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Beta2-agonists may be superior to epinephrine to relieve severe anaphylactic uterine contractions.

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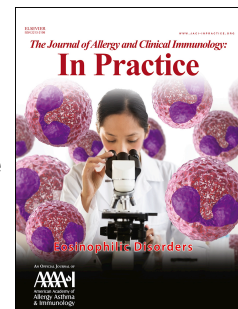
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ABSTRACT

Background:

Uterine contractions are recognized as a potential manifestation of anaphylaxis but literature on their proper management is limited. It is widely recognized that anaphylactic reactions can cause uterine contractions, but little is known about their optimal management.

Objective

Review potential treatments for painful uterine contractions associated with anaphylaxis or mast cell activation.

Method

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines. Pubmed, Embase and Cochrane were searched in English, French and Spanish for reports of uterine anaphylaxis published up until July 2020. The search strategy used a combination of boolean operators and included the following Medical Subject Heading terms and keywords: hypersensitivity; anaphylaxis; mastocytosis; uterus; uterine contraction; pelvic pain; labor, obstetric; labor, premature; and endometriosis.

Results

This systematic review identified 19 studies reporting on 31 cases of painful uterine contractions occurring during anaphylaxis or other events associated with mast cell activation.

Nine patients were pregnant. We present 2 additional cases in non-pregnant women, one associated with an oral food challenge and the other associated with oral food desensitization. The most frequent triggers were subcutaneous immunotherapy (14 cases), food (6 cases) and drugs (4 cases). Uterine cramps were associated with systemic symptoms in 24 cases and lasted in average for 2.4 hours. Pre-treatment with anti-histamines and montelukast generally failed to prevent recurrence, but non-steroidal anti-inflammatory drugs were used successfully in some reports. Response to intramuscular epinephrine was inconsistent. Data from ex vivo models indicate that epinephrine may paradoxically contribute to uterine contractions through alpha-receptor activity. A small number of cases showed good response to beta-2-agonists

Conclusion: There is a lack of quality data on painful uterine contractions occurring in the context of anaphylactic reactions and on their optimal management. In the absence of counter-indication, use of a beta-2 agonist and premedication with non-steroidal anti-inflammatory drugs could be the preferred options.

Keywords : Allergy, Anaphylaxis, Mast cell activation, Pelvic pain, Uterine contractions, uterus, Preterm labor, Endometriosis

64 Highlights box**65 What is already known about this topic?**

66 Uterine contractions are recognized as a potential manifestation of anaphylaxis but literature
67 on their proper management is limited.

68 What does this article add to our knowledge?

69 Reports indicate inconsistent response to epinephrine, possibly due to its alpha-adrenergic
70 action on uterus. Pre-treatment with anti-histamine is generally ineffective. A few cases were
71 successfully treated with beta-2-agonists. Pre-treatment with NSAID were also reported as
72 effective.

73 How does this study impact current management guidelines?

74 Use of beta-2-agonists and NSAID for the treatment of uterine contractions during anaphylactic
75 reaction warrant further investigation. Use of epinephrine could be ineffective to relieve severe
76 pain caused by uterus contraction.

77 **Abbreviations**

78 VIT : Venom immunotherapy

79 MC : Mast cells

80 NSAIDS :Non-steroidal anti-inflammatory drugs

81 PGE2 : Prostaglandin E 2

82 PGD2 : Prostaglandin D 2

83 PGF2 α : Prostaglandin F 2 α

INTRODUCTION

Anaphylaxis is a potentially severe and life-threatening event, which can occur as a result of an allergen entering the circulation and triggering degranulation of basophils and mast cells in multiple organ systems throughout the body. The manifestations of anaphylaxis most frequently involve the cutaneous (80%), respiratory (70%), gastro-intestinal (45%), cardiovascular (45%) and neurological (15%) systems (1). Mast cells are also present throughout the myometrium and most allergists and textbooks recognize uterine contractions as a potential manifestation of anaphylaxis (2, 3). They are however generally written off as miscellaneous manifestations and actual literature on the topic is limited, often focusing on the risk of preterm labor and fetal distress during pregnancy, rather than on the symptom of lower pelvic pain (1, 4-11).

The underrepresentation of gynecologic manifestations in anaphylaxis literature raises an important question of sex and gender bias, especially as women make for almost 2/3 of the clientele in adult allergy clinics (12). Uterine cramping can be extremely painful and may not readily respond to usual treatments of anaphylaxis. Here, we present two cases of uterine contractions from anaphylactic reactions during an oral food challenge and oral food desensitization that were refractory to intra-muscular epinephrine along with a systematic review of literature on the topic.

