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Pregnancy Outcomes in Patients Exposed to OnabotulinumtoxinA Treatment: A Cumulative 29-Year Safety Update

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Abstract

Background and Objectives: A previous publication of pregnancy outcomes in onabotulinumtoxinA-exposed mothers demonstrated that the prevalence of major fetal defects (0.9%, 1/110) was comparable to background rates in the general population. There is continued interest to better understand the safety of onabotulinumtoxinA during pregnancy. This analysis evaluated pregnancy outcomes following onabotulinumtoxinA exposure to provide a cumulative 29-year update.

Methods: The Allergan Global Safety Database was searched from 1/1/1990 to 12/31/2018. Data from women (<65 years or unknown) during pregnancy or ≤3 months prior to conception treated with onabotulinumtoxinA were assessed to estimate birth defect prevalence rates of live births only from prospective pregnancies.

Results: Of 913 pregnancies, 397 (43.5%) were eligible with known outcomes. Maternal age was known in 215 pregnancies: 45.6% were ≥35 years. Indication was known in 340 pregnancies: most frequent were aesthetic (35.3%) and migraine/headache (30.3%). Timing of exposure was known in 318 pregnancies: 94.6% were prior to conception or during the first trimester. OnabotulinumtoxinA dose information was known in 242 pregnancies; the majority (83.5%) were exposed to <200 U. Of 195 prospective pregnancies with 197 fetuses, there were 152 (77.2%) live births and 45 (22.8%) fetal losses (32 spontaneous, 13 elective). Of 152 live births, 148 (97.4%) had normal outcomes, 4 had abnormal outcomes. Among the 4 abnormal

outcomes, there were 1 major birth defect, 2 minor fetal defects, and 1 birth complication. The prevalence rate for overall fetal defects was 2.6% (4/152, 95% CI: 1.0-6.6%) and 0.7% (1/152, 95% CI: 0.1-3.6%) for major fetal defects (3-6% in the general population). Among cases of live births and known determinable exposure times, there was 1 birth defect with preconception exposure and 2 with first-trimester exposure.

Discussion: Although subject to reporting bias due to the nature of the post-marketing database review, this 29-year retrospective analysis of safety data in pregnant women exposed to onabotulinumtoxinA demonstrates that the prevalence rate of major fetal defects among live births is consistent with rates reported in the general population. Even though there are limited data available for second- and third-trimester exposure, this updated and expanded safety analysis provides important real-world evidence to healthcare providers and their patients.

Classification of Evidence: This analysis provides Class III data that demonstrate that the prevalence rate of major fetal defects among live births subsequent to in utero onabotulinumtoxinA exposure is comparable to reported background rates.

Search Terms: Birth defects, BOTOX, fetal defects, onabotulinumtoxinA, pregnancy outcomes

Introduction

OnabotulinumtoxinA (BOTOX/BOTOX Cosmetic, Allergan, an AbbVie Company, North Chicago, Illinois, USA) is a potent therapeutic neurotoxin that causes muscle relaxation and can provide clinical benefit for conditions characterized by the inappropriate contraction of skeletal and smooth muscles, pain (ie, chronic migraine), and the overstimulation of cholinergically innervated glands (ie, hyperhidrosis).[1] To date, onabotulinumtoxinA has been approved by the US Food and Drug Administration (FDA) and in the European Union (EU) for the treatment of 12 therapeutic indications and 3 aesthetic indications (**Table 1**).[2,3] Many of these indications are neurological conditions; therefore, neurologists are likely to account for a large proportion of healthcare providers who treat with onabotulinumtoxinA in clinical practice.[4] The high prevalence of migraine in the female population suggests that many exposed to onabotulinumtoxinA are expected to be women of childbearing age.[5] Recent reviews have concluded that there are limited data on the safety of onabotulinumtoxinA during pregnancy.[6-8] Taking into consideration that approximately 45% of pregnancies are unintended,[9] onabotulinumtoxinA exposure may inadvertently occur prior to conception or during the early stages of pregnancy in women undergoing routine treatment. Therefore, a greater understanding of the safety of onabotulinumtoxinA during pregnancy would be informative to healthcare providers, and their patients.

Given the additional pregnancy exposure since 2013 that was not included in the analysis conducted by Brin et al in 2016[2] and the increased use of onabotulinumtoxinA in neurological indications, this analysis was designed to replicate the methodology of that previous analysis including more recent data.

The objective of this analysis was to evaluate pregnancy outcomes following onabotulinumtoxinA exposure using an expanded dataset to provide a cumulative 29-year safety update.

Methods

The Allergan Global Safety Database contains individual safety reports received from pre- and post-approval sources worldwide, including Allergan- and partner-sponsored clinical trials, post-authorization studies, regulatory agencies, published literature, and post-marketing spontaneous reporting. The database includes prospective (fetal outcome unknown at initial reporting) and retrospective (fetal outcome known at initial reporting) pregnancies, in which the patient was exposed to onabotulinumtoxinA or botulinum toxin type A (BoNT/A) manufacturer unknown. When a pregnancy is reported, a minimum of three attempts are made to gather the following information: pregnancy exposure (including patient and treatment information), pregnancy outcome, consent to access medical information, and the physician's contact information (to gather additional pregnancy information).

