Pemphigus and Pregnancy

Abstract

Pemphigus in pregnancy is a special clinical scenario that has potential consequences on both maternal and fetal outcomes. Being an autoimmune disease with Th2 preponderance, pemphigus is expected to flare in pregnancy, especially in the first two trimesters. Fetal outcomes like stillbirth and neonatal pemphigus have been reported, the latter being a consequence of a transient transplacental transfer of autoantibodies. Management needs to be individualized keeping the risk/benefit ratios of therapies in mind while optimizing maternal and fetal health. It is crucial to have appropriate counseling regarding conception for women with pemphigus in the child-bearing period because the probability of adverse materno-fetal outcomes is higher if the disease is severe.

Keywords: *Neonatal pemphigus, pemphigus, pregnancy, pregnancy outcome*

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Introduction

Pemphigus is a group of autoimmune blistering disorders that are characterized by intraepidermal split and mucocutaneous blistering. Pemphigus in pregnancy poses special clinical challenges and warrants comprehensive management, especially in weighing the risk/benefit ratios of therapy while optimizing both maternal and fetal health. Pregnancy as a special state precludes the feasibility of conducting most research, leaving clinicians to refer to anecdotal case reports and series while making decisions on therapy. This review aims to consolidate available literature that discusses practical problems of pemphigus in pregnancy, with a special focus on its management.

Problem statement

Pemphigus vulgaris (PV) is the most common among the pemphigus group of disorders. Its incidence is variable across the globe and among various ethnicities.[1] Many studies show that there exists a female preponderance of PV with an approximate female-to-male ratio of 1.4:1.[2] The age of onset reported is between the fourth and sixth decades of life, with the exception of certain ethnicities like the Middle East and Asia that report disease onset earlier by about a decade.[2,3] Hence, women of these geographic regions of child-bearing potential, that is, 15–49 years of age as defined by the World Health Organisation (WHO), would naturally constitute a significant proportion of pemphigus cases. However, exact estimates of pemphigus in pregnancy are not determined due to the paucity of registries and incomplete reporting of cases. Pregnancy in pemphigus is generally reported to be rare.[4-7] This however may reflect rare occurrence of pemphigus in the general population or preferential and/or partial reporting of data. The estimated incidence of PV is 0.76–32 cases per million population, with an approximate incidence of 4.4 per million in India.[2,3] Theoretically, the occurrence of pregnancy in pemphigus should be more common than the sparse published data suggests.

Search strategy

The PubMed database was searched using the keywords "pemphigus" and "pregnancy." Publications from 1950 till May 11, 2023 were screened for eligibility. Articles in only the English language were included. Abstracts were individually screened to look for descriptions of issues especially related to pregnancy in pemphigus. Articles pertaining to the clinical presentation (s) of pemphigus in pregnancy, pregnancy outcomes, fetal outcomes and management of the disease in pregnancy and lactation were included. Those discussing pemphigoid gestationis, pregnancy dermatoses or not pertaining to pemphigus specifically in pregnancy were

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excluded. Of a total of 257 articles in the initial search, 83 were included in the review [Figure 1].

Alterations in immune system during pregnancy

Pregnancy has its own special immunological status because it has to maintain a balance between the mother's immune responses and fetal tolerance. To accommodate for the "allogenic fetus," there is a profound modulation of immune responses orchestrated by the hormonal milieu, particularly sex hormones and cortisol.[8] Pregnancy broadly is a Th2 lymphocyte-predominant status, which is quintessential for the development of tolerance to relatively foreign fetal antigens. Progesterone is mainly responsible for the suppression of the Th1 and Th17 immune responses. Along with maternal cytokines, it also switches the immune system toward the Th2 and Treg axes.[9,10] There is a transient Th1 environment during uterine implantation, which becomes Th2 predominant progressively along the course of pregnancy. The former Th1 pro-inflammatory responses enable trophoblast invasion in the peri-implantation period, while Th2 sets in the latter period for immune tolerance to the fetus.

