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A critical review of COVID-19 course and vaccination in dermatology patients on immunomodulatory/biologic therapy: recommendations should not differ between non-pregnant and pregnant individuals

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COVID-19 can have detrimental effects on immunosuppressed patients. Here, we evaluate the evidence regarding continuing immunomodulatory/biologic (IMBI) therapy in pregnant dermatology patients during the COVID-19 pandemic. Also, we discuss the risks of COVID-19 vaccination in pregnant dermatology patients on IMBI therapy. As indicated in this review, regarding continuing IMBI therapy in pregnant dermatology patients during the pandemic, there is no compelling reason for treating them differently than non-pregnant. The body of evidence indicates that mRNA COVID-19 vaccines are safe during pregnancy. Studies on rheumatology patients, a group that overlaps significantly with the dermatology group, provided essential findings. IMBI in a non-pregnant rheumatology patient was not associated with COVID-19 mortality (except for rituximab), and vaccination of the rheumatology patient during pregnancy improved the obstetric outcomes compared to the unvaccinated patient. Based on this data, it can be stated that after weighing the benefit–risk profile of the available COVID-19 vaccines, the recommendation for the pregnant dermatology patient speaks in favor of the COVID-19 vaccination. COVID-19 vaccine recommendations in pregnant dermatology patients on IMBI should not differ from those for their non-pregnant counterparts.

KEYWORDS

COVID-19, immunomodulator, biologic, COVID-19 vaccine, risks, dermatology, pregnancy, immunosuppressive therapy

1. Introduction

Since the beginning of the COVID-19 pandemic there have been increasing concerns about the effects of the infection on vulnerable groups, such as patients on immunomodulatory/biologic (IMBI) therapy (immunomodulatory drugs are categorized into immunostimulators or immunosuppressives, and biologics are drugs with a targeted action on the immune system) and pregnant persons. Similar concerns were raised about the safety and efficacy of COVID-19 vaccination in these groups. Such individuals have been traditionally excluded from clinical trials, which made formulating recommendations challenging.

The modulations of the maternal immune system in pregnancy may affect the response to viral infections such as COVID-19 (1). The altered inflammatory response to viruses during pregnancy is thought to be mediated, at least in part, by the following: a shift toward the T helper 2 (Th2) phenotype over Th1 (2); a decrease in circulating natural killer cells (3); a decrease in circulating plasmacytoid dendritic cells (4) that are key for type 1 interferon production against viruses; and an increase in circulating progesterone levels (5). Progesterone can enhance lung repair of damage induced by the influenza virus (6). However, in mouse models, progesterone challenge resulted in a decrease in virus-specific antibody levels and virus-specific CD8+ T cells (7) and alterations in the innate immune system, including the pattern recognition receptors Toll-like receptors (TLRs) during pregnancy (8). COVID-19 infection causes pyroptosis of host cells and release of endogenous molecules created upon tissue injury called damage-associated molecular patterns (DAMPs), which can be TLR ligands and further enhance inflammation. These modulations in the maternal immune system have consequences for the clinical trajectory of COVID-19 and for the treatment and prevention of COVID-19 in pregnancy. However, it remains to be determined whether these adaptations result in a higher susceptibility and/or morbidity, or are in fact, protective against COVID-19 (2).

Here we discuss the effects of COVID-19 on maternal and fetal/neonatal outcomes and evaluate the evidence regarding the continuation of IMBI therapy for dermatologic conditions in pregnant persons diagnosed with COVID-19. We also discuss the evidence relevant to the risks of COVID-19 vaccination in pregnant patients on IMBI therapy for dermatologic conditions. Furthermore, we compare such evidence to that of non-pregnant patients on IMBI therapy.

The scarcity of data and heterogeneity of articles precluded a systematic review. Our literature search focused on articles with information on COVID-19 in pregnant women on IMBI. We searched PubMed and Google Scholar databases since inception using terms including "COVID-19 OR SARS-CoV-2," "COVID-19 vaccine OR COVID-19 vaccination," "risks," "complications OR adverse events," "immunosuppressive," "immunomodulator," "biologic," "dermatology OR dermatologic," "skin disease" "pregnancy OR gestation." Expert opinions and medical society guidance were considered. The reference lists of selected articles were reviewed. The discussion here is limited to IMBI therapies that may be used in pregnancy, including systemic corticosteroids, cyclosporin, tumor necrosis factor alpha inhibitors (TNFαI) (e.g., adalimumab, certolizumab pegol, etanercept), interleukin (IL)-17 (e.g., secukinumab), IL-4/13 inhibitors (dupilumab), and anti-IL-12/23 (ustekinumab) (9). Supplementary Tables S1 and S2 detail the pregnancy labeling of these drugs. IMBI that may not be prescribed in pregnancy, such as methotrexate, azathioprine, mycophenolate mofetil, and rituximab is not included.

2. COVID-19 effects on maternal course, pregnancy, and neonatal outcomes

2.1. Maternal course

The SARS-CoV-2 infection affects 3–20% of pregnant women presenting for labor and delivery (10, 11). In a systematic review, 6–8% of pregnant people universally screened for COVID-19 tested positive, 54–77% of these individuals were asymptomatic, and pregnant people were more likely to be asymptomatic than nonpregnant people of reproductive age with COVID-19 (12). Pregnant patients with asymptomatic infection are at higher risk only for maternal morbidity and preeclampsia (13). Symptoms resemble those in non-pregnant individuals (14, 15). The presence of symptoms increases the risk of severe infection and maternal complications (12, 13). Pregnant women do not appear more likely to contract the infection than the general population. However, pregnancy appears to worsen the clinical course of COVID-19 as indicated by increased risks for intensive care unit admission, need for mechanical ventilation and ventilatory support, and death (12, 14, 16, 17).

Data from 463 US hospitals demonstrated that maternal mortality during childbirth hospitalization increased compared to pre-pandemic (18). Population-based cohort studies have reported increased risks for severe maternal morbidity or mortality in patients with COVID-19 (19, 20). A meta-analysis of observational studies of SARS-CoV-2 infection during pregnancy noted that patients with COVID-19 had a 62% increased risk of developing preeclampsia (21). However, some laboratory findings of SARS-CoV-2 infection can be similar to those seen in severe preeclampsia and HELLP syndrome. Obesity, age greater than 35, hypertension, diabetes, multiple comorbidities, and being unvaccinated are risk factors for serious infection and death in pregnancy (22, 23). The SARS-CoV-2 Delta variant was associated with higher rates of severe maternal morbidity events compared with other strains (24).

2.2. Pregnancy and neonatal outcomes

Maternal infection following 20 weeks of gestation raises the risk of negative obstetric outcomes, and infection following 26 weeks raises the risk of unfavorable neonatal outcomes (25). Thus, early vaccination to decrease the risk of contracting SARS-CoV-2 infection is advised. Pregnant women should be given two doses of a mRNA vaccine for more robust maternal and fetal antibody responses (26). The body of evidence suggests that the risks of miscarriage and congenital anomalies are not increased above baseline (27–30). Preterm and cesarean birth rates have been increased in many studies (12, 19, 31, 32). In cohort studies, the increased risk appears to be limited to patients with severe or critical disease in late pregnancy (31, 33, 34), and underlying comorbidities may also play a role. Infection with the Delta variant during pregnancy may be associated with a higher risk

of placental dysfunction and fetal compromise than previous variants (35).