For this analysis, the database was searched from January 1, 1990 (start of recorded cases) to December 31, 2018 for eligible reports. To be included in this analysis, pregnancies had to meet the following criteria: 1) eligible pregnancy, defined as a case in which onabotulinumtoxinA treatment occurred during pregnancy or ≤3 months prior to the estimated date of conception, and the patient's age was <65 years (or unknown), and 2) known outcome, defined as a case in which the pregnancy had ended and birth type was known at the time of analysis. All pregnancies were reviewed by a medical safety physician to determine birth type, including live birth or fetal loss (resulting from spontaneous fetal loss or elective abortion and other causes of fetal loss [eg, stillbirths]). Elective abortions may have been due to known prior exposure and, therefore, a conservative approach was used to evaluate fetal loss. Additionally, the medical

safety physician determined the presence or absence of fetal defect(s). Fetal defects were categorized as follows[10]: minor birth defect (defined as a birth defect with mostly cosmetic significance; rarely medically significant or requiring surgical repair), major birth defect (defined as a birth defect with medical and/or social implications that often requires surgical repair), birth complication (defined as a complication during labor and/or delivery), genetic abnormality (defined as a pathogenic sequence variant or chromosome abnormality), and significant adverse event (defined as an event[s] considered to be significant by the medical reviewer). In addition to birth type and fetal defects, maternal characteristics were assessed, including age (grouped as <35 years or ≥35 years [advanced maternal age]), indication, timing of exposure (grouped by stage of pregnancy), and dose utilized (grouped by 50 U increments). Due to missing maternal characteristic data in some of the reports, results are expressed as the percentage of individuals with known information. To determine if maternal characteristics varied between prospective pregnancies with live births and those with spontaneous fetal loss, group differences were evaluated using chi-square tests in SAS v9.4 (SAS Institute, Cary, NC, USA).

Due to inherent bias associated with retrospective pregnancy reports,[11,12] only prospective pregnancies were used to estimate prevalence rates of fetal defects among live births, which is consistent with FDA guidance[13] and the approach utilized in other reports.[11,14] Retrospective analyses of pregnancy outcomes have an inherent reporting bias caused by the tendency to report abnormal over normal outcomes, which can lead to a potential inflation of the true prevalence rate. The prevalence rate of overall and major birth defects for prospective pregnancies with live births were calculated using Poisson distributions in SAS and expressed as 95% confidence intervals (CI). This methodology is consistent with that utilized previously[2] and the data reported in this manuscript are inclusive of, and expand upon, those reported by Brin et al in 2016.[2]

Standard Protocol Approvals, Registrations, and Patient Consents

Similar to other published analyses[2,15] utilizing de-identified and anonymous data, informed consent was not required.[2,15]

Data Availability Statement

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (eg, protocols, clinical study reports, analysis plans), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications.

These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal, Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time after approval in the US and Europe and after acceptance of this manuscript for publication. The data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: https://www.abbvieclinicaltrials.com/hcp/data-sharing/.html.

Results

Distribution of pregnancies

In total, 913 pregnancies were retrieved (1/1/90-12/31/18) from the Allergan Global Safety Database (**Figure**). After excluding pregnancies that failed to meet the inclusion criteria (461 pregnancies did not have a known outcome [labeled “unknown”] and 55 were not eligible [labeled “ineligible” because the injection date was >3 months prior to the estimated date of

conception]), 397 (397/913, 43.5%) eligible pregnancies with a known outcome were included in this analysis (**Figure**). Most eligible pregnancies reported exposure to onabotulinumtoxinA (357/397, 89.9%), with the remainder BoNT/A manufacturer unknown (40/397, 10.1%). Of the 397 pregnancies, 195 (195/397, 49.1%) were prospective and 202 (202/397, 50.9%) retrospective. All BoNT/A manufacturer unknown were retrospective pregnancies.

Maternal characteristics

Characteristics of pregnancies with a known outcome are shown in **Table 2**. Advanced maternal age (≥35 years) was observed in 45.6% of total pregnancies (98/215). Neurological conditions were reported in 180/340 (52.9%) of pregnancies, including migraine/headache (103/340, 30.3%), and movement disorders (41/340, 12.1%). The other most frequently reported indication was aesthetic (120/340, 35.3%). The most common dose categories of onabotulinumtoxinA were 100 to <200 U (40.1%, 97/242) and <50 U (32.2%, 78/242). Approximately 95% of onabotulinumtoxinA exposure occurred during the first trimester or prior to the estimated date of conception.

