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Case: This is a 23-year-old with narcolepsy and cataplexy, treated with methylphenidate in the third trimester, resulting in an improvement of episodes of cataplexy. A review of the literature reveals information regarding options for medical management and the mode of delivery for these women.
Conclusion: Type 1 Narcolepsy can be treated with medications after consideration of risks and benefits. For patients who are symptomatic at the time of birth, cesarean section may be the preferred mode of delivery in women with type 1 narcolepsy.

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Type 1 Narcolepsy in Pregnancy: A Case Report and Review of Literature

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Conclusion: Type 1 Narcolepsy can be treated with medications after consideration of risks and benefits. For patients who are symptomatic at the time of birth, cesarean section may be the preferred mode of delivery in women with type 1 narcolepsy.

Keywords: Type 1 Narcolepsy, Cataplexy, Pregnancy, Delivery, Obstetric, Morbidity, Hospitalization

Introduction:

Narcolepsy affects 0.05% of the United States population and 1 in 2000 people globally. It is one of the most common causes of disabling daytime sleepiness after obstructive sleep apnea (OSA). There is no variation in gender, and symptoms can start at any point in life. It is estimated that only 25% of patients are diagnosed and receiving treatment for narcolepsy. [1] The focus of this case series is on a pregnant patient with type 1 narcolepsy, the medical management, and method of delivery.

Narcolepsy is a chronic clinical syndrome that affects the ability to regulate the sleep-wake cycle. Symptoms include hypersomnia, hypnagogic hallucinations, and sleep paralysis. [2] Orexin/Hypocretin A and B are neuropeptides that promote normal wakefulness, inhibition of REM sleep occurrence, and regulation of muscle tone. Losing hypocretin-producing neurons causes narcolepsy in humans. [3,4]

The diagnosis is divided into subtypes: Type 1 narcolepsy (previously known as narcolepsy with cataplexy) and Type 2 narcolepsy (previously known as narcolepsy without cataplexy). Type 1 narcolepsy is based on the individual either having low hypocretin levels (< or 110 pg/mL) in the lateral hypothalamus or manifesting as cataplexy. Type 2 narcolepsy

patients experience excessive daytime sleepiness but usually do not have muscle weakness triggered by emotions. They usually also have less severe symptoms and have hypocretin within a normal range (> 200 pg/ml). [5] The National Institute of Neurological Disorders and Stroke termed cataplexy as a "sudden loss of muscle tone while the person is awake that leads to feelings of weakness and a loss of voluntary muscle control." This can occur with emotions such as laughter and sadness and in women reported with sexual activity and during labor and delivery. [6] Narcolepsy is considered autoimmune in origin, but recent research also shows a genetic component. This is seen with A variation in this gene, called HLA-DQB1*06:02, which increases the chance of developing narcolepsy, particularly type 1 narcolepsy [5].

During pregnancy, physiologic changes in sleep can exacerbate underlying sleep disorders. A pregnant patient may experience fatigue and increased awakening during the night. Cataplexy has been known to worsen with poor sleep and fatigue, both common during pregnancy and postpartum .[7]

Case:

This is a 23-year-old primigravida who presented for prenatal care at nine weeks of gestation. She was diagnosed with type 1 narcolepsy two years before conceiving by a daytime sleep study. She was started on armodafinil and venlafaxine by a sleep specialist, which she discontinued from 9 weeks to 30 weeks gestation. During this time, she admitted to 3 episodes of cataplexy daily. Prior to the pregnancy, she would report up to 30 episodes daily. Her cataplexy would be triggered by excitement, such as when her husband returned home from work. She would bring herself to safety beforehand and had managed until the third trimester without any falls. She admitted to depression and anxiety surrounding her disorder, which worsened her

cataplexy. At 30 weeks of gestation, the patient complained of worsening cataplexy, sometimes reaching more than ten episodes daily, accompanied by severe fatigue. After consultation with the sleep specialists, maternal-fetal medicine, and counseling regarding the risks and benefits of the medication, she was initiated on the lowest effective dose of methylphenidate, 5 mg, which she continued until delivery. She continued to have 1 episode of cataplexy daily.