Still, more than 95% of newborns of affected mothers are uninfected and in good health (36, 37). Affected newborns tend to present a benign disease course despite the increased need for mechanical ventilation (38). The risk of developing severe COVID-19 appears to be higher in preterm infants and neonates with comorbidities (38). Neonatal morbidity (e.g., need for mechanical ventilation) has been predominantly related to prematurity and adverse uterine environments resulting from critical maternal COVID-19 (12). A systematic review reported that the incidence of neonatal deaths was equivalent between SARS-CoV-2-positive females compared with seronegative counterparts admitted to labor and delivery (39). A US study of over 8,000 stillbirths suggested that pregnant females with COVID-19 have a higher risk of stillbirth than pregnant females without COVID-19 (40). However, data on stillbirths are affected by several confounders and remain inconclusive (36). Some newborns of affected mothers developed a transient rash (41). One reported infant had a diffuse, maculopapular rash that disappeared in one day, while another infant had a diffuse, miliaria-like eruption that resolved in 10 days without therapy (42).

The average rate of SARS-CoV-2 congenital infection (i.e., intrauterine transmission) is less than 2% of maternal infections (43). Shah and colleagues' criteria suggest that congenital infection be identified by a polymerase chain reaction in umbilical cord blood, neonatal blood, or amniotic fluid obtained during the first 12 h of birth (44). A systematic review that used Shah and *colleagues*' criteria on 47 studies revealed that vertical transmission was confirmed in 0.3%, probable in 0.5%, and possible in 1.8% (45). Individuals with COVID-19 mostly have transient, low-viremia rates (46), which explains why *in-utero* transmission is uncommon (47). However, *in-utero* transmission has been documented (48). The angiotensin-converting enzyme 2 receptors and serine protease TMPRSS2 required for SARS-CoV-2 cell entry are weakly co-expressed in the placenta (49, 50). These findings could explain the rarity of placental SARS-CoV-2 infection and fetal transmission.

3. COVID-19 in the dermatology patient on IMBI therapy

There have been two essential questions in the medical community: a) whether IMBI therapy increases the risk of COVID-19 or subsequent mortality and b) whether IMBI should be postponed or discontinued in patients diagnosed with COVID-19. Regarding the first question, a retrospective matched cohort study from Massachusetts showed that, overall, biologics were not associated with COVID-19 (OR, 0.88; 95% confidence interval [CI], 0.71–1.09; $p¼0.25$), adjusting for demographics, comorbidity burden, and local infection rates (51). Patients treated with TNFαI were less likely to be diagnosed with SARS-CoV-2 infection than matched controls (OR, 0.69; 95% CI, 0.48–0.98; $p¼0.04$). Mortality rates were similar in the group of patients on biologics and matched controls. In another study, IMBI therapy was not associated with increased COVID-19 severity in patients with hidradenitis suppurativa (52). A retrospective chart review from the Houston greater area adds to the evidence that patients on biologics are not at increased risk of contracting COVID-19 or have worse outcomes, except for those on rituximab (shown to increase hospitalization rate) (53). Interestingly, the study's results suggested that patients on biologics have a lower rate of COVID-19 positivity than the general population, suggesting a possible protective effect.

Most guidelines of professional bodies concur that discontinuation of treatment for the concern of contracting COVID-19 is not supported because it may lead to decreased efficacy outcomes with reintroduction or a flare of conditions such as psoriasis (54, 55). The guidance of the American Academy of Dermatology (AAD) and other medical societies do not recommend routine discontinuation of IMBI therapy in patients who have not tested positive for COVID-19 or exhibited signs/symptoms of the disease (55, 56). However, one should consider risk vs. benefit in each patient, considering the severity of the dermatologic condition and risk factors for severe manifestations of COVID-19 disease (including age > 60, cardiovascular disease, hypertension, and diabetes) (56, 57). Also, patients with dermatologic disorders, including psoriasis, hidradenitis suppurativa, and atopic dermatitis that are associated with metabolic syndrome, older age, or comorbidities such as respiratory disorder have poorer prognosis if they become infected with COVID-19 (58). A higher risk of all-cause pneumonia has been reported in patients with severe skin disorders such as psoriasis.

AAD and *National Institute for Health and Clinical Excellence (NICE) Guideline 169* for dermatologic conditions recommend the discontinuation of biologics in COVID-19-positive patients (55, 56, 59). However, when deciding whether to stop treatment, the healthcare provider should consider the severity of COVID-19, the risks and benefits of stopping treatment, the severity of the dermatologic condition, and the effect of withholding treatment on concomitant non-dermatologic conditions (59). Patient may re-initiate IMBI therapy after complete recovery from COVID-19. Some authors recommend continuing biologic, especially TNFαI medications that are known to suppress cytokine storms if viral symptoms are mild (60). A recent systematic review of professional bodies' immunosuppressant guidelines during the COVID-19 pandemic stated that steroid usage should not be stopped abruptly (55). Also, it advised an individualized risk–benefit analysis considering the risk of the effect of COVID-19 infection, including the psychological burden, and the likelihood of relapse of the condition treated with IMBI.

The British Association of Dermatologists (BAD) recommends shielding for patients at the highest clinical risk: patients taking ⩾20 mg prednisolone (or equivalent) per day for >4 weeks or ⩾5 mg prednisolone (or equivalent) per day combined with another immunosuppressant, patients taking a combination of two or more immunosuppressants, patients taking cyclophosphamide, and patients on rituximab or infliximab for primarily skin conditions (61).

4. COVID-19 vaccination in the dermatology patient on IMBI therapy

Most professional associations concur that COVID vaccines are safe in the dermatology patient on IMBI (62–66). As none of the COVID-19 vaccines developed are live attenuated vaccines, they do not pose the risk of vaccine-induced infection, a significant concern in immunosuppressed patients. No data support that patients on IMBI exhibit a higher frequency of adverse effects from COVID-19 vaccines

compared to persons not on IMBI (67). In patients with a history of anaphylaxis to vaccinations, systemic mastocytosis or idiopathic anaphylaxis, an allergy diagnostic work-up should be performed prior to vaccination (68, 69). Dermatologic complications of COVID-19 vaccines are typically mild and self-limited (70, 71).

A study suggested that there might be an association between COVID-19 vaccination and exacerbation of autoimmune bullous diseases (AIBDs) (72). Three-fourths of patients were on systemic therapy, mostly prednisolone (73.1%), at the time of vaccination. Patients vaccinated in the active phase of the disease were more likely to experience post-vaccine disease exacerbation, with a number needed to harm of 3. Still, the authors indicated that the benefits of vaccination outweigh the potential risk of complications. Vaccination is recommended for such patients, but preferably in the remission/controlled phase of the disease.

Although there are no direct supporting data, based on studies with other vaccines, there has been a concern that some immunomodulators, particularly if more than one is being used, may diminish COVID-19 vaccine efficacy (64). However, newer generation biologic agents used in chronic plaque psoriasis and atopic dermatitis showed little to no interference with seasonal influenza, pneumococcal, or tetanus vaccine (73–75). Variable humoral responses to hepatitis B (HBV) vaccine were reported in patients on IMBI (76, 77). Good antibody levels were observed after vaccination for patients on IL-17 (e.g., secukinumab) and IL-4/13 inhibitors (dupilumab) (62). TNFαI (adalimumab, certolizumab, etanercept) and anti-IL-12/23 (ustekinumab) biologics have been associated with a decrease in antibody levels. Prednisone at a dose of >20 mg per day diminished humoral responses to influenza vaccines in patients with systemic lupus erythematosus (78). While cyclosporin treatment results in severely disturbed humoral responses to vaccines in kidney transplant recipients, this may not be generalized to patients with dermatology immune disease (62).

