

Clinical Impact of Pregnancy in Mastocytosis: A Study of the Spanish Network on Mastocytosis (REMA) in 45 Cases

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Key Words

Anaphylaxis • Mast cell-related symptoms • Mastocytosis • Pregnancy

Abstract

Background: The impact of pregnancy on mast cell (MC)-related symptoms and newborn outcome in women with mastocytosis is not well described. We report a series of 30 women who had 45 pregnancies. **Methods:** Patients completed a specific questionnaire concerning MC mediator release symptoms graded according to their frequency to detect clinical changes occurring during pregestation and pregnancy as well as postpartum. Information about the medications received during pregnancy and labor and about newborn medical complications was also recorded. **Results:** Worsening of MC-related symptoms during pregnancy was observed in 10 cases (22%); additionally, 1 woman developed skin lesions as a manifestation of indolent systemic mastocytosis (ISM) within the third trimester of pregnancy. Conversely, 15 cases (33%) experienced clinical improvement during pregnancy, with a complete resolution of pregestational symptoms in 7 cases. MC mediator release symptoms intrapartum were observed in 5 cases (11%) without any fatal outcome. Newborn medical complications (e.g.

prematurity, low birth weight, and respiratory distress) were detected in 7 infants (16%) who were all successfully managed with conservative measures. One infant developed cutaneous mastocytosis several years after birth. **Conclusions:** Mastocytosis has a heterogeneous clinical behavior during pregnancy: the profile of MC-related symptoms remained unchanged in half of the cases, while in the other half pregnant women experienced either an improvement or an exacerbation of the symptoms, with the manifestation of ISM during pregnancy in 1 case. To prevent potential life-threatening MC-related symptoms, adequate prophylactic antimediator therapy intrapartum should be systematically administered. The absence of both maternal and infant severe complications suggests that patients with nonaggressive categories of mastocytosis should not be advised against pregnancy.

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Introduction

Mast cells (MC) play a key role in inflammatory reactions in allergic and nonallergic processes [1–5]. MC activation through the cross-linking of high-affinity Fc receptors for IgE (FcεRI) is a critical step in immediate

hypersensitivity reactions; however, other immunologic and nonimmunologic stimuli which include aggregated IgG [6], complement proteins [7], peptides [8], and hormones [9], among others, are also involved in MC activation and its functional regulation. Physiological MC activation and degranulation in the functional layer of the endometrium occurs just before and during menstruation [10], suggesting that MC may contribute to premenstrual exacerbations of allergic conditions such as asthma, angioedema, and atopic dermatitis. A higher MC density in pregnant versus nonpregnant tissues [11], an association between the increased contractility of myometrium and serum histamine and other MC mediators in mice and humans during pregnancy [12–14], and some cases of breast feeding-related anaphylaxis [15, 16] have been reported. Altogether, these observations suggest that MC could be involved in the regulatory mechanisms of the physiological female reproductive states including the menstrual cycle, pregnancy, labor, and puerperium.

Mastocytosis is characterized by an abnormal proliferation and accumulation of MC in several tissues. Symptoms are mostly due to the effects of the MC mediators released due to known and unknown triggers after MC activation through immunologic and nonimmunologic pathways. Sexual hormone serum levels change throughout pregnancy and after delivery, which might translate into changes in the profile of MC mediator release-associated symptoms. Moreover, the compulsory discontinuation of antimediator drugs during pregnancy because of safety concerns, the stress of labor, and the potential administration of anesthetic and analgesic drugs in its management, may also worsen MC mediator-related symptoms. However, information on pregnant women with mastocytosis is restricted to a small patient series [17] and some case reports [18–22].

Here we report a retrospective study on 45 pregnancies in 30 women with nonaggressive categories of mastocytosis (mostly with systemic involvement) in order to investigate the impact of pregnancy on the clinical course of mastocytosis and the potential effects of mastocytosis on the outcome of pregnancy.