Fetal outcomes

Of the 195 prospective pregnancies (197 fetuses, including 2 sets of twins), there were 152 live births (152/197, 77.2%) (**Figure**). Most live births were normal (148/152, 97.4%); 4 were characterized as abnormal (4/152, 2.6%). Fetal loss was largely due to spontaneous fetal loss (32/45, 71.1%) and the remainder due to elective abortion (13/45, 28.9%). There were 4 cases of intrauterine death and 3 premature births. Of those live births with known fetal defects and known timing of exposure, 1 pregnancy was observed with onabotulinumtoxinA exposure during the preconception period (ventricular septal defect), and 2 pregnancies were observed with exposure during the first trimester (talipes equinovarus and cardiac murmur).

Of the 202 retrospective pregnancies (207 fetuses, including 5 sets of twins), there were 160 live births (160/207, 77.3%) (**Figure**). Similar to prospective pregnancies, most live births were normal (155/160, 96.9%); 5 had abnormal outcomes (5/160, 3.1%). Of the 202 retrospective pregnancies (207 fetuses), 22.7% had fetal loss (47/207). Fetal loss was largely due to spontaneous fetal loss (40/47, 85.1%) and the remainder due to elective abortion (7/47, 14.9%). There was 1 premature birth and no intrauterine deaths. Of those with known fetal defects and known timing of exposure, 1 was exposed to onabotulinumtoxinA during the preconception period (laryngomalacia), and 2 were exposed during the first trimester (tracheoesophageal fistula/esophageal atresia and brain neoplasm).

Fetal loss

Among all prospective and retrospective pregnancies, 69 (72 fetuses, including 3 sets of twins) resulted in fetal loss due to spontaneous fetal loss (cases with known data shown in **eTable 1** in the Supplement; see **Figure** for flow chart). Of the total pregnancies, a higher proportion of women who experienced spontaneous fetal loss were of advanced maternal age (≥35 years; 32/53, 60.4%). The most frequently treated indications were aesthetic (35/66, 53.0%), migraine/headache (16/66, 24.2%), and movement disorders (9/66, 13.6%). The majority of onabotulinumtoxinA exposure occurred during the first trimester (41/52, 78.8%). The most frequently reported dose was <50 U (21/44, 47.7%). Approximately half of pregnancies reported a gestational age of 1 to <2 months at the time of fetal loss (26/49, 53.1%).

A comparison of maternal characteristics in prospective pregnancies with live births (n=152) versus prospective pregnancies with spontaneous fetal loss (n=32) (**Table 3**) revealed a non-significant statistical trend for patients who experienced spontaneous fetal loss to be of advanced maternal age (≥35 years; 14/24, 58.3%) compared to those with live births (41/108, 38.0%; comparison, *P*=.067). No statistical differences were found between prospective

pregnancies of live births and spontaneous fetal loss for timing of onabotulinumtoxinA exposure (*P*=.990) or dose (*P*=.205).

For completeness, the characteristics of eligible prospective (n=434) and retrospective (n=22) pregnancies with known and unknown fetal outcomes are presented in **eTables 2–3** in the Supplement. Briefly, the pregnancies with and without known outcomes had similar maternal characteristics, aside from a trend toward lower onabotulinumtoxinA doses in the latter group.

In all prospective and retrospective pregnancies, there were 20 elective abortions (pregnancies with known data shown in **eTable 3** in the Supplement; see **Figure** for flow chart). In contrast to the higher maternal age observed in pregnancies of spontaneous fetal loss, elective abortions were more common in women <35 years of age (9/15, 60.0%). The following indications were observed most often among pregnancies with elective abortion: aesthetic (5/16, 31.3%), migraine/headache (4/16, 25.0%), and urological disorders (3/16, 18.8%). Similar to spontaneous fetal loss, the majority of onabotulinumtoxinA exposure occurred during the first trimester (14/17, 82.4%). The most frequently reported dose was ≥200 U (5/12, 41.7%). The most common gestational age at the time of elective abortion was 1 to <2 months (6/15, 40.0%). The most common reasons reported for elective abortion were personal/social (8/15, 53.3%) and fetal disorder (4/15, 26.7%). There were 4 fetal defects reported in elective abortion cases (2 prospective cases, 2 retrospective cases). Both prospective cases reported timing of exposure as first trimester (agenesis of corpus callosum and Down syndrome); 1 of the retrospective cases reported timing of exposure as first trimester (Down syndrome), and the other retrospective case had unknown timing of exposure (neural tube defect).

Fetal defects

Of all prospective and retrospective pregnancies (n=397), 13 fetal defects were reported (**Figure**; **Table 4**). There were 6 major fetal defects: 2 prospective pregnancies (1 live birth, 1

elective abortion) and 4 retrospective pregnancies (3 live births, 1 fetal loss). Of the prospective pregnancies, ventricular septal defect was reported in a case of live birth, which was asymptomatic and did not require intervention, and a case of agenesis of the corpus callosum, in which the fetus was electively aborted at 7 months gestation. Of the retrospective pregnancies with live births, there was a report of tracheoesophageal fistula/esophageal atresia, which was successfully repaired with surgery, a case of cleft lip and cleft palate, and a case of diaphragmatic hernia, which underwent surgical repair and required prolonged intubation. Lastly, a retrospective case of neural tube defect resulted in an elective abortion at week 19 of gestation.