Case 1

The first patient was a 29-year-old woman followed at the allergy clinic for multiple food allergies, allergic rhinitis, oral allergy syndrome, and severe asthma. Her regular medication

included cetirizine and a combination of salmeterol and high dose inhaled fluticasone. She had also been diagnosed with endometriosis (grade I) by laparoscopy in 2012.

In fall 2018, she was scheduled for an open challenge to soy milk (specific IgE at 3.5kUA/L). The challenge started with a dose of 15mL. Thirty minutes later (T+30m), she reported non-objective symptoms of throat pruritus, sensation of lip edema, and reflux. Indirect laryngoscopy was normal. The challenge was stopped and local symptoms were treated with 20 mg of rupatadine, 300 mg of ranitidine and 15mL of magnesium hydroxide.

Ninety minutes later, after discussion with patient, because symptoms had rapidly resolved and were compatible with her oral allergy syndrome and that she normally takes anti-histamines regularly at home, it was decided to proceed with the next step of the challenge to document tolerance to higher amounts while under anti-histamine.

After a second dose of 60 mL of soy milk (T+120m), she started to clear her throat and reported a change in her voice. The examination revealed mild conjunctivitis with nasal congestion and mild facial flushing. Challenge was stopped again. The patient was administered ophthalmic bepotastine 1.5%. She was also administered montelukast 10 mg and prednisone 50 mg to prevent a subsequent asthma exacerbation, as well as pantoprazole 40 mg for the recurrence of acid reflux.

Twenty minutes later (T+140m), she suddenly reported rapidly progressing nausea and abdominal pain and was administered 0.5 mg of intramuscular (IM) epinephrine. This was followed by 50 mg of dimenhydrinate and 50 mg of ranitidine intravenously (IV) to try to

alleviate the severe nausea. She vomited once and then left for the bathroom for urgent diarrhea.

At that point, the patient reported severe lower abdominal pain, described as 10/10, that radiated to both legs. She was clearly distressed with tremors of the lower extremities classically associated with post-partum uterine contractions. All other symptoms from the anaphylaxis had resolved within 15 minutes of the first adrenaline injection. Blood pressure and auscultation were completely normal. She was administered a 1L bolus of normal saline with ondansetron 40 mg IV and hydromorphone 1mg subcutaneously (SC). Given the absence of response, she was administered a second dose of hydromorphone 1mg SC, epinephrine 0.5 mg IM and methylprednisolone 40 mg IV. At T+180m, there was still no significant effect of the medication on the lower abdominal pain. After discussion with obstetrics, she was administered a dose of 0.8 mg sublingual (SL) nitroglycerine and 500 mg of naproxen with second bolus of 1L of NaCl 0.9%. The pain decreased over 10 minutes to 6/10, with resolution of the pain radiating to her legs and the vital signs remained normal. At T+240m, the pain returned to 10/10 and the patient was in tears. Nitroglycerine 0,4 mg SL and hydromorphone 1 mg SC were repeated. At T+280min, the pain was down to 2/10 and the patient care was taken over by the gynecology team. The pelvic exam was normal and beta-hCG was negative. She was asymptomatic when discharged at T+10h. An ultrasound performed 2 weeks later was normal.

Case 2

Case 2 was a 17-year-old female patient having undergone omalizumab-enabled accelerated oral immunotherapy to peanut, sesame, walnut, and cashew. Her initial specific IgE to these

foods were 41, 4.0, 10.3 and 5.1 kUA/L, respectively. She had reached a daily maintenance dose of 500 mg per food in January 2019 and successfully discontinued omalizumab in February 2019.

In August 2019, she was awoken at 3 am by a lower abdominal pain described as the worst in her life. She had taken her dose at 11pm the previous night. She was immediately taken to the ER by her parents. Upon arrival at the emergency room, 30 minutes after the onset of the pain, hives appeared on the torso and neck and the patient felt shortness of breath without wheezing. She immediately used her epinephrine auto-injector, which was followed by rapid relief of cutaneous and respiratory symptoms. The abdominal pain however persisted for another 4 hours before subsiding. It was only treated with acetaminophen due to the instruction to avoid non-steroidal anti-inflammatory drugs (NSAIDS) during OIT.

Following this episode, an individualized action plan was implemented, which instructed the patient to immediately use 800 mcg of inhaled salbutamol rather than epinephrine in case of isolated uterine cramping. The patient experienced three subsequent similar episodes, all of which fully resolved within 5 minutes of administration of suprathreshold doses of inhaled salbutamol. All episodes occurred after taking the dose very late at night and during the patient's menstrual periods. The patient was therefore instructed to take the dose in the morning to avoid the co-factor of sleep deprivation and to actively control menstrual cramping with naproxen (13).

Because she had had generalized anaphylaxis (without uterine cramping) a few months earlier during a cofactor challenge to her food dose performed with aspirin and alcohol, she was

deemed at risk of NSAID-induced food-dependent anaphylaxis. She was therefore instructed to take cromoglycate with her food dose on the days she would take naproxen (14). The uterine symptoms did not reoccur with these precautions.