The inference that Th2-dominant autoimmune diseases like pemphigus would flare during pregnancy can be drawn from this theoretical prevalence of Th1/Th2 predominance during phases of pregnancy. In reality, the pemphigus–pregnancy interaction appears nonlinear and complex. There are oscillations in the immune responses throughout pregnancy mediated by estrogen and progesterone, as well as by other hormones like dehydro-epiandrosterone, cortisol and norepinephrine.[11]

Maternal risks: Effects of pregnancy on pemphigus

Effects on disease course

Preponderance of Th2 immune responses essentially implies worsening of pemphigus in pregnancy akin to other autoimmune diseases like systemic lupus erythematosus. Flare of pemphigus is usually seen during the first and second trimesters. During the last trimester, there is an increase in the bound as well as unbound fractions of endogenous corticosteroids produced by chorion, which may possibly abate the autoimmune responses.[12] Immediate postpartum flare of the disease is also noted due to sudden withdrawal of this cortisol activity. Apart from being a factor that exacerbates the disease, pregnancy itself may also be a precipitating factor of pemphigus.[13]

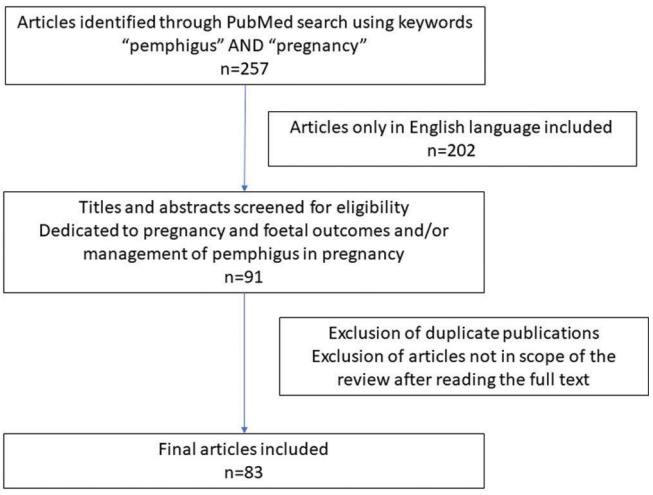

Figure 1: Search strategy used in the narrative review to find articles pertaining to pemphigus in pregnancy

It is difficult to estimate or predict the percentage of pemphigus patients who would flare during pregnancy since there are multiple variables, including the clinical status at conception. Patients of pemphigus who have been in remission before pregnancy may not show any worsening of their disease.[14,15] In two large case series, pemphigus flared in 53.8 and 61.9% of pregnant patients, respectively; an unchanged course of the disease was seen in 28.8 and 28.6% patients, respectively; while approximately 9% cases also reported improvement during pregnancy in both series.[16,17]

There can be varied morphology of pemphigus in pregnant patients owing to hormonal and/or immunological changes. There have been case reports on PV with polycyclic lesions, only mucosal/cutaneous variants, as well as concurrence with pemphigoid gestationis.[18-22] Anecdotal reports of paraneoplastic pemphigus, pemphigus herpetiformis and pemphigus foliaceous triggered during pregnancy are also available.[23-25] Postpartum de novo pemphigus vegetans is reported to occur, and a single case report described an association with myasthenia gravis in which a therapeutic abortion was induced due to complications from worsening myasthenia.[26,27] A single case report on pregnancy complicated with herpes simplex co-infection and pemphigus is reported.[28] Therapeutic abortion for severe pemphigus was contemplated in old literature, which has no role in the present times.[29]

Effects on the mode of delivery

Theoretically, trauma that would occur during vaginal delivery can lead to the extension of the erosions. On the contrary, there is a possibility of delayed wound healing after cesarean section due to corticosteroid use for pemphigus. Hence, the mode of delivery is left at the discretion of the obstetrician with no special necessity of a cesarean section only for pemphigus as an indication.[30]