Patients and Methods

Patients

Medical records from 292 childbearing women diagnosed with mastocytosis by the Spanish Network on Mastocytosis (REMA) up to 2009 were reviewed in order to identify patients who had had 1 or more successful pregnancies after the onset of mastocytosis. Thirty women who had had a total of 45 pregnancies

(1 pregnancy in 16 patients, 2 in 13, and 3 in 1) were contacted and gave their informed consent to participate in this retrospective study. A total of 21 pregnant women (referred to as cases from now on) were referred to the REMA before getting pregnant, and 16 of them had been on scheduled antimediator therapy before pregnancy; by contrast, only 5/24 cases (9a, 9b, 23a, 29, and 30b) referred after they became pregnant had been receiving treatment for mastocytosis before the referral according to the criteria of their treating physicians from centers other than REMA (table 1). Four patients (13%) had suffered a total of 6 miscarriages before their first full-term pregnancy, 3 of which occurred within a 2-year interval in 1 patient; by contrast, 3 additional women suffered 1 miscarriage, each after previous successful pregnancies. All of these miscarriages occurred within the first trimester of pregnancy.

Diagnosis of mastocytosis was made upon referral by the REMA on the basis of skin and bone marrow (BM) biopsy findings according to World Health Organization (WHO) criteria [23]. Overall, 25/30 patients were diagnosed with indolent systemic mastocytosis (ISM). Two had an absence of skin lesions (ISMs–) and 23 had cutaneous involvement (ISMs+); 1 had well-differentiated systemic mastocytosis (WDSM) [24] and the remaining 4 patients had cutaneous mastocytosis (CM).

All 45 cases were single pregnancies; 1 pregnancy was achieved by in vitro fertilization due to a history of infertility. The median age at pregnancy was 31 years (range 26–40), while the median time from the onset of mastocytosis to the beginning of pregnancy was 9 years (range 1–28). The study was approved by the local ethics committee.

Mastocytosis-Related Symptoms

Information about the clinical symptoms was obtained from the medical history as well as from specific questionnaires filled out by the participants. MC mediator release-associated symptoms such as pruritus, flushing, gastrointestinal symptoms, and anaphylaxis (a severe, life-threatening, generalized or systemic episode of MC-related symptoms) were recorded during 3 periods: (1) pregestational (baseline), (2) pregnancy (first, second, and third trimester), and (3) postpartum. All symptoms were graded according to REMA criteria on the basis of their frequency: (1) absent, (2) daily, (3) weekly (on >1 but <7 days per week), (4) monthly, and (5) occasionally (<once a month). Any changes in the frequency of pregestational MC-related symptoms were recorded during pregnancy and puerperium. Worsening of symptoms was defined as a predominant increase in the frequency of symptoms and/or the development of new MC-related symptoms which had been previously absent (in any of the trimesters of the pregnancy period). Those cases with clinical improvement were categorized as: (1) complete resolution (CR) if all MC mediator release-associated symptoms disappeared, (2) partial resolution (PR) if at least 1 MC-related symptom disappeared, (3) major resolution (MR) if a decrease in the frequency of pregestational MC-related symptoms was observed, and (4) minor resolution (mR) if at least 1 pregestational MC-related symptom disappeared or decreased but other symptoms or this one worsened in the following trimesters of pregnancy. Anaphylaxis was the most severe symptom recorded; thus, cases with changes in this symptom, but also in others, were classified according to the evolution of anaphylaxis following the criteria described above.