METHODS

Human cases of painful uterine contractions during anaphylaxis or mast cell activation were identified by a systematic review of the literature in Medline, Embase and Cochrane. Reports of premature labor that would be induced by an anaphylaxis were included (Figure 1). Articles in English, French and Spanish were searched through July 2020. We searched the literature with the following MeSH terms in Medline and Cochrane: “Endometriosis”, “Uterus”, “Uterine Contraction”, “Labor, Obstetric”, “Pelvic pain”, “Obstetric Labor, Premature”, “Mastocytosis”, “Anaphylaxis” and “Hypersensitivity”. We used the following Keywords in Embase: “uterus contraction”, “pelvic pain”, “dysmenorrhea”, “endometriosis”, “labor”, “uterus”, “immature and premature labor”, “mastocytosis”, “anaphylaxis” and “hypersensitivity”.

RESULTS

Systematic review of clinical case studies

The literature search yielded a total 19 reports (13 articles and 6 abstracts) describing together 31 cases of uterine contraction, which are summarized in table 1. Nine of the case reports were in pregnant women and only one patient was known for endometriosis. Uterine cramping was

associated with other systemic symptoms of anaphylaxis in 24 cases (78%). Six reports also mentioned vaginal bleeding (19%). Two of the nine pregnant patients required an emergency caesarean section.

The most frequent trigger was venom immunotherapy (9 cases), followed by food allergens (6 cases), subcutaneous immunotherapy to environmental allergens (5 cases), medication (4 cases), mast cell related diseases (3 cases) and latex (1 case). Of the mast cell related diseases, there was one patient with mast cell activation syndrome and two with cutaneous mastocytosis. The trigger was unknown or not mentioned in 2 cases.

Antihistamine were used the most frequently (16 cases), followed by intramuscular epinephrine (11 cases), corticosteroids (9 cases), nebulized terbutaline (8 cases), subcutaneous epinephrine (4 cases), NSAID (2 cases), ephedrine (1 case) and magnesium sulfate (1 case). Symptoms lasted between 10 minutes and 8 hours, with an average of 2.4 hours.

Ex vivo models

Given limited clinical data on anaphylactic uterine contractions, the information provided by ex vivo models can be particularly useful to inform on the potential effect of anti-allergy interventions in this specific context.

The first such experiments took place in 1910 and 1913 by Schultz (15) and Dale (16), who demonstrated that smooth muscle from the myometrium of sensitized animal contracted when challenged with their specific allergen. The reaction was called “the Schultz and Dale reaction” (17). Schultz also showed sustained increased contractility in post-mortem uterine tissue from animal having undergone fatal anaphylaxis (15).

The Schultz and Dale experiment was later validated using human myometrium strips from ragweed-allergic women (2). It was then noted that samples from pregnant women contracted with increased frequency and intensity compared to those from non-pregnant donor. Passive transfer experiments using myometrium strips from non-ragweed allergic women that were pre-incubated with serum from ragweed-allergic patients were also performed to demonstrate the specificity of the reaction and its dependence on IgE.

Antihistamines and montelukast

Histamine and serotonin have been shown to exert a synergic dose-dependent effect on myometrial strip contraction (2, 18-20). Histamine-induced contraction can be fully prevented with diphenhydramine but not cimetidine, indicating this mechanism is mediated through the H₁-receptor (21). However, diphenhydramine only partially suppresses contractility when sensitized myometrium strips are directly challenged with an allergen, suggesting that other mediators are independently involved in IgE-mediated uterine contraction (2). Similarly, chlorpheniramine, another H₁-antagonist, but not cimetidine slightly attenuated contractile response induced by mast cell degranulation with compound 48/80 (22). In the same experiment, contractility was fully inhibited by pre-treatment with cromolyn, a mast-cell stabilizer. In clinic however, the use of oral cromolyn to treat anaphylactic uterine contractions is made moot by its negligible gastro-intestinal absorption (23).

In contrast, leukotrienes (LTC₄, LTD₄, LTE₄ and LTB₄) seem to have little to no effect on the contractility of animal or human myometrium in vitro (24, 25).

Anti-histamine have been used in most cases of anaphylactic uterine contractions but their relative efficacy is difficult to assess (26-33). In two cases, pre-medication with antihistamine and montelukast was attempted and found ineffective at preventing further episodes of painful uterine contractions on subsequent injections of subcutaneous immunotherapy (30).

NSAIDS

Prostaglandins are well-recognized mediators of uterine contraction. In parturition, prostaglandin $F_{2\alpha}$ is directly produced by the endometrial cells in response to oxytocin and is a potent enhancer of myometrium contractility (24, 34, 35).

