

SHORT REPORT

Botulinum toxin A during pregnancy: a survey of treating physicians

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Botulinum toxin A (btxA) is widely used for cosmetic purposes, headaches, dystonia, spasticity, pain and other on and off label uses. Despite the widespread use of btxA in women of childbearing potential, there are few data on the effects of this drug on pregnant women and the fetus. The goal of this study was to survey physicians who use btxA, to determine their experience with pregnant women. We surveyed 900 physicians who used commercially available btxA. The questionnaire asked treating physicians if they had knowingly or unknowingly injected pregnant women and what was the outcome of each pregnancy. In total, 396 physicians (44%) returned questionnaires, of whom only 12 physicians reported injecting pregnant women with btxA. Sixteen pregnant women were injected, mostly in the first trimester, and only one patient, who had prior spontaneous abortions, suffered a miscarriage. Another woman had a therapeutic abortion. All other pregnancies went to term and there were no fetal malformations. Based on this limited survey of treating physicians in the USA, btxA appears to be relatively safe for both expectant mother and fetus. We need further data, however, and we would recommend that physicians and patients carefully consider the risks and benefits before using btxA in pregnant women.

The effects of botulinum toxin A (btxA) administration during human pregnancy are largely unknown. There is only one prior report on the use of btxA during pregnancy.¹ FDA approved labeling for btxA indicates that this toxin is pregnancy risk category C, and recommends that it should be “administered during pregnancy only if the potential benefit justifies the potential risk to the fetus”.² We report the results of a survey of treating physicians who routinely use btxA for various disorders. Our survey results indicate that there is no obvious qualitative association of btxA injection with any adverse outcomes of pregnancy including miscarriages or fetal malformation.

MATERIALS AND METHODS

We mailed a one page survey (fig 1) to 900 US physicians identified from a national prescription database who had used btxA in late 1995 and 1996. Results of this survey were presented previously in abstract form.³ The questionnaire asked the physician to estimate the number of patients they had injected with btxA, whether or not they had knowingly or unknowingly injected pregnant women, the indication for btxA therapy, and how many units were used. We also wanted to know the trimester during which the patient had received the drug and what was the outcome of the pregnancy. We also questioned the physicians about their comfort level with administering btxA during pregnancy.

RESULTS

In total, 396 physician questionnaires were returned (44% response rate) and only 12 physicians (3% of responders) had knowingly or unknowingly injected pregnant women with btxA. Two physicians with considerable experience (they had injected 1900 and 2000 patients, respectively) had injected three pregnant women each. The other 10 physicians reported injecting only one pregnant woman each. In total, 16 women received btxA injections while pregnant; one patient received injections while carrying twins and another patient received injections repeatedly during three separate singleton pregnancies.

Of the 16 women, 12 were injected during the first trimester, 1 during the second, 1 during the third, and in 1 patient the duration of pregnancy at the time of injection was unknown. The woman who was injected with btxA during three separate pregnancies received 1–3 injections during each pregnancy, occurring over all three trimesters (approximately 300 U per treatment). The injected btxA dose ranged from 1.25 U to 300 U (of the Botox formulation). Indications were cervical dystonia (9 patients), strabismus (2), blepharospasm (2), limb dystonia (1), oromandibular dystonia (1), and spasmodic dysphonia (1).

Of the 19 pregnancies, one was terminated medically and another woman with a history of spontaneous abortion miscarried. The woman who had a miscarriage had received one series of injections for cervical dystonia and had received approximately 300 U of btxA. The other 17 pregnancies went to full term without complications and none of the infants needed special postnatal care.

Of the 12 physicians, only one (with over 2000 total patients injected) was “very comfortable” and five physicians were “somewhat comfortable” with using btxA during pregnancy.

DISCUSSION

Botulinum toxin A is produced by *Clostridium botulinum* as a single chain polypeptide with a molecular weight of 150 kDa.⁴ Studies of btxA injection in pregnant animals are limited; however, these studies suggest that btxA does not cross the placenta, perhaps due to its large size. In one study, the concentration of btxA was measured in different body fluids after administering a highly lethal intravenous dose to pregnant rabbits.⁵ There was no detectable level of btxA in the placenta or fetuses at the time of death of the rabbits.⁵ For pregnant mice and rats during organogenesis, the developmental NOEL (no observed effect level) was 4 U/kg.² This would roughly translate into a dose of 240 U for a 60 kg woman. Doses of 8 U/kg and 16 U/kg were associated with “reductions in fetal body weights and/or delayed ossification which may be reversible.”² In rabbits, however, daily doses of 0.125 U/kg from days 8–18 of gestation or 2 U/kg on day 6

Abbreviations: btxA, botulinum toxin A; EMG, electromyography; NOEL, no observed effect level

Use of Botox during pregnancy survey

1. Do you currently use Botox for any condition? _____yes _____no
(If yes, answer questions below)
2. Your name _____ Specialty _____
(optional)
3. Approximately how many patients have you injected Botox? _____
4. What conditions have you given Botox for?