Table 1. Antimediator therapy given to pregnant women with mastocytosis (n = 30) before, during, and after each pregnancy (n = 45)

Patient ID	Disease subtype	Age during pregnancy (years)	Drugs before pregnancy	Drugs during pregnancy	Drugs after delivery
1a	CM	33	–	–	–
1b	CM	36	–	–	–
2a	CM	28	–	–	–
2b	CM	33	H1, DC	–	–
3	CM	32	AZT ^b , 5ASA ^b	AZT ^b , 5ASA ^b	AZT ^b , 5ASA ^b , DC
4	CM	26	–	–	–
5	ISMs+	36	H1, H2, DC	H1 ^a	–
6a	ISMs+	35	–	–	–
6b	ISMs+	38	–	–	–
7	ISMs+	29	H1, DC	–	–
8	ISMs+	29	DC	–	DC
9a	ISMs+	29	H1 ^a	–	H1 ^a
9b	ISMs+	33	H1 ^a	H1 ^a	H1 ^a
10a	ISMs+	32	H1, H2, DC	–	H1, DC
10b	ISMs+	35	H1, DC	–	–
11	ISMs+	32	–	–	–
12a	ISMs+	29	DC	H1 ^a	DC
12b	ISMs+	31	DC	H1 ^a , H2	H2, DC
13a	ISMs+	28	H1, DC	–	H1, DC
13b	ISMs+	31	H1, DC	–	–
14	ISMs+	33	DC	–	–
15	ISMs+	38	DC	–	–
16	ISMs+	34	H1, DC	–	–
17	ISMs+	30	H1, CE ^a	–	DC, HU
18	ISMs+	30	–	–	H1 ^a , CE ^a
19	ISMs+	33	–	–	H1, CE ^a
20a	ISMs+	27	–	–	–
20b	ISMs+	31	–	CE ^a	–
21a	ISMs+	27	–	–	–
21b	ISMs+	29	–	–	–
22	ISMs+	30	–	–	–
23a	ISMs+	27	H1 ^a , CE ^a	H1 ^a , CE ^a	–
23b	ISMs+	29	–	–	–
23c	ISMs+	31	–	–	–
24a	ISMs+	35	–	–	–
24b	ISMs+	40	–	–	DC
25a	ISMs+	28	–	–	–
25b	ISMs+	31	–	–	H1
26a	ISMs+	30	–	–	–
26b	ISMs+	34	–	–	–
27	ISMs+	29	DC	–	–
28	ISMs–	31	H1, H2, DC, BD, HU, CE ^a , E ^a	H1	H1, H2, DC, BD
29	ISMs–	30	CE ^a	–	–
30a	WDSM	31	–	–	–
30b	WDSM	35	H1 ^a , CE ^a	–	H1 ^a , CE ^a

CM = Cutaneous mastocytosis; ISMs+ = indolent systemic mastocytosis with skin involvement; ISMs– = indolent systemic mastocytosis without skin involvement; WDSM = well-differentiated systemic mastocytosis; H1 = H1 antihistamine; H2 = H2 antihistamine; DC = disodium cromolyn; HU = hydroxyurea; BD = benzodiazepines; CE = corticosteroids; E = epinephrine; AZT = azathioprine; 5ASA = mesalazine.

^a Taken as needed.

^b Specific therapy for inflammatory bowel disease.

