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Mast cell activation syndrome in pregnancy, delivery, postpartum and lactation: a narrative review

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ABSTRACT

Mast cell activation syndrome (MCAS) is a chronic multisystem disease of aberrant constitutive and reactive mast cell mediator release causing generally inflammatory, allergic, and dystrophic issues. The pathobiology of MCAS drives extraordinary clinical complexity and heterogeneity, which led to only recent recognition despite increasingly apparent substantial prevalence, perhaps as high as 17%. It also has a strong female predilection. Thus, MCAS inescapably impacts pregnancy and the post-partum period in many women. No specific research in the pregnant or post-partum MCAS population has been performed yet. However, its prevalence and potential for driving substantial morbidity merit obstetric providers' acquaintance with this illness and its potential impacts on their patients during pregnancy, delivery, the post-partum period, and lactation. Extensive literature review across all medical specialties, plus direct experience in the authors' practices, provides guidance in recognising MCAS in pregnancy and diagnosing and effectively managing it. Described herein are manners in which MCAS, a protean multisystem disease, adversely affects all stages of pregnancy and post-partum. In order to reduce risks of MCAS causing complications before, during and after pregnancy, identifying and controlling the syndrome prior to pregnancy is best, but, even if the disease is not recognised until late, there may still be opportunities to mitigate its effects. There is precedent for improved outcomes if comorbid MCAS is recognised and controlled. This review provides the first comprehensive guide for obstetric providers regarding this emerging major comorbidity.

Introduction

Mast cells (MCs) play critical roles in innate and adaptive immunity, activating in response to any of a menagerie of triggers (including the classic IgE-mediated pathway and many others) and then quickly releasing their stores of potent mediators, driving a wide range of effects throughout the body (Figures 1 and 2). They are present in all vascularised tissues but are dominantly sited at the environmental interfaces (skin, respiratory tract, gastrointestinal tract and genitourinary tract) and vessel walls. Mast cell activation syndrome (MCAS) is a form of MC disease which, though recognised only recently, increasingly is appearing to be quite prevalent. Molderings et al. (2013) estimate prevalence of 1–17% in the general population, with 74% of patients also reporting similar symptoms in one or more first degree relatives. Both MCAS and the long previously recognised but rare entity of mastocytosis (the latter found in various cutaneous and systemic forms) are now both considered forms of MC activation disease (MCAD) because both MCAS and mastocytosis feature chronic inappropriate MC activation (i.e. inappropriate constitutive and reactive production and release of assorted MC mediators). However, only mastocytosis exhibits overtly neoplastic levels of MC proliferation. Mastocytosis, like any malignancy, is the product of mutations (almost always acquired/somatic) in genes regulating MC proliferation.

MCAS, too, appears to typically be of somatic mutational origin, though affecting activation more so than proliferation. Through the course of their routine practices, beginning several years ago, the authors – among other investigators – began realising many of their patients with large lists of problems of general themes of inflammation, allergic-type issues, and a wide variety of dystrophisms had a single issue underlying their spectra of morbidities, aberrant MC activation, and with such recognition came diagnoses of MCAS. This in turn led to successful MC-focused treatments of previously chronically, inexplicably ill (often long labelled 'psychosomatic'), seemingly unimprovable patients. Meanwhile, the authors came to appreciate that as aberrant MC activation had caused most or all of their MCAS patients' other morbidities, so, too, had it likely caused, or at least significantly contributed to, their morbidities in pregnancy and post-partum. Very little research has been performed regarding MCAS in pregnancy and post-partum, but the substantial benefits MCAS patients commonly gain in other aspects of their health create reasonable suspicion that similar improvements might be gained in the difficulties the disease might cause in pregnancy and post-partum. For this reason, and, given that initial treatments for MC disease are simple, inexpensive, and safe in pregnancy and post-partum, the authors aim to increase obstetrics professionals' familiarity with the
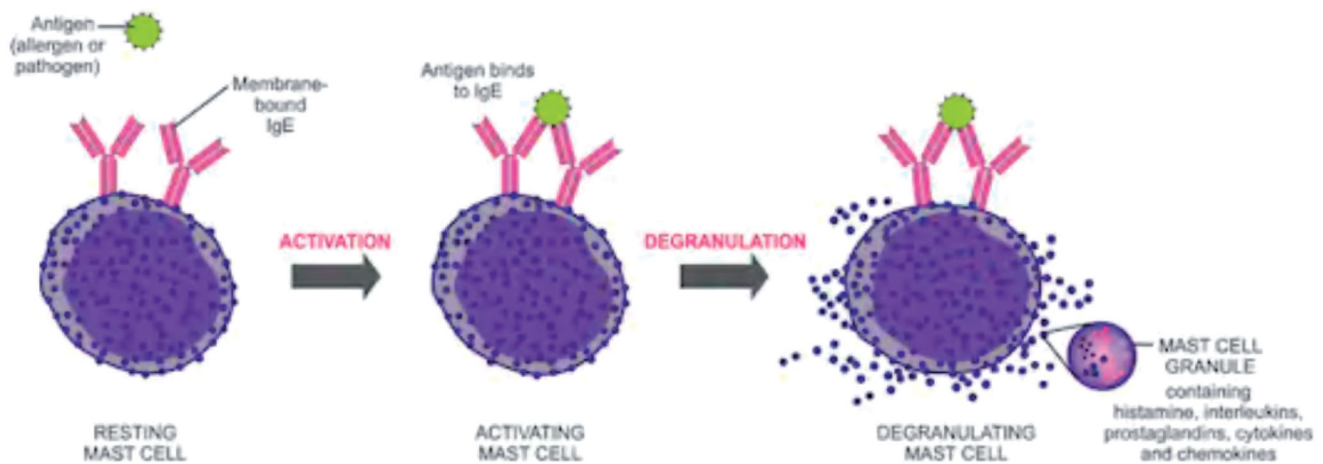
Figure 1. Classic pathway for mast cell activation and mediator release.
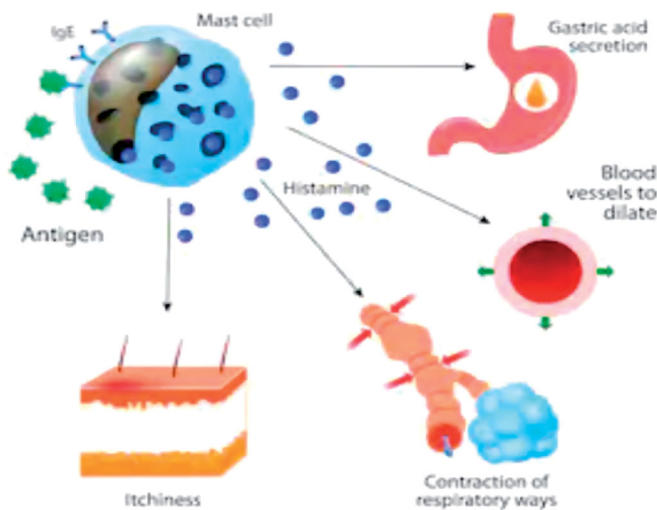

Figure 2. Examples of multi-systemic effects of mast cell mediator release.

disease, using methods of literature review and review of the authors' experiences in managing MCAS patients over the past 12 years.

Discovery of the mast cell and recognition of mast cell activation syndrome

In 1863, German pathologist Friedrich von Recklinghausen was the first to identify MCs (Recklinghausen 1863). A decade later, German anatomist Wilhelm Waldeyer described them in rat dura mater as 'embryonal' and 'plasma' cells (Waldeyer 1875). In 1877, Waldeyer's medical student, Paul Ehrlich, wrote in his Doctor of Medicine dissertation the same cells are found in human connective tissue, referring to them as 'mästzellen' (well-fed cells) due to further identifying their unique granulation utilising aniline-positive dyes (Ehrlich 1877). This was one of Ehrlich's many discoveries for which he was awarded the 1908 Nobel Prize in Medicine (Nobel Foundation 2018). To this day, special staining is required to identify MCs in tissue, as they usually are misidentified with routine haematoxylin and eosin staining as lymphocytes, plasma cells, macrophages, histiocytes, or spindle cells (Swieter et al. 1987). For roughly the first century since

discovery of the MC, the only forms of MC disease recognised were prevalent allergic phenomena and rare neoplasias called mastocytosis. As more MC mediators with broad ranges of effects were discovered, investigators increasingly suspected existence of a broad range of diseases featuring aberrant MC activation (i.e. MC mediator production and release) without the striking neoplasia of mastocytosis. Two decades after the first hypothesis of what is now called MCAS appeared in the literature (Roberts 1988), the first case reports were published (Akin et al. 2007; Sonneck et al. 2007; Valent et al. 2007).