The patient's medical history was also significant for ulcerative colitis. She was diagnosed five years prior. She was treated with mesalamine 300 mg. She had recurrent flares before conceiving and active disease during her pregnancy, treated with oral prednisone, rectal mesalamine, and rectal hydrocortisone. The patient followed up with her gastroenterologist throughout her pregnancy.

Recommendations were given regarding cesarean delivery due to active rectal involvement of her ulcerative colitis and the patient's concern about cataplexy during labor. Patient presented at 37 weeks with spontaneous rupture of membranes. At this time, the patient was on 25mg of prednisone. Stress dose steroids were given, and she underwent a cesarean delivery under spinal anesthesia. She delivered a viable male infant, weighing 3152g, with Apgar scores of 9 and 9. The patient and the infant were discharged home on postoperative day 3. The infant had no signs of amphetamine withdrawal.

Discussion:

Treatment for type 1 narcolepsy involves behavioral modifications, proper sleep hygiene, and medications geared toward alleviating symptoms. Behavioral modifications involve regularly scheduled naps and exercising. Sleep hygiene consists of maintaining regular sleep and

wake times and getting appropriate sleep each night. Medications include modafinil, stimulants, antidepressants, and sodium oxybate.

There are significant challenges during pregnancy and childbirth in women with type 1 narcolepsy. These challenges include decisions about medications, risk of trauma, increased risk of adverse perinatal outcomes, and determination regarding mode of delivery.

The potential teratogenicity of medications available for narcolepsy has not been fully established. The risks and benefits should be discussed in detail prior to the initiation or continuation of these medications during pregnancy. [8] [Table I] In the literature, Pascoe et al. conducted a survey assessing pregnant narcolepsy patients. The survey assessed prescription narcolepsy medication use and discontinuation during pregnancy. The survey results indicate that 33.3% of women discontinued medication during pregnancy. 82.9% of women discontinued due to fears of harming the fetus, and 58.5% discontinued due to the recommendation of a provider. Alternative management was recommended, such as sleep extension, increased caffeine intake, discontinuing work, and discontinued driving. [9] Our patient resumed medication during her 3rd trimester because the risk of trauma secondary to her increased cataplectic episodes outweighed the potential risks of the medication.

A cataplectic episode can lead to falls and trauma to the mother and the fetus. Trauma in pregnancy can lead to devastating outcomes for the mother and her unborn child, including maternal injury, placental abruption, and fetal death.

Recent data has emerged to suggest that narcolepsy can increase the risk of adverse perinatal outcomes, and more so with Type 1 narcolepsy as compared with Type 2. A retrospective cross-sectional analysis was performed using nationwide inpatient sample (NIS) data in pregnant women with type 1 and type 2 narcolepsy, revealing that type 1 narcolepsy has

an increased risk of gestational hypertension (5.3%), preeclampsia (4.8%), and cesarean sections (1.1%) than in pregnant patients without narcolepsy. [5]

Mode of delivery can be complex since there are more obstetric complications seen and higher rates of cesarean sections in these women. There are cases reported of cataplexy during vaginal delivery that led to emergency cesarean section. In fact, the majority of the successful outcomes in the case reports are women who delivered by cesarean section. Although vaginal delivery is not contraindicated, if there are multiple narcoleptic and cataplectic episodes during labor and delivery, a cesarean section may be indicated. [8]

There is a paucity of data and case reports of type 1 narcolepsy in pregnancy [Table II]. In their article, Ping et al. describe a case of a 32-year-old female with a history of type 1 narcolepsy triggered by sexual excitement. Her cataplectic episodes were described as an inability to speak and involved atonia of her limbs. She remained off of her medications during pregnancy and resumed postpartum. She had an emergency cesarean section at 39 weeks, secondary to prolonged cataplectic episodes following each uterine contraction. [10] Williams et al. describe a 16-year-old female with narcolepsy, controlled on fluoxetine and modafinil, and glutaric aciduria during pregnancy. She continued to have episodes of cataplexy that worsened as she neared her delivery date. Their patient had an elective cesarean section at 38 weeks with favorable outcomes. [11] Hoque et al.'s recommendations to a 25-year-old pregnant patient involved discontinuing stimulant use unless the risks of narcolepsy substantiated the use of the medication. They believe a patient with significant cataplexy should also consider an elective cesarean section due to the risk of labor-induced cataplexy. [12]

We reported a case of a woman with type 1 narcolepsy during pregnancy, controlled on medication for worsening cataplexy in the third trimester. In total, the literature describes one

other case that continued medication during pregnancy with favorable outcomes. Comprehensive counseling of the patient regarding the risks and benefits of the individual medications during pregnancy is recommended. Our patient was successfully managed with the lowest effective dose of methylphenidate, 5 mg, and had an elective cesarean section with a successful maternal and neonatal outcome.