Fetal risks: Effects of pemphigus on pregnancy and fetal outcomes

Pemphigus can adversely affect fetal outcomes, especially when the disease is severe in the mother and/or associated with high titers of maternal autoantibodies. Clinically severe, refractory disease and maternal indirect immunofluorescence titers equal to or higher than 1:160 have been associated with poor fetal outcomes.[31] Neonatal pemphigus is also

associated with prematurity.[32,33] Neonatal pemphigus has not been shown to have a correlation with maternal disease activity and may occur even when the mother is in remission, suggesting that neonates may be sensitive to maternal autoantibodies irrespective of their titres.[31-39]

Most of the pemphigus patients can have normal, full-term deliveries when they are treated in appropriate liaison between obstetrician and dermatologist. The probability of an event-free pregnancy is higher if pemphigus is well controlled. Normal outcomes may be under reported in literature due to preferential reporting of adverse events or neonatal pemphigus.[34,35]

The rate of stillbirth is variably reported between 1.4 and 27% in the literature.[16,17,34,36,40] In some cases of stillbirth, positive direct immunofluorescence of skin and the presence of autoantibodies in fetal sera have been demonstrated.[32,33] The cause of stillbirth directly due to pemphigus or its therapies is unclear since pregnant patients with active disease also have normal fetal outcomes. Despite of disputable causality of stillbirth, it may be prudent to enhance antenatal surveillance. Intrauterine death has also been reported, highlighting the importance of intrauterine fetal monitoring.[41-43]

Neonatal pemphigus can occur due to transplacental transfer of pathogenic anti-desmoglein IgG4 autoantibodies, resulting in transient mucocutaneous blistering that resolves in two to six weeks of life.[32,33,41-46] Neonatal pemphigus has been reported in the literature with variable disease severity in the mother, hence it is important to counsel about its likelihood irrespective of the maternal disease.[47-62] Although rare, neonatal pemphigus foliaceous and neonatal pemphigus herpetiformis have also been reported.[63-65] Neonatal pemphigus may have a delayed presentation, as late as 13 days postpartum.[66]

There are differences in the expression of desmogleins in neonatal and adult skin and mucosa[37,67] [Figure 2]. Unlike the skin of adults where Dsg3 is suprabasal in expression, neonates express Dsg3 throughout the epidermis which is similar to desmoglein expression of adult mucosa. Hence, Dsg3 is able to compensate for the blistering induced by anti-Dsg1 autoantibodies, making PF a rarity in neonates. On the contrary, this Dsg3 overexpression results in more widespread blistering when anti-Dsg3 autoantibodies are passively transferred to the newborn. Hence, neonatal PV often shows widespread cutaneous blistering compared with adults.[67]

Management with topical therapy suffices and most cases resolve within the first few weeks of life, with no long-term sequelae. Autoantibodies are passively transferred and not synthesized by the neonate. These transferred autoantibodies are catabolized with time.

Other maternal/fetal outcomes include abortion, recurrent pregnancy loss, pre-eclampsia, low birth weight, intrauterine growth retardation and congenital anomalies. These are usually multifactorial in nature and the role of pemphigus or its management in the same is unclear.

Pemphigus at the child-bearing age and counseling regarding conception

Women of child-bearing potential should be adequately counseled regarding the planning of conception. The recommendations are to plan pregnancy carefully after the disease goes into remission. Throughout pregnancy, maternal and fetal monitoring should be done and there should be preparedness for outcomes like a flare of maternal disease or neonatal blistering and preterm birth even if the maternal disease is under control.[37,68] Owing to the risk of such complications, every case of pemphigus in pregnancy, either triggered de novo or a worsened pre-existing disease, is a potential "high-risk pregnancy." Drugs like methotrexate, mycophenolate mofetil (MMF) and cyclophosphamide are to be discontinued before conception by a minimum period of 12 weeks, 6 weeks and 4 weeks, respectively.[69,70] Pregnancy should be deferred for 1 year after rituximab as per standard recommendation.[70,71] Potential risks of disease flare, wound-related complications during delivery and limitations of using certain therapies during pregnancy should be explained to the patient as well as to the family. An uneventful maternal and fetal outcome is more likely if conception is planned considering all of these aspects. When pregnancy is planned a few months after both clinical and serological remission, reduction and/or delay in the pemphigus flare-up has been noted.[72] It is important to note that multiple case reports and case series have shown favorable fetal outcomes and every pemphigus patient may not have maternal/fetal complications.[73-78]