General presentation of MCAS

Symptoms of MCAS are confoundingly diverse due to the presence of MCs in every vascularised tissue (Figure 3) and because MCs produce and release more than 200 mediators, each with a unique array of direct and indirect, local and remote, and acute and chronic effects. Symptoms first appear at any point in a patient's life, though most often they initially present in childhood or adolescence (Afrin 2013). Symptoms significantly worsen shortly following major physical or psychological stressors which induce cytokine storms which in turn might induce further somatic mutations in MC regulatory genes leading to further MC dysfunction (Afrin 2013). Symptoms may even begin in infancy as vague, nonspecific findings, e.g. failure to thrive, colic, rashes, reflux, poor eating, poor sleeping, unusual reactivities, etc. Symptoms commonly driven by MCAS include fatigue, cognitive dysfunction (often termed by patients as 'brain fog', most commonly manifesting as issues with memory, concentration and word-finding), migraines, seizures, pseudo-seizures, dystonias, dysautonomias, paraesthesias, easy bruising and other odd bleeding problems (often mistakenly misdiagnosed as mild forms of assorted bleeding disorders such as von Willebrand disease), flushing, hair changes (such as hair loss), dermatographia, rashes, multiple (and often 'odd') allergies, eye irritation, acute vision changes, abdominal pain, nausea, diarrhoea (often alternating with constipation), splenomegaly, gastroesophageal reflux, menstrual abnormalities (including break-through bleeding), miscarriages, dysuria
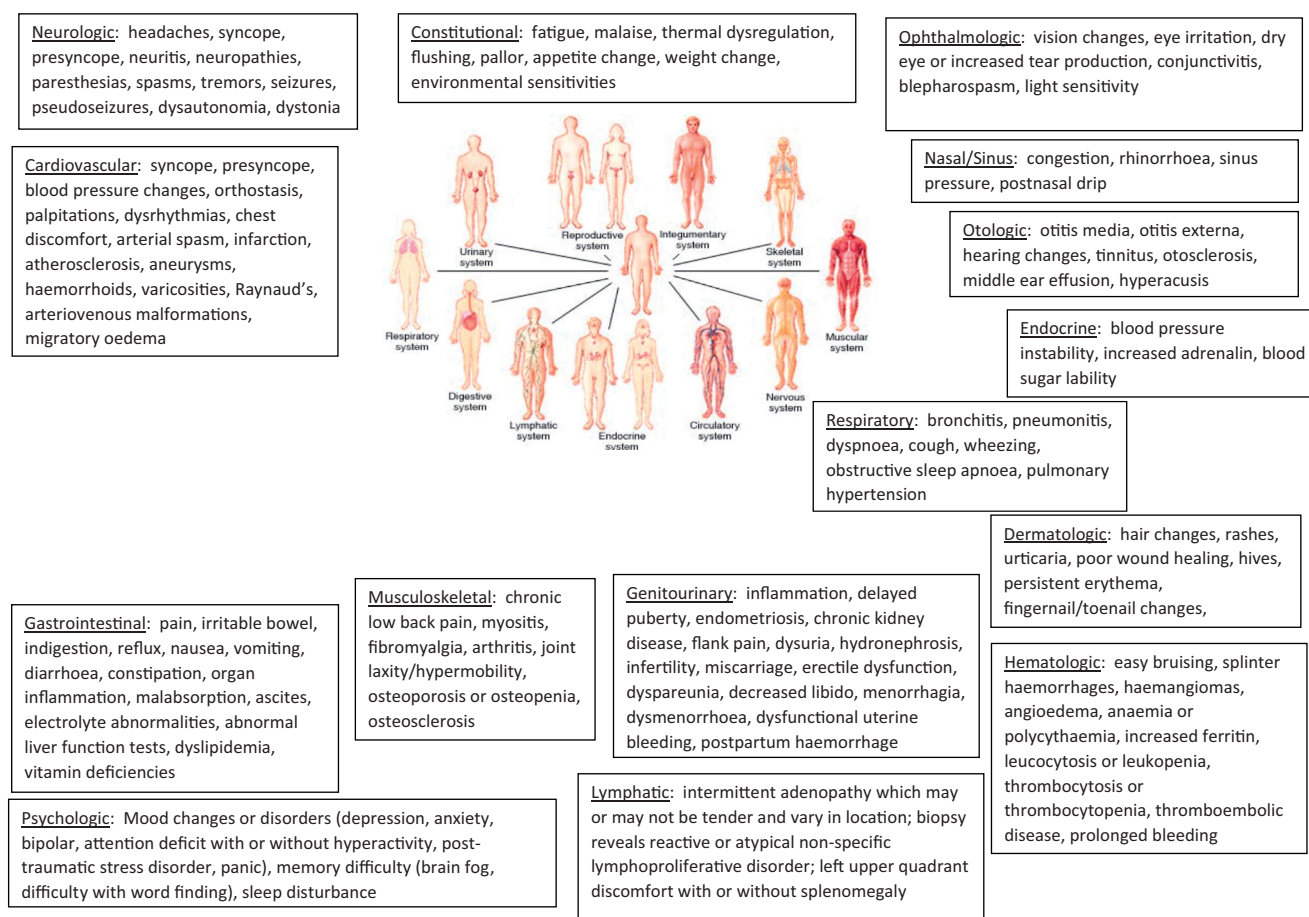
Neurologic: headaches, syncope, presyncope, neuritis, neuropathies, paresthesias, spasms, tremors, seizures, pseudoseizures, dysautonomia, dystonia

Constitutional: fatigue, malaise, thermal dysregulation, flushing, pallor, appetite change, weight change, environmental sensitivities

Ophthalmologic: vision changes, eye irritation, dry eye or increased tear production, conjunctivitis, blepharospasm, light sensitivity

Cardiovascular: syncope, presyncope, blood pressure changes, orthostasis, palpitations, dysrhythmias, chest discomfort, arterial spasm, infarction, atherosclerosis, aneurysms, haemorrhoids, varicosities, Raynaud's, arteriovenous malformations, migratory oedema

Nasal/Sinus: congestion, rhinorrhoea, sinus pressure, postnasal drip

Otologic: otitis media, otitis externa, hearing changes, tinnitus, otosclerosis, middle ear effusion, hyperacusis

Endocrine: blood pressure instability, increased adrenalin, blood sugar lability

Respiratory: bronchitis, pneumonitis, dyspnoea, cough, wheezing, obstructive sleep apnoea, pulmonary hypertension

Dermatologic: hair changes, rashes, urticaria, poor wound healing, hives, persistent erythema, fingernail/toenail changes,

Gastrointestinal: pain, irritable bowel, indigestion, reflux, nausea, vomiting, diarrhoea, constipation, organ inflammation, malabsorption, ascites, electrolyte abnormalities, abnormal liver function tests, dyslipidemia, vitamin deficiencies

Musculoskeletal: chronic low back pain, myositis, fibromyalgia, arthritis, joint laxity/hypermobility, osteoporosis or osteopenia, osteosclerosis

Genitourinary: inflammation, delayed puberty, endometriosis, chronic kidney disease, flank pain, dysuria, hydronephrosis, infertility, miscarriage, erectile dysfunction, dyspareunia, decreased libido, menorrhagia, dysmenorrhoea, dysfunctional uterine bleeding, postpartum haemorrhage

Hematologic: easy bruising, splinter haemorrhages, haemangiomas, angioedema, anaemia or polycythaemia, increased ferritin, leucocytosis or leukopenia, thrombocytosis or thrombocytopenia, thromboembolic disease, prolonged bleeding

Psychologic: Mood changes or disorders (depression, anxiety, bipolar, attention deficit with or without hyperactivity, post-traumatic stress disorder, panic), memory difficulty (brain fog, difficulty with word finding), sleep disturbance

Lymphatic: intermittent adenopathy which may or may not be tender and vary in location; biopsy reveals reactive or atypical non-specific lymphoproliferative disorder; left upper quadrant discomfort with or without splenomegaly

Figure 3. Common symptoms across the MCAS population. Most of the symptoms in the individual MCAS patient are a subset of the symptoms shown here. The disease is extremely heterogeneous, and the full symptom profile in the individual MCAS patient is virtually unique.

(often empirically but mistakenly diagnosed and treated as infection), mood disorders, chronic pain, mild dyspnoea and more. Symptoms often are episodic and/or fluctuate; different symptoms often manifest at different times. Providers seeing patients with such an array of inflammatory, allergic-like and dystrophic issues may serve those patients well by newly considering a unifying diagnosis of MCAS. MCAS potentially impacts every system in the body, and, though it may only cause clinically inconsequential problems in some, many MCAS patients suffer significant, sometimes even disabling or life-threatening consequences. Table 1 provides a comprehensive (but still far from exhaustive) list of symptoms.

General approach to diagnosing MCAS

The full diagnostic evaluation of MCAS is beyond the scope of this paper, but it is essential to confidently exclude mimicking conditions. Table 2 lists differential diagnostic considerations, but diagnoses explaining only subsets of a patient's problems generally should be disfavoured over more unifying diagnoses. However, if a comorbid 'traditional diagnosis' is clearly identified in an MCAS patient, then standard treatments for that diagnosis need to be prioritised regardless of whether that diagnosis is ultimately attributable to the MCAS. Although there is not yet a true consensus on diagnostic criteria for MCAS, the two principal proposals in the current literature are the commonly used Molderings et al.

