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OVERACTIVE BLADDER (U LEE AND S ADELSTEIN, SECTION EDITORS)

Treatment of Refractory Urinary Urgency, Frequency, and Incontinence in Pregnancy

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Abstract

Purpose of Review The prevalence of urinary symptoms such as urgency, frequency, and urge incontinence is high in pregnancy and often becomes more bothersome further in pregnancy. First-line treatment often includes behavioral modifications such as avoidance of caffeine and timed voiding. Treating incontinence refractory to these first-line measures poses a challenge to the clinician given the concern for fetal harm, miscarriage, and preterm labor from current treatment modalities. The purpose of this review article is to summarize the most up-to-date literature of second- and third-line treatment options for urge incontinence in pregnancy as well as address the known and theoretical risks.

Recent Findings The etiology of urge incontinence in pregnancy remains poorly understood and is likely multifactorial. Pelvic floor physical therapy, oral medications, and sacral neuromodulation have been used during pregnancy with some efficacy and outcome reporting. The use of percutaneous tibial nerve stimulation or intradetrusor onabotulinum toxin A injections specifically for the treatment of overactive bladder in pregnancy has not been reported. The current data is limited and comes mostly from case studies/series and registry data.

Summary With the exception of pelvic floor physical therapy, limited evidence exists to recommend one treatment modality over another in pregnancy. The safety prolife of oral medications, onabotulinum toxin A injections, and neural modulation in pregnancy has not been conclusively established. The decision to use one of these treatments during pregnancy must weigh the known and theoretical risks against the potential benefits and include informed decision making with the patient.

Keywords Overactive bladder · Urinary incontinence · Refractory incontinence · Pregnancy

Introduction

Urinary symptoms such urgency, frequency, and incontinence are common complaints among pregnant women [1]. Overactive bladder symptoms prevalence tends to be high and remain stable throughout pregnancy from 12 weeks gestation onward [2]. A majority of women, 63%, experienced urgency symptoms. Eighty-five percent of the women who reported urinary frequency at 36 weeks had previously reported urinary frequency at 12 weeks gestation. Morkved et al. reported that urinary incontinence of any type occurred in 30.7% of women at 20 weeks of gestation and 48% of women at 36 weeks of gestation [3]. Urinary symptoms tend to become more bothersome as pregnancy progresses [4]. While stress urinary incontinence is more common among pregnant women, urge urinary incontinence (UUI) has been reported in 5.8% of women in early pregnancy (12 weeks of gestation). The prevalence increases with gestational age to 7.5% of women at 28–32 weeks of gestation and of women at 15.9% of women in late gestation (36–38 weeks) [1, 2, 5]. As high as 6.7% of women in early gestation and 16.9% of women in late gestation will be bothered by UUI symptoms [2, 5]. Despite the high prevalence of symptoms, the majority of women report to not find these symptoms bothersome [2]. More specifically, the experience of OAB-wet appears to more adversely impact quality of life than OAB-dry [6]. The experience of OAB-wet negatively impacts quality of life assessment primarily under the "mobility" and "embarrassment" domains [6].

This article is part of the Topical Collection on *Overactive Bladder*

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The pathophysiology of overactive bladder and urge urinary incontinence remains poorly understood and even less so in pregnancy. The development of OAB in pregnancy is likely multifactorial. Often cited factors including the increasing pressure on the bladder by the gravid uterus, increase in glomerular filtration rate due to increasing progesterone levels, and changes in bladder capacity [7]. Interestingly, human chorionic gonadotropin (hCG) has been shown to reduce detrusor contractility and is currently being investigated as a potential therapeutic for OAB. As such, the incontinence experienced during pregnancy may actually have a component of overflow incontinence [8]. Urinary changes in pregnancy cannot be explained entirely by changes in hormone levels though. Improvement in patient's urinary symptoms after delivery has been noted including patients requiring sacral neuromodulation prior to pregnancy and then not needing it after delivery. The resolution in symptoms is likely from a combination of factors including hormonal effects, pelvic accommodation and changes during pregnancy, and neural circuit re-education [9].

The treatment of overactive bladder during pregnancy should begin with behavioral modifications. However, if these measures fail to resolve symptoms, pregnancy can pose a significant challenge given the concern for teratogenicity and subsequent fetal harm, miscarriage, and preterm labor.

