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Hypersensitivity to Laminaria: A Case Report and Review of Literature

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Abstract: An August 2014 literature search identified 10 cases of laminaria hypersensitivity, with 8 recognized as anaphylaxis. Included cases suggest limited epinephrine utilization in laminaria anaphylaxis and good outcomes with corticosteroids and antihistamines alone. Anaphylaxis risk appears elevated with prior laminaria exposure. Evidence suggests laminaria hypersensitivity is likely IgE mediated.

December 24, 2014

Carolyn L. Westhoff, MD
Contraception, Editor-in-Chief

Re: CONTRACEPTION-D-14-00337R1

Title: Hypersensitivity to Laminaria: A Case Report and Review of Literature

Dear Dr. Westhoff,

Thank you for your email dated December 1, 2014, in which you invited me and my co-authors to submit a revised manuscript for further consideration that addresses the points of the special expert referees and Editorial Board. We hope that our responses to every point raised and/or changes to the manuscript are satisfactory.

Reviewer Comment 1:

Line 37: You added that Dilapan-S is more costly. That is true per rod but typically fewer rods are needed so that the overall cost for dilators used is less. Remove the cost information as it is not pertinent in this case report. You can state it is an alternative product rather than more costly if you believe some other adjective is needed.

Response 1:

We agree that the Dilapan-S cost information is not pertinent to the case report and have therefore removed it from the manuscript.

Changes to Manuscript 1 (line 37-38):

Conversely, Dilapan-S is a faster-acting synthetic polyacrylate-based hydrogel rod without reported hypersensitivity reactions [3].

Reviewer Comment 2:

Line 44: You changed some of the information about the case patient. Previously, she had 3 prior terminations and now you state that she reported 2 prior spontaneous miscarriages and 2 terminations. You did not state in your cover letter that you made this change. Which is correct and why?

Response 2:

While reviewing the documents available in our electronic medical record system, we noticed a discrepancy in the patient's pregnancy history. It is very clear that the patient had indeed reported one episode of laminaria use for a D&E, as that is specifically noted by the initial interviewing physician. However, what was unclear was how many suction aspirations she had experienced, as one physician noted 3 terminations and another noted only 2, as well as 2 spontaneous losses. In order to determine which was correct, we found the scanned document of the patient's pre-operative history, which is necessary for booking cases at our institution. This hand-written document was produced at a different time from the first two physician interviews, making it unlikely to have been a "copy-

paste” electronic error, and it agreed with the history of 2 spontaneous losses and 2 surgical terminations, so we corrected the initial reporting of the patient’s pregnancy history.

Changes to Manuscript 2:
None

Reviewer Comment 3:

Lines 44-45: you added abbreviations without definitions that were not there previously and are not referred to in the cover letter. Please spell out definitions and used commonly accepted terms. D&A is likely a local pseudonym and you are probably referring to a D&C or a suction aspiration. Please clarify.

Response 3:

We have clarified the abbreviations. At the first use of the term “dilation & evacuation” we note the appropriate abbreviation “D&E”, and have removed “D&A” to avoid confusion, replacing it with “suction aspiration”.

Changes to Manuscript 3 (line 33-34 and 44-45):

Dilation and evacuation (D&E) at increasing gestational ages requires cervical preparation for safe uterine evacuation, typically accomplished with osmotic dilators.

She reported 2 prior spontaneous miscarriages and 2 terminations, consisting of suction aspiration and a D&E with laminaria use.

Reviewer Comment 4:

Line 62: You moved this information to the start of a new paragraph. With this change, it is unclear to exactly what you are referring. The sentence worked well in its location in the prior version. Do you mean patient characteristics of the cases in the review or of your case? Please clarify.

Response 4:

We moved the sentence back to its original location (from line 62 to line 59) in order to clarify the contents of Table 1, so that it is now clear that we are referring to all the cases in the review, not just our newly reported case.

Changes to Manuscript 4 (line 58-59):

This identified 6 published case reports covering 9 patients [4-9]. Patient characteristics and outcomes are summarized in Table 1.

