



Structural and functional comparison of mast cells in the pregnant versus nonpregnant human uterus

Robert E. Garfield, PhD,^{a,*} Anne-Marie Irani, MD,^b Lawrence B. Schwartz, MD, PhD,^c Egle Bytautiene, MD,^a Roberto Romero, MD^d

Division of Reproductive Sciences, Department of Obstetrics and Gynecology, University of Texas Medical Branch, Galveston, TX^a; Departments of Pediatrics^b and Internal Medicine,^c Virginia Commonwealth University Health Systems, Richmond, VA; Perinatology Research Branch, National Institute of Child Health and Human Development/ National Institutes of Health/Department of Health and Human Services, Bethesda, MD, and Detroit, MI^d

Received for publication December 24, 2004; revised March 16, 2005; accepted March 30, 2005

KEY WORDS

Pregnancy
Uterine contractility
Mast cells
Ragweed
Allergy
Myometrium

Objective: To characterize uterine mast cells and investigate uterine muscle strips contractile responses to challenge with an allergen in nonpregnant and pregnant women.

Study design: A double-antibody labeling technique was used to identify tryptase positive or chymase-tryptase-positive mast cells in uterine samples from term pregnant and nonpregnant women. Longitudinal myometrial strips were prepared from biopsies of hysterectomy specimens from patients undergoing procedures for benign indications and women who had elective cesarean sections. Responses to ragweed antigen were compared in uterine tissues from allergic and nonallergic patients and with passively sensitized tissues in the absence or presence of H₁ receptor antagonist and a cyclooxygenase inhibitor.

Results: Tryptase-chymase-positive mast cells were predominant in nonpregnant myometrium, whereas tryptase-positive cells were dominant in pregnant myometrium. Mast cell density was significantly higher in tissue from pregnant women than those of nonpregnant women. Studies in tissues from patients with known allergy to ragweed, as well as in passively sensitized tissues, showed an immediate and substantial increase in the frequency and force of myometrial contraction after a challenge with ragweed antigen. A similar response was observed to histamine. There was no contractile response to antigen challenge in tissues from nonallergic patients. An H₁ receptor antagonist partially inhibited the response to antigen, whereas a cyclooxygenase inhibitor had no effect.

Conclusion: Sensitized isolated pregnant and nonpregnant human uterine tissue is capable of responding to antigen challenge with strong myometrial contractions. This ability, along with the increased density of mast cells in pregnant tissues as compared with nonpregnant tissues, indicates a possible role for mast cells in mediating uterine contractility in pregnancy.

© 2006 Mosby, Inc. All rights reserved.

* Reprint requests: Robert E. Garfield, PhD, Division of Reproductive Sciences, Department of Obstetrics and Gynecology, University of Texas Medical Branch, 301 University Boulevard, Rt. J-62, Galveston, TX 77555-1062.

E-mail: rgarfiel@utmb.edu

The mast cell is considered to play a central role in immediate allergic reactions. After immunological activation via IgE receptors, the mast cell releases histamine, proteases, proteoglycans, lipid-derived mediators, cytokines, etc, all of which influence the biology of adjacent cells and the metabolism of the extracellular matrix. Thus, mast cells have a significant role in the biologic state of any tissues in which they are present.

Human mast cell (MC) can be defined on the basis of histologic, functional, compositional, and pharmacologic regulatory properties. Recognizing different types of mast cells is critical to the understanding of their biologic significance in view of the release of different mediators upon stimulation and differential responsiveness to degranulating agents.

Proteases are a quantitatively important component of mast cells. Several proteases, including tryptase, chymase, cathepsin G, and human MC carboxypepsidase, have been identified in human mast cells.¹ Immunohistochemical techniques performed using antibody preparations against each protease have shown the presence of 2 distinct types of human MCs, termed MC_T and MC_{TC}. MC_T cells stain positively with antitryptase antibody but lack binding to antichymase antibody as well as antibodies to cathepsin G and carboxypepsidase (tryptase positive, chymase negative MCs). This type predominates in the alveolar lining of the lung and the intestinal mucosa.¹ MC_{TC} mast cells stain positively with antibodies to tryptase and other proteases, including chymase, cathepsin G, and carboxypeptidase (tryptase-chymase positive MCs), and are the predominant type observed in the skin, heart, conjunctiva, and intestinal submucosa.¹

The presence of the mast cell in the human uterus was first described by D'Erchia in 1897.² Mast cells are very scanty in the endometrium but more abundant in the connective tissue and myometrium, especially in proximity to large blood vessels.^{3,4} Uterine MCs possess the same unique phenotypic characteristics and heterogeneity as other human mast cells.^{5,6} The greatest number of MCs are located in the inner half of the myometrium, with approximately equal proportions of MC_T and MC_{TC} cells.⁶ Isolated human uterine MCs release histamine, prostaglandin D₂, and leukotriene C₄ in response to anti-IgE and calcium ionophore A23187.⁷ This indicates the ability of human uterine mast cells to respond to FcεRI-dependent and FcεRI-independent stimuli, analogous to mast cells from lung, skin, or intestine.