In anaphylaxis, the main prostaglandin produced by mast cells is prostaglandin D_2 . In the Schultz and Dale reaction, it potentiates the effect of both histamine and serotonin on the myometrium strips (19). Its two receptors (DP1 and DP2) are expressed by the myometrium and whereas DP1 increases intracellular levels of cAMP (relaxation), they are decreased by the activation of DP2 (contraction) (36). The final effect on the myometrium is biphasic, with an excitatory phase followed by an inhibitory phase (35, 37).

In vitro, ibuprofen has been shown to only partially suppress myometrium contractility following compound 48/80-induced mast cell degranulation (22). In practice, however, NSAIDS are effective as first line tocolytics for pre-term labor or for the treatment of endometriosis.

It is possible that the full impact of contractility potentiating effect of prostaglandins is not fully captured by ex vivo experiments.

In one case report, ibuprofen and diclofenac were used successfully for the treatment and prevention of painful uterine contractions caused by venom immunotherapy in a patient with endometriosis (38). It should be noted that in the third trimester, the use of NSAIDS should not exceed 48h due to the risk of fetal ductus arteriosus closure.

Adrenergic agonists

Study of human myometrial strips from pregnant donors showed that adrenalin contributes to both the contraction of myometrium via the α -adrenergic receptors and its relaxation via the β -adrenergic receptors. The net effect of adrenalin is an initial relaxation followed by sustained contraction (39).

In line with this opposing action of adrenalin receptors, both α -antagonists and β -agonists have been shown to reduce uterine contractility. The mechanism has been shown to involve a decrease in the production of $\text{PGF}_{2\alpha}$ and PGE_2 and an increase in 6-keto-prostaglandin $\text{F}_{1\alpha}$ (40). Terbutaline, a pure β -agonists, is a potent tocolytic currently used off-label for the acute treatment premature labor (41). The FDA recommends against its continued use for more than 48-72h or in prophylaxis due to its metabolic and cardio-vascular side-effects (e.g. arrhythmias, pulmonary edema, hyperglycemia, hypokalemia) (42).

Cady and Weber presented a case series in the form of an abstract in 2009, describing the use of nebulized terbutaline for the treatment of uterine anaphylaxis(43). It was used successfully in combination with epinephrine in 4 patients presenting both uterine cramping and other manifestations of anaphylaxis. It was also found safe and effective when used without epinephrine in one patient with isolated uterine anaphylaxis. Terbutaline was also successfully

used by Wang et al. The patient responded 10 minutes after a dose of nebulized terbutaline and responded also to SC terbutaline(44). Donahue et al also used nebulized terbutaline, but the outcome is not known(45). Nebulized β -agonist was also used by Tsuzuki et al, but the specific drug was not mentioned (27). There is another case report where inhaled bronchodilator was used, but the specific medication and dosage was not mentioned (28). In both cases the intent appeared to be to treat the bronchospasm rather than the uterine anaphylaxis.

Non-adrenergic vasopressors

Ex vivo studies indicate that glucagon has no effect on uterine contractility(46) while methylene blue appears to relax the myometrium(47). Vasopressin, on the other hand, is more potent than oxytocin at inducing contractions of non-pregnant uterus, making it probably the least interesting vasopressor to treat anaphylactic shock in a patient with uterine contractions(48).

Corticosteroids

There is little literature on the effect of non-sexual corticosteroids on uterine contractility. In ex vivo models using myometrium from pregnant women, methylprednisolone has been shown to promote contractility at low concentrations but to inhibit it at high concentrations (49).

All case reports mentioning the use of systemic corticosteroids in the context of uterine anaphylaxis were administered in the context of concomitant respiratory and/or cardiovascular manifestations (27, 28, 31, 32, 50). In one case, it was administered to accelerate lung maturation in the context of eminent preterm labor (32).

Nitroglycerine

Intravenous nitroglycerine is used as a tocolytic in obstetrics but is less effective than calcium-channel blocker and β -agonist (51). Sublingual administration of nitroglycerin has not been shown to have an effect on uterine contraction during labor (52). In the context of primary dysmenorrhea however, transdermal administration was shown to be effective at decreasing pain (53). The effect was, however, short-lived (30 minutes) and it was significantly less effective than oral diclofenac at reducing pain 2 hours after administration (54). This short duration of clinical effect may explain the return of abdominal cramping in case number 1. There were no other reports of the use of nitroglycerine for the treatment of uterine anaphylaxis identified in the literature search.

Calcium

Karakurt and colleagues reported uterine anaphylaxis in a patient where hypocalcemia appeared to act as a co-factor (55). The patient was known for hypoparathyroidism secondary to a previous thyroidectomy. Thirty minutes after venom immunotherapy injection, she presented with cyclic uterine contractions every three minutes, despite pre-medication with anti-histamine which responded to calcium infusion. Calcium infusion before her injections prevented uterine contractions on subsequent injections.