(2017) criteria (updated from Molderings et al. 2011 and Afrin et al. 2016), shown in Figure 4, and a more restrictive proposal (Valent et al. 2019, updated from Valent et al. 2012) which has been criticised in a number of respects (e.g. Afrin and Molderings 2014). MC mediators commonly tested in evaluations for MCAS include tryptase, histamine, N-methyl-histamine, chromogranin A, prostaglandin D_2, 11-β-prosta-glandin-$F_{2\alpha}$, heparin, and leukotriene E4. Nonsteroidal anti-inflammatory drugs (NSAIDs) and proton pump inhibitors (PPIs) should be avoided for five days prior to specimen collection through the time of the 24-h urine due to confounding impacts on prostaglandin and chromogranin testing, respectively (Afrin 2013; Afrin and Molderings 2014). As most clinical laboratories are unfamiliar with these tests, physicians may need to educate laboratory staff to ensure specimens are handled with continuous chilling and sent to appropriate reference laboratories. Special staining (typically with CD117 immunohistochemical stain) of extracutaneous biopsies (most commonly from the gastrointestinal tract, sometimes also the genitourinary tract or dermatologic as discussed by Roberts and Oates (1991)) may show diagnostically helpful increased numbers of MCs (albeit not at the levels, or in the aberrant morphological and histological patterns, seen in mastocytosis). Marrow biopsies usually are not helpful (one of the many contrasts between MCAS and mastocytosis). It is not yet possible to predict, based on any known clinically observable parameters, which mediators will be elevated in a given

Table 1. Common symptoms of mast cell activation syndrome (MCAS) as discussed by several authors (Molderings et al. 2013; Ratner 2015; Weinstock et al. 2018).

Body system	Symptoms attributable to MCAS
General/constitutional	Fatigue, malaise, difficulty regulating body temperature, subjective sensation of most of the time feeling cold, intermittent sweats/diaphoresis, flushing, pallor, appetite change, weight change (with or without thyroid disease), environmental sensitivities (dyes, cleaning products, fragrances, medications, foods and more)
Neurologic	Headaches, syncope or presyncope, neuropathies (sensory or motor), paraesthesias, spasms, tremors, seizures or pseudo seizures, dysautonomia
Cardiovascular	Syncope or presyncope, blood pressure changes (may be associated with change in body position), palpitations, dysrhythmias, chest discomfort, arterial spasm, infarction, atherosclerosis, aneurysms, haemorrhoids, varicosities, Raynaud's, arteriovenous malformations, migratory oedema (with normal cardiac and renal function)
Dermatologic	Hair changes, rashes, urticaria, poor wound healing, hives, persistent erythema, fingernail/toenail changes and dermatographia
Otologic	otitis media (infectious or sterile), otitis externa (infectious or sterile), hearing changes (loss or hypersensitivity), tinnitus, otosclerosis, middle ear effusion
Nasal/sinus	Congestion, rhinorrhoea, sinus pressure and postnasal drip
Gastrointestinal	Pain (burning sensation to mouth, dental pain with or without decay, sore throat, dysphagia, anywhere along entire tract without or without diffuse abdominal pain), irritable bowel, indigestion, reflux, nausea, vomiting, diarrhoea, constipation, organ inflammation (hepatitis, gastritis, duodenitis, pancreatitis), malabsorption, ascites, electrolyte abnormalities, abnormal liver function tests, dyslipidemia and vitamin deficiencies
Lymphatic	Intermittent adenopathy that may or may not be tender and variable location, biopsy reveals reactive or atypical non-specific lymphoproliferative disorder, left upper quadrant discomfort with or without splenomegaly
Respiratory	Bronchitis, pneumonitis, dyspnoea, cough, wheezing, obstructive sleep apnoea and pulmonary hypertension
Genitourinary	Inflammation anywhere in the entire tract, delayed puberty, endometriosis, chronic kidney disease, flank pain, hydronephrosis, infertility, miscarriage (may also need evaluation for antiphospholipid antibody syndrome), erectile dysfunction, dyspareunia, decreased libido, menorrhagia, dysmenorrhoea, dysfunctional uterine bleeding and dysuria
Musculoskeletal	Chronic low back pain, myositis, fibromyalgia, arthritis, joint laxity/hypermobility, osteoporosis or osteopenia and osteosclerosis
Haematologic	Easy bruising, splinter haemorrhages, haemangiomas, angioedema, anaemia or polycythaemia, increased ferritin, leucocytosis or leukopoenia, thrombocytosis or thrombocytopenia, thromboembolic disease, prolonged bleeding. Bone marrow shows no malignancy in MCAS (unlike systemic mastocytosis). Increased risk for future malignancy is present though
Ophthalmologic	Vision changes, eye irritation, dry eye or increased tear production, conjunctivitis, blepharospasm and light sensitivity
Psychologic	Mood changes or disorders (depression, anxiety, bipolar, attention deficit with or without hyperactivity, post-traumatic stress disorder, panic), memory difficulty (brain fog, difficulty with word finding), sleep disturbance

Note: individual symptoms are not exclusive to MCAS and may be attributed to other conditions which need to be excluded.

Table 2. Some differential diagnoses which may be important to exclude in the MCAD diagnostic process depending on clinical presentation.

- Neuroendocrine tumour (e.g. carcinoid, pheochromocytoma, gastrinoma, VIPoma, insulinoma, glucagonoma)
- Chronic eosinophilic leukaemia or other hypereosinophilic syndrome
- Acute basophilic leukaemia (extremely rare)
- Other haematologic malignancy (e.g. Hodgkin lymphoma, B-cell or T-cell non-Hodgkin lymphoma, amyloidosis or other plasma cell dyscrasia, chronic myeloid leukaemia or other chronic myeloproliferative neoplasm, histiocytosis, acute myeloid leukaemia, hairy cell leukaemia)
- Other non-haematologic malignancy (e.g. primary brain tumour, renal cell carcinoma)
- Paraneoplastic effect of occult malignancy, erythromelalgia
- Non-malignant endocrine disease (e.g. thyrotoxicosis, hyperparathyroidism, adrenal failure)
- Hemophagocytic lymphohistiocytosis (HLH)
- Macrophage activation syndrome
- Porphyria
- Amyloidosis
- Sarcoidosis
- Endometriosis
- Epilepsy, anxiety/panic disorder, depression, bipolar affective disorder type II
- Cardiac dysrhythmia
- Infection (e.g. Epstein-Barr virus, hepatitis C, HIV, Lyme disease, *Helicobacter* pylori gastritis, other rickettsial or mycobacterial disease)
- Toxic exposure (e.g. alcoholism, heavy metal, organic chemicals)
- Connective tissue disease (e.g. systemic lupus erythematosus, Sjögren syndrome, mixed connective tissue disease, rheumatoid arthritis or Felty syndrome)
- Hereditary or acquired angioedema
- Behçet's disease
- Adult Still's disease
- Inborn autoinflammatory syndromes
- Inborn immunodeficiency syndromes
- Hyper-IgE (Job) syndrome
- Inborn disease of inappropriate heavy metal absorption (e.g. hemochromatosis, Wilson's disease
- Median arcuate ligament syndrome, mesenteric angina, fibromuscular dysplasia, coeliac disease, non-coeliac gluten intolerance, lactose intolerance
- Hypersensitivity drug reactions

Importantly, diagnosis of MCAD of course does not preclude development of other, independent processes. When old symptoms significantly change (in character, amplitude or frequency), or when new symptoms emerge, patients diagnosed with MCAD should first pursue timely evaluation and attribute such symptoms to MCAD only if consistent with mast cell mediator release and other reasonable diagnostic considerations have been ruled out.

MCAS patient. The heterogeneity of aberrant mediator expression in the pathobiology of MCAS is to be expected given the physiologic complexity of the MC. Biological and logistical challenges abound in this esoteric testing. Repeat testing not uncommonly is required to correct specimen handling errors yielding falsely normal/negative/low results. In areas of the world where difficulties accessing these tests impede diagnosis, demonstration of response to empiric MC-directed therapy is an acceptable substitute per some published MCAS diagnostic criteria (Molderings et al. 2017). Despite these challenges, diagnosis is worthwhile, helping patient and provider finally realise there is 'a real disease'

Major criteria

1. Constellation of clinical complaints attributable to pathologically increased MC activity (MC mediator release syndrome)

Minor criteria

1. Multifocal or disseminated infiltrates of MCs in marrow and/or extracutaneous organ(s) (e.g., gastrointestinal or genitourinary tract; >19 MCs/high power field)

2. Abnormal spindle-shaped morphology in >25% of MCs in marrow or other extracutaneous organ(s)

3. Abnormal MC expression of CD2 and/or CD25 (i.e., co-expression of CD117/CD25 or CD117/CD2)

4. MC genetic changes (e.g., activating KIT codon 419, 509 or 560 mutations) shown to increase MC activity

5. Evidence (typically from body fluids such as whole blood, serum, plasma, or urine) of above-normal levels of MC mediators including:

- tryptase
- histamine or its metabolites (e.g., *N*-methylhistamine)
- heparin
- chromogranin A (note potential confounders of cardiac, renal, or hepatic failure, neuroendocrine tumors, chronic atrophic gastritis, or recent proton pump inhibitor use)
- other relatively MC-specific mediators (e.g., eicosanoids including prostaglandin (PG) D_2, its metabolite 11-β-PGF$_{2\alpha}$, or leukotriene E4)