Functional studies on isolated uterine tissues have demonstrated that mediators known to be released from mast cells on degranulation, such as histamine and prostaglandin F_{2α}, can stimulate uterine contractility.^{4,8-11} Our laboratory has demonstrated that challenge with ovalbumin induces premature labor in ovalbumin-sensitized guinea pigs.¹² We also reported that mast cell

degranulation induced by compound 48/80 through IgE-independent pathways increased the spontaneous contractile activity of myometrial strips obtained from pregnant women.¹³

However, experiments to study the effect of IgE-dependent degranulation on human uterine contractility have not been performed yet. The present study was designed to fill that gap as well as to compare the distribution of MC_T and MC_{TC} cells in uterine tissues during pregnant and nonpregnant states.

Material and methods

Tissue samples from nonpregnant women were collected from hysterectomy specimens from patients undergoing procedures for benign indications. Approximately half of the nonpregnant patients were postmenopausal. We did not see any differences in MC levels/density in the uterine tissues between postmenopausal and reproductive-age women. Therefore, they are all grouped together as the nonpregnant group. Although we did not observe any hormonal associations, reports from the literature suggest that they do exist.^{6,14} Specimens were also collected from pregnant patients undergoing elective cesarean section at term. These patients had no history of maternal diabetes, hypertension, or autoimmune disease and no history of intrauterine growth retardation. All patients were questioned as to their allergic status with regard to ragweed and other allergens.

For structural studies, 1 × 1 × 0.5-cm, and for functional studies, 2 × 2 × 1-cm biopsy samples were removed from the superior aspect of the lower uterine segment at the time of cesarean section and from the same uterine segment from hysterectomy specimens. This study was approved by the Institutional Review Board of McMaster University (Hamilton, Ontario, Canada), and consent for the collection of tissues was obtained from each patient.

Structural studies

Samples from all tissues were fixed in Carnoy's solution for 3 hours and then placed in 70% ethanol for histological preparation. The Carnoy's fixed tissue was embedded in paraffin, cut at 6-μm thickness, placed on coated slides, and stained using the previously described double-antibody labeling technique to identify MC_T and MC_{TC} cells.¹⁵

Mast cell quantification

Sections of the uterine tissue were coded and read in a blind fashion by 1 investigator. Mast cells were counted under light microscopy at ×160 magnification. Mast cell concentrations were obtained using a Zeiss

videoplan apparatus (Carl Zeiss Inc, Thornwood, NY) and calculated according to the following formula:

$$\text{Mast cells/mm}^3 = [\text{mast cells/mm}^2] \times [9.5 \mu\text{m} + 6 \mu\text{m}].$$

The mean mast cell diameter is represented by 9.5 μm , and 6 μm represents the tissue section thickness. The percentages of MC_T and MC_{TC} cells were also calculated.

Preparation of uterine tissues for functional studies

All tissues for functional studies were treated as above. After obtaining the tissue samples, they were pinned into Petri dishes and immersed in Kreb's solution. Tissue strips (about 2 mm $\times$ 2 cm) parallel to the long axis of the uterus were cut. The ends of the strips were tied with silk threads, and each strip was hung in a 20 mL organ chamber containing Kreb's solution oxygenated with 5% CO₂ and 95% O₂. The tissues were allowed to equilibrate for 20 minutes; a resting tension of 2 grams was then placed on each strip. Force was monitored with a Grass FT 30D isometric transducer (Grass Instrument Co, Quincy, MA) connected to an 8-channel Grass recorder (Grass Instrument Co).

Procedures for passive sensitization

Tissue strips from nonallergic patients were passively sensitized to ragweed by incubating the strips for 18 hours at 4°C in serum from patients known to be allergic (4+ by radioallergosorbent test) to ragweed. Control strips from the same patients were incubated in Kreb's solution for 18 hours at 4°C and served as control tissues. Both sets of tissues were then suspended in the jacketed water chambers as above. For each patient, 6 tissue strips were passively sensitized and 2 strips used as controls.

