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Case Series of Botulinum Toxin Administered to Pregnant Patients and Review of the Literature

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Abstract

Objective: To evaluate a case series of patients who received medically necessary botulinum toxin during pregnancy.

Materials and Methods: Retrospective chart review of three patients who underwent repeated intralaryngeal injections of botulinum toxin during pregnancy. Chart reviews were also conducted on the children to further evaluate the safety.

Results: No evidence of harm to the mothers or fetuses were found in our series, including data from pregnancy and birth records using standard measures of gestation, APGAR scores, neonatal intensive care unit stay, and time until discharge. Clinical data for 3–5 years were available for the children. No evidence of muscular weakness was noted and all diagnoses were listed.

Conclusion: Botulinum toxin injection for functional airway issues was not associated with any adverse effects to the mother or fetus during pregnancy in any of the cases reviewed. We recommend further investigation to evaluate the current contraindication of elective botulinum toxin use in pregnancy.

Introduction

Botulinum neurotoxin A (BoNTA) was discovered in the early 1900s, receiving its first U.S. Food and Drug Administration (FDA) approval in 1989 and is now used to treat a multitude of conditions, both functional and cosmetic.[1–4] Pregnancy and lactation are relative contraindications for botulinum toxin injections. Owing to the elective nature of the injections for aesthetics, most patients and physicians have elected to delay treatment during pregnancy and nursing periods.[5] Botulinum toxin is also used in the field of laryngology to treat adductor spasmodic dysphonia, a condition that requires constant treatment to preserve the airway and voice.[6] To our knowledge, there are no published studies evaluating the safety of botulinum toxin injections that were administered knowingly and consistently throughout pregnancy.

A case series is presented of three patients who underwent botulinum toxin treatments before, during, and after pregnancy. All patients had previously established care with a laryngologist, and required botulinum toxin injections every 3–4 months for several years before the pregnancy. In addition, the children's medical records were available and reviewed to fully evaluate the safety of the treatments.

Materials and Methods

In compliance with the University of Utah IRB and after approval was granted, a retrospective medical record review of patients who had undergone intralaryngeal injection of botulinum toxin A during pregnancy was performed. The analyzed data included gravida, parity, age, gender, diagnosis, comorbid condition, time of injections during pregnancy, health at time of birth of mother and infant were reviewed by using intrapartum records, complications at time of injection or birth, neonatal intensive care unit (NICU) stay, and appearance, pulse, grimace, activity, and respiration (APGAR) scores. In addition, the children's medical records were also reviewed for all medical problems listed through all available follow-up.

Results

Case #1

A 37-year-old woman with adductor spasmodic dysphonia was treated with onabotulinum toxin A injections during her second pregnancy. Her first pregnancy had been

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KEY POINTS

Question: Is botulinum toxin safe during pregnancy? The safety of botulinum toxin use in pregnancy has not been thoroughly studied due to the ethical constraints related to the possible risks to the mother and fetus. We review three cases of medically necessary intralaryngeal use of botulinum toxin administered before, during, and after pregnancy.

Findings: No adverse events were noted in the mother or the fetus. Review of the current literature sheds further light into the safety of botulinum toxin use in pregnancy for both functional and cosmetic indications.

Meaning: We recommend further investigation before the restrictions are adjusted for cosmetic procedures, although this adds to the growing literature of the safety of botulinum toxin during pregnancy.

aborted. Past medical history included migraines. Based on the due date used during her pregnancy, she underwent botulinum toxin A injections at 4 weeks and again at 34 weeks, with 3.37 total units injected each time to the thyroarytenoid muscles. She received all routine prenatal care, including anatomy scan, blood type and Rh screening, immunizations, infectious screening, gestational diabetes screen, and sexually transmitted infection screen. She was diagnosed with intrauterine growth restriction with concern for possible coarctation of the aorta. She was noted to have an active fetus on all prenatal visits, and at 37.1 weeks delivered a 2454 g female vaginally, without complications. APGAR scores were 8 at 1 min, with the loss of one point for pale blue color, and 9 at 5 min. The infant was observed overnight in the NICU as a precaution for possible coarctation of the aorta and echocardiography was performed without evidence of any abnormalities. Vitals remained stable throughout her 48 h well-baby nursery stay. She was breastfed. Three years of medical records were available for review, revealing a herpes simplex virus infection at 14 days old, requiring a peripherally inserted central catheter, and infectious disease follow-up, ultimately resolving within 10 days with treatment. She was also diagnosed with recurrent otitis media. The child was noted to meet all growth and developmental milestones.