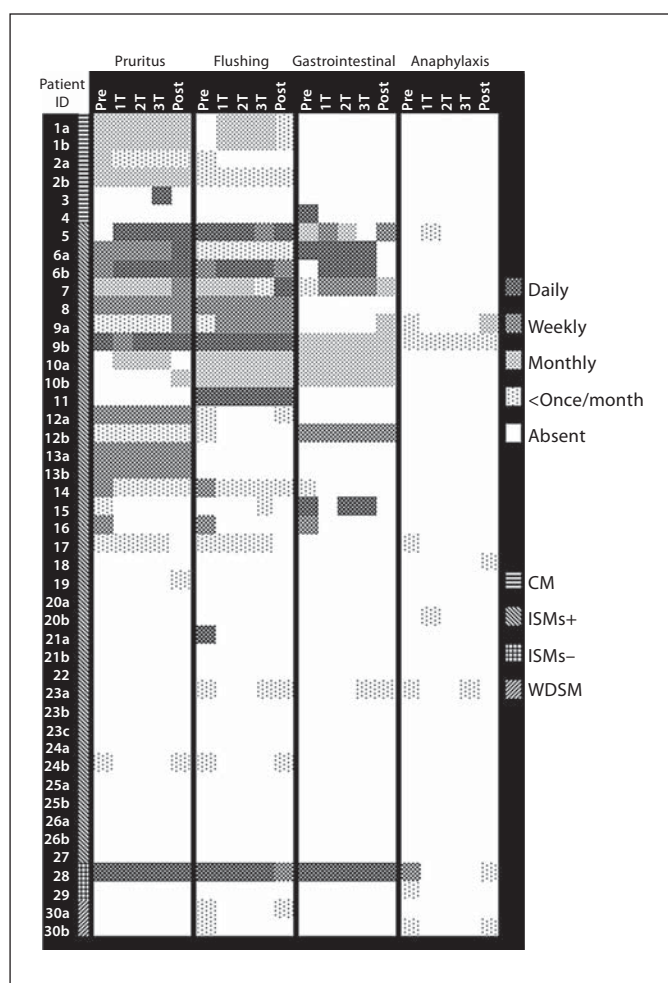


Fig. 1. Pregnancy in women with mastocytosis (n = 45). Pregestational MC mediator release symptoms (Pre) and their changes throughout the first (1T), second (2T), and third (3T) trimesters of pregnancy and after delivery (Post). Idiopathic anaphylaxis was the most responsive MC-related symptom throughout the whole pregnancy (2/4 cases; 50%), followed by flushing, (8/23; 35%), gastrointestinal symptoms (3/12; 25%), and pruritus (3/20; 15%). By contrast, worsening of MC-related symptoms during pregnancy (including the development of symptoms which had been absent before) was observed in a minority of cases: pruritus in 4 cases (3, 5, 6b, and 10a), flushing in 5 cases (1a, 1b, 6b, 9a, and 15), gastrointestinal symptoms in 4 cases (5, 6b, 7, and 23a), and idiopathic anaphylaxis in case 5. In most cases, MC-related symptoms remained unchanged throughout pregnancy and after delivery compared to the pregestational clinical profile.

Follow-Up of Pregnancy and Management of Delivery

Because patients were referred from different centers, the follow-up of pregnancy and management of delivery were carried out under the criteria of gynecologists and anesthesiologists from each center. Once pregnancy had been confirmed, the use of medications without well-established safety at this point was dis-

continued, except for a woman who had an inflammatory bowel disease and continued on azathioprine plus mesalazine therapy throughout pregnancy and after delivery. In this sense, usage of dexchlorpheniramine and ranitidine scheduled or taken as needed, and of corticosteroids or epinephrine when strictly required, was allowed in cases of severe MC mediator release-associated symptoms during pregnancy following a careful evaluation of the risk-benefit ratio. Table 1 shows medications given to the patients before, during, and after pregnancy. Moreover, multivitamins, folic acid, and ferrous sulphate were also allowed to be administered throughout pregnancy and puerperium according to the gynecologist's criteria. Information on the type of delivery and the anesthesia used, as well as on the administration of prophylactic antimediator drugs for labor and delivery, was obtained from admission medical reports and recorded.

Additionally, newborn outcomes such as stillbirths, prematurity, and a low birth weight, as well as the presence of relevant diseases at birth (including mastocytosis) or their development during the following years, were also recorded.

Results

Mastocytosis-Related Symptoms throughout Pregnancy and after Delivery

Mastocytosis-related symptoms observed throughout pregnancy included pruritus in 20 cases (45%), flushing in 18 (40%), gastrointestinal symptoms in 11 (24%), and anaphylaxis triggered by a hymenoptera sting (case 20b) or of idiopathic origin (cases 5, 9b, and 23a) in 4 cases (9%).