6. Symptomatic response to inhibitors of MC activation or MC mediator production or action

Figure 4. Proposed diagnostic criteria for mast cell activation syndrome (Molderings et al. 2017, updated from Molderings et al. 2011 and Afrin et al. 2016) when all other diagnoses which could better explain the full range and chronicity of the findings in the case have been excluded. The diagnosis mast cell activation syndrome is made upon fulfilment of the major criterion plus at least one minor criterion.

present and potentially reducing the great financial and social costs posed by the chronic mysterious illness. Frequent co-morbidities of MCAS (many of which are likely consequential to chronic inappropriate MC activation rather than truly independent co-morbidities) include seasonal and environmental allergies, hypermobile Ehlers Danlos Syndrome (hEDS), postural orthostatic tachycardia syndrome (POTS), dysautonomia, migraines, syncope, presyncope, seizures, pseudo-seizures, fibromyalgia, central sensitisation syndrome, gastroesophageal reflux disease (GERD), intestinal dysbioses

such as small intestinal bacterial overgrowth (SIBO) and small intestinal fungal overgrowth (SIFO), chronic diarrhoea, irritable bowel syndrome (IBS), chronic fatigue syndrome (CFS), interstitial cystitis (IC), vulvodynia, dyspareunia, recurrent miscarriages, dysmenorrhoea, menorrhagia, dysfunctional uterine bleeding, depression, dysthymia, anxiety, idiopathic pruritis, urticaria, eczema, asthma, and thermal dysregulation as discussed by several authors (Jakate et al. 2006; Afrin 2013; Molderings et al. 2013; Afrin and Molderings 2014; Ratner 2015; Regauer et al. 2015; Regauer 2016; Weinstock et al. 2018).

The substantial prevalence of MCAS, together with the great number of pregnancies each year in the U.S.A. (6.3 million according to the Centres for Disease Control [accessed Apr 2019]) and worldwide (211 million according to the World Health Organisation [accessed Apr 2019]), make it certain that many pregnant women have MCAS, though at present it is unrecognised in virtually all who have it. Based on MCAS prevalence estimates from Molderings et al. (2013), up to 1.1 million pregnancies in the U.S.A. and 35.9 million pregnancies worldwide may be affected annually. Again, given the presence of MCs in all vascularised tissues, the great numbers of MC mediators, and the great ranges of effects of those mediators, MCAS is highly likely a comorbidity of clinical significance in many pregnancies, whether recognised, diagnosed, and treated – or not.

General approach to treating MCAS

Management of MCAS is as complex as the disease itself, given that each patient is different, has unique sensitivities, and responds differently to various MC-stabilizing interventions. Unsurprisingly, given the complexity of MC biology and pathobiology, there is not a simple one-step intervention which cures or even controls it fully for every patient, as described by both Afrin (2013) and Molderings et al. (2013).

It is important to provide the patient with reassurance, i.e. despite the disease being only recently recognised, it is not new and the patient is far from alone. Patient support organisations exist and are growing. Referral of a patient suspected of having MCAS to a provider familiar with the condition is desirable but presently often impractical given the dearth of such providers. Many providers who suspect the presence of the condition will simply need to 'do their best' to diagnose and treat it, perhaps informally consulting remotely located specialists. Both the patient and the provider need appropriate expectations that, with such complex pathophysiology and yet such an immature state of the science in this area, attaining the (admittedly subjective) present goal of treatment of feeling significantly better than the pre-treatment baseline the majority of the time likely will require time and a number of intervention trials. The provider should counsel patience, persistence, and a methodical approach in stepping through trials of the assorted treatments. It often is difficult to 'sort things out' if multiple changes in the regimen are made around the same time and the patient either improves or worsens. As with cutaneous mastocytosis and indolent systemic mastocytosis, the average MCAS patient seems to live a lifespan equivalent to the general population, so the

average MCAS patient likely will have the time needed to achieve the above-stated goal. Patients often need reminders that MCAS management is a marathon, not a sprint, as there currently is no cure. Instead, control/palliation is the goal, with many treatments already found helpful.

Once MCAS is diagnosed, the first step for every patient – and continuing for the remainder of the patient's life – is to identify the substances, activities, physical forces, and/or stressors (physical or psychological) which may trigger reactive flarings of the patient's baseline/constitutive state of MC activation. Examples include infections, mould, dust, pollen, temperature or humidity changes, stress, and food or medication product excipients such as fillers, binders, dyes or preservatives typically listed as 'inactive ingredients' in product labelling. A pharmacist-assisted review of the ingredient list of a poorly tolerated product may help identify a potential triggering excipient, whereupon pursuit of a trial of an alternative formulation not containing that excipient to confirm (or refute) the suspicion becomes a crucial process given that many excipients are incorporated into an extraordinary number of products. If unable to avoid some environmental triggers of severe reactions, the patient may need to pursue a desensitisation protocol with an appropriate provider (e.g. an allergist).

The next step is to identify the patient's optimal anti-histamine regimen, meaning the particular histamine H1 and H2 receptor antagonists ('H1 and H2 blockers') which clearly improve the patient's symptoms better than other H1 and H2 blockers. Antihistamines bring significant improvement to the majority of MCAS patients, and they are inexpensive and appear safe for chronic use in most patients, making them an excellent choice for first-line pharmacologic intervention. Because the disease frequently causes chronic fatigue, H1 blocker trials in MCAS patients typically focus on the non-sedating H1 blockers, though sedating H1 blockers (e.g. diphenhydramine) do have roles to play, typically in management of flares. By methodically trying the available non-sedating H1 blockers (typically as a two-week-long trial of each drug tried at its standard dose taken twice daily), most MCAS patients can identify a specific H1 blocker which is more helpful than the others. After instituting regular use of the most helpful H1 blocker, similar rotating trials of the H2 blockers are added, whereupon most MCAS patients again manage to identify a particular one which is most helpful. Since H1 and H2 blockers, at routine doses, usually are very well tolerated drugs, an adverse reaction of any sort to the first formulation tried (name-brand or generic; gelcap, capsule, tablet, liquid, etc.) of any of these drugs almost certainly is an issue of excipient-directed reactivity, not drug-directed reactivity, creating an excellent opportunity for identifying, and thus avoiding, yet another of the patient's triggers. No methods currently exist for predicting which drug in any class of MC-targeting drugs will provide, among all the drugs of that class, the most benefit in the individual MCAS patient. Similarly, no methods yet exist for predicting which classes of therapy will best help the individual patient. There are not yet even any clear patterns as to which symptoms will necessarily be helped by which interventions. Thus – similar to many other diseases – there is much 'trial and error' at

present in managing this disease. Most MCAS patients eventually identify a particular MC-targeted regimen which allows them to reach the above-stated goal.

Further steps involve trying additional MC-targeted interventions as needed to reach the goal. Some patients may reach the goal quickly and inexpensively. Others may require many medication trials and eventually require trials of very expensive medications. However, in the authors' experience, with sufficient patience, persistent, and a methodical approach by both patient and physician, most MCAS patients eventually reach the goal. Examples of pharmacologic interventions in MCAS beyond antihistamines include leukotriene receptor antagonists, corticosteroids (preferably only short-term, helping with flares), benzodiazepines (potentially very effective via binding to MC-surface benzodiazepine receptors, though not first-line due to potential for abuse, misuse, dependence, etc.), NSAIDs (though caution may be required, as these drugs may trigger reactions in some patients), selective serotonin reuptake inhibitors (SSRIs, though the physician must be conscientious of risk for serotonin syndrome if the patient is on both an SSRI and H1 blockers), MC 'stabilizers' (such as cromolyn (a.k.a. cromoglicate) and pentosan that does not cross the placenta (Forestier et al. 1986)), anti-inflammatory flavonoids such as quercetin, ketotifen, vitamin C (reducing histamine production and release, among other effects), vitamin D, immunosuppressants, and many more. Of course, epinephrine (usually self-administered via auto-injectors) is the primary 'go-to' drug for frank anaphylaxis. Table 3 lists common pharmacologic interventions for MCAS, including pregnancy- and post-partum-related risks. Many MCAS patients achieve significant improvement simply with antihistamines, which are safe in pregnancy, post-partum and lactation. 'Advanced' treatments appropriate in some patients include the anti-IgE monoclonal antibody omalizumab and certain tyrosine kinase inhibitors, such as imatinib, which, when effective, typically are tolerated well and require only low doses. Many novel treatments for mastocytosis are in development and may prove useful in MCAS as well.

Polypharmacy easily arises in MCAS patients, but potential for excipient-directed reactivity only heightens the importance of manoeuvres aimed at reducing polypharmacy and eliminating agents with minimal benefit.

To date, there have been no data published (of any level of evidence) regarding treatment specifically of MCAS in pregnancy, and there have been no reports yet of the impacts of MCAS on post-partum issues. The authors leveraged their combined clinical experience in more than 3000 MCAS patients to present below the first comprehensive consideration of impacts of MCAS on pregnancy and post-partum issues.