An essential study investigated the effect of immunosuppression on the immunogenicity of mRNA COVID-19 vaccines in patients with chronic inflammatory disease (79). The authors noted that S-specific antibody titers observed in patients on TNFαI were similar to those in patients with rapid recovery from COVID-19 and may provide sufficient humoral protection. However, anti-S IgG antibody titers after vaccination were lower in participants receiving glucocorticoids than in those not. A US study indicated that mRNA vaccine efficacy against COVID-19-associated hospitalization was lower in patients with a rheumatologic or inflammatory disorder (81%) than in immunocompetent persons (90%) (80). The authors concluded that immunocompromised persons benefit from mRNA COVID-19 vaccination but are less protected from severe COVID-19 outcomes than immunocompetent persons.

A study by Simon and *colleagues* indicated that immune responses against the SARS-CoV-2 are delayed and reduced in patients with immune-mediated inflammatory diseases (81). This effect was attributed to the disease itself rather than concomitant treatment. A study of 50 patients with stable plaque psoriasis treated with biologics for at least 2 months examined mRNA vaccine safety (participants received 2 doses) and subsequent psoriasis flares (82). All patients discontinued their biological therapy 10 days before and 10 days after each vaccine dose. Of these, 24 patients were treated with TNFαI, 14 with anti-IL17, 7 with anti-IL12-23, and 5 with anti-IL23. All patients were evaluated on days 2, 7, and 14 post-vaccination for local and/or systemic side effects and/or reactions to the vaccine. None of the patients experienced adverse effects or a psoriatic flare. Only one patient treated with infliximab biosimilar referred an exacerbation of psoriasis after vaccination. These findings supported that SARS-CoV-2 mRNA vaccines are safe for patients with chronic plaque psoriasis treated with biologics and do not trigger psoriasis. However, these data should be validated in a larger sample.

A multidisciplinary committee provided guidance on the safety and efficacy of SARS-CoV-2 vaccination for dermatologists and other clinicians when prescribing IMBI therapies (62). It concluded that the SARS-CoV-2 vaccines approved are expected to be safe for dermatology patients on IMBI. There is variability in vaccine efficacy, depending on the degree of immunosuppression which in turn depends on the type of IMBI therapy, dose, duration, general condition of the patient, and the type of vaccine administered. Data generally support a possible decrease in antibody titers with TNFαI, rituximab, ustekinumab, and many oral immunotherapies, including corticosteroids. The risk–benefit ratio may favor immunization if immunosuppression is low and there is a significant risk of COVID-19 development. One may consider checking antibody titers after vaccination and using additional vaccinations, if needed, to boost protective antibodies. If protective antibody titers are inadequate and skewed to a T helper type 2 phenotype, vaccine-associated enhanced respiratory disease (VAERD) can develop (83).

Regarding the timing of COVID-19 vaccination, AAD and BAD do not recommend expediting vaccination before planning IMBI therapy for skin disease (62, 63). However, guidance from other authorities, such as the EADV and Australasian Medical Dermatology Group, recommends that vaccination be expedited and administered prior to initiation of IMBI (64, 65).

5. COVID-19 in the pregnant patient on IMBI therapy

There exists limited data surrounding the trajectory of COVID-19 in pregnant women on IMBI. A theoretical concern is that IMBI therapies causing moderate to severe immunosuppression may increase maternal/fetal risks from COVID-19 because of delayed clearing of the viral mRNA. However, there is hardly any supporting evidence in the literature. In one case study, a pregnant patient with severe ulcerative colitis and COVID-19 infection experienced a spontaneous abortion following treatment of COVID-19 with azithromycin and hydroxychloroquine and treatment of ulcerative colitis with intravenous cyclosporine (84). However, the cause of the spontaneous abortion was unclear. Several authors suggest that there is no need to abruptly discontinue IMBI therapy in pregnancy in patients with quiescent inflammatory bowel disease (IBD) (85).

Biologics such as TNFαI decrease cytokine storms and, therefore, may be associated with minimal risk in the pregnant patient and can be handled as in the non-pregnant person. There have been no safety signals in the literature regarding TNFαI use in pregnancy in the context of COVID-19. A retrospective study included 244 pregnant women with IBD, of which 75 (30.7%) were on biologics; in 22 of those (29.3%), the treatment was stopped at a median of 28 weeks' gestation (85). Twenty-two (9%) of patients

were on systemic corticosteroids. Despite high levels of immunosuppression, only a single COVID-19 infection occurred. Adverse pregnancy outcomes were infrequent and not associated with IMBI.

Antenatal systemic corticosteroids are administered to women at threat of preterm birth and fetal lung maturity and confer significant morbidity and mortality benefit for neonates (86). The RECOVERY trial recommends administering prednisolone 40 mg orally or intravenous hydrocortisone 80 mg twice daily in COVID-19 patients who require oxygen supplementation or ventilatory support (87). However, this trial included only six pregnant patients. Other authors recommended methylprednisolone because of its limited placental transfer and documented efficacy in cases of acute lung injury (88). Most authors concur that corticosteroid administration should continue in the context of iatrogenic preterm delivery in pregnant COVID-19 patients due to maternal condition (2). While these findings cannot be extrapolated to the use of corticosteroids for non-obstetric reasons, such as a severe flare of a dermatologic condition, they indicate that short courses of systemic steroids should not be excluded in the management of dermatologic conditions in pregnancy, and a risk–benefit analysis should be conducted, as in the non-pregnant patient. Controlling the dermatologic condition is often crucial to the successful completion of pregnancy and minimizing fetal risks associated with the condition. When using a systemic steroid, the provider should assess the therapeutic effect as soon as possible and try to taper the dose of systemic steroid rapidly.

6. COVID-19 vaccination in the pregnant woman on IMBI therapy

Most authorities recommend that all unvaccinated people planning a pregnancy or those who are pregnant or recently pregnant undergo COVID-19 vaccination, and those who are vaccinated should receive booster doses when eligible (36, 89, 90). The recommendation for vaccination during pregnancy is based on data showing vaccine safety and efficacy in pregnant people and data that pregnancy is associated with an increased risk of severe infection (36). Studies on vaccination among pregnant women (most participants vaccinated in the third trimester) show no evidence of harmful fetal/perinatal effects such as neonatal death, stillbirth, congenital anomalies, decreased fetal growth, preterm birth, or miscarriage (91–93). Several studies reported worse pregnancy outcomes in unvaccinated COVID-19-positive patients (94). In a US study, mRNA COVID-19 vaccination series during pregnancy was associated with reduced risk for COVID-19 hospitalization among infants (95). Vaccine efficacy against admission to an ICU for COVID-19 was 70 percent, 90 percent of the infants admitted to an ICU for COVID-19 were born to unvaccinated mothers, and the only two infants who died were born to unvaccinated mothers.

Experts suggest that women during pregnancy or postpartum should opt for mRNA vaccines, if accessible, as viral vector vaccines may cause thrombosis associated with thrombocytopenia (91). If mRNA vaccines are unavailable, any viral vector vaccine is deemed better than no vaccine (36). Regarding the timing of a pregnancy after undergoing the first or both COVID-19 vaccine doses, experts maintain that there is no impact on pregnancy and that vaccination against SARS-CoV-2 infection should occur or continue based on standard protocols (36, 96).