Overall prevalence rates of fetal defects

Consistent with FDA guidance[13] and other reports,[11,14] only prospective pregnancies were used to estimate prevalence rates of fetal defects in live births (N=152). In this analysis, the prevalence rate for overall fetal defects among live births (including all defects regardless of severity) was 2.6% (4/152, 95% CI: 1.0-6.6%) and for major fetal defects was 0.7% (1/152, 95% CI: 0.1-3.6%) (see **eTable 4** in the Supplement). In those with known timing of exposure, the prevalence rate of fetal defects in those exposed during the preconception period was 3.1% (1/32, 95% CI: 0.6-15.7), and in those exposed during the first trimester was 2.0% (2/98, 95% CI: 0.6-7.1).

Neurological Conditions

Approximately 65% (220/340) of pregnancies had a therapeutic indication, of which 81.8% (180/220) were neurologic (see **eTable 5** in the Supplement). A total of 57.2% (103/180) and 22.8% (41/180) of those with neurological conditions were being treated for migraine/headache and movement disorders, respectively. Of prospective pregnancies with any

neurological indication, 2 were characterized as abnormal (2/74, 2.7%). Similarly, of retrospective pregnancies with any neurological indication, 2 were characterized as abnormal (2/106, 1.9%).

This analysis provides Class III data that demonstrate that the prevalence rate of major fetal defects among live births subsequent to in utero onabotulinumtoxinA exposure is comparable to reported background rates.

Discussion

This manuscript summarizes pregnancy outcomes following onabotulinumtoxinA exposure using the Allergan Global Safety Database to provide a cumulative 29-year safety update. In total, 913 pregnancies were retrieved from the database, with 397 pregnancies eligible with known outcome, which were nearly evenly distributed between prospective (n=195) and retrospective (n=202) pregnancies. Analysis of maternal characteristics revealed that age was slightly skewed toward women <35 years old compared to those of advanced maternal age (≥35 years). The most common indications were aesthetic and migraine or headache, with onabotulinumtoxinA dosing consistent with typical use.[3,16] The majority of onabotulinumtoxinA exposure occurred during the first trimester, followed by preconception exposure. There were 3 fetal defect events among those with preconception exposure and 5 among those with first-trimester exposure.

This retrospective safety analysis expands upon a previous publication[2] that summarized safety data from the Allergan Global Safety Database over a 24-year period and included 232 eligible pregnancies with known outcomes. This 29-year update, encompassing the previous data, includes 397 eligible pregnancies with known outcomes. This updated analysis added 165 eligible pregnancies (58 prospective and 107 retrospective), an approximate 71% increase. In the original report, aesthetic was the most common reason for using onabotulinumtoxinA

(50.5% of total pregnancies), followed by movement and pain disorders (16.8% and 14.2%, respectively). In the current manuscript, therapeutic treatment with onabotulinumtoxinA (64.7%) was more common than aesthetic treatment (35.3%). Neurological conditions (52.9%), such as migraine/headache (30.3%) and movement disorders (12.1%), were the most frequently reported therapeutic indications. In this updated analysis, there was a large increase in the number of migraine or headache cases (n=103) compared to the previous study (n=24).[2] OnabotulinumtoxinA was approved for the treatment of chronic migraine in 2010, allowing for 8 years of post-approval data in the current manuscript compared to only 3 years in the original. Taking into consideration that the prevalence of migraine is highest in women of reproductive age, that women report migraines negatively impacting their plans for pregnancy, that up to 80% of women who had migraines prior to conception will continue to have manifestations during pregnancy requiring intervention, and that women with chronic migraine who discontinued onabotulinumtoxinA treatment during pregnancy showed a relapse in their condition,[17,18] this expanded analysis can provide important real-world evidence to healthcare providers and patients.

Most fetal outcomes from prospective (77.2%) and retrospective (77.3%) pregnancies resulted in live births. The incidence of spontaneous fetal loss was 16.2% (32/197) for prospective pregnancies and 19.3% (40/207) for retrospective. In the general population, spontaneous fetal loss is expected to occur in approximately 10-28% of known pregnancies,[19] with increased risk with advanced maternal age.[20] In this analysis, the incidence of fetal loss due to elective abortion was 6.6% (13/197) for prospective pregnancies and 3.4% (7/207) for retrospective. According to surveillance data from the Centers for Disease Control and Prevention (CDC), the rate of US legal induced abortion is 11.6 abortions per 1,000 women (aged 15-44 years).[21] Direct comparisons between the abortion rate found in this analysis and the US rate are not possible due to differences in how the denominators were defined. In this

analysis, the denominator included only pregnant women, while the CDC denominator included all women of childbearing potential (aged 15-44 years).