Case #2

A 32-year-old woman with adductor spasmodic dysphonia was treated with onabotulinum toxin A injections during her first pregnancy. Past medical history included asthma. Based on the due date used during her pregnancy, she underwent botulinum toxin A injections at 9 weeks, at 34 weeks, and again 7 weeks after pregnancy, with 2.5 total units injected into the thyroarytenoid muscles each time. She received all routine prenatal care, including anatomy scan, blood type and Rh screening, immunizations, infectious screening, gestational diabetes screen, and sexually transmitted infection screen. She was noted to have an active fetus on all prenatal visits, and at 38.6 weeks delivered a 2530 g female vaginally, without complications. APGAR scores were 8 at 1 min, with the loss of one point for pale blue color, and 9 at 5 min. Five years of clinical data were available on the child. The infant was not breastfed. She was worked up for difficulty gaining weight; however, all workup was found to be normal, and the conclusion from the pediatrician was that it was genetic, as both parents are thin and had similar difficulty gaining weight as young children. The child was also diagnosed with sleep disordered breathing and adenotonsillar hypertrophy, requiring an adenotonsillectomy at age 3. She was followed for lead exposure, folliculitis, and eczema, although she was noted to be meeting all her growth and developmental milestones.

Case #3

A 33-year-old woman with adductor spasmodic dysphonia was treated with onabotulinum toxin A injections during her second pregnancy. Her first child had been born full term and was living. Past medical history included anemia of pregnancy, tremor, depression and anxiety, abnormal pap smear requiring LEEP, former tobacco use quit 3 years prior, and alcohol use. Based on the due date used during her pregnancy, she underwent injections of the thyroarytenoid muscles and thyrohyoid muscles on the day of conception, and during pregnancy at 14 weeks, and 3 weeks after giving birth. A total of 10 U of botulinum toxin A were used, divided between injection sites. She received all routine prenatal care, including anatomy scan, blood type and Rh screening, immunizations, infectious screening, gestational diabetes screen and sexually transmitted infection screen. She was noted to have an active fetus on all prenatal visits. She experienced preterm labor at 35 weeks and was treated with tocolysis for 1 week. At 36.2 weeks she delivered a 3175 g male vaginally, without complications. APGAR scores were 8 at 1 min, with the loss of one point for pale blue color, and 9 at 5 min. He was given supplemental oxygen briefly for increased work of breathing. He did not require NICU support. He was breastfed. Records for the child through 5 years were followed, medical problems diagnoses included congenital anomaly of the kidney and vesicoureteral reflux diagnosed after an episode of urosepsis at 4 months of age that resolved with inpatient treatment. He was also noted to have tobacco smoke exposure, an accidental ingestion of a potentially harmful entity, and asthma noted to be well controlled with medications. The child was noted to meet all growth and developmental milestones.

Discussion

Today, with >6.6 million treatments annually, BoNTA is the most frequently performed nonsurgical cosmetic procedure

Table 1. Impact of onabotulinumtoxinA in pregnant animals

Animal model	*Dose*	*Administration schedule*	*Developmental stage*	*Effect*
Mice, rats	4 U/kg	2× daily	Gestation days 5 and 13	No effect
Rats, rabbits	1 U/kg (rats) 0.25 U/kg (rabbits)	1× daily	Gestation period	No effect
Rats, rabbits	≥4 U/kg (rats) ≥8 U/kg (rabbits)	1× daily	Gestation period	Maternal toxicity
Rats	1, 4, or 16 U/kg	1×	Before implantation, implantation, or organogenesis	No effect

Data from onabotulinumtoxinA prescribing information, Allergan, Inc.[22]

in the United States.[7] In the past two decades, numerous studies have established the safety and efficacy of BoNTA both in therapeutic and in cosmetic treatments.[8–19] The majority of reported adverse events (AEs) associated with BoNTA injections have been relatively mild and resolved without requiring any intervention. The most common AEs have involved injection site effects with the cosmetic use. Muscle paresis is an expected effect of BoNTA as the release of acetylcholine neurotransmitter is inhibited at the neuromuscular junctions near the site of injection, which may, consequently, lead to temporary local weakness. Thus, whereas nearly 30 years of clinical application and extensive research may seem to support the wide therapeutic index and safety profile of this product, concerns over yet undefined severe AEs and complications still exist, specifically in groups that are typically excluded from studies such as pregnant patients.