There are inadequate data on vaccine safety and efficacy in pregnant patients on IMBI. In a descriptive study, unvaccinated pregnant women with rheumatic and musculoskeletal diseases (RMD) and COVID-19 had a greater number of pre-term births compared with those fully vaccinated against COVID-19 (97). Additionally, the need for COVID-19 pharmacological treatment was uncommon in pregnant women with RMD regardless of vaccination status. These results support active promotion of COVID-19 vaccination in women with RMD who are pregnant or planning a pregnancy. Of note, a study of 113 patients with rheumatic disease (68% of the patients were on IBMI and 2% pregnant) did not show any association between the medications and COVID-19 mortality (except for rituximab); mortality in this cohort was associated with comorbidities, especially diabetes, obesity, and interstitial lung diseases (98).

In a report of two pregnant COVID-19-positive systemic lupus erythematosus patients, both women delivered healthy babies (99). One patient presenting at 38 weeks of gestation did not discontinue or decrease the use of azathioprine, hydroxychloroquine, and prednisone but was induced on the same day as her positive COVID-19 test. The other patient, who was taking hydroxychloroquine, azathioprine, and etanercept, tested positive for COVID-19 at 19 weeks of gestation and discontinued azathioprine and etanercept, but resumed both soon after. Etanercept was stopped at 30 weeks of gestation. She later received triamcinolone acetonide injections for oligoarthritis. She underwent cesarean section complicated by a placenta accrete resulting in a massive hemorrhage; however, the patient and newborn were both discharged in good health 3 days after delivery.

No data support that the COVID-19 vaccine response in a pregnant patient on IMBI differs from that in a non-pregnant counterpart. There is evidence that vaccination of a non-pregnant patient on IMBI provokes substantial humoral responses, even if the antibody titers generated are lower in patients on certain medications such as systemic corticosteroids. Most importantly, looking at the rheumatic disease group of patients, which overlaps significantly with the dermatologic disease group, IMBI in a non-pregnant patient was not associated with COVID-19 mortality (except for rituximab), and vaccination of the rheumatic patient during pregnancy improved the obstetric outcomes compared to the unvaccinated patient. Based on this data, it can be stated that after weighing the benefit–risk profile of the available COVID-19 vaccines, the recommendation for the pregnant dermatology patient speaks in favor of the COVID-19 vaccination.

7. Counseling the pregnant patient on IMBI therapy

Several issues should be included in a consultation about the risks and benefits of discontinuing IMBI therapy:

- Scarcity of data on pregnancy during COVID-19 clinical trials
- Studies showing that IMBI may not affect the course of COVID-19 in immunocompetent patients with dermatologic conditions (51–53)

- Data showing that adverse pregnancy outcomes were infrequent and not associated with IMBI in IBD patients (85)
- Risk of COVID-19 complications due to pregnancy (increased risk to a pregnant person of severe disease and death) or underlying conditions (e.g., diabetes, obesity, heart disease)
- Risk of COVID-19 to the fetus or newborn (preterm birth rate appears to be increased)

The above issues should also be discussed in a consultation about COVID-19 vaccination during pregnancy (100). Additionally, the healthcare provider should discuss the following:

- Risk of vaccine reactogenicity, including fever (treatment with antipyretic medications such as acetaminophen decreases this risk) and dermatologic adverse effects (self-limited) (70)
- Time of planned vaccination during pregnancy (fever in the first trimester caused by the vaccine may increase the risk of congenital defects)
- Extensive evidence for safety of other vaccines during pregnancy
- Studies favoring vaccination in pregnancy in a similar group, the rheumatology patients (97, 98)
- A potential protective effect for the neonate from the placental transfer of antibodies to the fetus (101)
- Risk of exposure to SARS-CoV-2 and potential for mitigation with working from home, wearing masks, and physical distancing.

The above maternal and fetal risks need to be weighed against the risks of COVID-19 itself.

The pregnant individual should be advised that there are no biologic reasons to believe that the vaccines currently approved are harmful to the pregnant person or fetus (102, 103). A case of normal delivery in a pregnant female vaccinated for COVID-19 during third trimester showed the presence of antibodies in the baby indicating a possible protective effect for the neonate (101, 104). The available evidence, theoretical considerations, FDA evaluation, Centers of Disease Control (CDC), and professional medical society guidance point in the same direction: the real benefits of COVID-19 immunization in the immunocompetent pregnant individual outweigh the scant theoretical safety concerns in pregnancy. The risk of having a lowered response to COVID-19 vaccine because of concomitant IMBI therapy taking exists, but a lowered response is better than lack of protection (vaccine not administered). This should be discussed in the consultation. A shared decision-making among the mother, her family, and health care provider is warranted pending further data from clinical trials and vaccinated pregnant persons outside clinical trials (100, 103).

8. Conclusion

There is insufficient evidence regarding the continuation of IMBI therapy for dermatologic conditions in pregnant persons diagnosed with COVID-19. However, available data indicate that there is no compelling reason for treating pregnant patients differently than non-pregnant. The risks of COVID-19 vaccination in pregnant patients on IMBI therapy for dermatologic conditions can be extrapolated from experimental studies and studies in overlapping populations such as rheumatology patients. Current guidelines on COVID-19 vaccination for immunosuppressed dermatologic patients and pregnant patients separately recommend vaccination in both groups. The body of evidence indicates that mRNA COVID-19 vaccines are safe during pregnancy. Along the same lines, many biologics can be safely administered during COVID-19–some TNFαI can even benefit the course of the disease. Based on the evidence presented here, COVID-19 vaccine recommendations in pregnant patients on IBMI for dermatologic conditions should not differ from those for their non-pregnant counterparts. Collecting data for post-vaccine surveillance will help address some of the unanswered questions.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1121025/full#supplementary-material

References

1. Silasi M, Cardenas I, Kwon JY, Racicot K, Aldo P, Mor G. Viral infections during pregnancy. *Am J Reprod Immunol*. (2015) 73:199–213. doi: 10.1111/aji.12355

2. Wastnedge EAN, Reynolds RM, van Boeckel SR, Stock SJ, Denison FC, Maybin JA, et al. Pregnancy and COVID-19. *Physiol Rev*. (2021) 101:303–18. doi: 10.1152/physrev.00024.2020

3. Veenstra van Nieuwenhoven AL, Heineman MJ, Faas MM. The immunology of successful pregnancy. *Hum Reprod Update*. (2003) 9:347–57. doi: 10.1093/humupd/dmg026

4. Yang M, Yang L, Wang X, Wang Y, Wei Y, Zhao Y. Decline of plasmacytoid dendritic cells and their subsets in normal pregnancy are related with hormones. *J Reprod Med*. (2015) 60:423–9.