Impacts of mast cell activation syndrome on pregnancy

Given the complex, multisystem nature of MCAS and the normal prominent presence of MCs at all environmental interfaces, including the genitourinary tract, it stands to reason the

Table 3. Pregnancy/post-partum considerations regarding medications potentially used to manage mast cell activation disease, according to product information and United States National Library of Medicine Toxnet (United States National Library of Medicine 2013).

Pharmacologic class / Class specific risks	Medication	Dose	Pregnancy Safety Category	Lactation Safety Category
H1 antihistamine Sedation, reduced foetal movement, reduced weight gain, reduced milk production	Cetirizine	10–20 mg	Not assigned	Caution
	Diphenhydramine	25–50 mg	B, though caution in third trimester	Not recommended, some sources state contraindicated though in some settings benefits to mother outweigh risks
	Fexofenadine	80–160 mg	C	Not recommended though in some settings benefits to mother outweigh risks
	Hydroxyzine	50–100 mg	Contraindicated in first trimester, caution in second and third trimester without category assigned	Contraindicated
	Ketotifen (oral and ophthalmic)	1 mg (oral), 1 drop (ophth)	Not assigned	Caution
	Levocetirizine	5–10 mg	B	Caution
	Loratadine	10–20 mg	Not assigned	Not recommended though in some settings benefits to mother outweigh risks
H2 receptor blocker Increased prolactin and transient growth suppression at toxic doses	Cimetidine	300–1600 mg	B	Caution
	Famotidine	20–40 mg	B	Caution, some sources state contraindicated though in some settings benefits to mother outweigh risks
	Ranitidine	75–150 mg	B	Caution
Leukotriene receptor antagonists Restricted foetal growth at toxic doses, congenital limb defects	Montelukast	10–20 mg	B	Caution
	Zafirlukast	10–20 mg	B	Use should be avoided
Mast cell stabilizer Decreased foetal weight	Cromolyn (ophthalmic, inhaled, oral, or topical)	1–2 drops (ophth), 20 mg (inh), 100 mg to 40 mg/kg/d (oral)	B	Unknown, No studies
Nonsteroidal anti-inflammatory May impair fertility, spontaneous abortion/ miscarriage (SAB), gastroschisis and cardiac malformations in early pregnancy, patent ductus arteriorsis (PDA) if administered in third trimester	Aspirin	60–650 mg	Not assigned, avoid in third trimester, unless low dose for severe pre-eclampsia at risk for preterm delivery	Caution 75–162 mg occasionally, avoid higher doses or routine/prolonged use
	Celecoxib	100–400 mg	C up to 30 weeks then D	Caution
	Ibuprofen	200–800 mg	C in 1st & 2nd trimester, avoid in 3rd trimester	Caution
	Meloxicam	7.5–15 mg	C prior to 30 weeks then D	Not recommended
	Naproxen	250–500 mg	Not assigned, avoid in third trimester	Not recommended
Corticosteroid Hypoadrenalism	Budesonide	1–2 puffs (inhaled), 3–9mg (oral or rectal)	B (inhaled), C (oral or rectal)	Acceptable (inhaled), Caution due to lack of data (oral or rectal)
	Clobetasol	Up to 50 g	C	Caution and avoid application to nipple, thoroughly wipe off breast prior to breastfeeding
	Methylprednisolone	40–120 mg (IM or IV), 4–48 mg (oral)	C	Avoid breastfeeding for 2–8 h after 1 g IV dose, Oral doses up to 40 mg/day not likely to cause problems but higher doses may cause adrenal suppression
	Prednisone	5–60 mg	C (short acting) D (long acting)	Caution (lowest dose should be prescribed; theoretically, if high maternal dose necessary, avoid breastfeeding for 4 h following dosing or use prednisolone.)
	Triamcinolone	2.5–80 mg (intraarticular), 40–160 mg (IM), one application (topical)	Not assigned	Caution
Opioid receptor antagonist Only found to be embryotoxic in animal studies when animals given doses 30–60 times higher than the maximum human dose and no retrospective studies have found harm in humans	Low dose naltrexone	0.5–5 mg	C	Caution

Table 3. Continued.

Pharmacologic class / Class specific risks	Medication	Dose	Pregnancy Safety Category	Lactation Safety Category
Heparinoid Does not cross the placenta and unknown if excreted in breastmilk	Pentosan	100 mg	B	Caution
Selective serotonin reuptake inhibitor Cardiovascular defect risk in infants exposed in utero 2% compared to 1% for general population.	Citalopram	20–40 mg	C	Not recommended, though if needed by mother, then is not a contraindication to breast feeding
Exposure late in pregnancy may increase risk of persistent pulmonary hypertension in newborn (exact risk unknown).	Fluoxetine	20–80 mg	C	Not recommended, though if needed by mother, then is not a contraindication to breast feeding
	Paroxetine	20–50 mg	D	Caution
30% of neonates with prolonged exposure had dose related symptoms of withdrawal (tremor, gastrointestinal disturbance, sleep disturbance, hypertonicity, high-pitched cry) and should be monitored at least 48 hours.	Sertraline	50–200 mg	Not assigned	Not recommended, though if needed by mother, then is not a contraindication to breast feeding
Benzodiazepine Hypotonia, respiratory depression, hypothermia, addicting, and withdrawals in neonates exposed in utero, may also impair skeletal formation	Alprazolam	0.25–4 mg	Not assigned	Not recommended
	Clonazepam	0.25–4 mg	Not assigned	Caution
	Diazepam	2–10 mg	Not assigned	Not recommended
	Lorazepam	0.5–4 mg	Not assigned	Not recommended
	Midazolam	0.07–2.5 mg	D	Caution
	Triazolam	0.125–0.25 mg	X	Contraindicated
Tyrosine kinase inhibitor SAB and congenital abnormalities	Bosutinib	100–600 mg	D	Not recommended
	Dasatinib	100–140 mg	D	Not recommended
	Imatinib	100–400 mg	Not assigned, associated with spontaneous abortion and congenital abnormalities	Not recommended
	Nilotinib	150–200 mg	D	Not recommended
	Ponatinib	15–45 mg	Not assigned	Not recommended
Anti-C5 monoclonal antibody Increased rate of developmental abnormalities and foetal death at doses two to eight times higher than standard dose	Eculizimab	600–1200 mg (IV)	Not assigned	Caution
	Mepolizumab	100 mg (SQ)	Not assigned	Caution
IgG monoclonal antibody No known harm seen though currently undergoing research through a drug registry and animal studies have found 0.15% of the maternal serum level present in the infant following injections during the pregnancy	Omalizumab	150 mg (SQ) q4weeks to 375 mg (SQ) q2 weeks (dose depends on weight and IgE levels)	B	Not recommended
Other or cytotoxic Severe foetal malformations and potentially foetal death	Hydroxyurea	15 mg/kg/day (max 35 mg/kg/day)	Not assigned, though recommended to avoid pregnancy the entire time on the medicine through 6 months after discontinuation	Contraindicated
	Thalidomide	50–200 mg	Not assigned, though used to be considered category X and currently recommended to not get pregnant or donate blood entire time on medicine through 4 weeks after discontinuation	Contraindicated

Note: Only U.S. Food and Drug Administration-approved medications are listed. Use of any medication in pregnancy and/or lactation must consider the risks and benefits to both mother and baby. The lowest effective dose is recommended to be administered.

disease could significantly impact pregnancy. Stress, whether psychological or physical, is a prominent activator of MCs (Afrin 2013). The hormonal changes of pregnancy result in significant physical stresses, and pregnancy commonly brings significant psychological stresses, too. There are many known complications of pregnancy. Most are idiopathic, such as breast tenderness, morning sickness, hyperemesis gravidarum (HG), spontaneous abortion, threatened miscarriage, subchorionic haemorrhage, uterine irritability/contractions with or without cervical change, fatigue, pruritic urticarial papules and plaques of pregnancy (PUPPP), pre-eclampsia, eclampsia, and more. When the female patient is previously diagnosed with MCAS, the pregnancy provider is best able to care for the patient if s/he not only practices standard obstetric care for these conditions but also keeps in mind the potential for added success in controlling symptoms upon improving MC disease control. Precedent for such added success has already been seen in oncologic settings as discussed by Valent et al. (2007), Afrin and Molderings (2014) and Molderings et al. (2017). Furthermore, for patients not previously evaluated for MCAS but who present otherwise complex medical history of general themes consistent with MCAS, the possibility of MCAS should not be ignored and evaluation should be pursued, whether by the treating obstetrics provider or upon referral to another MCAS-aware consultant. There are not yet any globally accepted definitions of dermatographism, but it nevertheless is an extremely common physical exam finding in MCAS (Figure 5). If a patient with the above-described complex history is seen to quickly (within 1–2 min) manifest erythroderma in the track of a light scratch, and if that erythroderma then persists for at least another 5–10 min, it is difficult to attribute such a response to any process other than aberrant triggering of dysfunctional MCs in the skin. This results in immediate (and aberrantly sustained) release of vasodilatory mediators, giving cause to further evaluate for MCAS, presumably via the above-described laboratory testing. Table 4 presents common complications potentially attributable to MCAS which the authors have observed in each stage of pregnancy in their patients who have come to be definitively diagnosed with MCAS.