Pelvic Floor Physical Therapy

When behavioral modifications, such as timed voiding and avoidance of caffeine, fail to improve urinary urgency and frequency, conservative measures such as pelvic floor physical therapy should be considered.

As the uterus expands during pregnancy to accommodate the growing fetus, pelvic organs are pushed downwards thereby continuously exposing pelvic floor muscles to stress, weakening them. Sonography performed throughout early pregnancy demonstrates the pelvic floor to be displaced downward [10]. Additionally, during this time, reduced pelvic floor contractions and increased mobility of the urethra and bladder are seen [10]. Pelvic floor muscle thickness and strength protect against development of urinary incontinence. Pelvic floor physical therapy (PFPT) is commonly recommended during pregnancy and in the postpartum period both for the prevention and treatment of urinary incontinence [11].

Decreased pelvic floor muscle strength has been noted in late pregnancy (36–38 weeks); however, women who underwent PFPT were found to have a significant increase in muscle strength during pregnancy. Women who underwent PFPT experienced significant improvement in urinary loss and significant reduction in urinary frequency, urgency, nocturia, and urge incontinence symptoms [11].

A Cochrane review by Boyle et al. (2013) evaluated the effectiveness of pelvic floor muscle training in the prevention or treatment of urinary and fecal incontinence in pregnant and postnatal women. It reviewed and summarized comparisons of 22 studies testing PMPT versus usual antenatal/postnatal care for prevention and treatment of both urinary and fecal incontinence. Pelvic floor muscle therapy was shown to be effective in treating urinary incontinence. Research demonstrates that whether treatment was initiated during or after pregnancy, for women experiencing incontinence symptoms at either point, fewer women were incontinent in PFMT groups than in control groups with a risk reduction of 58%. When PFMT is utilized in mixed prevention or treatment in the antenatal setting, the prevalence of urinary incontinence is reduced by 20% in the late pregnancy period but does not extend after delivery [12].

Anticholinergic and Beta-3 Agonist Medications

Few studies exist regarding the safety of anticholinergic and the newer beta-3 agonist medications during pregnancy. A small retrospective cohort study described use of oxybutynin IR in four pregnancies among women with neurogenic bladder due to spinal cord injury. No pregnancy complications were noted (Table 1) [13].

OnabotulinumtoxinA Injection

Intravesical injection with onabotulinumtoxinA (obtxA) is a US Food and Drug Administration-approved third-line treatment option for overactive bladder (OAB). There are no case reports of intravesical obtxA injection specifically for the treatment of OAB during pregnancy; however, there are case reports of obtxA use during pregnancy, albeit at lower doses than those used for OAB, for indications such as migraine prophylaxis (71 U used at 18 weeks gestation), severe achalasia (80 U used at 33 weeks gestation), and facial cosmetic purposes (54 U used at 5 weeks; 65 U used at 6 weeks) [14–16]. None of the case reports reported any neuromuscular junction blockade at birth or birth defects. Newman et al. published a case report of women with severe cervical dystonia. During her four pregnancies she received 300 U of obtxA in the 3 months prior to conception and then between 300 and 900 U during the pregnancy including two pregnancies during which she received 300 U during the first trimester for a total of 600–1200 U in the pre-conception/antenatal period. APGAR scores were not available; however, there were no reported complications or birth defects, and all the children were noted to have normal neurocognitive development [17].

Table 1 summaries pregnancy categories and breast feeding information for commonly used medications for the treatment of overactive bladder/urge urinary incontinence

Medication	Pregnancy category	Breastfeeding
Oxybutynin	B	No information available, may reduce breast milk production; manufacturer reports cases of lactation suppression in some immediate-release formulation in post-marketing surveillance
Tolterodine	C	No information available, may reduce breast milk production; long half-life of 55 h
Solifenacin	C	
Fesoterodine	Not assigned	No information available, may reduce breast milk production
Trospium	C	No information available
Darifenacin	C	No information available
Mirabegron	Not assigned	

The largest study on pregnancy outcomes used the Allergan Global Safety Database to identify pregnancies during which women were exposed to either onabotulinumtoxinA or botulinum toxin. Approximately 574 pregnancies were identified, of which 276 had a known outcome; 232 pregnancies (137 prospective and 95 retrospective) were included in the analysis. The majority of exposure was during the first trimester, and almost half of the women received ≥ 100 U. They reported outcomes for both the prospective and retrospective cases; however given concern for recall bias, prevalence and risk assessment were interpreted from the prospective cases. Rates of spontaneous abortion and fetal defects among pregnant women treated with onabotulinumtoxinA were similar to the general population. The rates of elective and spontaneous abortion were 5.8% and 15.1%, respectively. The observed rate of any fetal defect was 2.7%, while the rate of major fetal defect was 1.8% [18].