In this analysis, the prevalence rate of overall fetal defects in prospective live births, which includes all defects regardless of severity, was 2.6% (4/152, 95% CI: 1.0-6.6%) and for major fetal defects was 0.7% (1/152, 95% CI: 0.1-3.6%). Among cases of live births and known determinable exposure times were 1 birth defect (1/32, 3.1%, 95% CI: 0.6-15.7) with preconception exposure and 2 birth defects (2/98, 2.0%, 95% CI: 0.6-7.1) with first-trimester exposure. In addition, an exploratory sensitivity analysis was conducted that included pregnancies with unknown birth outcomes. The prevalence rate was 3.9% (6/154, 95% CI: 1.8-8.2%), suggesting that including these data, which assumed that a fetal defect occurred in unknown cases, had no effect on the prevalence of fetal defects.

Published fetal birth defect rates vary between countries and reporting centers. The CDC reported that major structural and genetic birth defects occur in approximately 3% of US births.[22] The Texas Birth Defects Registry reported structural or chromosomal birth defects in 4.3% of live births.[23] Registry data from the UK found a slightly lower incidence, with major and system-specific congenital anomalies occurring in approximately 1.7-2.0% of children less than 1 year of age.[24] The March of Dimes Foundation estimates that 6% of total births worldwide have a serious birth defect of genetic or partially genetic origin.[25] Given these data, the prevalence rate of major birth defects in live births found in this analysis (0.7%) is within/below that observed in the general population. Compared to the previous analysis[2] (overall defects: 2.7% [3/110, 95% CI: 0.6-8.0%]; major defects: 0.9% [1/110, 95% CI: 0.02-5.1%]), the prevalence rates in this expanded analysis were slightly lower than those reported previously.

Of 397 pregnancies with known outcomes, 13 fetal defects were reported. No discernible patterns in characteristics were observed, as fetal defects were reported for prospective and retrospective pregnancies, in cases of live birth and fetal loss, and in patients treated for a

variety of indications. Additionally, no consistent types of malformation by organ were observed. Compared to the previous analysis,[2] four additional fetal defects (major) were identified: corpus callosum agenesis (prospective elective abortion), cleft lip and cleft palate (retrospective live birth), diaphragmatic hernia (retrospective live birth), and neural tube defect (retrospective elective abortion).

Published reports of fetal exposure to botulinum toxin from botulism (17 publications describing 19 pregnant women, which have been summarized previously[2,26]) found no evidence of infantile botulism nor any direct adverse effects on the pregnancy or fetus. A literature search of BoNT/A treatment during pregnancy (or up to 3 months prior to conception) for therapeutic or aesthetic indications, which may be inclusive of the pregnancies reported in this analysis, revealed 21 publications describing 109 women and 118 pregnancies.[18,27-46] Some reports described other BoNT/A products, or did not specify the manufacturer, and we acknowledge the non-interchangeability of these findings. Of the published pregnancies, there was one report of a therapeutic abortion[29] and five reports of spontaneous fetal loss.[18,28,29,36,46] Of the spontaneous fetal loss, two were in women with a history of previous miscarriage without BoNT/A treatment,[28,29] one was "a result of an inherent anembryonic pregnancy, most likely without any relation to the BoNT/A injection,"[36] and the last two were medically unremarkable.[18,46] There were two reports of premature birth, with one "not thought to be related to the drug"[39] and the other was "within background average statistics."[46] In addition to the pregnancies above, a recent retrospective study evaluated the safety of onabotulinumtoxinA for the treatment of chronic migraine during pregnancy and concluded that all 10 pregnancies assessed resulted in "live full-term births to healthy babies with no organ malformations."[47]

A significant strength of this analysis, which increases the external validity of these results, is the large number of pregnancies within the Allergan Global Safety Database. Nearly 400 eligible pregnancies across both aesthetic and therapeutic indications from US and international

sources are described in this manuscript. The safety of onabotulinumtoxinA during pregnancy remains an important topic for healthcare providers and their patients and this update provides additional real-world information. Due to differences in manufacturing, formulation, and potency evaluation amongst BoNT/A products, which can impact clinical dosing, duration of action, and adverse events, these onabotulinumtoxinA safety data are not interchangeable with that of other products.[48,49]

As is common to retrospective database analyses, this analysis has several limitations. First, to ensure potentially important safety data were not overlooked, reports of BoNT/A manufacturer unknown were included in this analysis; therefore, data in this manuscript may not be exclusive to pregnancies associated with onabotulinumtoxinA exposure. Nevertheless, none of these cases were in the prospective cohort. Second, this analysis is restricted to data within the Allergan Global Safety Database, which includes only reported pregnancies and does not represent all onabotulinumtoxinA-exposed pregnancies. Additionally, the database may not contain full details, limiting in-depth analyses on risk factors in this population, including concomitant medication exposure, comorbidities, and other potentially relevant covariates. Third, most onabotulinumtoxinA exposure data are from the first trimester, which is important, as it is the period of most organogenesis; however, consequently, less is known about onabotulinumtoxinA exposure throughout the later stages of pregnancy. Based on preclinical data, it is unclear whether a level of potential systemic onabotulinumtoxinA exposure would be significant enough to impact the fetus of treated mothers.[50] Fourth, exposure was primarily (83.5%) <200 U (per labeling, the maximum dose is 400 U), so the effects of higher doses could not be evaluated. The majority of exposed mothers were treated for neurological and aesthetic conditions, which may limit generalizability. Fifth, abnormal outcomes were assessed at the time of birth, but data for later time points during postnatal development were often unavailable. This was not a comparative or controlled study, and although the analysis adds to the evidence

base, conclusions about the safety of onabotulinumtoxinA during pregnancy should be made with caution and continue to be monitored.