5. Siiteri PK, Febres F, Clemens LE, Chang RJ, Gondos B, Stites D. Progesterone and maintenance of pregnancy: is progesterone nature's immunosuppressant? *Ann N Y Acad Sci*. (1977) 286:384–97. doi: 10.1111/j.1749-6632.1977.tb29431.x

6. Hall OJ, Klein SL. Progesterone-based compounds affect immune responses and susceptibility to infections at diverse mucosal sites. *Mucosal Immunol*. (2017) 10:1097–107. doi: 10.1038/mi.2017.35

7. Hall OJ, Nachbagauer R, Vermillion MS, Fink AL, Phuong V, Krammer F, et al. Progesterone-based contraceptives reduce adaptive immune responses and protection against sequential influenza a virus infections. *J Virol*. (2017) 91:e02160–16. doi: 10.1128/JVI.02160-16

8. Young BC, Stanic AK, Panda B, Rueda BR, Panda A. Longitudinal expression of toll-like receptors on dendritic cells in uncomplicated pregnancy and postpartum. *Am J Obstet Gynecol*. (2014) 210:445.e1–6. doi: 10.1016/j.ajog.2013.11.037

9. Wilmer E, Chai S, Kroumpouzos G. Drug safety: pregnancy rating classifications and controversies. *Clin Dermatol*. (2016) 34:401–9. doi: 10.1016/j.clindermatol.2016.02.013

10. LaCourse SM, Kachikis A, Blain M, Simmons LE, Mays JA, Pattison AD, et al. Low prevalence of severe acute respiratory syndrome coronavirus 2 among pregnant and postpartum patients with universal screening in Seattle, Washington. *Clin Infect Dis*. (2021) 72:869–72. doi: 10.1093/cid/ciaa675

11. Vintzileos WS, Muscat J, Hoffmann E, John NS, Vertichio R, Vintzileos AM, et al. Screening all pregnant women admitted to labor and delivery for the virus responsible for coronavirus disease 2019. *Am J Obstet Gynecol*. (2020) 223:284–6. doi: 10.1016/j.ajog.2020.04.024

12. Allotey J, Stallings E, Bonet M, Yap M, Chatterjee S, Kew T, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. *BMJ*. (2020) 370:m3320. doi: 10.1136/bmj.m3320

13. Villar J, Ariff S, Gunier RB, Thiruvengadam R, Rauch S, Kholin A, et al. Maternal and neonatal morbidity and mortality among pregnant women with and without COVID-19 infection: the INTERCOVID multinational cohort study. *JAMA Pediatr*. (2021) 175:817–26. doi: 10.1001/jamapediatrics.2021.1050

14. Zambrano LD, Ellington S, Strid P, Galang RR, Oduyebo T, Tong VT, et al. Update: characteristics of symptomatic women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status - United States, January 22-October 3, 2020. *MMWR Morb Mortal Wkly Rep*. (2020) 69:1641–7. doi: 10.15585/mmwr.mm6944e3

15. Karaçam Z, Kizilca-Çakaloz D, Güneş-Öztürk G, Çoban A. Maternal and perinatal outcomes of pregnancy associated with COVID-19: systematic review and meta-analysis. *Eur J Midwifery*. (2022) 6:42. doi: 10.18332/ejm/149485

16. Qeadan F, Mensah NA, Tingey B, Stanford JB. The risk of clinical complications and death among pregnant women with COVID-19 in the Cerner COVID-19 cohort: a retrospective analysis. *BMC Pregnancy Childbirth*. (2021) 21:305. doi: 10.1186/s12884-021-03772-y

17. DeBolt CA, Bianco A, Limaye MA, Silverstein J, Penfield CA, Roman AS, et al. Pregnant women with severe or critical coronavirus disease 2019 have increased composite morbidity compared with nonpregnant matched controls. *Am J Obstet Gynecol*. (2021) 224:510.e1–510.e12. doi: 10.1016/j.ajog.2020.11.022

18. Molina RL, Tsai TC, Dai D, Soto M, Rosenthal N, Orav EJ, et al. Comparison of pregnancy and birth outcomes before vs during the COVID-19 pandemic. *JAMA Netw Open*. (2022) 5:e2226531. doi: 10.1001/jamanetworkopen.2022.26531

19. Ferrara A, Hedderson MM, Zhu Y, Avalos LA, Kuzniewicz MW, Myers LC, et al. Perinatal complications in individuals in California with or without SARS-CoV-2 infection during pregnancy. *JAMA Intern Med*. (2022) 182:503–12. doi: 10.1001/jamainternmed.2022.0330

20. Metz TD, Clifton RG, Hughes BL, Sandoval GJ, Grobman WA, Saade GR, et al. National Institute of Child Health and Human Development maternal-fetal medicine units (MFMU) network. Association of SARS-CoV-2 infection with serious maternal morbidity and mortality from obstetric complications. *JAMA*. (2022) 327:748–59. doi: 10.1001/jama.2022.1190

21. Conde-Agudelo A, Romero R. SARS-CoV-2 infection during pregnancy and risk of preeclampsia: a systematic review and meta-analysis. *Am J Obstet Gynecol*. (2022) 226:68–89.e3. doi: 10.1016/j.ajog.2021.07.009

22. Kleinwechter HJ, Weber KS, Mingers N, Ramsauer B, Schaefer-Graf UM, Groten T, et al. Gestational diabetes mellitus and COVID-19: results from the COVID-19-related obstetric and neonatal outcome study (CRONOS). *Am J Obstet Gynecol*. (2022) 227:631.e1–631.e19. doi: 10.1016/j.ajog.2022.05.027

23. Smith ER, Oakley E, Grandner GW, Rukundo G, Farooq F, Ferguson K, et al. Clinical risk factors of adverse outcomes among women with COVID-19 in the pregnancy and postpartum period: a sequential, prospective meta-analysis. *Am J Obstet Gynecol*. (2022) S0002-9378:00680–9. doi: 10.1016/j.ajog.2022.08.038

24. Mupanomunda M, Fakih MG, Miller C, Ottenbacher A, Winegar AL, Roberts P, et al. Comparison of severe maternal morbidities associated with delivery during periods of circulation of specific SARS-CoV-2 variants. *JAMA Netw Open*. (2022) 5:e2226436. doi: 10.1001/jamanetworkopen.2022.26436

25. Badr DA, Picone O, Bevilacqua E, Carlin A, Meli F, Sibiude J, et al. Severe acute respiratory syndrome coronavirus 2 and pregnancy outcomes according to gestational age at time of infection. *Emerg Infect Dis*. (2021) 27:2535–43. doi: 10.3201/eid2710.211394

26. Pratama NR, Wafa IA, Budi DS, Putra M, Wardhana MP, Wungu CDK. mRNA Covid-19 vaccines in pregnancy: a systematic review. *PLoS One*. (2022) 17:e0261350. doi: 10.1371/journal.pone.0261350

27. Woodworth KR, Olsen EO, Neelam V, Lewis EL, Galang RR, Oduyebo T, et al. Birth and infant outcomes following laboratory-confirmed SARS-CoV-2 infection in pregnancy - SET-NET, 16 jurisdictions, march 29-October 14, 2020. *MMWR Morb Mortal Wkly Rep*. (2020) 69:1635–40. doi: 10.15585/mmwr.mm6944e2

28. Elshafeey F, Magdi R, Hindi N, Elshebiny M, Farrag N, Mahdy S, et al. A systematic scoping review of COVID-19 during pregnancy and childbirth. *Int J Gynaecol Obstet*. (2020) 150:47–52. doi: 10.1002/ijgo.13182

29. Yan J, Guo J, Fan C, Juan J, Yu X, Li J, et al. Coronavirus disease 2019 in pregnant women: a report based on 116 cases. *Am J Obstet Gynecol*. (2020) 223:111.e1–111.e14. doi: 10.1016/j.ajog.2020.04.014