Figure 5. Dermatographism, a very common finding in MCAS, showing erythroderma in the track of a light scratch. Note Darier's sign, an even more vibrant demonstration of mast cell activation in the skin, is actual urticaria (i.e. a raised wheal) in the track of a scratch and not commonly seen in MCAS.

In patients with acute and chronic gastrointestinal illnesses (whether due to MCAS or not), the marked hormonal fluctuations and physical demands of pregnancy alone could bring worsening or relapse of symptoms. If the patient is experiencing large volume or frequent diarrhoea or emesis, it is essential to monitor levels of medications (as feasible) due to malabsorption or even excessive excretion or fluid shifts. Constipation, too, may have significant effects on drug levels and dosing needs. The increased plasma volume associated with pregnancy may further affect medication dosing needs. Kimpinski et al. (2010) reported early orthostasis in many pregnant patients improves in the second and third trimesters after transiently worsening in the first trimester; Woidacki et al. (2014) reported transient improvement in orthostasis in the early post-partum period. It is currently unknown if these changes in orthostasis are strictly due to POTS vs. MCAS vs. a combination of both (unsurprising given increasing suspicions that MCAS may be a key driver of POTS in some POTS patients). Many patients have both conditions and see worsening of POTS emerge concomitantly with instability of MCAS, such as when marked gastrointestinal complications of MCAS impede water and salt absorption (to help regulate POTS) and medication absorption (to help MCAS and other comorbidities).

NSAIDs have long been known to be efficacious in controlling MCAS in some patients, and no clear aetiology for pre-eclampsia has yet emerged. The literature has long demonstrated the benefits of NSAIDs in reducing the complications of pre-eclampsia and thus raises a legitimate question as to whether MCAS might be the primary driver in some proportion of the pre-eclamptic population, particularly pre-eclamptics whose comprehensive history aligns well with the complexity and general themes previously described for MCAS. The CLASP (1994) multi-centre study was performed to identify ways to manage pre-eclampsia and improve outcomes for both mother and child. It noted prior small trials showed 75% reductions in pre-eclampsia and some avoidance of intrauterine growth retardation (IUGR) with low dose anti-platelet regimens, though larger studies had failed to confirm similar results. The CLASP investigators ultimately concluded routine use of low dose aspirin prophylactically or therapeutically is not indicated but is appropriate for women with severe pre-eclampsia who will need significantly early delivery. Specifically, CLASP showed 9364 pregnant women given 60 mg aspirin daily beginning in the second trimester reduced preterm delivery, potentially due, at least in part, to reduction of MC activation. It also did not increase placental bleeding but slightly increased blood transfusions post-partum. Low dose aspirin is unlikely to contribute significantly to post-partum bleeding (PPB), and instead PPB in the setting MCAS may simply be due to aberrant release (as provoked by all the physical and psychological stresses of delivery) of significant portions of the MCs' great stores of endogenous heparin. MC activation induces fibrinolysis, too (Seidel et al. 2011). While taking care to note that there are some MCAS patients in whom NSAIDs such as aspirin are triggers of MC activation, nevertheless, in the absence of more definitive research, low dose aspirin seems to be a reasonable intervention to try (from the point of

recognition of pregnancy) in the aspirin-tolerating pregnant MCAS population, especially those who previously suffered pregnancy-related complications such as repeated early miscarriages, HG, pre-eclampsia/eclampsia, or post-partum depression/anxiety.

General pregnancy prescribing guidelines of fewest and lowest doses of medications which accomplish the goal of treating condition(s) to functional levels match the management strategy in MCAS. Additional considerations in pregnancy and lactation of course include foetal and infant exposure to drugs across the placenta and via breastmilk, respectively. Table 3 provides pregnancy/post-partum-related considerations of drugs commonly utilised in the management of MCAS.

Impacts of MCAS on labour and delivery

General guidelines for perioperative management of MCAS are applicable to management of MCAS in labour and delivery, too. Labour and delivery obviously are major physical (and, often, psychological) stressors and clearly have potential not only to cause acute flares of MC activation in the gravid MCAS patient but also to trigger permanent escalations of baseline MC dysfunction during, or even in the few months following, pregnancy. Acute flares of MC activation generally are managed with extra doses of H1 and H2 histamine receptor blockers with or without steroids and/or benzodiazepines as determined clinically warranted by healthcare provider. Prophylactic dosing can be given, too, if felt warranted to try to prevent a flare. Patients should undergo peripartum and post-partum clinical monitoring for flares including monitoring for rashes, flushing, liability in vital signs and verifying the medication products administered do not have any excipient ingredients to which the patients are known to react. Patients should be maintained in the least stressful environment possible. If any signs of MC activation develop, support staff should notify the doctor or administer histamine H1 ± H2 receptor antagonists if already ordered. There are no data on short or long term outcomes of vaginal delivery vs. caesarean section delivery for either female MCAS patients or the children they deliver, though Thompson et al. (2002), Borders (2006) and Villar et al. (2007) affirmed caesarean delivery to be generally more physically stressful than vaginal delivery, with several studies showing surgical delivery results in increased risks of hysterectomy, haemorrhage, anaemia, infection, thrombosis, fatigue, headache, insomnia, polyuria and post-partum depression within the first 8 weeks after delivery (Thompson et al. 2002; Borders 2006; Villar et al. 2007). Potentially, fatigue, headache, insomnia, and other symptoms could be attributed to MC mediator release but also could be attributed to hormones, surgical blood loss, pain from surgical recovery, demands of caring for a newborn, etc. Therefore, all other factors being equal, vaginal delivery theoretically would be preferable in an MCAS patient, though analysis of preferred delivery method may be significantly weighted by the severity and type of comorbid EDS. Overall, obstetricians are recommended to prioritise their existing suite of assessment tools (other maternal comorbidities, foetal heart tones, contraction patterns, cervical change, prior caesarean sections, placental location, etc.) over consideration of MCAS in deciding which method of delivery to pursue in the individual patient.

Impacts of mast cell activation syndrome in the post-partum period

Both providers and patients would like to have MCAS symptoms arising during pregnancy cease upon delivery, but that is often not the case. There is further physical and psychological stress during recovery from pregnancy and delivery as well as adjustment to having a neonate, including attendant hormonal changes. Again, some of the fundamental pathobiological behaviours of MCAS stem from the MC's normal acute and chronic responses to stress, including degranulation with release of a cornucopia of pro-inflammatory mediators. The post-partum time period is generally defined as immediately following delivery through the first 6–8 weeks or longer. MCAS patients in theory could be at higher risk for post-partum haemorrhage with or without prolonged post-partum rubra lochia from endogenous heparin release from MCs or enhanced fibrinolysis driven by activated MCs (Seidel et al. 2011). Incidence of 'baby blues', post-partum depression, and post-partum anxiety also could be increased in the post-partum MCAS population, as psychiatric comorbidities often wax during flares of MCAS (Afrin et al. 2015). When genitourinary tract MCs are overactive, inflammation may be stoked in segments, or the entirety, of the genitourinary tract and may result in vaginitis, incontinence, dyspareunia, endometritis, dysuria with or without interstitial cystitis, dysfunctional uterine bleeding, cervicitis, and more (Afrin et al. 2019). Table 4 lists further potential complications. Medications may be more difficult to tolerate when the patient is more inflamed, too. It is important to investigate potential excipient issues if an MCAS patient adversely reacts to a medication product being newly tried, particularly if the drug in the product is ordinarily a well-tolerated drug.

Impacts of mast cell activation syndrome on lactation

MCAS can complicate lactation, too. As Raynaud's phenomenon results in distal discolouration with reduced blood flow, it also can affect nipples, resulting in pallor and cyanosis upon exposure to cold temperatures, or upon uncovering the breast to express milk or colostrum, and result in marked pain. Raynaud's phenomenon often is triggered later by removing a wet nipple from an infant's mouth to either switch breasts, finish nursing, trying to wake baby, or begin/end pumping. This pain in the general post-partum population usually can be managed with nifedipine (Anderson et al. 2004), but its use may be limited in certain MCAS patients also suffering baseline borderline hypotension. Unfortunately, this pain greatly limits lactation for mothers and subsequently reduces passive immunity for the baby. Anaphylaxis from lactation is rare but may occur (Shawkat et al. 2011). Additionally, newborns and infants may react to breast milk,

Table 4. Complications of MCAS during pregnancy, delivery, post-partum, and lactation as identified by several authors (Clasp 1994; Thompson et al. 2002; Anderson et al. 2004; Borders 2006; Jakate et al. 2006; Valent et al. 2007; Villar et al. 2007; Kimpinski et al. 2010; Afrin 2013; Molderings et al. 2013; Ratner 2015; Regauer et al. 2015; Woidacki et al. 2014; Regauer 2016, Weinstock et al. 2018).