Conclusions

This 29-year retrospective analysis of safety data in onabotulinumtoxinA-exposed mothers demonstrates that the prevalence rate of major fetal defects among live births is consistent with rates reported in the general population. Most of the exposures were in the preconception period and first trimester of pregnancy, with limited data available for second- and third-trimester exposure. This updated and expanded safety analysis provides important real-world evidence to healthcare providers and their patients.

http://links.lww.com/WNL/C790

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Figure Legend

Figure. Distribution of pregnancies.

[a]Pregnancies in which onabotulinumtoxinA injection occurred >3 months prior to the estimated date of conception were considered ineligible.

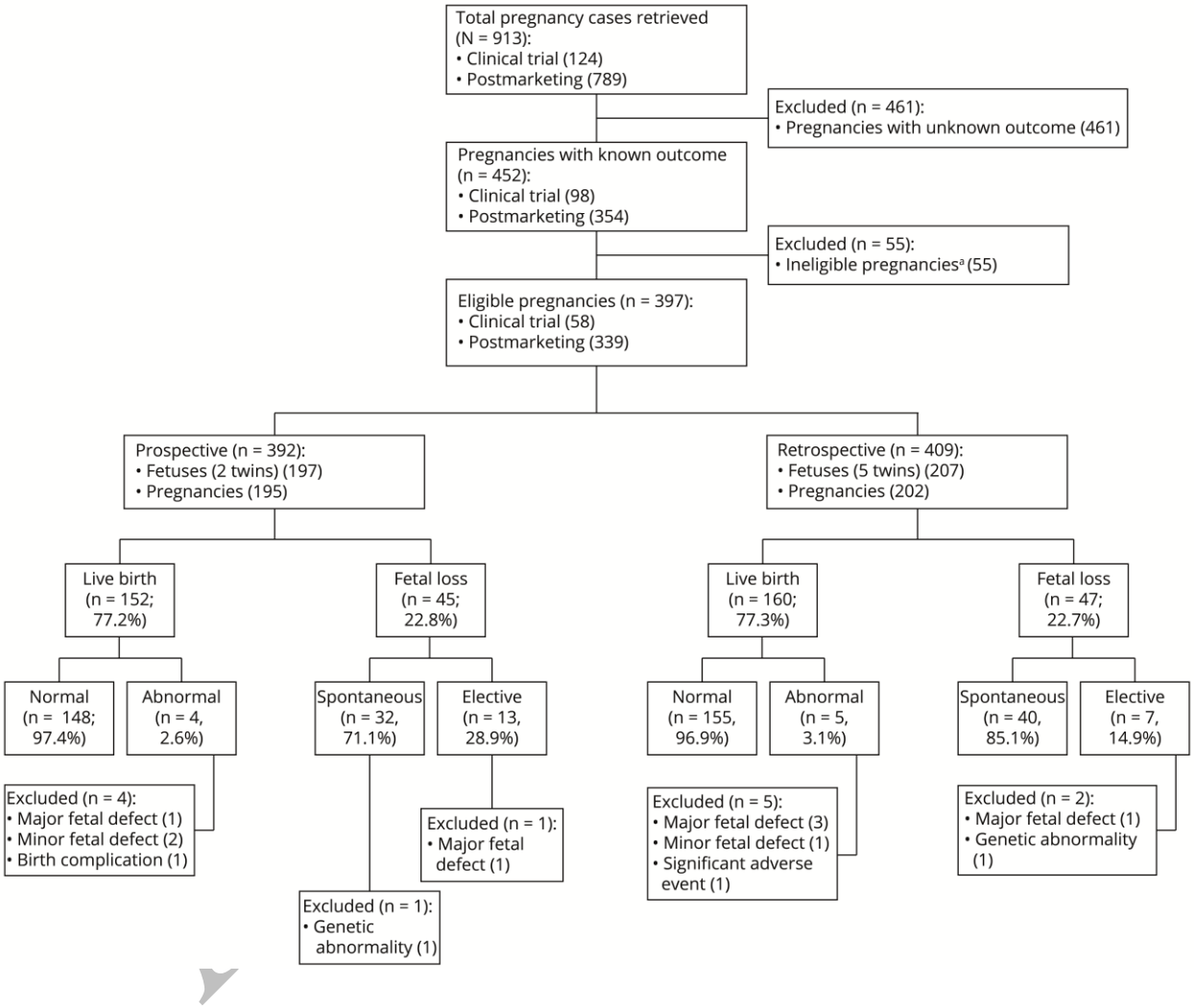

Table 1. Approved indications for onabotulinumtoxinA treatment[a]