30. Hernández-Díaz S, Smith LH, Wyszynski DF, Rasmussen SA. First trimester COVID-19 and the risk of major congenital malformations-international registry of coronavirus exposure in pregnancy. *Birth Defects Res*. (2022) 114:906–14. doi: 10.1002/bdr2.2070

31. Metz TD, Clifton RG, Hughes BL, Sandoval G, Saade GR, Grobman WA, et al. Disease severity and perinatal outcomes of pregnant patients with coronavirus disease 2019 (COVID-19). *Obstet Gynecol*. (2021) 137:571–80. doi: 10.1097/AOG.0000000000004339

32. Wang X, Chen X, Zhang K. Maternal infection with COVID-19 and increased risk of adverse pregnancy outcomes: a meta-analysis. *J Matern Fetal Neonatal Med*. (2022) 35:9368–75. doi: 10.1080/14767058.2022.2033722

33. Smith LH, Dollinger CY, VanderWeele TJ, Wyszynski DF, Hernández-Díaz S. Timing and severity of COVID-19 during pregnancy and risk of preterm birth in the international registry of coronavirus exposure in pregnancy. *BMC Pregnancy Childbirth*. (2022) 22:775. doi: 10.1186/s12884-022-05101-3

34. Lokken EM, Huebner EM, Taylor GG, Hendrickson S, Vanderhoeven J, Kachikis A, et al. Washington state COVID-19 in pregnancy collaborative. Disease severity, pregnancy outcomes, and maternal deaths among pregnant patients with severe acute respiratory syndrome coronavirus 2 infection in Washington state. *Am J Obstet Gynecol*. (2021) 225:77.e1–77.e14. doi: 10.1016/j.ajog.2020.12.1221

35. Shook LL, Brigida S, Regan J, Flynn JP, Mohammadi A, Etemad B, et al. SARS-CoV-2 placentitis associated with B.1.617.2 (Delta) variant and fetal distress or demise. *J Infect Dis*. (2022) 225:754–8. doi: 10.1093/infdis/jiac008

36. Berghella V, Hughes BL. COVID-19: overview of pregnancy issues. UpToDate (2021). Available at: https://www.uptodate.com/contents/covid-19-overview-of-pregnancy-issues (accessed November 25, 2022)

37. Dumitriu D, Emeruwa UN, Hanft E, Liao GV, Ludwig E, Walzer L, et al. Outcomes of neonates born to mothers with severe acute respiratory syndrome coronavirus 2 infection at a large medical Center in new York City. *JAMA Pediatr*. (2021) 175:157–67. doi: 10.1001/jamapediatrics.2020.4298

38. Kim DH. Clinical implications of coronavirus disease 2019 in neonates. *Clin Exp Pediatr*. (2021) 64:157–64. doi: 10.3345/cep.2020.01795

39. Huntley BJF, Mulder IA, Di Mascio D, Vintzileos WS, Vintzileos AM, Berghella V, et al. Adverse pregnancy outcomes among individuals with and without severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): a systematic review and meta-analysis. *Obstet Gynecol*. (2021) 137:585–96. doi: 10.1097/AOG.0000000000004320

40. DeSisto CL, Wallace B, Simeone RM, Polen K, Ko JY, Meaney-Delman D, et al. Risk for stillbirth among women with and without COVID-19 at delivery hospitalization - United States, march 2020-September 2021. *MMWR Morb Mortal Wkly Rep*. (2021) 70:1640–5. doi: 10.15585/mmwr.mm7047e1

41. Zimmermann P, Curtis N. COVID-19 in children, pregnancy and neonates: a review of epidemiologic and clinical features. *Pediatr Infect Dis J*. (2020) 39:469–77. doi: 10.1097/INF.0000000000002700

42. Chen Y, Peng H, Wang L, Zhao Y, Zeng L, Gao H, et al. Infants born to mothers with a new coronavirus (COVID-19). *Front Pediatr*. (2020) 8:104. doi: 10.3389/fped.2020.00104

43. Allotey J, Chatterjee S, Kew T, Gaetano A, Stallings E, Fernández-García S, et al. SARS-CoV-2 positivity in offspring and timing of mother-to-child transmission: living systematic review and meta-analysis. *BMJ*. (2022) 376:e067696. doi: 10.1136/bmj-2021-067696

44. Shah PS, Diambomba Y, Acharya G, Morris SK, Bitnun A. Classification system and case definition for SARS-CoV-2 infection in pregnant women, fetuses, and neonates. *Acta Obstet Gynecol Scand*. (2020) 99:565–8. doi: 10.1111/aogs.13870

45. Jeganathan K, Paul AB. Vertical transmission of SARS-CoV-2: a systematic review. *Obstet Med*. (2022) 15:91–8. doi: 10.1177/1753495X211038157

46. Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, et al. Detection of SARS-CoV-2 in different types of clinical specimens. *JAMA*. (2020) 323:1843–4. doi: 10.1001/jama.2020.3786

47. Edlow AG, Li JZ, Collier AY, Atyeo C, James KE, Boatin AA, et al. Assessment of maternal and neonatal SARS-CoV-2 viral load, transplacental antibody transfer, and

placental pathology in pregnancies during the COVID-19 pandemic. *JAMA Netw Open*. (2020) 3:e2030455. doi: 10.1001/jamanetworkopen.2020.30455

48. Vivanti AJ, Vauloup-Fellous C, Prevot S, Zupan V, Suffee C, Do Cao J, et al. Transplacental transmission of SARS-CoV-2 infection. *Nat Commun*. (2020) 11:3572. doi: 10.1038/s41467-020-17436-6

49. Pique-Regi R, Romero R, Tarca AL, Luca F, Xu Y, Alazizi A, et al. Does the human placenta express the canonical cell entry mediators for SARS-CoV-2? *elife*. (2020) 9:e58716. doi: 10.7554/eLife.58716

50. Hecht JL, Quade B, Deshpande V, Mino-Kenudson M, Ting DT, Desai N, et al. SARS-CoV-2 can infect the placenta and is not associated with specific placental histopathology: a series of 19 placentas from COVID-19-positive mothers. *Mod Pathol*. (2020) 33:2092–103. doi: 10.1038/s41379-020-0639-4

51. Pahalyants V, Murphy WS, Klebanov N, Lu C, Theodosakis N, Klevens RM, et al. Immunosuppressive biologics did not increase the risk of COVID-19 or subsequent mortality: a retrospective matched cohort study from Massachusetts. *J Am Acad Dermatol*. (2022) 86:252–5. doi: 10.1038/s41379-020-0639-4

52. Naik HB, Alhusayen R, Frew J, Guilbault S, Hills NK, Ingram JR, et al. Biologic therapy is not associated with increased COVID-19 severity in patients with hidradenitis suppurativa: initial findings from the global hidradenitis Suppurativa COVID-19 registry. *J Am Acad Dermatol*. (2022) 86:249–52. doi: 10.1016/j.jaad.2021.09.016

53. Lee KP, Koshelev MV; D3CODE Team, Pacha O. The effect of biologic therapy for immune-mediated inflammatory diseases on clinical outcomes of COVID-19 in the greater Houston area: a retrospective chart review. *J Am Acad Dermatol*. (2022) 87:658–60. doi: 10.1016/j.jaad.2021.12.054

54. Georgakopoulos JR, Mufti A, Vender R, Yeung J. Treatment discontinuation and rate of disease transmission in psoriasis patients receiving biologic therapy during the COVID-19 pandemic: a Canadian multicenter retrospective study. *J Am Acad Dermatol*. (2020) 83:1212–4. doi: 10.1016/j.jaad.2020.07.021

