

CASE REPORT

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Anaphylaxis-induced premature uterine contractions: a case report and literature review

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Abstract

Background Preterm labor is caused by multiple etiologies, including intra-amniotic infection and/or intra-amniotic inflammation, vascular disorders, cervical disease, decidual senescence, and breakdown of maternal–fetal tolerance. Accumulating evidence *in vivo* and *in vitro* has shown that an allergic reaction, including anaphylaxis, can induce preterm uterine contractions. This report describes a case of a pregnant woman who developed anaphylaxis and regular uterine contractions after the ingestion of a strawberry-coated biscuit. We also review the mechanism of allergic reaction (hypersensitivity)-induced preterm labor.

Case presentation

A 31-year-old woman (gravida 1, para 0) at 30⁺² weeks of gestation was admitted to the labor and delivery unit with regular uterine contractions and anaphylactic symptoms after she ingested a strawberry-coated biscuit as a snack. The uterine contractions resolved after the treatment of anaphylaxis by administering antihistamines and epinephrine. The patient subsequently delivered at 39⁺³ weeks of gestation. The amniotic fluid profile showed no infection or inflammation. A postpartum skin-prick test confirmed a positive type 1 hypersensitivity reaction to the strawberry-coated biscuit.

Conclusions We report a case of anaphylaxis-induced uterine contractility in which uterine contractions subsided after the treatment of anaphylaxis. The absence of intra-amniotic infection and/or intra-amniotic inflammation and the cause of the anaphylaxis were confirmed. Our findings indicate that maternal allergic reactions may be one of the mechanisms of preterm labor.

Keywords Allergy, Amniotic fluid, Anaphylaxis, Contractility, Contraction, Hypersensitivity, Myometrial contraction, Pregnancy, Preterm, Uterine allergy

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Background

Preterm birth is the leading cause of neonatal mortality globally [1–7]. Multiple pathological mechanisms, such as intra-amniotic inflammation, intra-amniotic infection, vascular disorders, cervical disease, decidual senescence, and breakdown of maternal–fetal tolerance, lead to spontaneous preterm delivery [1, 8–11]. Among these mechanisms, intra-amniotic infection and/or intra-amniotic inflammation is causally linked to preterm delivery [10, 12–17]. Accumulating evidence has shown that a maternal allergic reaction, including anaphylaxis, can induce preterm uterine contractions, which resolve after treatment of the allergic reaction, and the patient subsequently delivers at term gestation [18, 19]. The mechanism responsible for uterine contractions is thought to be myometrial contractility induced by degranulation of mast cells (effector cells of type 1 hypersensitivity) [18]. Anaphylaxis is a rare complication of pregnancy with an incidence rate ranging from 1.6 to 2.7/100,000 deliveries [20–23]. Common causes of anaphylaxis during pregnancy include the use of antibiotics and food allergies [21, 23]. This condition is associated with maternal hypotension and hypoxemia, which are potentially life-threatening to the mother and fetus [23]. Anaphylaxis is initially managed by immediate improvement of the maternal airway, eliminating causative agents, and administering drugs, such as anti-histamines, epinephrine, glucocorticoids, and vasopressors [19–23]. These drugs can be used safely without major side effects in pregnancy.

We report a case of a pregnant woman who developed systemic anaphylaxis and regular uterine contractions after ingestion of a strawberry-coated biscuit. Her uterine contractions subsided after the administration of antihistamines and epinephrine without the administration of tocolytic agents. Subsequently, she delivered uneventfully at term (39⁺³ weeks' gestation). No intra-amniotic infection or intra-amniotic inflammation was associated with the uterine contractions. The cause of anaphylaxis was confirmed at postpartum. We also discuss the mechanism of anaphylaxis implicated in preterm labor.