Indication	Year of FDA approval	Year of EU/EMA approval
Therapeutic		
Strabismus	1989	N/A
Blepharospasm	1989	1994
Cervical dystonia	2000	1995
Primary axillary hyperhidrosis	2004	2001
Adult upper limb spasticity	2010	2001
Chronic migraine	2010	2010
Adult detrusor overactivity associated with a neurologic condition	2011	2011
Overactive bladder	2013	2013
Adult lower limb spasticity	2016	2014
*Pediatric upper limb spasticity	2019	2009
*Pediatric lower limb spasticity	2019	1997
*Pediatric detrusor overactivity associated with a neurologic condition	2021	N/A
Aesthetic		
Glabellar lines	2002	2003
Lateral canthal lines	2013	2014
*Forehead lines	2017	2017

EMA = European Medicines Agency; EU = European Union; FDA = US Food and Drug Administration; N/A = not applicable.

[a]Asterisks (*) indicate new FDA approvals since previous 2016 report.[2] Detailed information pertaining to indication statements approved by the FDA can be found in the package insert.[3]

Table 2. Characteristics of prospective and retrospective pregnancies with a known outcome[a]

	Prospective pregnancies (n=195)	Retrospective pregnancies (n=202)	Total (N=397)
Maternal age, n	142	73	215
Missing data	53	129	182
<35 years	84 (59.2)	33 (45.2)	117 (54.4)
≥35 years[b]	58 (40.8)	40 (54.8)	98 (45.6)
OnabotulinumtoxinA indication,[c] n	182	158	340
Missing data	13	44	57
Aesthetic	89 (48.9)	31 (19.6)	120 (35.3)
Skin wrinkling	88	31	119
Skin cosmetic procedure	1	0	1
Therapeutic	93 (51.1)	127 (80.4)	220 (64.7)
Migraine/headache[d]	49 (26.9)	54 (34.2)	103 (30.3)
Migraine	46	54	100
Headache	3	0	3
Movement disorders[d]	17 (9.3)	24 (15.2)	41 (12.1)
Torticollis	8	16	24
Spasmodic dysphonia	1	5	6
Dystonia	4	0	4
Blepharospasm	1	1	2
Muscle hypertrophy	2	0	2
Hemiparesis	1	0	1
Muscle contracture	0	1	1
Strabismus	0	1	1
Hyperhidrosis	12 (6.6)	15 (9.5)	27 (7.9)
Hyperhidrosis	12	15	27
Urological disorders	6 (3.3)	1 (0.6)	7 (2.1)
Neurogenic bladder	4	1	5
Hypertonic bladder	1	0	1
Cystitis interstitial	1	0	1
Gastrointestinal disorders	1 (0.5)	5 (3.2)	6 (1.8)
Oesophageal achalasia	0	5	5
Anal fissure	1	0	1
Spasticity[d]	5 (2.7)	1 (0.6)	6 (1.8)
Muscle spasticity	5	1	6
Pain disorders[d]	3 (1.6)	0 (0.0)	3 (0.9)
Muscle spasms	2	0	2
Pelvic pain	1	0	1
Miscellaneous disorders[d]	0 (0.0)	27 (17.1)	27 (7.9)
Nervous system disorder	0 (0.0)	27 (17.1)	27 (7.9)
Timing of exposure,[e] n	177	141	318
Missing data	18	61	79
Prior to conception			
0-1 month	22 (12.4)	4 (2.8)	26 (8.2)
>1-2 months	11 (6.2)	4 (2.8)	15 (4.7)
>2-3 months	7 (4.0)	3 (2.1)	10 (3.1)
First trimester	129 (72.9)	121 (85.8)	250 (78.6)
Second trimester	7 (4.0)	5 (3.5)	12 (3.8)
Third trimester	1 (0.6)	4 (2.8)	5 (1.6)
OnabotulinumtoxinA dose, n	142	100	242

Missing data	53	102	155
<50 U	54 (38.0)	24 (24.0)	78 (32.2)
50 U to <100 U	19 (13.4)	8 (8.0)	27 (11.2)
100 U to <150 U	19 (13.4)	13 (13.0)	32 (13.2)
150 U to <200 U	27 (19.0)	38 (38.0)	65 (26.9)
200 U to <250 U	10 (7.0)	9 (9.0)	19 (7.9)
250 U to <300 U	2 (1.4)	0 (0.0)	2 (0.8)
300 U to <350 U	9 (6.3)	3 (3.0)	12 (5.0)
350 U to <400 U	2 (1.4)	0 (0.0)	2 (0.8)
≥400 U	0 (0.0)	5 (5.0)	5 (2.1)

n or N = number of pregnancies; U = units of onabotulinumtoxinA.

[a]Known data are shown and expressed as n or n (% among those with known information).

[b]Advanced maternal age was defined as ≥35 years.