55. Barlow-Pay F, Htut TW, Khezrian M, Myint PK. Systematic review of immunosuppressant guidelines in the COVID-19 pandemic. *Ther Adv Drug Saf*. (2021) 12:2042098620985687. doi: 10.1177/2042098620985687

56. American Academy of Dermatology. Guidance on the use of immunosuppressive agents. (2021). Available at: https://www.aad.org/member/practice/coronavirus/clinical-guidance/Biologics

57. Brownstone ND, Thibodeaux QG, Reddy VD, Myers BA, Chan SY, Bhutani T, et al. Novel coronavirus disease (COVID-19) and biologic therapy in psoriasis: infection risk and patient counseling in uncertain times. *Dermatol Ther (Heidelb)*. (2020) 10:339–49. doi: 10.1007/s13555-020-00377-9

58. Seirafianpour F, Sodagar S, Pour Mohammad A, Panahi P, Mozafarpoor S, Almasi S, et al. Cutaneous manifestations and considerations in COVID-19 pandemic: a systematic review. *Dermatol Ther*. (2020) 33:e13986. doi: 10.1111/dth.13986

59. National Institute for Health and Clinical Excellence. COVID-19 rapid guideline: dermatological conditions treated with drugs affecting the immune response. Available at: https://www.nice.org.uk/guidance/ng169/chapter/4-Patientsknown-or-suspected-to-have-COVID-19 (accessed November 22, 2022)

60. Price KN, Frew JW, Hsiao JL, Shi VY. COVID-19 and immunomodulator/immunosuppressant use in dermatology. *J Am Acad Dermatol*. (2020) 82:e173–5. doi: 10.1016/j.jaad.2020.03.046

61. British Association of Dermatologists. Dermatology advice regarding medication acting on the immune system: adults, paediatrics and young people. Available at: https://www.skinhealthinfo.org.uk/covid-19-provisional-guidance-on-vaccination-subject-to-approval-and-supply-of-vaccines/ (accessed November 22, 2022)

62. Gresham LM, Marzario B, Dutz J, Kirchhof MG. An evidence-based guide to SARS-CoV-2 vaccination of patients on immunotherapies in dermatology. *J Am Acad Dermatol*. (2021) 84:1652–66. doi: 10.1016/j.jaad.2021.01.047

63. British Association of Dermatologists. COVID-19: provisional guidance on vaccination. Available at: https://www.skinhealthinfo.org.uk/covid-19-provisional-guidance-on-vaccination-subject-to-approval-and-supply-of-vaccines

64. Wang C, Rademaker M, Tate B, Baker C, Foley P. SARS-CoV-2 (COVID-19) vaccination in dermatology patients on immunomodulatory and biologic agents: recommendations from the Australasian medical dermatology group. *Australas J Dermatol*. (2021) 62:151–6. doi: 10.1111/ajd.13593

65. Covid-19 Vaccination: Advice of the EADV task forces. Available at: https://www.eadv.org/covid-19/task-force (accessed November 22, 2022).

66. Das A, De A, Godse K, Sangolli P, Zawar V, Sharma N, et al. Evidence-based guidelines for SARS-COV-2 vaccination of patients of skin allergic diseases and patients on immuno-therapeutics. *Indian J Dermatol*. (2022) 67:314. doi: 10.4103/ijd.ijd_440_21

67. Jones ME, Kohn AH, Pourali SP, Rajkumar JR, Gutierrez Y, Yim RM, et al. The use of biologics during the COVID-19 pandemic. *Dermatol Clin*. (2021) 39:545–53. doi: 10.1016/j.det.2021.05.010

68. Untersmayr E, Förster-Waldl E, Bonelli M, Boztug K, Brunner PM, Eiwegger T, et al. Immunologically relevant aspects of the new COVID-19 vaccines-an ÖGAI (Austrian Society for Allergology and Immunology) and AeDA (German Society for Applied Allergology) position paper. *Allergo J Int*. (2021) 30:155–68. doi: 10.1007/s40629-021-00178-2

69. Munisamy M, Singh BSTP, Pandhi D. Recommendations for COVID vaccination for dermatological patients on immunosuppressive/immunomodulatory therapy (IADVL academy). *Indian Dermatol Online J*. (2021) 12:4–S11. doi: 10.4103/idoj.idoj_412_21

70. Kroumpouzos G, Paroikaki ME, Yumeen S, Bhargava S, Mylonakis E. Cutaneous complications of mRNA and AZD1222 COVID-19 vaccines: a worldwide review. *Microorganisms*. (2022) 10:624. doi: 10.3390/microorganisms10030624

71. Lim RK, Kalagara S, Chen KK, Mylonakis E, Kroumpouzos G. Dermatology in a multidisciplinary approach with infectious disease and obstetric medicine against COVID-19. *Int J Womens Dermatol*. (2021) 7:640–6. doi: 10.1016/j.ijwd.2021.08.008

72. Kianfar N, Dasdar S, Salehi Farid A, Balighi K, Mahmoudi H, Daneshpazhooh M. Exacerbation of autoimmune bullous diseases after severe acute respiratory syndrome coronavirus 2 vaccination: is there any association? *Front Med (Lausanne)*. (2022) 9:957169. doi: 10.3389/fmed.2022.957169

73. Brodmerkel C, Wadman E, Langley RG, Papp KA, Bourcier M, Poulin Y, et al. Immune response to pneumococcus and tetanus toxoid in patients with moderate-to-severe psoriasis following long-term ustekinumab use. *J Drugs Dermatol*. (2013) 12:1122–9.

74. Chioato A, Noseda E, Stevens M, Gaitatzis N, Kleinschmidt A, Picaud H. Treatment with the interleukin-17A-blocking antibody secukinumab does not interfere with the efficacy of influenza and meningococcal vaccinations in healthy subjects: results of an open-label, parallel-group, randomized single-center study. *Clin Vaccine Immunol*. (2012) 19:1597–602. doi: 10.1128/CVI.00386-12

75. Blauvelt A, Simpson EL, Tyring SK, Purcell LA, Shumel B, Petro CD, et al. Dupilumab does not affect correlates of vaccine-induced immunity: a randomized, placebo-controlled trial in adults with moderate-to-severe atopic dermatitis. *J Am Acad Dermatol*. (2019) 80:158–167.e1. doi: 10.1016/j.jaad.2018.07.048

76. Richi P, Alonso O, Martín MD, González-Hombrado L, Navío T, Salido M, et al. Evaluation of the immune response to hepatitis B vaccine in patients on biological therapy: results of the RIER cohort study. *Clin Rheumatol*. (2020) 39:2751–6. doi: 10.1007/s10067-020-05042-2

77. Haykir Solay A, Eser F. High dose hepatitis B vaccine is not effective in patients using immunomodulatory drugs: a pilot study. *Hum Vaccin Immunother*. (2019) 15:1177–82. doi: 10.1080/21645515.2019.1574151

78. Huang Y, Wang H, Wan L, Lu X, Tam WW. Is systemic lupus erythematosus associated with a declined immunogenicity and poor safety of influenza vaccination? A systematic review and meta-analysis. *Medicine (Baltimore)*. (2016) 95:e3637. doi: 10.1097/MD.0000000000003637