Myometrial contractility studies

After spontaneous contractions had stabilized, strips were incubated with a histamine H₁ receptor antagonist (diphenhydramine, 10⁻⁵ M), a cyclooxygenase inhibitor (indomethacin, 10⁻⁵ M), or Krebs buffer (control) for 10 minutes before ragweed antigen (final concentration, 1 mg/mL) was added to the organ chamber.

Data analysis

Student *t* test was used for statistical analysis; *P* < .05 was considered statistically significant.

Chemicals

Glucose, sodium chloride, potassium chloride, magnesium sulfate, potassium phosphate, sodium bicarbonate, sodium ethylenediamine tetra acetic acid, calcium chlo-

ride, histamine, diphenhydramine, indomethacin, and ragweed antigen were obtained from Sigma (St. Louis, MO). The serum from patients with ragweed allergy was kindly provided by Dr. J. Dolovich (Department of Pediatrics, McMaster University, Hamilton, Ontario, Canada).

Results

Structural studies

Double-antibody labeling of the uterine tissue showed the presence of both MC_{TC} and MC_T cells in both the pregnant and nonpregnant preparations (Figure 1A). The percentage of MC_{TC} cells tended to be higher in nonpregnant uterine tissue, whereas the percent of MC_T cells tended to be higher in pregnant uterine tissue, but these differences did not reach statistical significance. During pregnancy, a substantial and significant increase in the density of both types of mast cells was observed (Figure 1B).

Functional studies

A summary of the patients studied and the responses of their uterine strips to the ragweed antigen are presented in the Table. Eight tissue strips per patient were studied from 35 pregnant and 9 nonpregnant patients. The patients in each group were further subdivided into allergic, nonallergic, and passively sensitized groups.

Allergic patients

There were 3 pregnant patients with a history of ragweed allergy. Challenge with ragweed antigen elicited an increase in contractility in 9 of 11 strips from these patients (Table and Figure 2A). Both an increase in frequency and intensity of contraction occurred on antigen exposure. There were no allergic patients in the nonpregnant group.

Nonallergic patients

Tissues from pregnant (*n* = 22) and nonpregnant (*n* = 9) patients who had no known history of ragweed allergy were studied in this group (Table). Two strips from each patient were incubated in Kreb's solution and used as the control. They did not show any response to the challenge with ragweed antigen (Figure 2B). Only 1 strip of 25 strips tested from the nonpregnant group responded with an increased contractility to ragweed challenge.

Patients with passive sensitization

Tissues from both pregnant (*n* = 10) and nonpregnant (*n* = 7) nonallergic patients were passively sensitized. Significant responses to the antigen exposure were