Case presentation

A 31-year-old gravida 1, para 0, Thai woman at 30⁺² weeks of gestation presented to the labor and delivery unit with regular uterine contractions together with an acute onset of generalized hives, pruritus, flushing, and swollen lips. Her antenatal care had been unremarkable. Prior to this pregnancy, she had several episodes of urticaria, but she had never investigated the cause of the rash. Six hours before hospital admission, she developed nasal and throat itching, tightness in the chest, shortness of breath, nausea, and vomiting. She also developed swollen lips and tongue, and an itchy, urticarial rash that began at her face and trunk and radiated to the upper and lower extremities (Fig. 1). These symptoms occurred suddenly after snacking on a strawberry-coated biscuit. She also reported an episode of regular abdominal cramping every 3 minutes. Her physician administered chlorpheniramine 10 mg intravenously and referred the patient to our hospital because of the presentation of preterm uterine contractions.

At the labor and delivery unit (6 hours after the onset of symptoms), the patient complained of shortness of breath and abdominal cramps. Her vital signs showed tachycardia with a heart rate of 120 beats/minute and tachypnea with a respiratory rate of 24 breaths/minute. Her blood pressure was 100/60 mmHg. At a physical examination, inspiratory and expiratory wheezing in both lungs was observed. Facial swelling, erythema, edema, and a generalized pruritic erythematous maculopapular rash on the chest wall and abdomen and over both extremities were also observed (Fig. 1). The size of her uterus was appropriate for gestational age with the presence of regular uterine contractions occurring every 3 minutes and 40 seconds with moderate intensity (Fig. 2). A digital examination showed a closed cervical os with no effacement. The fetal heart rate status was reassuring, as shown by a baseline fetal heart rate of 140 beats/minute. An ultrasonographic examination revealed a single fetus appropriate for gestational age, the amniotic fluid and placenta

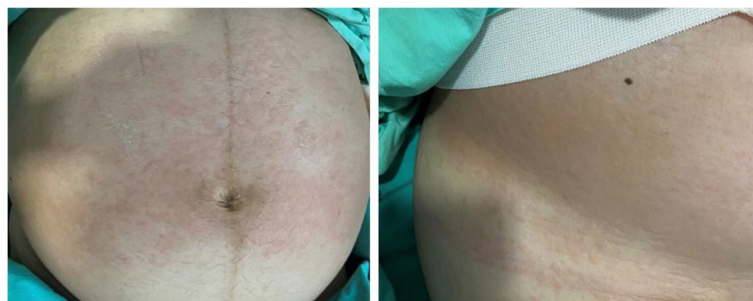


Fig. 1 Urticarial rash on the patient's abdomen. Photo courtesy of Dr. Piya Chaemsaitong, with permission

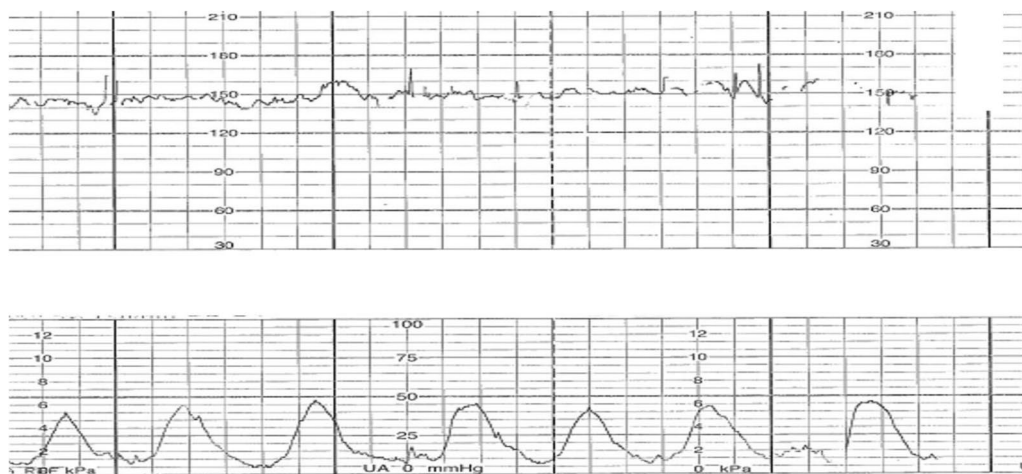


Fig. 2 External fetal monitoring. Uterine contractions occurred every 3 minutes and 40 seconds with moderate intensity

appeared normal, and the patient's cervical length was 30.2 mm.