79. Deepak P, Kim W, Paley MA, Yang M, Carvidi AB, Demissie EG, et al. Effect of immunosuppression on the immunogenicity of mRNA vaccines to SARS-CoV-2: a prospective cohort study. *Ann Intern Med*. (2021) 174:1572–85. doi: 10.7326/M21-1757

80. Embi PJ, Levy ME, Naleway AL, Patel P, Gaglani M, Natarajan K, et al. Effectiveness of 2-dose vaccination with mRNA COVID-19 vaccines against COVID-19-associated hospitalizations among immunocompromised adults - nine states, January-September 2021. *MMWR Morb Mortal Wkly Rep*. (2021) 70:1553–9. doi: 10.15585/mmwr.mm7044e3

81. Simon D, Tascilar K, Fagni F, Krönke G, Kleyer A, Meder C, et al. SARS-CoV-2 vaccination responses in untreated, conventionally treated and anticytokine-treated patients with immune-mediated inflammatory diseases. *Ann Rheum Dis*. (2021) 80:1312–6. doi: 10.1136/annrheumdis-2021-220461

82. Musumeci ML, Caruso G, Trecarichi AC, Micali G. Safety of SARS-CoV-2 vaccines in psoriatic patients treated with biologics: a real life experience. *Dermatol Ther*. (2022) 35:e15177. doi: 10.1111/dth.15177

83. Polack FP. Atypical measles and enhanced respiratory syncytial virus disease (ERD) made simple. *Pediatr Res*. (2007) 62:111–5. doi: 10.1203/PDR.0b013e3180686ce0

84. Rosen MH, Axelrad J, Hudesman D, Rubin DT, Chang S. Management of acute severe ulcerative colitis in a pregnant woman with COVID-19 infection: a case report and review of the literature. *Inflamm Bowel Dis*. (2020) 26:971–3. doi: 10.1093/ibd/izaa109

85. Selinger CP, Fraser A, Collins P, Gunn M, Chew TS, Kerry G, et al. Impact of the coronavirus infectious disease (COVID-19) pandemic on the provision of inflammatory bowel disease (IBD) antenatal care and outcomes of pregnancies in women with IBD. *BMJ Open Gastroenterol*. (2021) 8:e000603. doi: 10.1136/bmjgast-2021-000603

86. Kemp MW, Newnham JP, Challis JG, Jobe AH, Stock SJ. The clinical use of corticosteroids in pregnancy. *Hum Reprod Update*. (2016) 22:dmv047–59. doi: 10.1093/humupd/dmv047

87. RECOVERY Collaborative GroupHorby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med*. (2021) 384:693–704. doi: 10.1056/NEJMoa2021436

88. Saad AF, Chappell L, Saade GR, Pacheco LD. Corticosteroids in the management of pregnant patients with coronavirus disease (COVID-19). *Obstet Gynecol*. (2020) 136:823–6. doi: 10.1097/AOG.0000000000004103

89. American College of Obstetricians and Gynecologists. COVID-19 vaccination considerations for obstetric–gynecologic care. Available at: https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2020/12/covid-19-vaccination-considerations-for-obstetric-gynecologic-care?utm_source=higher-logic&utm_medium=email&utm_content=sept-14&utm_campaign=acog2022-digest (Accessed on September 15, 2022).

90. Royal College of Obstetricians & Gynecologists. COVID-19 vaccines, pregnancy and breastfeeding FAQs. Available at: https://www.rcog.org.uk/guidance/coronavirus-covid-19-pregnancy-and-women-s-health/vaccination/covid-19-vaccines-pregnancy-and-breastfeeding-faqs/ (Accessed November 22, 2022)

91. Prasad S, Kalafat E, Blakeway H, Townsend R, O'Brien P, Morris E, et al. Systematic review and meta-analysis of the effectiveness and perinatal outcomes of COVID-19 vaccination in pregnancy. *Nat Commun*. (2022) 13:2414. doi: 10.1038/s41467-022-30052-w

92. Hillson K, Clemens SC, Madhi SA, Voysey M, Pollard AJ, Minassian AM, et al. Fertility rates and birth outcomes after ChAdOx1 nCoV-19 (AZD1222) vaccination. *Lancet*. (2021) 398:1683–4. doi: 10.1016/S0140-6736(21)02282-0

93. Shimabukuro TT, Kim SY, Myers TR, Moro PL, Oduyebo T, Panagiotakopoulos L, et al. Preliminary findings of mRNA Covid-19 vaccine safety in pregnant persons. *N Engl J Med*. (2021) 384:2273–82. doi: 10.1056/NEJMoa2104983

94. Stock SJ, Carruthers J, Calvert C, Denny C, Donaghy J, Goulding A, et al. SARS-CoV-2 infection and COVID-19 vaccination rates in pregnant women in Scotland. *Nat Med*. (2022) 28:504–12. doi: 10.1038/s41591-021-01666-2

95. Halasa NB, Olson SM, Staat MA, Newhams MM, Price AM, Pannaraj PS, et al. Maternal vaccination and risk of hospitalization for covid-19 among infants. *N Engl J Med*. (2022) 387:109–19. doi: 10.1056/NEJMoa2204399

96. Emanoil AR, Stochino Loi E, Feki A, Ben AN. Focusing treatment on pregnant women with COVID disease. *Front Glob Womens Health*. (2021) 2:590945. doi: 10.3389/fgwh.2021.590945

97. Maguire S, Al-Emadi S, Alba P, Aguiar MC, Lawati TA, Alle G, et al. COVID-19 global rheumatology Alliance. Obstetric outcomes in women with rheumatic disease and COVID-19 in the context of vaccination status. *Rheumatology (Oxford)*. (2022) 62:1621–6. doi: 10.1093/rheumatology/keac534. Epub ahead of print

98. Al-Adhoubi NK, Ali M, Wahshi HA, Salmi IA, Al-Balushi F, Lawati TA, et al. COVID-19 mortality in patients with rheumatic diseases: a real concern. *Curr Rheumatol Rev*. (2022) 18:234–42. doi: 10.2174/1573397118666220412114514

99. Smeele HT, Perez-Garcia LF, Grimminck K, Schoenmakers S, Mulders AG, Dolhain RJ. Systemic lupus erythematosus and COVID-19 during pregnancy. *Lupus*. (2021) 30:1188–91. doi: 10.1177/09612033211002270

100. Rasmussen SA, Kelley CF, Horton JP, Jamieson DJ. Coronavirus disease 2019 (COVID-19) vaccines and pregnancy: what obstetricians need to know. *Obstet Gynecol*. (2021) 137:408–14. doi: 10.1097/AOG.0000000000004290

101. Gill L, Jones CW. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies in neonatal cord blood after vaccination in pregnancy. *Obstet Gynecol*. (2021) 137:894–6. doi: 10.1097/AOG.0000000000004367

102. Male V. Are COVID-19 vaccines safe in pregnancy? *Nat Rev Immunol*. (2021) 21:200–1. doi: 10.1038/s41577-021-00525-y

103. Blumberg D, Sridhar A, Lakshminrusimha S, Higgins RD, Saade G. COVID-19 vaccine considerations during pregnancy and lactation. *Am J Perinatol*. (2021) 38:523–8. doi: 10.1055/s-0041-1726390

104. Tariq J, Gupta L. Safety and efficacy of COVID-19 vaccines in pregnant women with rheumatic diseases: an immunologic perspective. *Rheumatol Int*. (2021) 41:1545–7. doi: 10.1007/s00296-021-04918-z