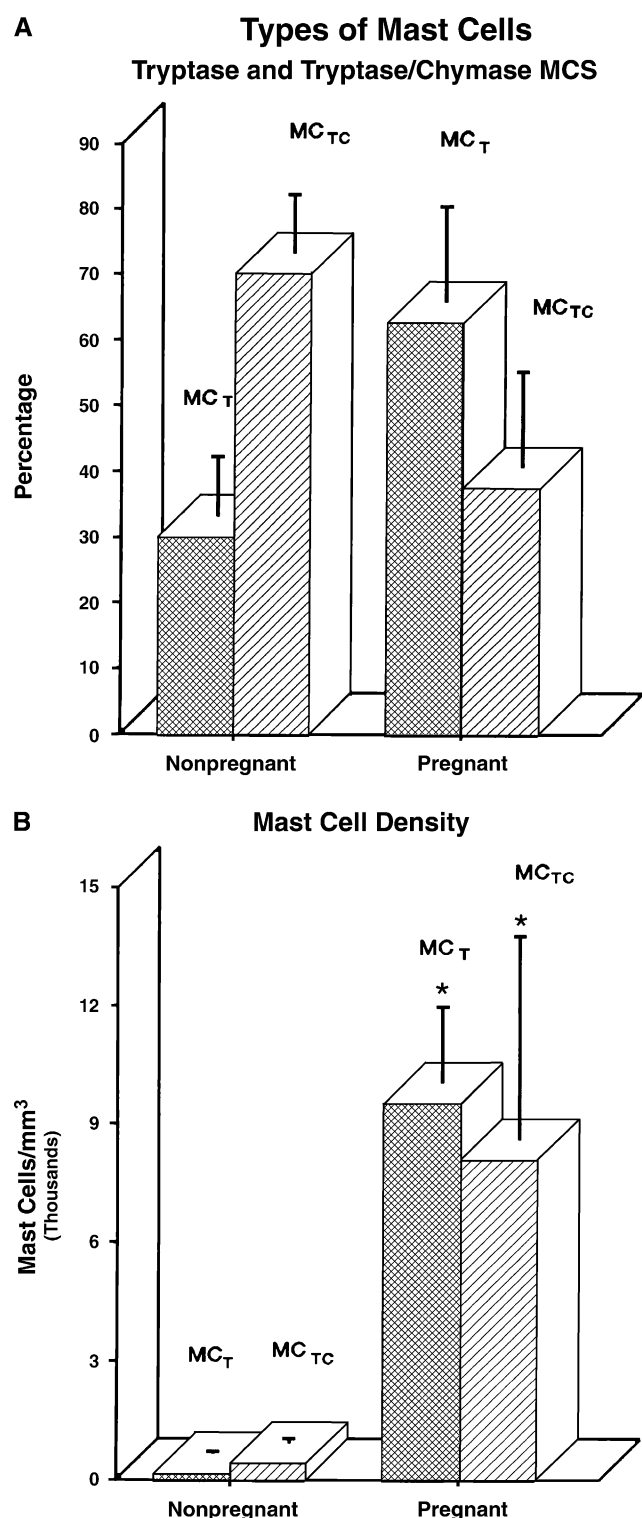


Figure 1 A. Distribution of MC_T and MC_{TC} cells (by percent) in uterine tissues from nonpregnant and pregnant women. B. MC_T and MC_{TC} cell densities in the uterine samples from nonpregnant and pregnant women. The results are shown as mast cells in thousands per mm³. *Indicates significantly ($P < .05$) higher numbers of mast cells in pregnant tissues.

Table Contractile responses to ragweed antigen in uterine strips from pregnant and nonpregnant patients

	Allergic*	Nonallergic*	Passively sensitized*
Pregnant			
Number of patients	3	22	10
Response to ragweed antigen	9 [†] /11 [‡] (3) [§]	1/25 (17)	20/22 (10)
Nonpregnant			
Number of patients	0	9	7
Response to ragweed antigen	0/0	0/14 (9)	14/15 (7)

* Response to ragweed antigen was measured as increased contraction.

[†] Number of tissue strips responding.

[‡] Total number of tissue strips challenged.

[§] The number in the parentheses represents the total number of patients from whom uterine tissue strips were collected.

observed in 20 strips from pregnant women of 22 challenged (Table and Figure 2B). In the preparations from nonpregnant tissues, 14 strips of 15 strips showed a response to antigen challenge (Figure 2B). In both pregnant and nonpregnant tissues, the control preparations that were incubated in Kreb's solution demonstrated no response to the antigen challenge (Figure 2B).

Effects of various mediators and their inhibitors

To determine the mediators responsible for the contractile responses to ragweed antigen, agents inhibiting the effect of known MC mediators were used. Figure 3A shows the effects of histamine on uterine contractility. The addition of histamine consistently elicited a contractile response in both pregnant and nonpregnant tissues. The addition of a histamine H₁ receptor antagonist, diphenhydramine, blocked the histamine effect and partially suppressed the response to ragweed. Because prostaglandins are known to be released at the time of MC degranulation, the effect of a cyclooxygenase inhibitor, indomethacin, was investigated. As seen in Figure 3B, responses to the antigen challenge were not inhibited by indomethacin.

Comment

The present study shows that MCs are abundant in the human uterus and that the degranulation of MCs by IgE-dependent pathways can lead to substantial changes in the myometrial contractility. By demonstrating that an antigen challenge can result in an increase in myometrial contractility, this study establishes a direct link to the immune system as an effector of such contractility. The demonstration that the immune system has the ability to modulate myometrial contractility both in the

nonpregnant and pregnant states is an important finding and may prove significant for a variety of physiological and pathological situations.

The influx of inflammatory cells such as macrophages, lymphocytes, and granulocytes to the uterus and cervix during pregnancy has been reported by other authors.^{16,17} In our study we observed that both MC_T and MC_{TC} types of MCs are present in pregnant and nonpregnant uterus with a significant increase in density during pregnancy. Thus, our study provides evidence that infiltration of MCs into the uterus during pregnancy occurs as well.