Calcium channel blockers are recommended as first line tocolytics (56). However, their use has never been reported or studied in the context of uterine anaphylaxis.

DISCUSSION

Severe uterine cramping is a rare but potentially severe manifestation of anaphylaxis in women, which can be challenging to manage. The exact incidence of uterine contractions during anaphylactic reactions is unknown and it is likely that mild and moderate cases are underreported. As a result, specific literature to guide its specific management is direly missing. Clinical data obtained through this systematic review was uncontrolled and heterogeneous making it difficult to interpretor to conclude as to the efficacy of any intervention.

Therefore, the first conclusion that should be drawn from this systematic review is the need epidemiological data as well as high-quality prospective intervention studies on the management of anaphylactic uterine contractions. In the absence of such high-quality data, the most informative data to guide practice appears to be from reports where different interventions were attempted in the context of repeated exposures to the allergen and from ex vivo models (Figure 2).

An important finding from the studies is that severe uterine contractions may not respond to the standard treatment of anaphylaxis with intramuscular epinephrine and that the latter may in fact contribute to increase uterine contractions. When given early, epinephrine likely helps prevent uterine contractions by inhibiting mast cell activation through their beta-2 receptor, but it could become a double-edge sword once contractions have started. In cases where uterine cramping is the main symptom of anaphylaxis, clinical judgment is required to determine whether beta-2 agonists may be a more adapted intervention, balancing the risk and

benefit of foregoing alpha-adrenergic effect. In such cases, close monitoring of any vascular manifestation is important to determine if rescue treatment with epinephrine is warranted.

The use of NSAIDS is another potential option that can be considered. In the second case, suboptimal treatment of menstrual cramping with acetaminophen was identified as a relevant risk factor contributing to food-induced uterine contractions. Treatment with naproxen was encouraged to minimize end-organ reactivity, following the same logic as with asthma control. However, the use of NSAIDs can be problematic in the context of OIT since they can also increase gut barrier permeability and act as co-factors for anaphylaxis. This problem was circumvented here by the use of sodium cromoglycate, which was shown to prevent this effect in a murine model (14).

Sublingual nitroglycerin was used to alleviate uterine contraction in the first case presented. It had modest and short-lived effect, which is in line with its pharmacologic profile. There seems to be little advantage in its use in terms of efficacy or accessibility when compared to inhaled beta2-agonist.

Given the lack of epidemiological data, it is difficult to assess the role of endometriosis and whether it is a risk factor for increased uterine contractions in the context of anaphylaxis or if it contributes to the severity of the pain. It is however worth noting that endometriosis is a risk factor for allergic disease in general (57). Mast cells are abundant in endometriotic implants and often located close to nerve endings (58).

Finally, an argument could be made to the effect that the lack of literature on anaphylactic uterine contractions may be an example of sex and gender bias. Sex bias is based on biological

differences while gender bias is based on socio-cultural difference between male and female patients. Low reports could be due to a gender effect if systematically dismissed by patients or allergists as irrelevant. In the absence of an equivalent manifestation in male patients, one can only hypothesize as to whether these would be more promptly reported or addressed. It is also important to distinguish literature on uterine anaphylaxis from obstetrical anaphylaxis. While there is an appreciable amount of literature on obstetrical anaphylaxis, the presentation does not necessarily involve uterine cramping and the concern is much more with severe refractory hypotension than with abdominal cramping (8-11). While obstetrical anaphylaxis appears relatively rare (10, 11), uterine contractions in non-pregnant patients could be more frequent than literature leads to believe (7). The fact that most reports are of severe cases suggests that they represent the tip of the iceberg and that many female patients could be experiencing mild to moderate episodes of anaphylactic uterine contractions that are not captured by the literature. Allergists and researchers both have a role in prioritizing this gap of knowledge.

CONCLUSION

In conclusion, there is a lack of quality data on anaphylactic uterine contractions and its proper management. Available case studies and pharmacologic data from ex vivo model indicate that epinephrine may in some cases be ineffective to treat this symptom and may even contribute to myometrium contraction. In the absence of cardio-vascular instability, use of a beta-2 agonist could be a preferred option. More research on this manifestation is needed to ensure proper management of anaphylaxis in women.

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FIGURES LEGENDS

Figure 1 – Study selection. PRISMA diagram describing study selection for review.