[c]Medical Dictionary for Regulatory Activities (MedDRA) preferred terms shown in italics.

[d]For a complete list of neurological disorders, see eTable 5 in the Supplement.

[e]If exposed to onabotulinumtoxinA multiple times during pregnancy, the patient was categorized closest to estimated date of conception.

Table 3. Comparison of characteristics between prospective pregnancies with live births and spontaneous fetal loss[a]

	Pregnancies with live births (n=152)	**Pregnancies with spontaneous fetal loss (n=32)**	***P* values**
Maternal age, n	108	24	.067
Missing data	44	8	
<35 years	67 (62.0)	10 (41.7)	
≥35 years	41 (38.0)	14 (58.3)	
OnabotulinumtoxinA indication, n	142	29	.009
Missing data	10	3	
Aesthetic	65 (45.8)	21 (72.4)	
Therapeutic	77 (54.2)	8 (27.6)	
Timing of exposure, n	138	26	.990
Missing data	14	6	
Prior to conception	32 (23.2)	6 (23.1)	
First/second trimester	106 (76.8)	20 (76.9)	
OnabotulinumtoxinA dose, n	115	20	.205
Missing data	37	12	
<50 U	41 (35.7)	11 (55.0)	
50 U to <100 U	16 (13.9)	3 (15.0)	
≥100 U	58 (50.4)	6 (30.0)	

n = number of pregnancies; U = units of onabotulinumtoxinA.

[a]Known data are shown and expressed as n or n (% among those with known information).

Table 4. Summary of fetal defects in prospective and retrospective pregnancies

Adverse event[a]	Pregnancy details	Indication	Time of exposure	Dose	Maternal age
Prospective fetal defects in live births					
Major fetal defect (n=1)					
Congenital ventricular septal defect *(Ventricular septal defect)*	C-section; asymptomatic, no intervention required	Axillary hyperhidrosis	37 days pre-conception	100 U	28 years
Minor fetal defects (n=2)					
Metatarsus adductus *(Talipes)*	Induced vaginal delivery (decreased fetal movement); no other abnormalities	Chronic migraine	15 days post-conception	155 U	19 years
Innocent heart murmur[b] *(Cardiac murmur)*	Family history of cardiac murmur	Blepharospasm	Trimesters 1, 2, 3	8 U, 12 U, 14 U	23 years
Birth complication (n=1)					
Horner's syndrome *(Horner's syndrome)*	C-section, placenta previa, and uterine varicosities; no abnormalities reported 11 months later	Axillary hyperhidrosis	"Few days" before conception	100 U (50 U each axilla)	Unknown
Prospective fetal defects in abortions					
Major fetal defect (n=1)					
Agenesis of corpus callosum *(Congenital central nervous system anomaly)*	Elective abortion at 7 months	Skin wrinkling	4 days post-conception	Not reported	37 years
Genetic abnormality					
Down syndrome *(Fetal chromosome abnormality)*	Miscarriage at gestation month 5	Skin wrinkling (glabella)	40 days post-conception	12 U	38 years
Retrospective fetal defects in live births					
Major fetal defects (n=3)					
Tracheoesophageal fistula *(tracheo-oesophageal fistula)* and esophageal atresia (*oesophageal atresia)*	Pre-term labor at ~33 weeks, resulting in C-section; surgical repair successful	Facial wrinkles	3 days post-conception	35 U	30 years
Cleft lip *(Cleft lip)* and Cleft palate (*Cleft palate)*	Live birth; limited information reported	Unknown	During pregnancy, specific timing not indicated	Not reported	Unknown
Diaphragmatic hernia *(Diaphragmatic hernia)*	Surgical repair with prolonged intubation	Chronic migraine	During pregnancy, specific timing not indicated	Not reported	Unknown

Minor fetal defect (n=1)					
Laryngomalacia *(Laryngomalacia)*	Planned C-section at 38 weeks; settled spontaneously over several months	Facial wrinkles	1 week pre- & 2 weeks post-conception	Not reported	38 years
Significant adverse event (n=1)					
Benign brain tumor[c] (*Brain neoplasm)*	Successful surgical resection	Cervical dystonia	Within 1 week before conception	100 U	25 years
Retrospective fetal defects in abortions					
Major fetal defect (n=1)					
Neural tube defect *(Neural tube defect)*	Elective abortion at week 19	Unknown	During pregnancy, specific timing not indicated	Not reported	Unknown
Genetic abnormality (n=1)					
Down syndrome (*Foetal disorder)*	Elective abortion at week 20	Skin wrinkling (glabella)	"Immediately after injection"	25 U	40 years

C-section = caesarean section; n = number of pregnancies; U = units of onabotulinumtoxinA.

[a]The event(s) as reported is (are) shown, followed by the Medical Dictionary for Regulatory Activities (MedDRA) preferred term(s) in italics.

[b]Diagnosed at 7 days.

[c]Diagnosed at 13 months.

Pregnancy Outcomes in Patients Exposed to OnabotulinumtoxinA Treatment: A Cumulative 29-Year Safety Update

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