Symptom/condition	First trimester	Second trimester	Third trimester	Delivery	Post-partum	Lactation
Fatigue (excess)	X	X	X	X	X	X
Hyperemesis gravidarum	X	X	X			
Uterine irritability	X					
Cervicitis	X				X	
Growth restriction, small for gestational age (SGA), intrauterine growth restriction (IUGR)		X	X			
Pregnancy induced hypertension		X	X			
Pruritic urticarial papules and plaques of pregnancy (PUPPP)	X	X	X		X	
Subchorionic haemorrhage	X	X				
Spontaneous abortion (SAB)	X	X				
Dysautonomia	X	X	X		X	X
Unstable vitals of mother or baby / unstable foetal heart tones				X		
Preterm premature rupture of membranes (PPROM)		X	X			
Premature rupture of membranes (PROM)			X			
Pre-eclampsia		X	X			
Eclampsia		X	X			
Preterm labour		X	X			
Stillborn delivery			X			
Vaginal tears (1st–4th degree), haemorrhage or surgical complication from C-section				X		
Hives, pruritis and urticaria					X	
Post-partum haemorrhage, prolonged bleeding, dysfunctional uterine bleeding					X	
Dyspareunia					X	
Endometritis					X	
Breast feeding anaphylaxis						X
Reduced milk supply						X
Baby blues, post-partum depression, post-partum anxiety						X
Raynaud's of nipple						X
Mastitis						X

requiring the mother to adjust her diet and/or wean early, reducing passive immunity (Brill 2008; Caminoa et al. 2010; Lifschitz and Szajewska 2015). MCAS also may drive mastitis and suppression of lactation. See Table 4 for additional complications of lactation in MCAS.

Conclusions

MCAS is a diverse, complex, multisystem disease (many symptoms seen in various patients are shown in Table 1 and Figure 3, but these certainly are not comprehensive lists) and likely is highly prevalent. Treatment is challenging due to absence so far of studies of this newly recognised disease identifying subpopulations likely to respond to specific treatments. However, patient, persistent, methodical trials of the large number of interventions found helpful in assorted MCAS patients usually results in identifying a regimen, unique to the individual patient, which helps achieve satisfactory improvement/control of this presently incurable disease. Although pregnancy and post-partum often provide female MCAS patients more challenges than faced by women without MCAS, most of these challenges appear manageable. Recognition and diagnosis of the disease are critical prior to developing patient-specific strategies for effective management. Many pregnant women with suspected or proven MCAS see improvement overall, as well as improved pregnancy outcomes, simply with addition of antihistamines and/or low dose aspirin or cromolyn to their regimens. The ultimate goals are safety and wellbeing of both mother and baby, generally accomplished by accurate diagnosis and timely identification and application of effective treatment. Most questions regarding MCAS in pregnancy and post-partum are unanswered and constitute fertile ground for rigorous research (e.g. might recognition and treatment of MCAS prior to pregnancy reduce HG or miscarriages). Our review found key management options with specific safety classifications for pregnancy and lactation (see Table 3 for details with all the product information labelling references directly from manufacturers, Committee on Drugs (1994), Forestier et al. (1986), Somogyi and Gugler (1979), Roberts et al. (1989) and Roberts and Oates (1991)) but also found many areas where additional research is needed. The limited amount of time the disease has been known to exist (approximately a decade) and the small number of studies to date further limit the strength of this review, but obstetrics providers nevertheless will find utility from this review in helping them recognise, diagnose, and treat the disease, thus hopefully beginning to 'move the needle' on addressing a wide variety of formerly quite idiopathic and frustrating complications in pregnancy and post-partum.

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References

ACOG Committee on Obstetric Practice. 2006. ACOG Committee Opinion No. 354: treatment with selective serotonin reuptake inhibitors during pregnancy. Obstetrics & Gynecology 108:1601–1603.

Afrin LB, Butterfield JH, Raithel M, Molderings GJ. 2016. Often seen, rarely recognized: mast cell activation disease – a guide to diagnosis and therapeutic options. Annals of Medicine 48:190–201.

Afrin LB, Molderings GJ. 2014. A concise, practical guide to diagnostic assessment for mast cell activation disease. World Journal of Hematology 3:1–17.

Afrin L. 2013. Presentation, diagnosis, and management of mast cell activation syndrome. Happauge (NY): Nova Science Publishers.

Afrin LB, Dempsey TT, Rosenthal L, Dorff SR. 2019. Successful mast-cell-targeted treatment of chronic dyspareunia, vaginitis, and dysfunctional uterine bleeding. Journal of obstetrics and gynaecology: the journal of the Institute of Obstetrics and Gynaecology 39:664–669.

Afrin LB, Pöhlau D, Raithel M, Haenisch B, Dumoulin FL, Homann J. 2015. Mast cell activation disease: an underappreciated cause of neurologic and psychiatric symptoms and diseases. Brain, Behavior, and Immunity 50:314–321.

Akin C, Scott LM, Kocabas CN, Kushnir-Sukhov N, Brittain E, Noel P, et al. 2007. Demonstration of an aberrant mast-cell population with clonal markers in a subset of patients with "idiopathic" anaphylaxis. Blood 110:2331–2333.

Anderson JE, Held N, Wright K. 2004. Raynaud's phenomenon of the nipple: a treatable cause of painful breast feeding. Pediatrics 113:e360–4.

Available from: http://www.who.int/whr/2005/chapter3/en/index3.html [cited 2019 Apr 21].

Available from: http://www.worldometers.info/world-population/us-population/ [cited 2019 Apr 21].

Available from: https://www.cdc.gov/nchs/products/databriefs/db136.htm [cited 2018 Feb 28].

Available from: https://www.un.org/development/desa/publications/world-population-prospects-the-2017-revision.html [cited 2018 Feb 28].

Borders N. 2006. After the afterbirth: a critical review of postpartum health relative to method of delivery. Journal of Midwifery & Women's Health 51:242–248.

Brill H. 2008. Approach to milk protein allergy in infants. Canadian Family Physician Medecin de Famille Canadien 54:1258–1264.

Caminoa M, Martín-Muñoz MF, Pineda de la Losa F, García-Parrado García G, Bobolea I, Larco J, et al. 2010. Hidden allergens in breast milk. Journal of Allergy and Clinical Immunology 125:1-AB221.

CLASP. 1994. Clasp: a randomised trial of low-dose aspirin for the prevention and treatment of preclampsia among 9364 pregnant women. Lancet 343:619–629.

Committee on Drugs. 1994. The transfer of drugs and other chemicals into human milk. Pediatrics 93:137–150.

Ehrlich P. 1877. Beitrage zur Kenntnis der Anilinfarburgen und ihrer Verwendung in der Mikroskopischen Technik. Archiv Für Mikroskopische Anatomie 13:263–277.

Forestier F, Fischer AM, Daffos F, Beguin S, Diner H. 1986. Absence of transplacental passage of pentosan polysulfate during mid trimester of pregnancy. Thrombosis and Haemostasis 56:247–249.

Jakate S, Demeo M, John R, Tobin M, Keshavarzian A. 2006. Mastocytic enterocolitis: increased mucosal mast cells in chronic intractable diarrhea. Archives of Pathology & Laboratory Medicine 130:362–367.

Kimpinski K, Iodice V, Sandroni P, Low P. 2010. Effect of pregnancy on postural tachycardia syndrome. Mayo Clinic Proceedings 85:639–644.

Lifschitz C, Szajewska H. 2015. Cow's milk allergy: evidence-based diagnosis and management for the practitioner. European Journal of Pediatrics 174:141–150.

Molderings GJ, Brettner S, Homann J, Afrin L. 2011. Mast cell activation disease: a concise practical guide for diagnostic workup and therapeutic options. Journal of Hematology & Oncology 4:10.

Molderings GJ, Haenisch B, Bogdanow M, Fimmers R, Nöthen MM. 2013. Familial occurrence of systemic mast cell activation disease. PLoS One 8:e76241.

Molderings GJ, Zienkiewicz T, Homann J, Menzen M, Afrin LB. 2017. Risk of solid cancer in patients with mast cell activation syndrome: results from Germany and USA. F1000Research 6:1889.

Nobel Foundation. 2018. All nobel laureates in physiology or medicine [cited 10 Aug 2018]. Available from http://www.nobelprize.org/nobel_prizes/medicine/laureates/.

Product Information. Accolate (zafirlukast). Zeneca Pharmaceuticals, Wilmington, DE.

Product Information. Actonel (risedronate). Procter and Gamble Pharmaceuticals, Cincinnati, OH.

Product Information. Allegra (fexofenadine). Hoechst Marion-Roussel Inc., Kansas City, MO.

Product Information. Ativan (lorazepam). Wyeth-Ayerst Laboratories, Philadelphia, PA.

Product Information. Benadryl (diphenhydramine). Parke-Davis, Morris Plains, NJ.

Product Information. Boniva (ibandronate). Roche Laboratories, Nutley, NJ.

Product Information. Bosulif (bosutinib). Pfizer U.S. Pharmaceuticals Group, New York, NY.

Product Information. Celebrex (celecoxib). Searle, Chicago, IL.

Product Information. Celexa (citalopram). Forest Pharmaceuticals, St. Louis, MO.

Product Information. Claritin (loratadine). Schering Laboratories, Kenilworth, NJ.

Product Information. Cromolyn Sodium (cromolyn (sodium cromoglycate)). Teva Pharmaceuticals (formerly IVAX), Miami, FL.