The patient was diagnosed with anaphylaxis and threatened preterm labor. To treat her anaphylaxis, intravenous chlorpheniramine 10 mg, intramuscular epinephrine (1:1000) 0.5 mg, and intravenous dexamethasone 5 mg were administered. Two hours after the administration of epinephrine, the patient still had uterine contractions. A digital examination was performed and the cervical os was closed with 50% effacement. Therefore, preterm labor was diagnosed. Preterm labor syndrome is associated with intra-amniotic inflammation and/or intra-amniotic infection. Therefore, the patient was counseled about amniocentesis (under the IRB approval protocol COA. MURA2021/254). Written informed consent was obtained from the patient before collecting specimens. Second doses of intramuscular epinephrine (1:1000) 0.5 mg and intravenous dexamethasone 5 mg were administered to remedy the persistent dyspnea and wheezing. Her dyspnea and uterine contractions improved within 1 hour after administering the second doses of epinephrine and dexamethasone (Fig. 3). The maculopapular rash and swelling subsided within a few days.

At the admission (6 hours after the onset of symptoms), her maternal white blood cell (WBC) count was 16,580 cells/mm³ (neutrophils: 84.2%, lymphocytes: 5.9%, and monocytes: 6.9%). An amniotic fluid analysis showed a WBC count of 105 cells/mm³ (polymorphonuclear cells: 46%, mononuclear cells: 54%). Hematoxylin and eosin staining for a cell differential was not performed. Amniotic fluid Gram staining, culture, and 16S ribosomal RNA gene polymerase chain reaction results were negative for microorganisms, and the amniotic fluid interleukin-6

concentration was within the normal range (0.41 ng/mL; cut-off > 2.6 ng/mL). These negative findings were consistent with no finding of intra-amniotic infection or intra-amniotic inflammation. The pregnancy progressed uneventfully, and the patient subsequently had a vaginal delivery of a female neonate weighing 3,480 g at 39⁺³ weeks of gestation. The neonate's Apgar score was 9, 10 and had no complication.

Three months after the delivery, the patient experienced similar symptoms (i.e., tightness in the chest and a maculopapular rash) after ingesting another snack of the same brand. The cause of the allergy was investigated. A skin-prick test result at 6 months after the delivery showed a positive wheal and flare for a strawberry-coated biscuit.

Discussion

This report suggests that maternal anaphylaxis can induce the onset of preterm uterine contractions, and these can be resolved by the administration of antihistamine agents, adrenergic drugs, and steroids. Although several reports have described the association between an allergic reaction and uterine contractions, only a few investigations proved the cause of allergy [18, 19]. Additionally, none of these reports determined the status of intra-amniotic infection and/or intra-amniotic inflammation, which is frequently observed in women presenting with symptoms of preterm labor.

Anaphylaxis during pregnancy

Anaphylaxis occurring during pregnancy is a rare event with an incidence of approximately 3.8/100,000 hospitalizations [20–22]. The mortality rate of anaphylaxis is



Fig. 3 Resolved uterine contractions after antihistamine and epinephrine administration

approximately 0.09/100,000 live births [23]. According to diagnostic criteria amended by the World Allergy Organization in 2020 [24], anaphylaxis is a clinical diagnosis based on the criteria shown in Table 1.

A recent systematic review and meta-analysis of 47 pregnant women with anaphylaxis showed that the most common clinical manifestations are hypotension and tachycardia (100%), followed by urticaria (57%) [22]. In addition, anaphylaxis is more commonly observed during the period of labor (approximately 80%) than prior to the onset of labor. Antibiotics, anesthetic drugs, latex, oxytocin, misoprostol, and rubber

contained in a Foley catheter are common allergens. Anaphylaxis can be associated with a 3.2% (95% confidence interval: 0.4–11) maternal mortality rate and a 14.3% (95% confidence interval: 4.8–30.3) neonatal encephalopathy rate [21]. Nevertheless, approximately half of the reported cases were solely diagnosed based on clinical symptoms and allergological tests without a proven allergen [22]. In the current case, the criteria of anaphylaxis were met. Therefore, we concluded that the anaphylaxis induced preterm uterine contractions. Indeed, uterine contractions are recognized as