OnabotulinumtoxinA is considered pregnancy category C due to animal studies that showed fetal body weight reduction and decreased skeletal ossification when administered during organogenesis at daily doses exceeding 8 U/kg (approximately 480–570 U for an average adult female) [19]. However, no adverse effects on fetal development were noted when rats received a single intramuscular injection of obtxA at doses of 1, 4, or 16 U/kg (approximately 60–72 U, 240–288 U, 960–1152 U for an average adult female) prior to implantation, at implantation, or during organogenesis [19]. OnabotulinumtoxinA has not been shown to circulate in peripheral blood as measurable levels after intramuscular or intradermal injection at recommended doses [20]. Additionally, the obtxA molecule is a large protein (150 kDa), and it is not felt that it crosses the placenta [21]. While not currently recommended, the use of obtxA during pregnancy must weigh the known and unknown risks against the potential clinical benefits. Additionally, the risk of urinary retention after intravesical obtxA injection must also be addressed with the patient as a patient may need to then perform clean intermittent catheterization which may be difficult to do and also potentially increase the risk of urinary tract infection which can cause its own set of problems during pregnancy.

Sacral Neuromodulation

Sacral neuromodulation (SNM) is an FDA-approved treatment for urinary frequency/urgency, urinary retention, and fecal incontinence. The mechanism of action of SNM has not been fully elucidated; however, it likely involves modulation of excitatory and inhibitory signal between the bladder and the spinal cord [22, 23]. The effect SNM on pregnancy, fetal status, and parturition has not been well evaluated [24]. Medtronic Inc., the manufacturer of Interstim™, recommends that the device be turned off once pregnancy is diagnosed.

Given the close proximity of the pelvic organs and cross-innervation of the pelvic plexus, there is theoretical concern that electrical stimulation of the pelvic plexus could induce uterine contractions resulting in miscarriage or preterm birth. An ultrasound study found that pre- and post-menopausal women treated with SNM did have wave-like uterine activity detectable on ultrasound [25]. However, animal studies have shown that direct electrical stimulation of the uterus can decrease contractility during delivery [26]. There is also concern that electrical stimulation to the fetus, especially during the critical period of organogenesis, may result in teratogenicity and subsequent congenital anomalies. A study of electrical stimulation in pregnant rats showed that there was no effect on the pregnancy; all rats had a healthy pregnancy without fetal anomalies or miscarriage, and fetal weight was not affected [27].

Another concern for SNM during pregnancy is that the SNM electrodes may be damaged or displaced by the gravid uterus or during parturition [9]. Additionally, the site of the SNM device may interfere with patient placement during delivery.

Multiple case reports and small case series have been published on SNM during pregnancy [9, 28–30]. The most current literature review was published by Mahran et al. in 2017 and reported on 22 patients with SNM that had 26 pregnancies. The SNM device was deactivated for 18 of the pregnancies, but remained active for the other eight. Of the 18 women who had their device deactivated, two women requested that the device be reactivated in the second trimester due to bothersome symptoms. In the 26 pregnancies, there was one miscarriage; however, this was in women who underwent in vitro

fertilization and whose device was deactivated prior to embryo transfer. Eighteen (72%) of the pregnancies resulted in full-term deliveries, while seven (28%) were preterm. Of the 25 pregnancies that result in birth, 16 were delivered via cesarean delivery, seven were spontaneous vaginal deliveries, and two were operative vaginal deliveries. Two of the 25 neonates were noted to have a birth defect or a neurocognitive disorder; one developed a motor tic disorder and was born with a congenital pilonidal sinus. Of note, both infants were the first two offspring born to the same mother, and the development of the pilonidal sinus was attributed to maternal gestational diabetes [31••].