Figure 1 shows the specific clinical changes observed throughout pregnancy and after delivery versus the pregestational profile of MC mediator release-associated symptoms. Overall, a worsening of MC-related symptoms throughout pregnancy was observed in 10 cases (22%) including an increase in their frequency (case 7), the development of symptoms which had been absent before pregnancy (cases 1a, 1b, 3, 10a, 15, 20b, and 23a), or both (cases 5 and 6b). New symptoms appeared in the first (n = 6) or third (n = 3) trimesters of pregnancy while the increase in the frequency of previous symptoms (n = 3) was systematically reported in the first trimester. A worsening of symptoms throughout pregnancy was observed among CM (3/6 cases) and ISMs+ patients (7/35 cases). In addition, a previously healthy woman (case 11) developed skin lesions typical of mastocytosis during the third trimester; diagnosis of ISMs+ was confirmed in this patient through BM studies performed several months after delivery. Cases 5, 9b (mR), and 23a had idiopathic anaphylaxis episodes, and case 20b had anaphylaxis triggered by a hymenoptera sting. They experienced symptoms such as generalized erythema, pruritus on the palms

and soles, flushing, facial swelling, tachycardia, dizziness, hypotension, nausea, abdominal pain, and diarrhea; in none of these cases were uterine contractions reported during the anaphylactic episode, and epinephrine was not used for the treatment of anaphylaxis (table 1).

Fifteen cases (33%) experienced an overall clinical improvement during pregnancy including CR (cases 4, 16, 21a, 24b, 29, 30a, and 30b), PR (cases 2a, 12a, 12b, 14, 17, and 28), and mR (cases 9a and 9b); no cases with MR were found. All resolutions were observed during the first trimester and they lasted throughout the whole pregnancy, except for case 9b. Anaphylaxis was absent during pregnancy in 2/4 cases (9a and 28) who suffered idiopathic episodes in the pregestational period; in another 3 cases (17, 29, and 30b) anaphylactic episodes before pregnancy were triggered by a hymenoptera sting or kiwifruit ingestion, a hymenoptera sting, and codeine, respectively; thus, the absence of anaphylaxis can not be attributed to pregnancy itself. Furthermore, resolution was also achieved in 8/23 (35%) cases with flushing, 3/12 (25%) cases showing gastrointestinal symptoms, and 3/20 (15%) cases with pruritus.

CR was observed in 2/2 pregnancies corresponding to the only patient with WDSM and in 1/2 ISMs-, 3/35 (9%) ISMs+, and 1/6 (17%) CM. In turn, PR was achieved in 1/2, 4/35 (11%), and 1/6 (17%) pregnancies in ISMs-, ISMs+, and CM patients, respectively; the mR corresponded to 2/35 (6%) ISMs+ patients.

In the remaining 20 cases (45%) no changes in MC-related symptoms were observed during pregnancy (19/35 ISMs+ and 1/6 CM). Nevertheless, case 24a experienced a significant improvement of her skin lesions from the first trimester of pregnancy.

Compared to the pregestational profile, MC mediator release-associated symptoms remained worse after delivery in 5/10 cases who worsened during pregnancy (cases 1a, 1b, 5, 6b, and 7); they also became worse in 3 additional cases (10b, 18, and 19) who did not experience any clinical changes during pregnancy and in 1 case (9a) who showed mR during pregnancy. In turn, the resolutions observed during pregnancy remained after delivery in 4/7 cases (4, 16, 21a, and 29) and in 3/6 cases (2a, 12b, and 14) who developed CR and PR during pregnancy, respectively. In addition, CR was also observed after delivery in cases 15 and 17; they had worsened and achieved PR during pregnancy, respectively. Finally, PR and MR were observed after delivery in cases 30b and 28 who showed CR and PR during pregnancy, and mR was found in another 2 cases who had either remained stable (case 6a) or worsened (case 23a) during pregnancy. Sixteen of 20 cases

(80%) who did not show any variation in their clinical symptoms throughout pregnancy remained without changes after delivery, while 3/10 cases (3, 10a, and 20b) who worsened, 1/6 (case 12a) with PR, 2/7 (cases 24b and 30a) with CR, and 1/2 (case 9b) with mR during pregnancy returned to their pregestational clinical profile after delivery. Anaphylaxis at this period was idiopathic in cases 9a, 9b, and 28, and it was triggered by nonsteroidal anti-inflammatory drugs and codeine in cases 18 and 30b, respectively.