Table 1 Diagnostic criteria of anaphylaxis [24]

Criteria 1	Acute onset of an illness (minutes to several hours) with simultaneous involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula) and at least one of the following:
	<ul style="list-style-type: none"> a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia) b. Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia, syncope, incontinence) c. Severe gastrointestinal symptoms (e.g., severe crampy abdominal pain, repetitive vomiting), especially after exposure to non-food allergens
Criteria 2	Acute onset of hypotension or bronchospasm or laryngeal involvement after exposure to a known or highly probable allergen (minutes to several hours), even in the absence of typical skin involvement

a manifestation of anaphylaxis and, importantly, the cause of anaphylaxis can be proven after delivery.

Allergy as a mechanism of disease of preterm labor

Evidence supportive of an allergic reaction (hypersensitivity) as one of the mechanisms implicated in preterm labor has been reported as follows.

1. In 1910, Schultz reported that the exposure of a specific allergen to a sensitized guinea pig induced contractions of the ileum [25]. Subsequently, a contractile response was demonstrated in the uterus of the sensitized guinea pig [26]. The “Schultz-Dale phenomenon” was then characterized by a standard technique in which antigen-induced contractions of the smooth muscles *in vitro* induced anaphylactic hypersensitivity [27]. Schultz-Dale anaphylactic contractions have been shown in the uterus of the guinea pig [28–46], rat [44, 47–49], mouse [50, 51], and human [52]. The Schultz-Dale experiment was later demonstrated in human myometrial strips collected from women with an allergy to ragweed. In addition, a higher frequency and intensity of myometrial contractions were observed in pregnant donors and then compared with non-pregnant donors [53]. Moreover, preincubation of myometrial strips in human serum led to the sensitization of the myometrial strips of non-allergic women, and this was mediated by immunoglobulin E [53].
2. Mast cells, which are the effector cells of an allergic reaction, have been found in the uterus [54]. Furthermore, histamine and prostaglandins produced by mast cell degranulation can induce myometrial contractility [54, 55].
3. Pharmacological degranulation of mast cells with a compound called “48/80” induces myometrial contractility [56–58]. Histamine and serotonin induce myometrial contractions in a dose-dependent manner [53, 54, 59, 60]. Diphenhydramine, chlorpheniramine, and antihistamine agents partially suppress myometrial contractility of sensitized myometrium strips challenged with an allergen, suggesting a histamine receptor-mediated mechanism [61, 62]. In addition, pre-treatment with cromolyn, which is a mast cell stabilizer, inhibits myometrial contractility, suggesting a role of mast cells, especially degranulation, in myometrial contractions [61, 62].
4. Incubation of myometrial strips from sensitized and non-sensitized rats with an anti-immunoglobulin E antibody increases myometrial contractility [56].
5. A challenge with ovalbumin results in an increase in the uterine tone of non-pregnant guinea pigs sensitized with ovalbumin [56–58].
6. The autopsy report of a guinea pig, performed immediately after its death caused by anaphylactic shock, showed increased uterine contractility [25].
7. Eosinophils identified in the amniotic fluid were found to represent the majority of WBCs in a subset of women with preterm labor [63]. Eosinophil-rich inflammation is associated with allergic diseases, such as asthma, atopic dermatitis (eczema), and allergic rhinitis [64–68]. Additionally, patients with an increase in amniotic fluid eosinophils (WBC count differential containing > 20% of eosinophils) are at an increased risk of preterm delivery. However, some patients with eosinophils detected in samples of amniotic fluid deliver at term and show no evidence of complications [63].
8. Preterm labor and delivery can be induced in a guinea pig model of type I hypersensitivity [18]. In addition, a study showed that pretreatment with a histamine H1 receptor antagonist (ketotifen) to ovalbumin-sensitized guinea pigs increased the duration of gestation and prevented preterm labor and delivery [61].
9. Previous studies showed that guinea pigs that were sensitized with chicken egg ovalbumin were at greater risk to deliver a preterm pup than those challenged with normal saline [18, 61].
10. Prior studies have suggested an association between patients with an allergic disease, such as asthma or allergic rhinitis, and increased preterm delivery [69–71].
11. Several case reports have shown that exposure to an allergen can induce uterine contractions and that these contractions are ameliorated after the treatment of anaphylaxis together with the standard treatment of preterm labor pain [22, 72–74]. Collectively, type I hypersensitivity reactions can induce preterm labor and delivery.