Figure 2 – Pharmacologic effect of anaphylactic reaction mediators and medications on myometrium. Red arrows indicate action that promote myometrium contraction and green arrows indicate actions that promote relaxation. (+) indicates agonist effect and (-) indicate antagonist effect. *NSAID: non-steroidal anti-inflammatory drug, cAMP: cyclic adenosine monophosphate, cGMP: cyclic guanosine monophosphate, PD: prostaglandin D2 receptor.*

	Patient	Context	Presentation	Treatments	Response to treatment	Final outcome
Klein et al. 1984 (26)	32 y.o., 29 weeks pregnant Unremarkable history	Reaction following the ingestion of crab and cherries	Pruritus and urticaria, palmoplantar erythema, hypotension and uterine contraction every 2-3 minutes. Fetal heart rate 138 bpm then 150 bpm with repetitive decelerations.	Diphenhydramine 50 mg, IV fluids, oxygen, ephedrine 5 mg IV ephedrine 10 mg IV	The contraction continued despite the treatment, the deceleration diminished gradually within 25 minutes with complete resolution after 2 hours.	She had caesarean section at 40,5 weeks. The baby had an Apgar 9-9, 3780 g and a normal neurologic exam.
Gbolade and Jackson 1991 (59)	19 y.o. Egg allergy Dysmenorrhoea	Few minutes following ingestion of fish	Multiple episodes of pelvic pain often associated with nausea and vomiting.	n/a	n/a	She was diagnosed with a cod allergy. Symptoms did not recur after eviction of fish from diet.
Barry, Madan and Hewitt 1992 (33)	31 y.o. Scheduled for an elective caesarean section	30 minutes after ranitidine 150 mg po	Dyspnea, chest and loin pain, pruritus, angioedema of the face and tongue, tachycardia 120.	Oxygen via facemask Chlorpheniramine 10 mg IV	After the initial symptoms resolved, she developed intermittent abdominal pain and underwent caesarean section.	Caesarean section was performed 7h hour after the onset of reaction without complication.
Donahue, Lupton et al. 1995 (45)	26 y.o. 19 weeks pregnant Telangiectasia macularis eruptiva perstans	New onset of telangiectasia macularis eruptive perstans	Consulted for chest tightness, dyspnea, uterine contraction, vaginal bleeding and maculopapular rash.	Chlorpheniramine Terbutaline aerosols Promethazine	Efficacy of immediate treatment not described. Continued treatment with hydroxyzine and imipramine relieved her dyspnea and uterine cramps.	Preterm labor at 24 weeks treated with magnesium sulfate. A normal baby was born by caesarean section at 36 weeks. 2840 g. Apgar 8-8.
Simpson, Roomes, and Humphrey 2001 (29)	37 y.o. allergy to dust mites and cockroach	2 episodes of anaphylaxis occurring on day 3 of menstrual period to unknown trigger	Lower abdominal pain, hypotension, diffuse erythema, pruritus and facial swelling	IV fluids, epinephrine IM and antihistamines.	n/a	Menstruations were suppressed with medroxyprogesterone and she was treated with regular NSAIDs.
Toubi, Kessel et al. 1997 (60)	47 y.o. Allergy to yellow jacket venom.	40 minutes after 20 μ g of yellow jacket venom extract	"A severe contraction of her uterus" followed by vaginal bleeding ten minutes later.	Epinephrine SC	The symptoms subsided gradually in 15 minutes.	She had another episode with 20 μ g of yellow jacket venom extract. She finally tolerated the weekly dose of 20 μ g after several weak of 15 μ g.
	23 y.o. Allergic rhinitis and asthma.	30 minutes after 0,3 cc of 1:2000 w/v of <i>Parietaria</i> extract	Flushing of the face and pruritus. Thirty minutes later, she developed severe lower abdominal pains and vaginal bleeding.	n/a	The symptoms subsided gradually.	She had a milder episode with a dose of 0,2 cc of 1:2000 w/v. She could not increase her doses beyond 0,5 cc of 1: 20000 w/v.
Shingai et al. 2002 (50)	33 y.o. 38 weeks pregnant. Atopic dermatitis. Fetal growth retardation	Few minutes after vaginal examination with a latex glove	General urticaria, facial congestion and dyspnea which improved with the treatment.	Hydrocortisone 1000 mg, intratracheal epinephrine and oxygen.	Two hours later, she developed regular uterine contractions with late decelerations and had caesarian section.	A latex allergy was confirmed. The baby had an Apgar of 5-8, weighed 2,227g and had rigidity of extremities at birth.