It is important to note that a worsening of skin lesions after delivery was observed in cases 7, 9b, 10b, 11, and 12a, while another 2 cases (1a and 9a) experienced cutaneous improvement; interestingly, the skin lesions of case 9a improved in the setting of a worsening of her MC mediator release-associated symptoms.

Labor Characteristics and MC Mediator-Related Symptoms Intrapartum

Thirty-five infants (78%) were born by vaginal delivery and 10 (22%) had a caesarean birth. Labor induction was carried out for 9 vaginal deliveries using oxytocin (n = 8) or dinoprostone (n = 1). Additionally, prophylactic antimediator therapy for labor was given in 17 cases (38%), according to each anesthesiologist's criteria, using different combinations of antihistamines and corticosteroids. Anesthetic procedures for labor and delivery were carried out in 37 cases (82%) including epidural, local, and general anesthesia (n = 32, n = 3, and n = 2, respectively). Amide-derivative anesthetic drugs were used in the local and epidural techniques associating fentanyl in 4 cases. MC mediator release symptoms during or immediately after labor were observed in 5 cases (11%); symptoms included pruritus (cases 11 and 25b), generalized erythema (cases 9a and 9b), and flushing (case 16); antimediator therapy was given only in case 16, and anesthesia was administered in cases 9b, 16, and 25b using epidural techniques. In addition, 1 patient had fever and the patient who received dinoprostone suffered from vomiting and diarrheas.

Perinatal Outcomes and Infants' Health

Stillbirths were not observed in this series. Three of the 45 newborns were preterm, corresponding to case 6b and another 2 pregnancies (cases 10b and 25a) with a worsening and stabilization of MC-related symptoms during pregnancy, respectively. Four infants were born with low birth weights (cases 7, 17, and 26a after full-term pregnancies), and the evolution of their mothers' symptoms during pregnancy was: worsening in cases 6b and 7,

PR in case 17, and no change in case 26a. Respiratory distress was observed after caesarean delivery at full term in case 26b and after vaginal delivery in case 17 who had fetal growth restriction during the pregnancy and was diagnosed at birth with Down syndrome. The mothers of these last 2 cases remained stable and had PR during pregnancy, respectively. Additionally, nonreassuring fetal heart rate tracing was detected in case 22 immediately before delivery, and case 27 developed a transient neonatal physiological jaundice. All of these cases achieved successful recovery with conservative management measures, and none of them corresponded to mothers who had suffered from anaphylaxis during pregnancy. Skin lesions were not detected at birth in any of the 45 newborns, but development of CM at the age of 5 years was observed in case 30a; the median age of the newborns in June 2010 was 59 months (range 7–377).

Discussion

Little is known about the impact of pregnancy and postpartum on the clinical course of mastocytosis; similarly, limited information exists about the potential impact of mastocytosis on the outcome of pregnancy. In the present study, we report on the largest series of pregnancies in women with mastocytosis, mostly with systemic involvement.