Reviewer Comment 5:

Line 102: remove "future."

Response 5:

“Future” has been removed from the concluding sentence.

Changes to Manuscript 5 (line 102-104):

Studies on the mechanism of laminaria anaphylaxis could help develop protocols to identify patients at risk and standardize treatment of laminaria-associated anaphylaxis.

Reviewer Comment 6:

You did not yet put the references into the correct format for this journal as requested. Look at published articles from this journal to make sure you match that format.

Response 6:

We changed the references format to match that of recently published articles.

Changes to Manuscript 6 (line 105-127):

References

- [1] Newmann SJ, Dalve-Endres A, Diedrich JT, et al. Cervical preparation for second trimester dilation and evacuation. *Cochrane Database Syst Rev* 2010. (8):CD007310.
- [2] Lichtenberg ES. Complications of osmotic dilators. *Obstet Gynecol Surv* 2004; 9:528-36.
- [3] Fox MC, Krajewski CM. Cervical preparation for second-trimester surgical abortion prior to 20 weeks' gestation: SFP Guideline #2013-4. *Contraception* 2014; 89:75-84.
- [4] Nguyen MT, Hoffman DR. Anaphylaxis to Laminaria. *J Allergy Clin Immunol* 1995; 95:138-9.
- [5] Cole DS, Bruck LR. Anaphylaxis after laminaria insertion. *Obstet Gynecol* 2000; 95:1025.
- [6] Chanda M, Mackenzie P, Day JH. Hypersensitivity reactions following laminaria placement. *Contraception* 2000;62:105-6.
- [7] Knowles SR, Djordjevic K, Binkley K, Weber EA. Allergic anaphylaxis to Laminaria. *Allergy* 2002;57:370.
- [8] Kim SH et al. Two cases of anaphylaxis after laminaria insertion. *J Korean Med Sci* 2003;18:886-8.
- [9] Kim MS, Kim DY, Chang YH, Cho YJ. A case of anaphylaxis to laminaria. *J Asthma Allergy Clin Immunol* 1999;19:601-5.
- [10] Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;117:391-7.

Reviewer Comment 7:

Please explain exactly if you made all of the changes requested in the table from the initial review:

- a. *Please provide a title. The title should describe the table so that a reader will comprehend the content of the table without having the rest of the article.*
- b. *All abbreviations need to be defined in a footer for the table (e.g. ARDS, ELISA).*
- c. *For your case, replace "unpublished" with "current report."*
- d. *The reference number should be included after the authors' names.*

Response 7:

The updated table has a title, “Characteristics and outcomes of laminaria hypersensitivity.” All abbreviations are defined in the footer, e.g. U = unreported, ARDS = acute respiratory distress syndrome, ELISA = enzyme-linked immunosorbent assay. We also replaced “unpublished” with “current report” for our case and changed the format of the first column, such that the reference number is included after the author’s names.

Changes to Manuscript 7:

[The updated table is attached in the submission.]

My coauthors and I look forward to your response to this revised manuscript.

Sincerely,

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1 Hypersensitivity to Laminaria: A Case Report and Review of Literature

2

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16

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Abstract

We report a case of laminaria hypersensitivity treated with diphenhydramine and corticosteroids. A literature review identified 10 previously reported cases, with 8 recognized as anaphylaxis, and good outcomes with corticosteroids and antihistamines despite limited epinephrine utilization. Laminaria hypersensitivity is likely IgE mediated with an increased anaphylaxis risk with prior exposure.

Keywords: abortion, allergy, anaphylaxis, anaphylactoid, evacuation

Introduction

Dilation and evacuation (D&E) at increasing gestational ages requires cervical preparation for safe uterine evacuation, typically accomplished with osmotic dilators. Derived from the seaweed *Laminaria japonica* or *digitata*, laminaria complications include infection, ruptured membranes, device fragmentation or retention and rarely anaphylaxis [1, 2]. Conversely, Dilapan-S is a faster-acting synthetic polyacrylate-based hydrogel rod without reported hypersensitivity reactions [3]. Since laminaria placement is frequently an outpatient procedure, risk factor identification, early recognition and rapid treatment of hypersensitivity reactions is imperative.

