encompass the spectrum.

Rotterdam Criteria

In 2003, a consensus workshop, sponsored by the European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM) in Rotterdam, the Netherlands, proposed that a woman has PCOS if she has at least two of the following criteria and if symptoms are not caused by other disorders:[5]

- Oligo-ovulation and/or anovulation
- Excess androgen activity
- Polycystic ovaries (confirmed with gynecologic ultrasound)

This definition would include women with classic PCOS, as well as women with polycystic ovaries and clinical and/or biochemical evidence of androgen excess, but no ovulatory dysfunction, and women with polycystic ovaries and ovulatory dysfunction, but without signs of androgen excess. The Rotterdam diagnostic criteria are internationally accepted.

Androgen Excess and Polycystic Ovary Syndrome Society Criteria

In 2006, the Androgen Excess and Polycystic Ovary Syndrome Society (AE-PCOS) suggested restricting the diagnostic criteria so that a woman would have to have all of the following features for a diagnosis of PCOS:[6]

- Excess androgen activity
- Oligo-ovulation/anovulation and/or polycystic ovaries
- Symptoms are not caused by other disorders that cause excess androgen activity.

Therefore, the prevalence of PCOS varies, depending on the diagnostic criteria used. For example, Bozdag et al.[7] found a prevalence of 6%, 10%, and 10%, based on the criteria of the National Institutes of Health (NIH), the Rotterdam Consensus Workshop Group, and the Androgen Excess and Polycystic Ovary Syndrome Society (AE-PCOS), respectively. Sirmans et al.[8] found that the prevalence estimates using the Rotterdam criteria are two to three times greater than those obtained when using the NIH/NICHD criteria. In general, the prevalence of PCOS is estimated to be 5%–13%.[7] The Office on Women's Health estimates that approximately one in 10 women of childbearing age are affected by PCOS.[9]

THE OSA–PCOS CONNECTION

OSA may worsen symptoms of PCOS

In OSA, upper airway muscles relax excessively during sleep, which allows structures supported by the muscles to collapse into and block (i.e., obstruct) the upper airway. This restricts airflow, thereby decreasing the amount of oxygen in the blood. When the oxygen level falls to a certain point, the respiratory center in the brain triggers a brief arousal (lasting for a few seconds) during which the upper airway muscle tone is restored. At this point, the person is able to take some deep, quick breaths to restore the blood oxygen level.

In people with OSA, frequent episodes of hypoxia and arousals from sleep increases sympathetic nervous system activation, which may contribute to hypertension and alter lipid metabolism. In addition, OSA has long been associated with insulin resistance, impaired glucose metabolism, metabolic syndrome, and increased risk of developing NAFLD.[10-14]

In women with PCOS, the presence of OSA may make features of PCOS worse or more difficult to treat. For example, Tock and colleagues[15] demonstrated that the presence of OSA in women with PCOS strongly predisposed them to developing NAFLD and having a worse metabolic profile. Simon and colleagues[16] found that, among obese teen girls with PCOS, sleep-disordered breathing was more prevalent in girls with PCOS and metabolic syndrome than in girls with PCOS and no metabolic syndrome; they further found that a higher apnea-hypopnea index was correlated with higher triglyceride levels and that poor sleep efficiency was correlated with a higher percentage of liver fat, waist circumference, and higher triglyceride level.

PCOS creates the "perfect storm" for the development of OSA

Various features of PCOS may contribute to the development of OSA. For example, an enlarged fatty liver or excess abdominal fat due to hyperandrogenism may impact respiratory movements and contribute to upper airway collapse. Excess androgen levels and low progesterone levels that occur in PCOS may increase the risk of OSA by increasing upper airway collapsibility.[17] Obesity in women with PCOS may contribute to airway collapsibility in several ways: increased fat tissue in upper airway structures (e.g., tongue, soft palate) may narrow the pharyngeal airway size, thereby increasing the risk of airway collapse; fatty depos-

its in upper airway muscles may decrease the activity in these muscles that would normally protect against airway collapse; and central adiposity may reduce the tracheal traction needed to maintain a patent airway during sleep.[18,19]

TREATMENT OF OSA: A HELPFUL ADJUNCT

The extent that OSA treatment can improve PCOS has not been researched extensively. However, the findings of some research are encouraging. Tasali and colleagues[20] measured insulin sensitivity and secretion at baseline and after eight weeks of continuous positive airway pressure (CPAP) treatment in young women with both PCOS and OSA. Tasali found that CPAP treatment modestly improved insulin sensitivity and that the change in insulin sensitivity was positively correlated with CPAP use but negatively correlated with body mass index. The magnitude of this effect was impacted by adherence with CPAP use and the degree of a woman's obesity.

Scientists estimate that the risk for OSA is at least 5- to 10-fold higher in women with PCOS than in similarly obese women without PCOS.[21] In addition, some research indicates that women with PCOS are twice as likely to have OSA than are women without PCOS, regardless of the degree of obesity (however, the risk increases as weight increases).[17]

WHAT SHOULD BE DONE?

Despite such statistics, OSA in women with PCOS, as well as in women in general, is often underrecognized by clinicians.[20,22] A reason for this lack of awareness may be that most published studies of PCOS have not included OSA as a potential contributor to PCOS symptoms or pathophysiology.[23] As a consequence, clinicians are more likely to be aware of the greater prevalence of obesity, abnormal metabolic findings, and NAFLD, but less likely to be aware of the greater prevalence of OSA, among their patients with PCOS and less likely to be aware that the co-occurrence of OSA and PCOS may worsen symptoms associated with PCOS (e.g., insulin resistance, metabolic syndrome, hypertension, dyslipidemia). Thus, clinicians may not think to ask women with PCOS about symptoms of OSA (e.g., snoring, witnessed apneas, daytime sleepiness). This oversight may thwart efforts to control a patient's blood glucose levels, hypertension, and other PCOS symptoms. To what extent treating OSA could be helpful in controlling symptoms of PCOS is unknown and future studies are needed to clarify this issue. A greater understanding of the interplay between OSA and PCOS could potentially lead to more effective treatment for women with both disorders. ■

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