It has been determined that normal pregnancy is associated with a type 2 cytokine profile with preferential production of interleukin (IL)-4, IL-5, and IL-10, the cytokines that strengthen humeral immunity, whereas type 1 cytokines (interferon- γ , tumor necrosis factor- α , IL-2) responsible for cell-mediated immunity are down-regulated.¹⁸ Mast cells, together with CD4-positive T cells among others, are one of the sources of type 2 cytokines. Therefore, mast cell the influx into the uterus could be associated with the need for type 2 cytokines to strengthen humeral immunity during pregnancy.

Previously it was reported that mast cell density in the human uterus significantly decreases in pregnancy at term when compared with the nonpregnant state.¹⁷ The discrepancy between the 2 studies can be explained by the different fixation methods. In our experiments, tissues were fixed in Carnoy's solution, whereas other investigators used buffered formalin.¹⁷ Significant differences in the distribution of mast cell subtypes, as well as the influence of fixation method, have been observed before. For example, chymase-positive mast cells were detected in the canine uterus only after fixation in Carnoy's fluid, and all types of MCs had a tendency to be higher in number in sections fixed in Carnoy's solution.¹⁹ Similar increases in MC density and histamine content toward the end of the gestational period have been shown in mice and rats.^{20,21}

Double-antibody labeling experiments revealed a difference in the type of MC dominating in pregnant and nonpregnant uterine tissues. The dominant type in nonpregnant tissues were tryptase-chymase positive cells (MC_{TC}), whereas in pregnant tissues the opposite was