Blepharospasm _____	How many patients? _____
Hemifacial spasm _____	How many patients? _____
Cervical dystonia _____	How many patients? _____
Limb dystonias _____	How many patients? _____
Spasmodic dysphonia _____	How many patients? _____
5. Have you knowingly or unknowingly injected pregnant patients(s) with Botox?
_____yes _____no
6. If yes, how many patients have you injected during pregnancy? _____
7. For which condition/conditions was Botox given? _____
8. What stage of pregnancy were these patients?
1–14 weeks _____ 14–28 weeks _____ 28 weeks–term _____ Unknown _____
9. What dosages did you inject? _____
10. What was the outcome of the pregnancy? Miscarriage _____ Went to term _____
11. Were there any problems with the infant in the immediate postnatal period? _____
12. How comfortable do you feel based upon your experience to inject pregnant patients? _____ Uncomfortable _____ Somewhat comfortable _____ Very comfortable

Figure 1 Survey that was mailed to 900 US physicians who used commercially available botulinum toxin A.

and day 13 of gestation produced severe maternal toxicity, abortions, and/or fetal malformations.² Given these data, product labelling also indicates that “if the drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential risks, including abortion or fetal malformations which have been observed in rabbits”.²

There are multiple case reports of pregnant women developing botulism unrelated to therapeutic use of btxA. One pregnant woman with botulism was totally paralysed and required mechanical ventilation; the movements of the 5 month fetus were normal and she had a normal spontaneous delivery at term.⁶ Other pregnant women with botulism delivered at term or slightly prematurely.^{7–10} Despite premature delivery in two cases, there was no evidence of clinical botulism and no detectable botulinum toxin in either infant’s serum.^{7–8} Some authors have suggested that btxA may be useful in preventing preterm labour in pregnant women following fetal surgery, based upon *in vitro* evidence that btxA inhibits myometrial activity in a potentially reversible manner.¹¹

BtxA would have to diffuse from distant sites to affect the myometrium or reach the placenta after intramuscular or subcutaneous injection. Some reports indicate that btxA can diffuse from distant sites such as facial musculature to the arm as detected by single fibre electromyography (EMG),¹²

especially at higher doses.¹³ However, the effects appear subclinical, as no weakness was detected in the affected muscles.^{12–14} Other studies have found that btxA does not spread to distant structures including the eye and contralateral musculature when injected into rabbit eyelids or the gastrocnemius muscle of rats, respectively.¹⁵ Another study using single fibre EMG indicated that there was no evidence of remote re-innervation or subclinical remodelling of motor units in the vastus lateralis muscles of patients treated with btxA.¹⁶

The methodological limitations of our study are those that are inherent to questionnaire/survey studies. Firstly, there could be sample selection bias, as the sample of physicians we surveyed was identified by their use of commercially available btxA, and perhaps some end users in a group practice were not identified to participate. Secondly, our response rate of 44%, while higher than many published questionnaire studies,¹⁷ is not optimum, and the responses received may represent a biased sample. Thirdly, those responding to the questionnaire may have been more likely to respond due to good outcomes. Those who did not respond may have been embarrassed about injecting pregnant women or had had unfavourable outcomes in btxA injected pregnant women that they did not wish to report. Fourthly, recall bias is possible in a survey; however, given the importance and the impact of pregnancy in patients’ (and physicians’) lives, it

would be less likely in our survey than in surveys involving less significant events (urination, bowel movements, diet, medication timing). Despite these limitations, this survey should serve as an initial exploration of the topic, given that there is only one previously reported case of btxA injections during pregnancy.¹

Given the widespread use of btxA for cosmetic purposes, dystonia, spasticity, migraine and tension headaches, pain syndromes, and multiple other on and off label uses, we feel that inadvertent exposure of pregnant women and fetuses will certainly occur at a greater frequency over time. In some cases, women may have worsening of conditions such as hemimasticatory spasm during pregnancy,¹⁸ perhaps necessitating btxA therapy. From our limited data, we can find no clear qualitative association of fetal harm with maternal exposure to btxA injections. We do not recommend injection of pregnant women (as per product labelling), however, until more data are available. It is also unknown if btxA passes into breast milk, so it would be important for nursing mothers not to receive injections until further information is gathered. If a pregnant patient requires injections and she is made aware of the possible risks according to good neurological practice,¹⁹ then it would be between the patient and the treating physician(s) to decide if the benefits outweigh the possible risks to the fetus.

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