Case Report

An African American 28-year-old P2042 presented for termination at 21 weeks gestation. She reported 2 prior spontaneous miscarriages and 2 terminations, consisting of suction aspiration and a D&E with laminaria use. She denied allergies or medical history. Thirty

minutes after laminaria placement in the hospital clinic, after receiving routine pre-operative instructions, she noted an unusual sensation in her throat and developed facial hives and nausea. No angioedema was present. She became hypotensive and tachycardic and was urgently transferred to the emergency department (ED) on a stretcher after laminaria removal and administration of diphenhydramine 50mg intramuscularly. In the ED, she was given prednisone 60mg orally. After recovery she was discharged with a steroid taper. She chose to continue her pregnancy and has been lost to follow-up.

Comment

This patient is the tenth reported case of laminaria hypersensitivity. A search was conducted on PubMed, Embase, Web of Science and clinicaltrials.gov with the terms “laminaria” AND “anaphylaxis” OR “hypersensitivity” OR “allergy” from database inception through August 2014. This identified 6 published case reports covering 9 patients [4-9]. Patient characteristics and outcomes are summarized in Table 1. All articles but one were available in English. A Korean case report was translated by two natively bilingual Korean healthcare providers [8].

Age, gravidity, parity, gestational age, previous laminaria exposure, time to onset of reaction, management, maternal and surgical outcome, and laboratory studies supporting laminaria-specific reactions were extracted. The National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID/FAAN) definition for anaphylaxis was used to differentiate cases of anaphylaxis from hypersensitivity [10]. Anaphylaxis was diagnosed when any one of three criteria were met: (1) hypotension to a

known allergen, (2) at least two of the following reactions to a *likely* allergen: skin or mucosal involvement, respiratory compromise, hypotension or persistent gastrointestinal symptoms, or (3) for *naive* cases: skin or mucosal involvement and hypotension or respiratory compromise. Differentiating anaphylaxis from hypersensitivity is key for proper treatment.

Eight of the ten hypersensitivity reactions met NIAID/FAAN criteria for anaphylaxis. While most patients received anti-histamines and corticosteroids, only 4 anaphylactic patients received epinephrine. However, most experienced prompt resolution without sequelae. No maternal deaths were reported. One patient required hospital transfer for respiratory distress requiring intubation and was induced at 22 weeks following membrane rupture on hospital day 6 [5]. Four patients completed abortions 1-2 days after initial laminaria placement [6]; one case utilized synthetic osmotic dilators without further issues [4].

This review suggests that laminaria anaphylaxis likely necessitates prior exposure. Seven of 8 anaphylactic patients reported previous laminaria use, with the remaining case unreported. Furthermore, immunological testing (skin and/or IgE serum) in 6 consenting patients demonstrated an IgE-mediated allergy, which requires allergen re-exposure. Inferences are limited based on the sample size of this review, however replacement of laminaria with Dilapan-S could be considered in patients with prior laminaria exposure.

Overall, care should be taken by clinicians to monitor outpatients for this rare but serious complication. In this review, time to onset of hypersensitivity ranged from immediately to 3 hours after placement.

Epinephrine is first-line treatment for anaphylaxis, followed by adjunctive medications like anti-histamines, corticosteroids, and bronchodilators [10]. In suspected cases, with removal of the inciting agent, intramuscular epinephrine should be rapidly administered and repeated every 5-10 minutes as needed. While this review suggests mostly favorable outcomes, our small sample size render it impossible to determine whether these reactions were mild forms of anaphylaxis or if laminaria-related anaphylaxis may be sufficiently treated with antihistamines and corticosteroids. Therefore, epinephrine remains key in early management and is recommended to avoid potential under treatment of anaphylaxis. Studies on the mechanism of laminaria anaphylaxis could help develop protocols to identify patients at risk and standardize treatment of laminaria-associated anaphylaxis.