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Table I: Medications used in the treatment of narcolepsy and cataplexy [13,14,15,16,]

Medication	***Indication***	***Pregnancy category***	***Adverse events***	***Adverse events reported in neonates***
Modafinil	Excessive daytime sleepiness	C	Headache, nervousness, syncope, Steven-Johnson syndrome with higher incidence in pediatric patients	In June 2019, manufacturers stated to not give Modafinil to pregnant patients, as post marketing data showed 15% of congenital malformations detected

				in children exposed to Modafinil during pregnancy compared with 3% in the general population[14] 13% of 102 live births had major congenital malformations (MCMs) such as congenital heart disease, congenital torticollis, and hypospadias. Since there was no specific organ malformation pattern identified There cannot be an established association between use of modafinil and/or armodafinil and MCMs [13]

				May be excreted in breast milk.
Atomoxetine	Cataplexy	C	Dry mouth, xerostomia, headache, abdominal pain, decreased appetite, cough, somnolence, vomiting	No adequate controlled studies done in humans. Excreted in breast milk
Dextroamphetamine	Excessive daytime sleepiness	C	Loss of appetite, insomnia, abdominal pain, vomiting, fatigue, dizziness	Increased risk of premature delivery and low birth weight. May experience withdrawal symptoms. Excreted into breast milk.
Methylphenidate	Excessive daytime sleepiness	C	Headache, insomnia, abdominal pain	No controlled studies in humans. Excreted in breast milk. Associated with higher rates of prematurity, growth

				restriction, and neonatal withdrawal
Selective Serotonin Reuptake Inhibitors (SSRIs)	Cataplexy	C-D	Headache, nausea, insomnia, anorexia, anxiety, asthenia, diarrhea, decreased libido	Neonatal abstinence syndrome. Six-fold increase of persistent pulmonary hypertension in the newborn. Possible increase in frequency of pregnancy loss. Excreted in breast milk
Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)	Cataplexy	C	Headache, nausea, insomnia, asthenia, dizziness, somnolence, dry mouth, sweating	No controlled studies in humans. Possible drug discontinuation syndrome. Possibly associated with spontaneous abortion, low birth weight, prematurity, serotonin syndrome, and persistent pulmonary hypertension. Excreted in breast milk

Tricyclic Antidepressants (TCAs)	Cataplexy	C-D	Xerostomia, headache, constipation, fatigue, nausea, impotence, weight gain, mania, tremor	Associated with possible cardiac defects. Withdrawal symptoms: respiratory distress, cyanosis, tremor, and seizures. Excreted in breast milk.
Sodium Oxybate	Cataplexy associated with narcolepsy	B	Headache, nausea, dizziness, pain, somnolence, pharyngitis **Characterized as a schedule III controlled substance	No controlled data in human pregnancy

Table II: medication use, mode of delivery and outcomes of patients with narcolepsy during pregnancy

Author	***Age***	***Medication use in pregnancy***	***Mode of delivery***	***Outcome***
Hoque et al	25	No	Not stated,	Not stated

			advised their patient that cesarean may be preferred[2]	
Ping et al	32	No	Emergency cesarean due to cataplectic episodes during labor	Postpartum depression and excessive daytime sleepiness, resumed modafinil postpartum. Favorable recovery[5]
Williams et al	16	Yes: Fluoxetine and modafinil	Elective cesarean: due to increased cataplectic episodes	No complications, Apgar score of 7 and 9, mother and infant discharged after 3 days [4]
Our patient	23	Yes: methylphenidate	Elective cesarean: due to	No complications,

			active ulcerative colitis and worsening cataplexy	Apgar score of 9 and 9, mother and infant discharged after 3 days