Management of pemphigus in pregnancy

Management of pemphigus during pregnancy has to be planned keeping multiple factors in mind, including maternal disease severity, stage of pregnancy and risk/benefit ratios of various drugs on mother and fetus.[79-82] It is important for the mother as well as the family to be able to understand the connotations of various therapeutic options, for clinical and medicolegal purposes. It is equally important to counsel regarding not ceasing therapy on their own after learning about conception in expectant mothers.

Topical therapies

Topical corticosteroids are safe in pregnancy and can be used for minimal disease.[83] There are concerns regarding systemic absorption related to the application of superpotent corticosteroids over higher absorption sites like eyelids, flexures, or genitalia. Although controversial, low birth weight has been reported, with the use of potent or very potent topical corticosteroids exceeding 300 g during the whole pregnancy.[84] Topical calcineurin inhibitors may also be tried but used less commonly. Both are FDA

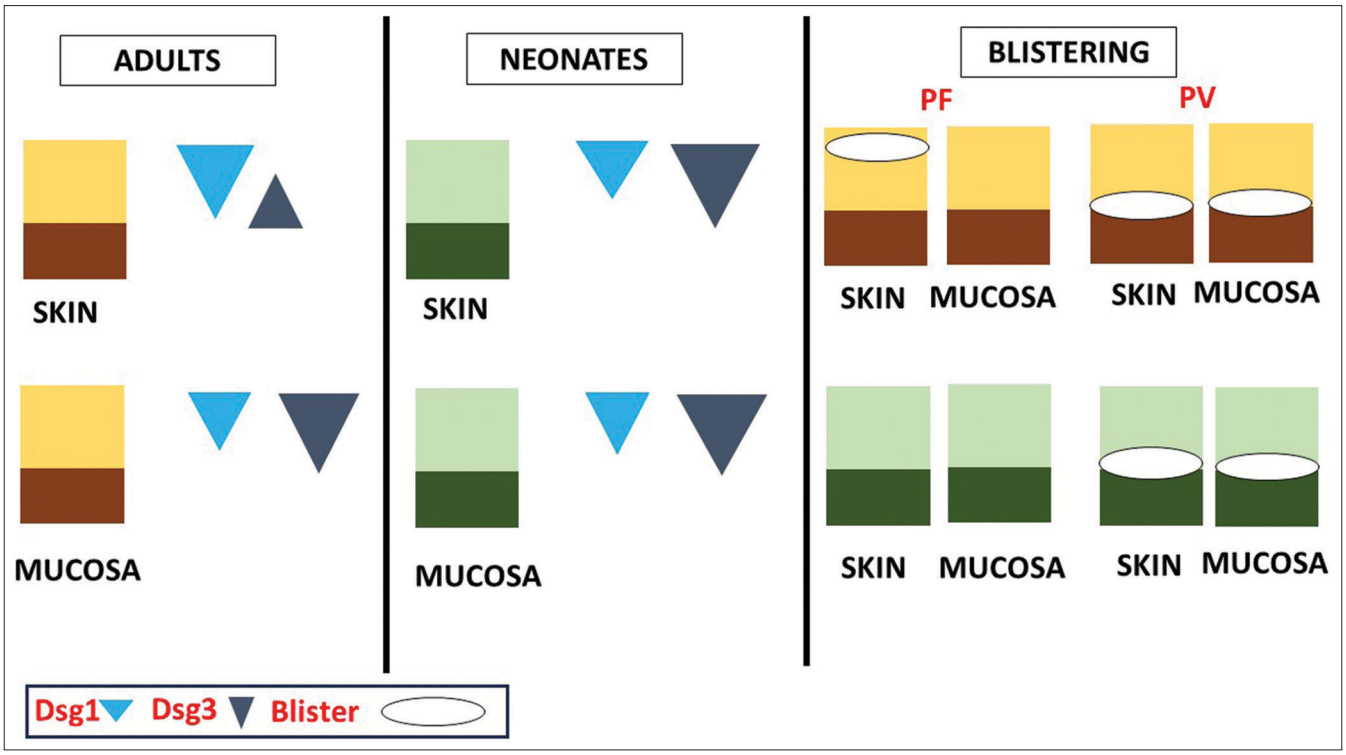

Figure 2: Dsg = Desmoglein, PV = Pemphigus vulgaris, PF = Pemphigus foliaceous. Distribution of desmogleins in neonates versus adults: Expression of Dsg3 is throughout the epidermis in neonatal skin, similar to adult mucosa. Hence, anti-Dsg1 autoantibodies usually do not cause blistering as they are compensated by Dsg3, while anti-Dsg3 autoantibodies can cause widespread blistering

Pregnancy Category C drugs and may be used standalone or in combination with systemic agents.

Systemic therapies

Oral corticosteroid prednisolone remains the first line of systemic treatment.[85,86] It has relatively better safety in pregnancy than other immunosuppressives. High 11 beta-hydroxysteroid dehydrogenase-2 activity of the placenta minimizes the fetal circulation of the drug by one-tenth of the maternal level by converting active prednisolone into inactive prednisone.[87] In contrast, fluorinated corticosteroids are minimally acted upon by this enzyme, resulting in higher transplacental transfer of the drug and subsequent fetal adverse events. Doses lower than 20 mg/day are safer.