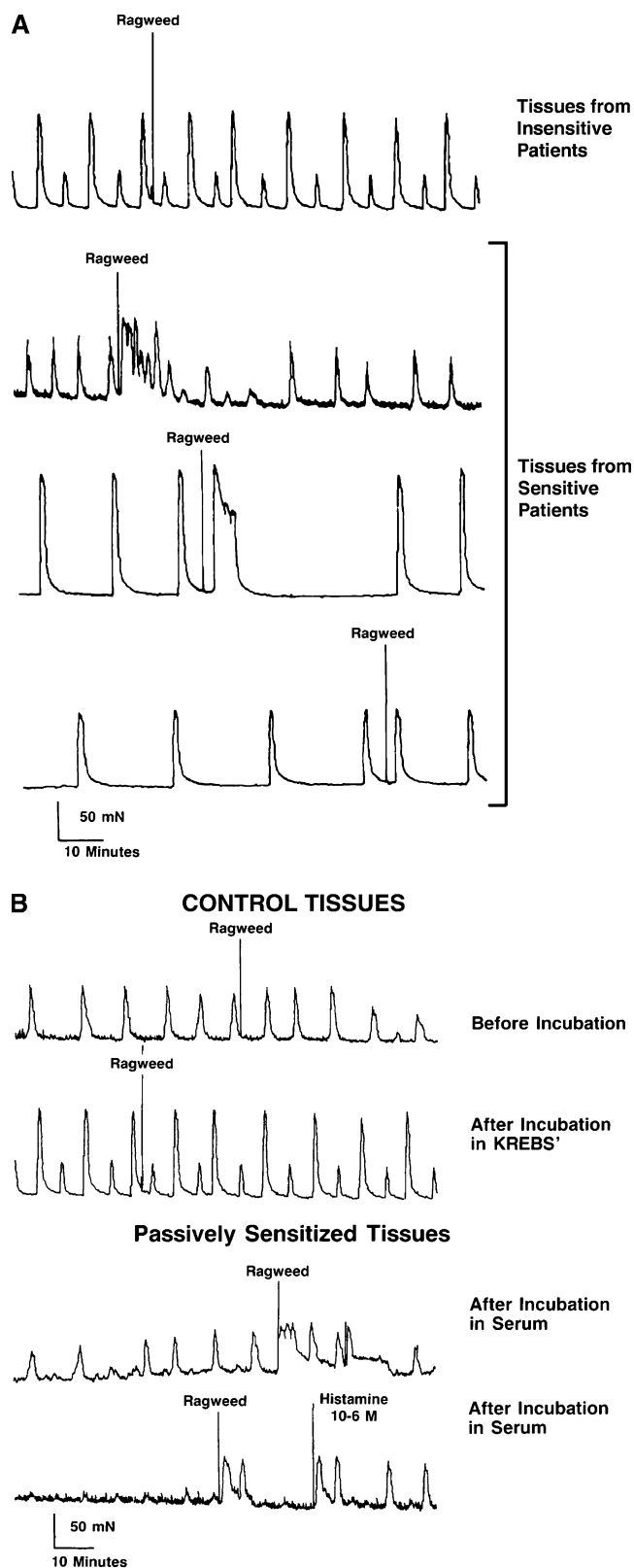


Figure 2 A. Contractile recordings from ragweed sensitive patients and nonsensitive control patients. The challenge of the tissue by ragweed antigen produces a substantial increase in spontaneous activity in the tissue from the sensitized patient, but has no effect on the tissue from the control, nonsensitized patient. B. Contractile recordings from the uterine samples of ragweed nonsensitive control patients before and after passive sensitization with serum from ragweed sensitive patients. The challenge of the tissue with ragweed produces a substantial increase in the spontaneous activity of the passively sensitized tissue, but does not do so in the control.

EFFECTS OF HISTAMINE AND DIPHENHYDRAMINE

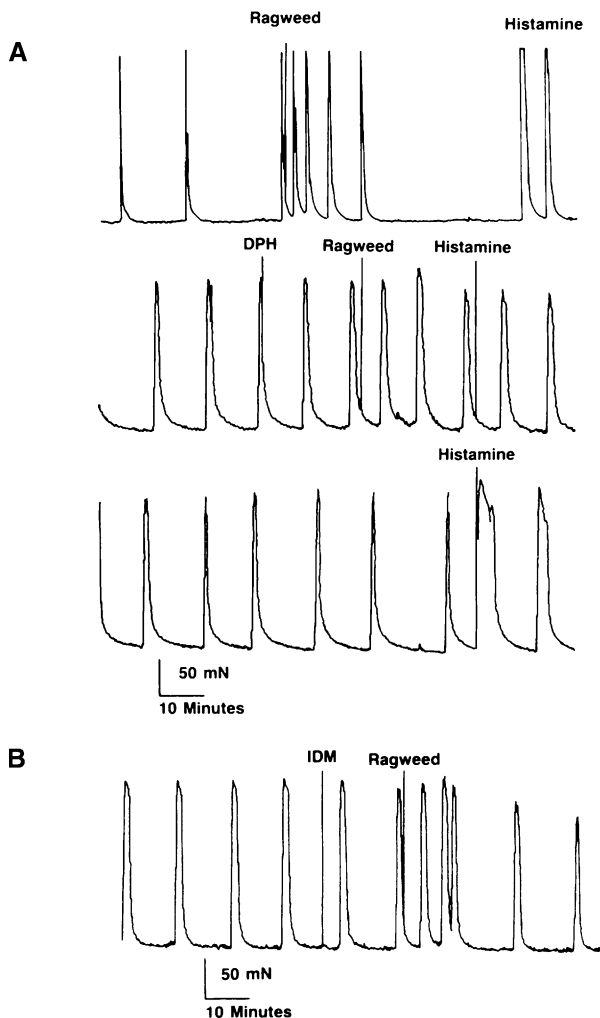


Figure 3 A. Effect of histamine and ragweed on uterine contractility from pregnant and nonpregnant women after the incubation of tissues with a histamine H_1 receptor antagonist (diphenhydramine - DPH). B. Effect of ragweed on uterine contractility after incubation of the tissues with a cyclooxygenase inhibitor (indomethacin - IDM).

observed, with tryptase-positive, chymase-negative cells (MC_T) being the predominant type, although these differences did not reach statistical significance. In nonpregnant uterine tissue, mast cell subtypes have been shown to be almost equally distributed in the inner myometrium, whereas fewer MCs were found in the outer myometrium and cervix, with the proportion of MC_{TC} cells significantly higher.⁶

Because biopsies for our experiments were obtained from the lower part of the uterus, in which cervical connective tissue extends into the myometrium, our data are in agreement with the above-described report about the predominance of MC_{TC} cells in nonpregnant human uterine tissues.⁶ The high percentage of MC_T cells seen in pregnant tissues could be relevant for the control of uterine contractility in pregnancy. Distribution of uter-

ine mast cell types has not been studied in pregnant human uterine tissues before. Mechanically dispersed human lung MCs, which consist of 90% MC_T cells,²² have been shown to be less responsive to immunological and nonimmunological stimuli and more sensitive to substances known to inhibit histamine release. Thus, we hypothesize that an increase in the number of MC_T cells that are less reactive to degranulation and more susceptible to a histamine release inhibitors could be a mechanism for protecting pregnancy late in gestation from immunological insults.