Cardona et al. 2003 (38)	47 y.o. Bee VIT premedicated with cetirizine Endometriosis Small uterine myoma	First reaction following the first of 2 injections of 20 µg of bee venom. Second reaction on next visit following the first of 2 injections of 40 µg.	Hypogastrium colic pain suggestive of uterine contractions. Associated menorrhagia on second episode.	Ibuprofen 600 mg Diclofenac 50mg IM Had premedicated with cetirizine 10 mg PO.	On both episodes, the patient was able to tolerate a second dose of VIT on the same day after resolution of initial symptoms with NSAIDs	At following visits, the patients would pre-medicate with ibuprofen 600mg and was able to reach the target maintenance dose of 100µg of <i>Apis mellifera</i> venom with no recurrence of symptoms.
Cady and Weber 2009 (43)	5 patients with hymenoptera venom allergy and 1 patient with food allergy	10-40 min after VIT injection or oral food challenge.	Uterine cramping 4 presented with other systemic manifestations of anaphylaxis	5 treated with epinephrine and nebulized terbutaline 1 treated with nebulized terbutaline only	Significant improvement within one hour for all patients	n/a
Gonzalo-Garijo et al. 2010 (28)	6 patients aged 35 to 52 y.o,	15-30 minutes after antibiotics (4), hymenoptera sting (1), SCIT (1), or unknown trigger (1)	Hypotension, bronchospasm, urticaria, nausea, diarrhea, abdominal pain and metrorrhagia	Corticosteroids and antihistamines (all) SC epinephrine (3)	Resolution in 2 to 8 hours, except one who reported symptoms for 4 days	n/a
Karakurt et al. 2010 (55)	45 y.o. Bee venom allergy Hypocalcemia from hypoparathyroidism post-thyroidectomy.	30 minutes after the first and second maintenance dose of VIT, despite premedication with levocetirizine.	Sudden cyclic uterine contractions every 3 minutes accompanied by hypocalcemia	Calcium infusion	The symptoms subsided after the calcium infusion.	On her third dose of maintenance immunotherapy, she received calcium infusion as premedication. She did not develop any contractions.
Madendag, Madendag et al. 2010 (61)	26 y.o. 27 weeks	Cutaneous mastocytosis	Premature uterine contraction and pruritic urticaria pigmentosa	Ringer's lactate Betamethasone for fetal lung maturation Magnesium sulfate Pheniramine IV	n/a	Resolution of the uterine contraction followed resolution of the skin manifestation. Timing not indicated.
Romero et al. 2010 (32)	28 y.o. 31 weeks pregnant	Shortly after ingestion of lobster	Generalized pruritic maculopapular rash, regular strong uterine contractions every three minutes	Chlorphenamine PO Betamethasone PO	n/a	She went into labor at 40 weeks. The infant weighed 3,8 kg and had an Apgar of 9 and 9. The child developed atopic disorders.
Nandigam, Eidelman, and Dimov 2016 (30)	4 patients. None with dysmenorrhea.	30-45 minutes after SCIT: Two during buildup phase and two during maintenance	One patient with uterine cramps only. Three patients with uterine cramps accompanied with urticaria, angioedema or diffuse erythema/flushing.	Reactions were treated with epinephrine and diphenhydramine. Premedication with antihistamine and montelukast was attempted on subsequent treatments.	Uterine contractions lasted for approximately one hour after the administration of treatment. The premedication was ineffective at preventing uterine anaphylaxis.	Two had recurrent episodes of uterine contractions despite the adjustment of the schedule and dosage of their SCIT.

Petkova et al. 2016 (31)	49 y.o. Mast cell activation syndrome	Reactions more prevalent with stress, menstruation and virus infections.	Recurrent nighttime attacks of acute abdominal cramps, diarrhea, urticaria fever, flushing, tachycardia, headache and uterine contractions.	Systemic corticosteroids and antihistamine	Symptoms would resolve within 10-15 min with vomiting.	Episodes controlled with regular administration of bilastine. Mild symptoms recurred when she tried to stop the antihistamine.
Tsuzuki 2016 (62)	26 y.o. 25 weeks Atopic dermatitis	After ingestion of buckwheat.	Dyspnea, itchy rash, abdominal pain and severe uterine contractions Threatened abortion	Intramuscular epinephrine (X2)	n/a	n/a
Garcia et al. 2017 (63)	A pregnant patient with latent syphilis	Desensitization to penicillin	"severe breakthrough reaction with uterine contraction"	n/a	n/a	Desensitization was discontinued
Tsuzuki et al. 2017 (27)	26 y.o. 25 weeks pregnant. Atopic dermatitis	15-30 min after meal	Bronchospasm with peripheral cyanosis, generalized itchy rash, abdominal pain and severe uterine contractions. No fetal distress at ultrasonography.	Oxygen Epinephrine 0,4mg IM Nebulized short-acting β 2-receptor agonist Manually displacement of the uterus to the left	Bronchospasm resolved, but the rash and the abdominal pain persisted. Epinephrine was repeated with antihistamine and methylprednisolone	Discharge after seven days of fetal monitoring and maternal treatment of threatened preterm labor. A normal baby was born at week 37. Investigation revealed buckwheat allergy.
Wang, Marshall et al. 2017 (44)	28 y.o. Fire ant and aeroallergen allergy	During rush immunotherapy	Itchy throat, facial flushing, coughing, wheezing. Then, rapidly developed severe pelvic cramps	Cetirizine, diphenhydramine, dexamethasone, nebulized epinephrine, formoterol and ipatropium. 1 mg nebulized terbutaline	Significant improvement of the pelvic pain 10 minutes after the first dose of terbutaline. She later had, rebound uterine cramps which improved with 0,25mg SC terbutaline. After 90 min, she developed flushing and urticaria that required epinephrine and IM corticosteroids.	Premedication with corticosteroids 3 days before VIT and ibuprofen 800mg was administered on subsequent visits