[88] Prednisolone is associated with stillbirth, low birth weight, and congenital anomalies, particularly cleft lip and cleft palate, although the statistical significance of this association remains unclear.[89] Dosing should be optimized to the lowest possible one as per disease severity. Prednisolone is an FDA Pregnancy Category C drug.

If the ongoing disease activity warrants high doses of corticosteroids, the use of steroid-sparing adjuvants is warranted. Most adverse fetal outcomes in pregnant pemphigus patients are related to disease activity rather than medications.[85-89] Azathioprine is an FDA Category D drug that has been tried as an adjuvant with relative safety in pregnancy.[34] Azathioprine use in pregnancy has been linked with congenital anomalies and preterm birth.[88-90]

High-dose intravenous immunoglobulin (IVIg) therapy is FDA Category C in pregnancy. This can be used as a second-line agent in cases that do not respond to corticosteroids. IVIg has been used with success in pemphigus patients at a dose of 2 g/kg given over 5 days, each cycle repeated monthly throughout pregnancy and initial 2- or 3-month postpartum. In addition to being efficacious and safe, it has also been reported to decrease the incidence of neonatal pemphigus by preventing the transplacental transfer of pathogenic autoantibodies from maternal to fetal circulation.[91,92] There is no risk of immunosuppression to both the mother and the newborn. Cost may be a deterrent to its use as a first-line therapy in India.

Methotrexate, cyclophosphamide and MMF should be avoided in pregnancy due to their teratogenicity. Dapsone, an FDA Category C drug, has been rarely used in pemphigus.[87,88] Despite relative safety, the neonate should be monitored for hemolytic anemia. Therapeutic plasma exchange, that is, plasmapheresis has been tried only in refractory cases in pregnancy and this modality is considered to be safe in pregnancy.[93-97]

Rituximab is an FDA Category C biological drug that targets CD20 and causes B-cell depletion. There is no evidence of it causing congenital malformations. However,