The sex steroids could modulate the density of mast cells during pregnancy. Pregnancy is associated with changes in estrogen and progesterone levels. Success of the pregnancy depends on the balance between the hormone levels. No changes in the number of human uterine MCs have been observed during the menstrual cycle when hormone levels are changing.⁶ However, progesterone, a hormone synthesized in large quantities by the placenta during pregnancy, has been known to be an immunosuppressive agent during pregnancy.²³ Therefore, estrogen and progesterone could exert a pregnancy-specific increase in MC density.

As demonstrated in this study, degranulation of MCs by a specific antigen results in a substantial increase in uterine contractility in isolated tissues from both pregnant and nonpregnant patients. We did not measure the degree of contractility in this study but have demonstrated this previously.^{13,21,24} Also, given the significant increase in MC density in pregnancy observed in our study and the report in the literature that pregnant human uterine preparations were more responsive to histamine (main mediator released from MCs) than nonpregnant ones⁹, we would speculate that the magnitude of the myometrial responses might have been higher in strips from pregnant uterus.

It has been shown that smooth muscle, including uterine, taken from sensitized animals contracts when challenged with a specific antigen.²⁴⁻²⁷ Mast cell mediators, such as serotonin, prostaglandins, and leukotrienes, are involved in the anaphylactic uterine response from actively sensitized animals.^{28,29} We have recently demonstrated that antigen challenge can induce premature labor and delivery in actively sensitized guinea pigs.¹² Therefore, our report, which for the first time presents data that isolated human uterine tissue contracts in response to antigen, is of significant importance.

The partial inhibition of the response to antigen by an H_1 receptor antagonist and no effect of a cyclooxygenase inhibitor indicate that neither histamine nor arachidonic acid-cyclooxygenase products are solely responsible for mediating the human myometrial response to antigen exposure. The effect of an H_1 receptor antagonist and cyclooxygenase inhibitor is similar to that described by us previously, in which we observed attenuation, although not significant, in the responses of

human isolated myometrium to mast cells degranulating agent compound 48/80.¹³

Our findings have important clinical implications in the regulation of uterine contractility in both the pregnant and nonpregnant states. Severe allergic reactions can produce uterine cramping. Therefore, local or systemic exposure to specific antigens may trigger a typical type I hypersensitivity reaction that includes substantial uterine contractions mediated locally by mast cell products. Such may be the case following intercourse in patients with antibodies to sperm or seminal fluid antigens. Furthermore, the ability of MCs and the immune system to influence uterine contractility may be important to the initiation of labor and the termination of pregnancy. Because many types of immune cells, such as macrophages, neutrophils, lymphocytes, and mast cells, are present in the uterine wall, a complex system probably regulates the relationship between the immune system and the uterus.

