

MOTHERISK ROUNDS

Medications for Restless Legs Syndrome in Pregnancy

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Abstract

According to epidemiological data, pregnant women have a two or three times higher risk of experiencing restless legs syndrome (RLS) than the general population. Current evidence suggests that dopaminergic dysfunction, impaired iron homeostasis, and genetic predisposition may be involved in the pathophysiology of RLS. Four classes of medications have been used for patients with RLS, but pregnancy elicits a therapeutic concern. Although two dopamine agonists, ropinirole and pramipexole, have been approved by the FDA for the treatment of RLS and are currently the first-line treatment for daily symptoms, there is very little information on the teratogenic risks of these new medications. Therefore, they are not currently recommended for use during pregnancy. Medications with a more extensive safety record in pregnancy include opioids; antiepileptics, such as carbamazepine and gabapentin; and certain benzodiazepines. Ruling out iron deficiency should be an integral part of a treatment plan for RLS in pregnancy. Before management with medication is introduced, every patient should be assessed for iron status with measurement of serum ferritin.

Résumé

Selon les données épidémiologiques, les femmes enceintes courent de deux à trois fois plus de risques de présenter le syndrome des jambes sans repos (SJSR) que la population générale. Les données actuelles semblent indiquer qu'une dysfonction dopaminergique, qu'une altération de l'homéostasie du fer et qu'une prédisposition génétique pourraient être mises en cause dans la pathophysiologie du SJSR. Quatre catégories de médicaments ont été utilisées pour les patientes présentant un SJSR; cependant, la grossesse soulève des préoccupations thérapeutiques. Bien que l'utilisation de deux agonistes de la dopamine (ropinirole et pramipexole) ait été approuvée par la FDA pour la prise en charge du SJSR et qu'elle constitue à l'heure actuelle le traitement de première intention contre les symptômes quotidiens, nous ne disposons que de très peu de données sur les risques tératogènes qu'engendrent ces deux médicaments. Ainsi, leur utilisation n'est actuellement pas recommandée au cours de la grossesse. Parmi les médicaments présentant un dossier d'innocuité plus étoffé pour ce qui est de la grossesse, on trouve les opioïdes, les antiépileptiques (tels que la carbamazépine et le gabapentine) et certaines benzodiazépines. Le fait d'écarter la présence possible d'une carence en fer devrait faire partie intégrante d'un plan de prise en charge du SJSR pendant la grossesse. Avant d'avoir recours à la médication, toutes les

patientes devraient faire l'objet d'une évaluation de leur état en ce qui concerne le fer (au moyen de la mesure du taux sérique de ferritine).

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INTRODUCTION

Restless legs syndrome (RLS) is a neurological disorder that is often associated with sleep disturbances and that results in reduced quality of life.^{1,2} Epidemiological evidence suggests that RLS is a common disorder with estimated prevalence ranging between 2.5% and 10% of the general population.^{3,4} The diagnosis of RLS is based on four major criteria established by the International RLS Study Group: the presence of an urge to move the legs, usually accompanied by unpleasant sensations; the occurrence of symptoms during inactivity or rest; relief with movement; and a worsening of symptoms in the evening or at night.⁵ Patients may describe the uncomfortable sensations as “creepy-crawly,” “like bugs (or worms) under the skin,” “burning,” “itching,” “grabbing,” or a variety of other sensations. Most people with RLS have sleep disturbances, largely because of limb discomfort and periodic limb movements.^{6,7} The result is daytime sleepiness and fatigue, especially in the severe forms of RLS.

RLS can occur as a primary disorder, with no apparent cause other than a possible genetic predisposition, or as a secondary condition, often related to iron deficiency, pregnancy, or end-stage renal disease.⁵ All of these secondary causes share a common factor of compromised iron status, supporting the concept that disturbed iron metabolism is a contributor to the development of RLS. However, the pathophysiology of RLS is complex and not yet fully elucidated. Current evidence suggests that three interrelated components may be involved: dopaminergic dysfunction, impaired iron homeostasis, and genetic predisposition.⁸⁻¹⁰

Key Words: Restless legs syndrome, pregnancy, dopaminergics, opioids, antiepileptics, benzodiazepines

Data from epidemiological studies suggest an 11% to 27% prevalence of RLS during pregnancy.¹¹⁻¹³ This observed risk in pregnant women is two to three times higher than in the general population.¹⁴ The last trimester of pregnancy seems to be the most critical, when the highest number of women develop symptoms, and when those with pre-existing RLS usually experience exacerbations.^{11,13,14} Up to 30% of affected women have a recurrence in subsequent pregnancies.¹³ However, Goodman et al.¹³ noted that symptoms disappeared in the postpartum period in the majority of patients.