Type I hypersensitivity reactions and uterine contractions in humans

A systematic review of clinical studies reported 31 cases of uterine contractions induced by anaphylaxis [19]. A total of 29% (9/31) of these cases were in pregnant women, of whom seven of nine of these women presented with an allergic reaction and preterm uterine contractions. Three cases were anaphylactic [73, 75]. Table 2 shows reported cases of type I hypersensitivity-induced preterm uterine contractions.

The first case of uterine contractions induced by hypersensitivity or anaphylaxis during pregnancy was

Table 2 Summary of cases with type I hypersensitivity-induced premature uterine contractions

Number	Authors/Year	Patient	Details of reaction	Presentation	Treatments	Response to treatment	Final outcome
1.	Klein et al. 1984 [72]	32 year-old, 29 weeks of gestation	Reaction following the ingestion of crab and cherries	Pruritus and urticaria, palmoplantar erythema, hypotension and uterine contractions. 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 contractions continued despite the treatment, the deceleration diminished gradually within 25 minutes with complete resolution after 2 hours.	Cesarean delivery at 40 ⁺⁵ weeks of gestation. The baby was normal.
2	Habek et al. 2000 [73]	23 year-old 27 weeks of gestation	Reaction following by a wasp sting	Swollen face, eyelids, lip, tongue. Tachypnea, dyspnea, bronchospasm, uterine contractions	Adrenaline 0.5 mg for 3 doses, IV fluids, oxygen, Methylprednisolone 500 mg IV, Aminophylline 250 mg IV, 10% calcium gluconate 10 ml IV	Facial edema and uterine contractions subsided Normal cardiotocography examination	Delivery at 35 weeks of gestation
3	Donahue et al. 1995 [76]	26 year-old 19 weeks of gestation	Telangiectasia macularis eruptiva perstans (rare type of mastocytosis)	Chest tightness, dyspnea, uterine contractions, vaginal bleeding and maculopapular rash	Chlorpheniramine, Terbutaline aerosols, Promethazine	Dysnea and uterine contractions relieved after treatment	Preterm labor at 24 weeks treated with magnesium sulfate. A normal baby was born by Caesarean delivery at 36 weeks
4	Kehoe et al. 2006 [77]	35-year-old 24 weeks of gestation	Systematic mastocytosis Anxiety and stress	Uterine cramping, peptic ulcer disease, diarrhea, flushing, fatigue, and rash	H1 and H2 blocker, proton pump inhibitor, leukotriene inhibitors	Relieved uterine contractions and other symptoms	Spontaneous delivery at term gestation with 3,310g female infant
5	Madendag et al. 2010 [78]	26-year-old 27 weeks of gestation	Cutaneous mastocytosis	Cutaneous manifestations with pruritus and premature uterine contractions	Pheniramine maleate 50 mg IV	Cutaneous manifestations and uterine contractions were resolved	Spontaneous vaginal delivery at 40 weeks of gestation
6	Romero et al. 2010 [18]	28 year-old 31 weeks of gestation	Symptoms occurred shortly after ingestion of lobster	Generalized pruritic maculopapular rash, regular strong uterine contractions every three minutes	Chlorphenamine and betamethasone orally	Rash and uterine contractions subsided	Cesarean delivery at 40 weeks of gestation and delivered infant weighed 3800 g. The child developed atopic disorders.
7	Tsuzuki et al. 2017 [75]	26 year-old 25 weeks of gestation	Symptoms occurred 15-30 min after meal	Bronchospasm with peripheral cyanosis, generalized itchy rash, abdominal pain and regular uterine contractions	Oxygen Epinephrine 0.4 mg intramuscular Nebulized short-acting β_2 -receptor agonist	Bronchospasm, rash and uterine contractions resolved	Delivery at 37 weeks of gestation. Skin prick test revealed buckwheat allergy.