Product Information. Deltasone (prednisone). Pharmacia and Upjohn, Kalamazoo, MI.

Product Information. Depo-Medrol (methylPREDNISolone acetate). Pfizer U.S. Pharmaceuticals Group, New York, NY.

Product Information. Elmiron (pentosan polysulfate sodium). Baker Norton Pharmaceuticals, Miami, FL.

Product Information. Entocort EC (budesonide). Perrigo, L. Company, Allegan, MI.

Product Information. Fosamax (alendronate). Merck & Co, Inc, West Point, PA.

Product Information. Gleevec (imatinib mesylate). Novartis Pharmaceuticals, East Hanover, NJ.

Product Information. Halcion (triazolam). Pharmacia and Upjohn, Kalamazoo, MI.

Product Information. Hydroxyurea (hydroxyurea (hydroxyUREA)). Par Pharmaceutical Inc, Chestnut Ridge, NY.

Product Information. Ibuprofen (ibuprofen). Par Pharmaceutical Inc., Spring Valley, NY.

Product Information. Iclusig (ponatinib). Ariad Pharmaceuticals Inc., Cambridge, MA.

Product Information. Klonopin (clonazepam). Roche Laboratories, Nutley, NJ.

Product Information. Medrol (methylprednisolone). Pharmacia and Upjohn, Kalamazoo, MI.

Product Information. Mobic (meloxicam) Boehringer-Ingelheim, Ridgefield, CT.

Product Information. Naprosyn (naproxen). Syntex Laboratories Inc., Palo Alto, CA.

Product Information. Nucala (mepolizumab). GlaxoSmithKline, Research Triangle Park, NC.

Product Information. Pamidronate Disodium (pamidronate). Teva Pharmaceuticals USA, North Wales, PA.

Product Information. Paxil (paroxetine). GlaxoSmithKline, Research Triangle Park, NC.

Product Information. Pepcid (famotidine). Merck & Co, Inc, West Point, PA.

Product Information. PredniSONE (predniSONE). Watson Pharmaceuticals, Parsippany, NJ.

Product Information. Prozac (fluoxetine). Dista Products Company, Indianapolis, IN.

Product Information. Pulmicort Flexhaler (budesonide). A-S Medication Solutions, Chicago, IL.

Product Information. Pulmicort Respules (budesonide). Astra-Zeneca Pharmaceuticals, Wayne, PA.

Product Information. Rayos (predniSONE). Horizon Pharma USA Inc., Northbrook, IL.

Product Information. ReVia (naltrexone). DuPont Pharmaceuticals, Wilmington, DE.

Product Information. Singulair (montelukast). Merck & Co, Inc., West Point, PA.

Product Information. Soliris (eculizumab). Alexion Pharmaceuticals Inc., Cheshire, CT.

Product Information. Solu-Medrol (methylPREDNISolone sodium succinate). Pfizer U.S. Pharmaceuticals Group, New York, NY.

Product Information. Solu-Medrol (methylprednisolone). Pharmacia & Upjohn, Kalamazoo, MI.

Product Information. Sprycel (dasatinib). Bristol-Myers Squibb, Princeton, NJ.

Product Information. Tagamet (cimetidine). SmithKline Beecham, Philadelphia, PA.

Product Information. Tasigna (nilotinib). Novartis Pharmaceuticals, East Hanover, NJ.

Product Information. Temovate (clobetasol). Glaxo Wellcome, Research Triangle Park, NC.

Product Information. Thalomid (thalidomide). Celgene Corporation, Warren, NJ.

Product Information. Uceris (budesonide). Santarus Inc, San Diego, CA.

Product Information. Valium (diazepam). Roche Laboratories, Nutley, NJ.

Product Information. Versed (midazolam). Roche Laboratories, Nutley, NJ.

Product Information. Vistaril (hydroxyzine). Pfizer US Pharmaceuticals, New York, NY.

Product Information. Xanax (alprazolam). Pharmacia and Upjohn, Kalamazoo, MI.

Product Information. Xolair (omalizumab). Genentech, South San Francisco, CA.

Product Information. Xyzal (levocetirizine). UCB Pharma Inc, Smyrna, GA.

Product Information. Zaditor (ketotifen ophthalmic). Ciba Vision Ophthalmics, Duluth, GA.

Product Information. Zantac (ranitidine). Glaxo Wellcome, Research Triangle Park, NC.

Product Information. Zilretta (triamcinolone). Flexion Therapeutics, Inc., Burlington, MA.

Product Information. Zoloft (sertraline). Roerig Division, New York, NY.

Product Information. Zyrtec (cetirizine). Pfizer US Pharmaceuticals, New York, NY.

Ratner V. 2015. Mast cell activation syndrome. Translational Andrology and Urology 4:587–588.

Recklinghausen F. 1863. Ueber eiter – und bindegewebskorperche. Archiv Für Pathologische Anatomie Und Physiologie Und Für Klinische Medicin 28:157–197.

Regauer S. 2016. Mast cell activation syndrome in pain syndromes bladder pain syndrome/interstitial cystitis and vulvodynia. Translational Andrology and Urology 5:396–397.

Regauer S, Eberz B, Beham-Schmid C. 2015. Mast cell infiltrates in vulvodynia represent secondary and idiopathic mast cell hyperplasias. APMIS 123:452–456.

Roberts LJ. 1988. Carcinoid syndrome and disorders of systemic mast-cell activation including systemic mastocytosis. Endocrinology and Metabolism Clinics of North America 17:415–436.

Roberts RJ, Blumer JL, Gorman RL, et al. 1989. American Academy of Pediatrics Committee on Drugs: transfer of drugs and other chemicals into human milk. Pediatrics 84:924–936.

Roberts LJ, Oates JA. 1991. Biochemical diagnosis of systemic mast cell disorders. Journal of Investigative Dermatology 96:19S–25S.

Seidel H, Molderings G, Oldenburg J, Meis K, Kolck U, Homann J, et al. 2011. Bleeding diathesis in patients with mast cell activation disease. Thrombosis and Haemostasis 106:987–989.

Shawkat E, Hussain N, Myers JE, Gillham J, Helbert M. 2011. Breast milk: friend or foe? BMJ Case Reports 2011:bcr0120113766.

Somogyi A, Gugler R. 1979. Cimetidine excretion into breast milk. British Journal of Clinical Pharmacology 7:627–629.

Sonneck K, Florian S, Müllauer L, Wimazal F, Födinger M, Sperr WR, Valent P. 2007. "Diagnostic and subdiagnostic accumulation of mast cells in the bone marrow of patients with anaphylaxis: Monoclonal mast cell activation syndrome.". International Archives of Allergy and Immunology 142:158–164.

Swieter M, Lee TD, Stead RH, Fujimaki H, Befus D. 1987. "Mast cell pleomorphism: properties of intestinal mast cells.". Advances in Experimental Medicine and Biology 216A:613–623.

Thompson JF, Roberts CL, Currie M, Ellwood DA. 2002. Prevalence and persistence of health problems after childbirth: associations with parity and method of birth. Birth 29:83–94. Available from: https://www.ncbi.nlm.nih.gov/pubmed/12051189

United States National Library of Medicine. 2013. Toxnet. Toxicology Data Network. Available from: http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT.

US Food and Drug Administration. 2018. Title 21—Food and Drugs, Chapter I—Food and Drug Administration, Department of Health and Human Services Subchapter D – Drugs for Human Use, Part 341 Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products FO [cited 2018 Feb 26]. Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=341.

Valent P, Akin C, Escribano L, Fodinger M, Hartmann K, Brockow K. 2007. Standards and standardization in mastocytosis: consensus statements on diagnostics, treatment recommendations and response criteria. European Journal of Clinical Investigation 37:435–453.

Valent P, Akin C, Arock M, Brockow K, Butterfield JH, Carter MC, et al. 2012. Definitions, criteria and global classification of mast cell disorders with special reference to mast cell activation syndromes: a consensus proposal. International Archives of Allergy and Immunology 157:215–225.

Valent P, Akin C, Bonadonna P, Hartmann K, Brockow K, Niedoszytko M, et al. 2019. Proposed diagnostic algorithm for patients with suspected mast cell activation syndrome. Journal of Allergy and Clinical Immunology 7:1125–1133.e.

Villar J, Carroli G, Zavaleta N, Donner A, Wojdyla D, Faundes A, et al. 2007. Maternal and neonatal individual risks and benefits associated with caesarean delivery: multicentre prospective study. BMJ 335:1025.

Waldeyer W. 1875. Ueber Bindegewebeszellen. Archiv Für Mikroskopische Anatomie 11:176–194.

Weinstock L, Brook J, Myers T. Goodman B. 2018. Novel treatment (new drug/intervention; established drug/procedure in new situation). CASE REPORT. Successful treatment of postural orthostatic tachycardia and mast cell activation syndromes using naltrexone, immunoglobulin and antibiotic treatment. BMJ Case Reports.

Woidacki K, Zenclussen AC, Siebenhaar F. 2014. Mast cell-mediated and associated disorders in pregnancy: a risky game with an uncertain outcome? Frontiers in Immunology 5:231.