TREATMENT

The goals of RLS treatment focus on improving symptomatology and hence quality of life. Pharmacological treatment is required only in moderate to severe forms of the disorder. It has been estimated that one third of patients have symptoms severe enough to warrant drug treatment.¹⁵ Pharmacologic treatment options for RLS can be classified into four categories: dopaminergic agents, opioids, benzodiazepines, and antiepileptics.

Dopaminergic Agents

In May 2005, the non-ergot dopamine agonist ropinirole became the first drug approved by the FDA for the treatment of RLS, followed by the second dopamine agonist pramipexole in November 2006. However, there is very limited evidence available regarding the overall safety of dopamine agonists in pregnancy, including those used for the treatment of restless legs syndrome (only one case report of pramipexole use during pregnancy, in a patient with Parkinson's disease, has been published¹⁶). Dopamine agonists (pramipexole, levodopa, and ropinirole) have been used very rarely during pregnancy, and safety data are lacking. Therefore, they are currently not recommended for use during pregnancy. Case reports of pregnant women with Parkinson's disease treated with a dopamine agonist are mainly restricted to women treated with levodopa. Levodopa appears to be safe to use during pregnancy, but case reports are still quite scarce.¹⁷

Alternative drugs with a better safety record that have been used more extensively for RLS during pregnancy include opioids and benzodiazepines.

Opioids

Opioids such as oxycodone, propoxyphene, and tramadol have been reported to be effective for treatment of RLS.^{18,19} Strong opioids, such as methadone, are recommended for the most severe cases.²⁰ Extensive published evidence documents the safety of using opioids in pregnancy; the only concern with their use is the possibility of a withdrawal syndrome in the neonate of a mother treated during the last

months of pregnancy.^{21,22} Nevertheless, at the usual therapeutic doses this is not usually a major concern.

The first clinical description of RLS is generally attributed to the 17th century British anatomist and physician Thomas Willis,²³ who was also the first to suggest opioids as a treatment. Nowadays, opioids are considered to be the safest of the drugs available to treat RLS during pregnancy.^{24,25} Although many clinicians may feel uncomfortable using long-term opioid therapy to treat symptoms for which there is no diagnostic test, these agents have been extensively used by patients with RLS with long-term benefit and little evidence of tolerance or addiction.^{24,26} Use of these drugs warrants consideration, because evidence suggests that sleep disruption caused by RLS may be associated with complications such as prematurity and difficult delivery.²⁷

Benzodiazepines

Data supporting the safety of benzodiazepines in pregnancy are less abundant, but still reassuring. The main concern with benzodiazepine use during pregnancy is the potential for an increased incidence of cleft palate, but this has not been proven and there is evidence, including a meta-analysis by Motherisk, suggesting that the risk is negligible.²⁸ Such risk does not exist if the drug is used only after the first trimester. A withdrawal syndrome has rarely been observed in neonates of mothers taking benzodiazepines.²⁹ Clonazepam is the most frequently studied and used benzodiazepine for RLS,³⁰ although others, including temazepam and triazolam, may also be useful.

Antiepileptics

Gabapentin has also been proposed as an effective treatment of RLS³¹ and has demonstrated efficacy equivalent to ropinirole in one study.³² This drug's safety for the fetus is reassuring, although the available information is still limited.³³ Folic acid supplementation (preferably 5 mg daily), especially during the first trimester, is mandatory in pregnant women taking gabapentin, given the association of antiepileptic medications with neural tube defects (although this has not been proven to date in the case of gabapentin).

Finally, carbamazepine was the first anticonvulsant evaluated in a controlled double-blind study for the treatment of RLS.³⁴ Currently, however, it is not often prescribed for RLS. Nevertheless, given the large body of data available from epilepsy registries on carbamazepine use in pregnancy, and its relative safety both for the mother and the fetus, carbamazepine should be considered a valuable option for the treatment of RLS in pregnancy, particularly in the second and third trimesters. Carbamazepine is currently considered by many to be the antiepileptic drug of choice during pregnancy. Recently published data from the UK Epilepsy and Pregnancy Register have shown that, for

monotherapy exposures, carbamazepine was associated with the lowest risk of major congenital malformation.³⁵

Iron Supplementation

In some cases of RLS during pregnancy, especially those associated with iron deficiency, iron supplementation appears to lead to improvement in symptoms. Because it is possible to have decreased iron stores without overt anemia, serum ferritin levels should be measured in patients with RLS.²⁴ Iron replacement appears to reduce or eliminate symptoms in patients who have serum ferritin levels < 45 µg/L.³⁶ Therefore, ruling out iron deficiency should be an essential part of the treatment plan for women with RLS in pregnancy.

CONCLUSION

Opioids currently have the best safety record of drugs available to treat women with RLS in pregnancy. Discontinuation near term should be considered because of the possibility of respiratory depression in the neonate. Carbamazepine and gabapentin may be useful alternatives, given their apparent fetal safety and large experience with their use in pregnancy. Attention to serum ferritin levels also is important.

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