Table 1 – Case reports of anaphylactic uterine contractions. VIT: Venom immunotherapy, SCIT: Subcutaneous immunotherapy

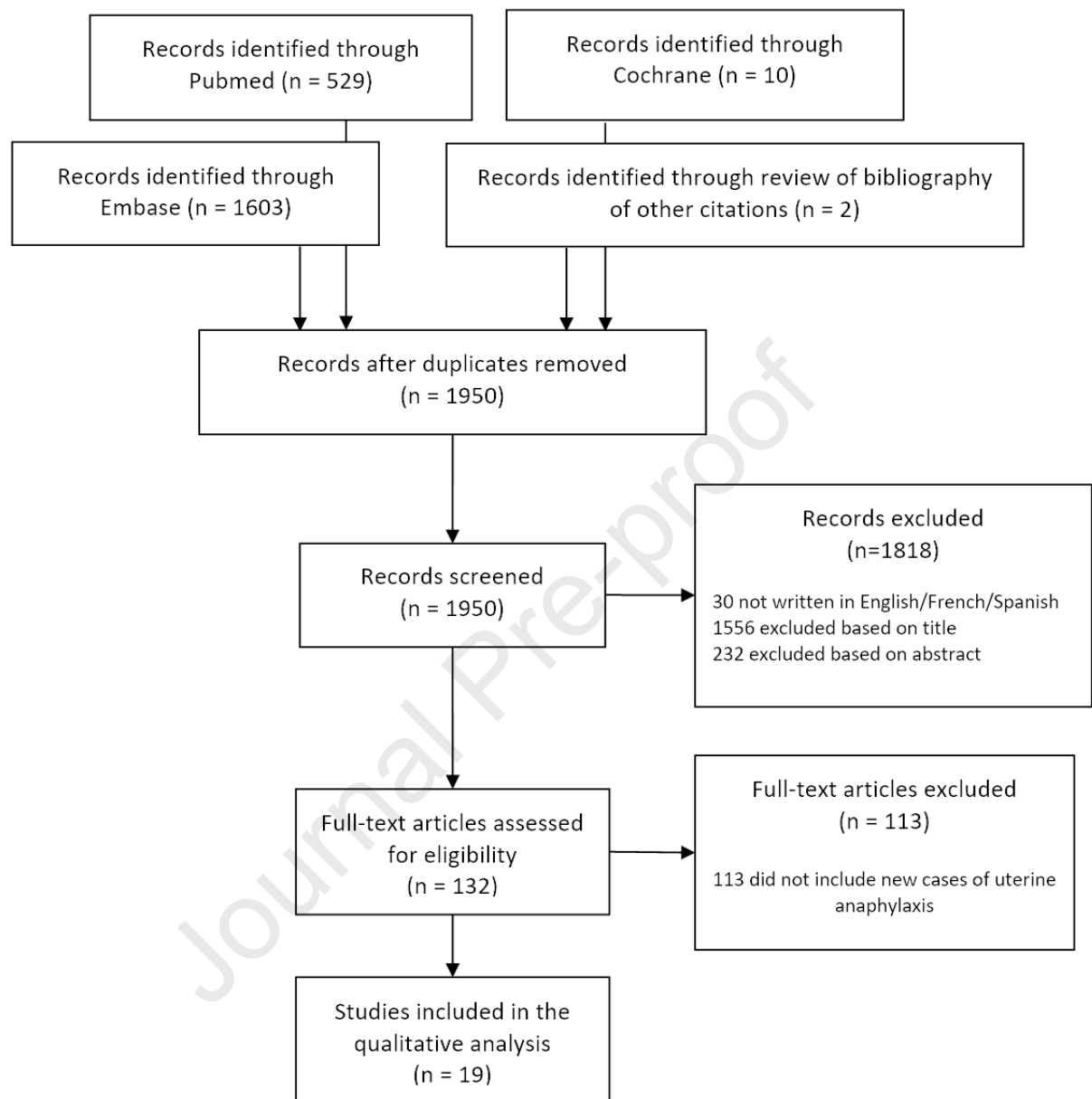


Figure 1 – Study selection. PRISMA diagram describing study selection for review.