The authors also reported on SNM function after delivery. Of the 25 patients, 14 still had functioning SNM devices. Three patients required reprogramming, one patient required revision, three patients required replacement, and four patients requested removal of the device. Sacral neuromodulation dysfunction was reported in eight out of the 25 deliveries; three after vaginal delivery and five after cesarean delivery. Two women were excluded from these numbers as they had been dissatisfied with their devices prior to delivery. Imaging was performed in two women who had recurrent symptoms postpartum. One of the women was noted to have a displaced and damaged lead, while the other woman's lead did not show evidence of lead displacement. One woman in the series complained of lower abdominal wall pain at the site of the pulse generator [31••]. It is likely that was due to compression from the gravid uterus and would not be seen among patients who had the pulse generator placed in the lower flank/buttock.

Yaiesh et al. (2016) published a literature review that included patients overgoing any type of electroneuromodulation while pregnant or trying to conceive. They reported on 75 patients, including 32 patients on SNM with 28 pregnancies, and 10 pregnancies in seven patients with spinal cord stimulation (SCS). Their results were generally similar to those of Mahran et al. They found that of the pregnancies that occurred while on SNM or SCS, most were unplanned, and diagnosis was made well into the first trimester—i.e., the fetus was exposed to weeks of electroneuromodulation. They concluded that there were no significantly reported congenital abnormalities or miscarriages that can be attributed solely to the prenatal neuromodulation, the presence of the implanted device during pregnancy, or even neuromodulation during pregnancy. Additionally, they cite work by Karsdon and Bernadini concluding that neuromodulation, either SNM or SCS, does not alter systemic levels of reproductive hormones nor do they affect maintenance of the gravid uterus or induction of labor [26, 32, 33]. Sacral neural stimulation does not appear to alter electronic fetal heart monitoring intrapartum [32, 33].

Current manufacturer guidelines recommend deactivation of the device once pregnancy is diagnosed. However, there is insufficient evidence to definitively recommend continued use versus deactivation of the device. The current evidence is limited and is derived from case studies and case reports. The first trimester is a critical window during pregnancy during which a fetus is most susceptible to teratogenic effect. In one of the largest case series, over 50% of women had the device active during some period of the first trimester, and approximately 30% of women had the device active during the entirety of their gestation [31••]. The decision to continue the use of sacral neuromodulation during pregnancy must weigh potential risks to the fetus against risks associated with return of symptoms. While a woman many tolerate the return of urinary urgency and frequency, women using sacral neuromodulation for chronic urinary retention may find that deactivation requires the use of clean intermittent catheterization or indwelling Foley catheter which can result in chronic urinary tract infection, pyelonephritis, and subsequent preterm delivery [34].

The most widely debated aspect of SNM during pregnancy is mode of delivery. Many authors advocate for cesarean delivery given concerns that maternal positioning during vaginal delivery, prolonged engagement of the fetal head, and increased pressure against the pelvis may cause lead displacement or damage to the implantable pulse generator [28]. However, among the multiple case series, there are higher rates of device dysfunction among patients who were delivered by cesarean section [29, 30]. There is not enough evidence to suggest one mode of delivery over another, and current clinical guidelines recommend proceeding with cesarean delivery for obstetric indications [35].

To our knowledge, there are no case reports of women who had the sacral neuromodulation device placed during pregnancy. The American College of Obstetricians and Gynecologists recommends that any elective surgery be postponed until after delivery [36]. The gravid uterus and the altered physiology of pregnancy may make the prone position necessary for sacral neuromodulation placement uncomfortable for the patient or even dangerous to the fetus. Additionally, prone positioning would make fetal heart rate monitoring and tocometry difficult if either of these were necessary.

Percutaneous Tibial Nerve Stimulation

No case reports or case studies are available regarding the use of percutaneous tibial nerve stimulation during pregnancy. Given the paucity of available data, no recommendations can be made for or against its use during pregnancy.

Conclusions

While urinary symptoms are common throughout pregnancy, most women do not find these symptoms bothersome. Treatment of these symptoms though is particularly challenging as there is concern for teratogenicity, miscarriage, and

preterm labor. With the exception of pelvic floor physical therapy, limited evidence precludes the recommendation of one treatment over another, and the safety profile of medications, onabotulinumtoxinA injections, and neural modulation in pregnancy has not be conclusively established. The decision to use one of these treatments during pregnancy must take into consideration the limited data available, the potential risks to the fetus versus the potential risks without the treatment, and the patient's informed decision-making.

Compliance with Ethical Standards

Conflict of Interest Jon F. Pennycuff declares that he has no conflict of interest. Joseph White declares that he has no conflict of interest. Amy Park has received speaker honorarium from Allergan.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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