there is a risk of B-cell depletion in the newborn, especially in the last trimester due to the transplacental transfer of the drug.[98,99] The timeline to understand the transplacental transfer of rituximab is given in Figure 3.[98-101] Rituximab has been used during pregnancy in other autoimmune diseases like refractory flares of systemic lupus erythematosus and ANCA-vasculitis, with variable fetal outcomes.[101,102] Preterm birth and spontaneous abortions are also reported after its use.[98,99] In a recent study on outcomes of pregnancy after exposure to rituximab before conception, 89% were live births and 17% were preterm deliveries. Amongst the latter, one case each of neonatal pemphigus, neonatal sepsis and hydronephrosis were noted.[70] Spontaneous abortion and termination due to Down's syndrome occurred in one pregnancy each out of 19 total pregnancies studied. Conception within 6 months of rituximab infusion was associated more with low birth weight, potentially confounded by higher dosing of corticosteroids and/or disease severity.[70] Another similar study showed favorable outcomes when rituximab was administered around pregnancy.[103] Literature is scarce to make a recommendation regarding the safety of the use of rituximab for pemphigus in pregnancy. Neonatal B-cell depletion and low birth weight remain potential consequences.

In patients of pemphigus with secondary infection, antibiotics may be required based on culture and sensitivity reports. Antibiotics considered relatively safe during pregnancy include penicillins, cephalosporins, and clindamycin. Most of the antibiotics are considered to be compatible with lactation and do not warrant interruption of breastfeeding.[104]

Pemphigus and postpartum period

Beyond pregnancy, there are several implications in the postpartum period as well. Topical therapies remain safe unless directly applied to the nipple-areola complex. Systemic corticosteroids are safe with negligible breast milk excretion; however, intake should be 4 hours before breastfeeding to minimize harm to the neonate.[105] IVIg is also a safe therapy, while MMF, methotrexate and cyclophosphamide are avoided likely in pregnancy. Azathioprine is usually compatible with breastfeeding, with cautious use in cases of maternal thiopurine methyltransferase (TPMT) polymorphisms.[106] TPMT polymorphisms in the mother can lead to higher levels of metabolites in breast milk, and in the infant may lead to the accumulation of metabolites. Newborn screening with TPMT is not recommended presently, because azathioprine is rapidly converted to 6-MP which may go to breastmilk in <1% amount, that too with poor oral bioavailability.[107] Rituximab levels in breastmilk are also negligible; however, data on lactation is scanty and usually it is avoided although the decision may be individualized.[108] A negligible portion of rituximab enters the fetal gastrointestinal tract, most