References

- [1] Newmann SJ, Dalve-Endres A, Diedrich JT, et al. Cervical preparation for second trimester dilation and evacuation. *Cochrane Database Syst Rev* 2010. (8):CD007310.
- [2] Lichtenberg ES. Complications of osmotic dilators. *Obstet Gynecol Surv* 2004; 9:528-36.
- [3] Fox MC, Krajewski CM. Cervical preparation for second-trimester surgical abortion prior to 20 weeks' gestation: SFP Guideline #2013-4. *Contraception* 2014; 89:75-84.
- [4] Nguyen MT, Hoffman DR. Anaphylaxis to Laminaria. *J Allergy Clin Immunol* 1995; 95:138-9.
- [5] Cole DS, Bruck LR. Anaphylaxis after laminaria insertion. *Obstet Gynecol* 2000; 95:1025.
- [6] Chanda M, Mackenzie P, Day JH. Hypersensitivity reactions following laminaria placement. *Contraception* 2000;62:105-6.
- [7] Knowles SR, Djordjevic K, Binkley K, Weber EA. Allergic anaphylaxis to Laminaria. *Allergy* 2002;57:370.
- [8] Kim SH et al. Two cases of anaphylaxis after laminaria insertion. *J Korean Med Sci* 2003;18:886-8.
- [9] Kim MS, Kim DY, Chang YH, Cho YJ. A case of anaphylaxis to laminaria. *J Asthma Allergy Clin Immunol* 1999;19:601-5.
- [10] Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;117:391-7.

Author (Reference)	Case	Age	Gravida Parity	Gestational Age (weeks)	Previous Exposure to Laminaria	Time to Onset of Reaction	Therapeutic Management	Maternal Outcome	Surgical Outcome	Allergy Labs	Reaction
Nguyen & Hoffman (4)	1	26	G5P1	U	3	"during insertion"	Epinephrine, antihistamine, corticosteroid	Biphasic reaction 48hrs later	Surgery completed with synthetic dilator	Yes, refused skin testing, IgE serum binding to laminaria extract	Anaphylaxis
Kim et al. (9)	2	42	G5P0	U	U	5min	Epinephrine, antihistamine, corticosteroid, dopamine	Resolved	U	Yes, skin testing	Anaphylaxis
Cole & Bruck (5)	3	32	G7P2	21	≥ 1	5min	Antihistamine, corticosteroid, beta---agonist nebulizer, complicated by intubation, aspiration & seizure, antibiotics	ARDS, Extubated 36hrs later	PPROM, labor induction	Indirectly (negative skin tests to latex & betadine)	Anaphylaxis
	4	21	G5P1	8	3	1h	Antihistamine, corticosteroid	Resolved	Surgery completed following day	Yes, skin testing	Hypersensitivity
Chanda et al. (6)	5	22	G3P1	20	1	3h	Antihistamine	Lost to follow---up	Lost to follow---up	Lost to follow---up	Hypersensitivity
	6	22	G6P3	1st trimester	2	2h	Antihistamine (home), beta---agonist nebulizer, epinephrine, antihistamine (hospital)	Resolved	Surgery completed following day	Lost to follow---up	Anaphylaxis
Knowles et al. (7)	7	34	U	U	3	30min	Antihistamine	Resolved	Surgery completed that day	Yes, skin testing	Anaphylaxis
	8	27	U	U	1	30min	Epinephrine, corticosteroid	Resolved	I	Yes, skin testing & ELISA for IgE to laminaria extract	Anaphylaxis
Kim et al. (8)	9	37	U	U	≥ 1	U	U	Recurrent episodes of urticaria	I	Yes, skin testing & ELISA for IgE to laminaria extract	Anaphylaxis
Sierra et al. <i>current report</i>	10	28	G8P2	21	≥ 1	30min	Antihistamine, corticosteroid	Resolved	Opted to cont nue pregnancy	Lost to follow---up	Anaphylaxis

Abbreviations: U = unreported, ARDS = acute respiratory distress syndrome, ELISA = enzyme---linked immunosorbent assay