The overall frequency of pregnancies with a worsening of MC-related symptoms during pregnancy was significantly lower in our series versus that of Worobec et al. [17], who reported an exacerbation of mastocytosis symptoms in 5/11 pregnancies (5 CM and 4 ISM patients). This apparent discrepancy could be explained by the relatively limited number of cases reported and/or the distribution of mastocytosis categories within these cases; in line with this latter hypothesis, we observed a greater frequency of cases with an exacerbation of MC mediator release-associated symptoms among CM patients versus ISM patients. Interestingly, 1 of our patients developed skin lesions of mastocytosis during the third trimester of pregnancy. To the best of our knowledge, no cases like this one have been reported so far, although 1 case of anaphylaxis at the onset of menstruation has been referred as an initial presentation of ISM [25]. Conversely, an improvement of MC-related symptoms was observed in one third of all pregnancies, including CR of all symptoms in a significant number of cases. It is important to note that case 28, who had had monthly episodes of severe idiopathic anaphylaxis before pregnancy, did not suffer any further

episode of anaphylaxis throughout pregnancy. Unfortunately, basal serum tryptase determinations were not systematically performed in all pregnancies; thus, the evolution of basal serum tryptase values was not evaluated.

Overall, these preliminary observations could suggest that hormonal changes occurring during pregnancy could have a potential effect on MC activation *in vivo*. In this sense, the binding of estradiol to estrogen receptor- α on the membrane of MC at physiological concentrations has proven to support the synthesis and release of MC mediators *in vitro* [26]; conversely, progesterone and some antiestrogen drugs (e.g. tamoxifen) inhibit MC secretion and proliferation [27, 28].

Treatment of MC mediator-related symptoms during pregnancy should be performed based on a careful risk/benefit evaluation; in this regard, the H1 antihistamines dexchlorpheniramine, cetirizine, and loratadine, as well as the H2 antihistamine ranitidine, are considered to have good safety profiles in pregnancy.

As previously described [17, 19, 22], our results show that anesthetic procedures and drugs given for inducing labor appear to be safe for the use in pregnant women with mastocytosis. In fact, only 3 women suffered from MC-related symptoms intrapartum when epidural anesthesia was used; interestingly, no prophylactic antimeediator therapy was given to 2 of them. In addition, the patient who received dinoprostone for the induction of labor suffered from symptoms considered typical drug adverse events rather than MC mediator release-associated symptoms. Despite the fact that, in our series, intrapartum symptoms were mild and usually restricted to the skin, life-threatening complications related to anesthesia or other labor factors may occur [29, 30]; thus, it seems reasonable to administer appropriate premedication to all pregnant mastocytosis patients during the initiation of labor.

The overall frequencies of spontaneous pregnancy loss during the first trimester, caesarean birth, prematurity, and low birth weight were not significantly different from those described for the general Spanish population (10–15, 25, 7.6, and 3–5.8%, respectively) [31–34]; based on these results and despite the limited number of mastocytosis cases analyzed in this study, it may be concluded that nonaggressive categories of mastocytosis do not seem to have a relevant impact on the outcome of pregnancy.

Although mastocytosis is considered to be a noninherited disease, several familial cases have been reported in the literature [35–40]. In our series, none of the newborns showed signs of congenital disease; however, 1 child de-

veloped CM several years after birth; this child is a 12-year-old female who refused a BM study. Interestingly, her mother was diagnosed with childhood onset WDSM which is a variant of mastocytosis characterized by round, well-granulated CD2-/CD25- BM MC infiltration [24] usually in the absence of mutations involving the activation loop of the KIT gene [41, 42]. In this sense, previous reports of familial mastocytosis lacking exon 17 KIT mutations have suggested the existence of inherited pathogenic mechanisms in a subgroup of mastocytosis patients lacking exon 17 KIT mutations [40, 43, 44].

In summary, from this study and the data available in the literature, it could be concluded that: (i) mastocytosis shows a heterogeneous clinical behavior during pregnancy, as happens in other diseases where MC play a relevant role (e.g. asthma) [45]; (ii) anesthetic drugs (or other com-

mon drugs used for labor) can be safely given to pregnant mastocytosis patients, and (iii) neither maternal nor infant severe complications were observed in this series, suggesting that patients with nonaggressive categories of mastocytosis should not be advised against pregnancy.

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