reported in 1984 [72]. A pregnant woman at 29 weeks of gestation developed erythema of the palms and urticarial areas on the face and abdomen, uterine contractions every 3 to 4 minutes, and maternal hypotension. Fetal heart rate tracing showed repetitive late decelerations. After the administration of diphenhydramine and ephedrine, the uterine contractions and the late decelerations of fetal heart rate were resolved. The patient underwent cesarean delivery at term because of a failure to progress in labor. The newborn had an Apgar score of 9-9, a birthweight of 3780 g, and a normal neurological exam [72]. The second case was an anaphylactic reaction in response to a wasp sting in a woman at 27 weeks of gestation, followed by preterm delivery at 35 weeks of gestation [73]. Three patients were diagnosed with mastocytosis, which is characterized by an abnormal accumulation of mast cells in several organs. These patients experienced pruritic urticaria pigmentosa and preterm uterine contractions at mid-gestation, which were resolved by the administration of intravenous pheniramine maleate, hydroxyzine hydrochloride, and imipramine hydrochloride. All patients eventually delivered at near term or at term gestation without complications [76–78].

Subsequently, Romero *et al* described a pregnant woman at 31 weeks of gestation with an episode of spontaneous preterm labor and a generalized pruritic maculopapular rash after the ingestion of shellfish [18]. Preterm labor subsided after the treatment of antihistamines and steroids. The patient eventually delivered at 40 weeks of gestation. Recently, Tsuzuki *et al* reported a pregnant woman at 25 weeks of gestation who presented with anaphylactic symptoms (i.e., dyspnea, generalized itchy rash, and regular uterine contractions) after consuming buckwheat noodles. Such symptoms subsided after the administration of epinephrine, antihistamine, and methylprednisolone. A healthy, neurologically intact neonate was delivered at term. Skin-prick and challenge test results of the mother confirmed a buckwheat allergy [75].

In this report, we describe the fourth case of pregnancy with anaphylaxis-induced preterm uterine contractions. Anaphylaxis is generally diagnosed based on clinical criteria, which were met in this patient (acute onset of skin and laryngeal involvement), even though tryptase concentrations were not measured in the samples of serum and amniotic fluid. Strengths of this report are the confirmation of the cause of the allergic status post-delivery and the finding that the patient's uterine contractions were not associated with intra-amniotic inflammation or intra-amniotic infection. Notably, an analysis of the types of cells in amniotic fluid by a flow cytometer or hematoxylin and eosin staining would be useful because a high number of eosinophils might be associated with type 1

hypersensitivity, including anaphylaxis, which can induce preterm labor [63].

Conclusions

We report a case of anaphylaxis-induced uterine contractions for which treatment of the anaphylaxis was followed by the resolution of uterine contractions. This evidence highlights a maternal allergic reaction as one of the mechanisms of preterm labor.

Abbreviation

WBC White blood cell

Acknowledgments

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Authors' contributions

Substantial contributions to sample collection, patient management, original draft preparation, and finalization of the manuscript: P.W. Conceptualization and finalization of the manuscript: R.R. Sample collection and patient care: W.L, T.K. Substantial contributions to laboratory assessment and finalization of the manuscript: P.V., P.M., R.S., P.P. Conceptualization, sample collection, patient management, original draft preparation, obtain funding and finalization: P.C. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed for this case report are included in this published article.

Declarations

Ethics approval and consent to participate

The collection and use of the materials for research purposes were approved by the Human Research Ethics Committee, Faculty of Medicine, Ramathibodi Hospital, Mahidol University (COA. MURA2021/254). All data were collected from the patient after obtaining written informed consent. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

Written informed consent for the photographs and their subsequent publication in this case report was obtained from the patient.

Competing interests

The authors declare no competing interests.

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