References

- Irani AM, Schwartz LB. Mast cell heterogeneity. *Clin Exp Allergy* 1989;19:143-55.
- Von Numers C. Über die Zellformen des Stromagewebes der menschlichen Gebärmutter-schleimhaut. *Acta Obstet Gynecol Scand* 1942;22:142.
- Sivridis E, Giatromanolaki A, Agnantis N, Anastasiadis P. Mast cell distribution and density in the normal uterus—metachromatic staining using lectins. *Eur J Obstet Gynecol Reprod Biol* 2001;98:109-13.
- Rudolph MI, Reinicke K, Cruz MA, Gallardo V, Gonzalez C, Bardisa L. Distribution of mast cells and the effect of their mediators on contractility in human myometrium. *Br J Obstet Gynecol* 1993;100:1125-30.
- Guo CB, Kagey-Sobotka A, Lichtenstein LM, Bochner BS. Immunophenotyping and functional analysis of purified human uterine mast cells. *Blood* 1992;79:708-12.
- Mori A, Zhai YL, Toki T, Nikaido T, Fujii S. Distribution and heterogeneity of mast cells in the human uterus. *Hum Reprod* 1997;12:368-72.
- Massey WA, Guo CB, Dvorak AM, Hubbard WC, Bhagavan BS, Cohan VL, et al. Human uterine mast cells. Isolation, purification, characterization, ultrastructure, and pharmacology. *J Immunol* 1991;156:1621-7.
- Bytautiene E, Vedernikov YP, Saade GR, Romero R, Garfield RE. Effect of histamine on phasic and tonic contractions of isolated uterine tissue from pregnant women. *Am J Obstet Gynecol* 2003;188:774-8.
- Cruz MA, Gonzalez C, Acevedo CG, Sepulveda WH, Rudolph MI. Effects of histamine and serotonin on the contractility of isolated pregnant and nonpregnant human myometrium. *Gynecol Obstet Invest* 1989;28:1-4.
- Castelli MC, Vadora E, Bacchi MA, Molina E. In vitro effects of histamine on human pregnant myometrium contractility. *Boll Soc Ital Biol Sper* 1993;69:783-9.
- Martinez-Mir I, Estañ L, Morales-Olivas FJ, Rubio E. Studies of the spontaneous motility and the effect of histamine on isolated myometrial strips of the nonpregnant human uterus: The influence of various uterine abnormalities. *Am J Obstet Gynecol* 1990;163:189-95.
- Bytautiene E, Romero R, Vedernikov Y, Saade G, Garfield RE. Induction of premature labor and delivery by allergic reaction and prevention by histamine H₁ receptor antagonist. *Am J Obstet Gynecol* 2004;191:1356-61.
- Bytautiene E, Vedernikov YP, Saade G, Romero R, Garfield RE. Degranulation of uterine mast cell modifies contractility of isolated myometrium from pregnant women. *Am J Obstet Gynecol* 2004;191:1705-10.
- Crow J, Wilkins M, Howe S, More L, Helliwell P. Mast cells in the female genital tract. *Int J Gynecol Pathol* 1991;10:230-7.
- Irani AM, Bradford TR, Kepley CL, Schechter NM, Schwartz LB. Detection of MCT and MCTC types of human mast cells by immunohistochemistry using new monoclonal anti-tryptase and anti-chymase antibodies. *J Histochem Cytochem* 1989;37:1509-15.
- Chwalisz K, Shao-Qing S, Garfield RE, Beier HM. Cervical ripening in guinea pigs after a local application of nitric oxide. *Hum Reprod* 1997;12:2093-101.
- Thomson AJ, Telfer JF, Young A, Campbell S, Stewart CJ, Cameron IT, Greer IA, Norman JE. Leukocytes infiltrate the myometrium during human parturition: further evidence that labour is an inflammatory process. *Hum Reprod* 1999;14:229-36.
- Marzi M, Trabattoni D, Vigano A, Villa ML, Salvaggio A, Clerici E, et al. Characterization of type 1 and type 2 cytokine production profile in physiologic and pathologic human pregnancy. *Clin Exp Immunol* 1996;106:127-33.
- Kube P, Audige L, Kuther K, Welle M. Distribution, density and heterogeneity of canine mast cells and influence of fixation techniques. *Histochem Cell Biol* 1998;110:129-35.
- Padilla L, Reinicke K, Montesino H, Villena F, Asencio H, Cruz M, et al. Histamine content and mast cells distribution in mouse uterus: the effect of sexual hormones, gestation and labor. *Cell Mol Biol* 1990;36:93-100.
- Tabb TN. Immune control of myometrial contractility: role of mast cells. In: Garfield RE, Tabb TN, editors. *Control of uterine contractility*. Boca Raton (FL): CRC Press; 1994. p. 355-73.
- Schwartz LB, Huff TF. Biology of mast cells. In: Middleton E, editor. *Allergy: principles and practice*. St. Louis: Mosby; 1998. p. 261-76.
- Siiteri PK, Stites DP. Immunologic and endocrine interrelationships in pregnancy. *Biol Reprod* 1982;26:1-14.
- Garfield RE, Bytautiene E, Vedernikov YP, Marshall JS, Romero R. Modulation of rat uterine contractility by mast cells and their mediators. *Am J Obstet Gynecol* 2000;183:118-25.
- Schultz WH. Physiological studies in anaphylaxis: the reaction of smooth muscle of the guinea pig sensitized with horse serum. *J Pharmacol Exp Ther* 1910;1:549-67.
- Dale HH. The anaphylactic reaction of plain muscle in the guinea pig. *J Pharmacol Exp Ther* 1913;4:167-223.
- Bytautiene E, Vedernikov Y, Saade G, Romero R, Garfield RE. Challenge with ovalbumin increases contractility of uterine and cervical strips from sensitized term pregnant guinea pigs. *J Soc Gynecol Invest* 2002;9:208A.
- Nielsen AT. Effect of methysergide and indomethacin on the anaphylactic contraction of the rat isolated uterus (Schultz-Dale response). *Acta Pharmacol Toxicol* 1977;40:321-8.
- Carraher R, Hahn DW, Ritchie DM, McGuire JL. Involvement of lipoxygenase products in myometrial contractions. *Prostaglandins* 1983;26:23-32.