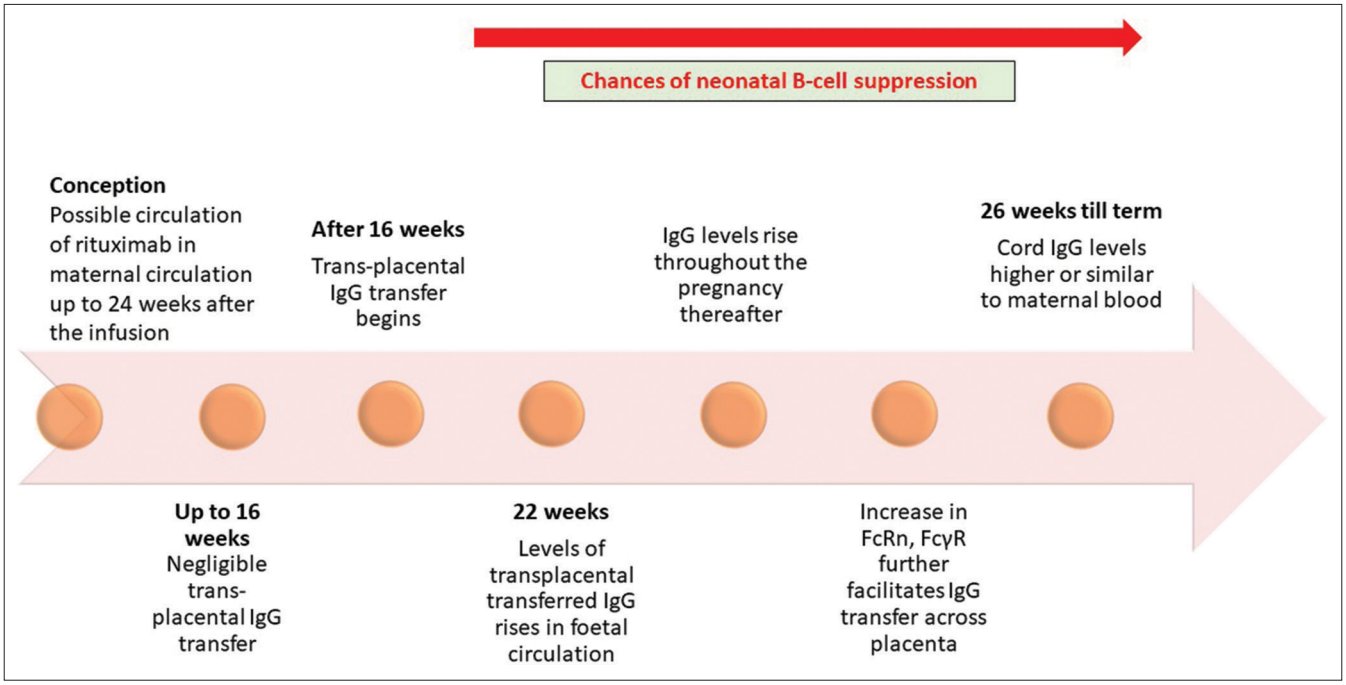

Figure 3: Timeline depicting the transplacental transfer of IgG antibodies, including rituximab from mother to fetus. The elimination pharmacokinetics are dynamic and a negligible amount of rituximab may be present as long as 6–9 months after the infusion; however, its clinical effects are unclear. The longest elimination half-life of rituximab is usually reported to be around 24 weeks.[98,99] Transplacental IgG transfer begins at 16 weeks of gestation, with fetal IgG levels <8% compared with average adult levels before 16 weeks.[100] Hence, strictly theoretically speaking, a plausible safe period for conception can be estimated to be as early as 2–3 months after the rituximab infusion, which would allow the time for maximal clearance of rituximab from maternal circulation and initial weeks of pregnancy with negligible transplacental transfer, although guidelines do recommend a safe period of 1 year for conception post the infusion.[101] (FcRn, Fcγ = neonatal Fc receptors and placental Fcγ receptors)

of which is likely to get degraded; while <25% reaches the stool the remainder is digested. Theoretically, the neonatal Fc receptors may enable the passage of undigested IgG molecules from the gastrointestinal tract to blood circulation and hence minuscule fetal exposure cannot be completely excluded.[109] In the immediate postpartum period, the disease may flare up necessitating therapy as per severity. Counseling regarding future pregnancies is also crucial.

There are some theoretical concerns about low lymphocyte subpopulations and responses to vaccination in infants with intrauterine exposure to immunosuppressives used by mothers. However, studies have demonstrated robust protective antibody responses even in infants born to mothers on immunosuppressives postrenal transplant.[110] Present recommendations do not preclude the administration of inactivated and live attenuated vaccines according to the local immunization schedule in infants breastfed by mothers on immunosuppressive therapies or exposed to immunosuppressives in-utero in the third trimester.[111] With regards to biologics, it is recommended that children exposed to biologics after the 22nd week of gestation should avoid live-attenuated vaccines (measles, mumps, oral poliomyelitis, oral typhoid fever, varicella zoster, yellow fever vaccines) in the first 6 months of life.[112] The rationale being that IgG crosses the placenta and is detectable as long as 6 months after birth in an infant's circulation, resulting in fetal immunosuppression and an increased risk of fatal, disseminated infections post live vaccination.[108] The ideal decision to vaccinate or not would be based on the detection of blood levels of the drug in a child's circulation. In the absence of such testing, it is prudent to avoid live vaccines in the first 6 months in children with intrauterine exposure to biologic drugs in the later half of pregnancy.

Conclusion

Pemphigus in pregnancy has repercussions on both the mother and the child, in terms of the course of disease, management options, and fetal outcomes. Since conducting clinical trials in this population is difficult, management decisions often rely on the clinical experience and limited and pertinent published literature. Larger registries reporting pregnancy outcomes are required to generate evidence and recommendations on management.

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Conflicts of interest

There are no conflicts of interest.

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