The data regarding the effects of BoNTA in pregnancy are scarce. As a result, BoNTA is considered a Category C drug by the FDA indicating that it should be used only if the potential benefits would justify the potential risks to the fetus.[5] Consequently, the standard of care in the United States is to avoid treating patients who are pregnant or are attempting to get pregnant with BoNTA, especially for the cosmetic indications. Unfortunately, there are limited studies examining the effects of BoNTA treatments in animal models of pregnancy. Hildebrand et al. measured the concentration of BoNTA in different body fluids of pregnant rabbits that were injected intravenously with a lethal dose of the toxin.[20] There were no detectable levels of BoNTA present in the placenta or the fetal blood at the time of the rabbits' death. From this study's results and the knowledge of molecular size constraints with human placental diffusion, it is believed that the active BoNTA molecule is too large to cross the human placenta barrier.[21]

Effects of BoNTA administration with various doses and schedules have been examined in animals using onabutulinmtoxinA (Table 1) and abobotulinumtoxinA (Table 2). Based on these studies, the no-effect dose for a single maternal injection of onabotulinumtoxinA in rats (16 U/kg) is ~50 times greater than the average cosmetic dosage generally administered in humans and, therefore, several hundred times higher than the doses used to treat the patients in this case series.[22] There have, however, been no formal studies examining the effects of BoNTA administration in pregnant woman, and the available evidence is mainly from various case studies.[23–26] Newman et al. first reported the case of a 26-year-old woman who experienced four apparently uncomplicated pregnancies while receiving treatments every 3–4 months with 300 U of onabotulinumtoxinA for idiopathic cervical dystonia, administered within 3 months of conception and during pregnancy, up to 1200 U in each pregnancy.[23] None of the children were breastfed. Although the children were not assessed directly, there were no suggestions of cognitive or motor developmental delays during the follow-up period, which was about 5 years for the oldest child.[23]

Bodkin et al. described two patients who were administered BoNTA in the first trimester of pregnancy.[26] Both patients suffered from cervical dystonia and had been receiving regular treatments of BoNTA for 3 years. The first patient, a 38-year-old woman, was administered 200 U of onabotulinumtoxinA at 2 weeks gestation. She did not receive any further injections during the pregnancy and was reported to deliver a healthy term baby by cesarean section.[26] The second patient, a 39-year-old woman, was administered 500 U of onabotulinumtoxinA when 4 weeks pregnant. An ultrasound performed 2 weeks postinjection revealed twin gestation of 10 weeks with no heartbeat. A causative relation between the BoNTA injection and the fetal demise, however, could not be established due to other high-risk factors, including the patient's age, medications, twin gestation, and a history of miscarriage.[26]

To determine the physicians' experience with BoNTA administration during pregnancy, Morgan surveyed 900 physicians who used commercially available BoNTA in

Table 2. Impact of abobotulinumtoxinA in pregnant animals

Animal model	*Dose*	*Administration schedule*	*Developmental stage*	*Effect*
Rats	2.2, 6.6, 22 U/kg	1× daily	From gestation days 6 through 17	Early embryonic death
Rats	44 U/kg	1×	Gestation day 6 and 12	Early embryonic death
Rats	22.2 U/kg	1× weekly	Gestation day 6 through parturition to weaning	No effect

Data from abobotulinumtoxinA prescribing information, Galderma Laboratories, L.P.[27]

their practice.[5] Among the 396 (44%) of the questionnaires returned, 12 physicians (3% of responders) had injected pregnant woman with BoNTA. Overall, 16 women had received 1.25 to 300 U of BoNTA for cervical dystonia, strabismus, blepharospasm, limb dystonia, oromandibular dystonia, and spasmodic dysphonia. Of the 19 total pregnancies (one woman had three separate pregnancies while receiving BoNTA injections), one was terminated medically and one was miscarried. The patient who miscarried was injected with 300 U of BoNTA for cervical dystonia and had a history of spontaneous abortion; therefore, a causal relationship between her miscarriage and the BoNTA injections could not be established. The other 17 pregnancies were reported to have gone to full term without complications and without any special postnatal care for the infants.[5]

The standard dose of BoNTA used in cosmetic procedures (20 or 85 U for glabellar and 24 U for lateral canthal lines) is a few folds lower than what is commonly administered for the therapeutic indications for dystonia and 10- to 20-fold higher than what is typically used for spasmodic dysphonia.[27] Thus, treatment-related AEs would be expected to be lower in the cosmetic applications, and even lower in therapeutic laryngeal injections. Considering its widespread cosmetics and therapeutic application, it is essential that the effects of BoNTA on pregnancy be determined in more detail. Currently many of the childbearing women who receive therapeutic treatments for disorders such as cervical dystonia, have to choose between continuing the benefits of their therapy and becoming pregnant. In addition, reasonable estimates $\sim$10 million injections annually on women who are, at least unknowingly, pregnant. To fully establish the safety and efficacy of BoNTA during pregnancy, more systematic studies are required.

Conclusion

BoNTA provides a broad range of therapeutic as well aesthetic benefits. Despite being a potent toxin, it has demonstrated a long history of safety when used properly. Although years of clinical research have examined its safety and efficacy, little research has been performed in pregnant women. Our case series is the first to fully evaluate the safety of treatment in pregnant women as well as the children. This study adds to the growing literature to further understand the effects of use during pregnancy. Given the small sample size and the low doses of medication used, we recommend further investigation before the restrictions are adjusted for cosmetic procedures.

Author Disclosure Statement

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