15.1 Physiological Changes in the Immune System in Pregnancy

Pregnancy is a unique immunological state. The common perception that normal pregnancy is a state of immune compromise (in order to avoid “rejecting” the fetus) is an oversimplification. In reality, the changes are more subtle, but several important changes occur in the maternal immune response during pregnancy.

In early pregnancy, changes occur in the local immune response within the uterus. Macrophages, dendritic cells, neutrophils and natural killer (NK) cells participate in a coordinated, controlled inflammatory response, which is essential for implantation and progression of the pregnancy [1]. Therefore, early pregnancy is actually a pro-inflammatory phase, mediated by an active (rather than a suppressed) innate immune system.
The innate immune response also provides a defence against infection. The inflammatory state may (in combination with hormonal and other factors) contribute to systemic illness such as nausea and vomiting of pregnancy [1].

The adaptive immune system undergoes more complex changes, including diminished cytotoxic responses and enhanced regulatory responses. As part of the normal adaptive immune response, the Th1 subgroup of CD4 T-cells express cytokines such as IFN-γ and TNF-α and play a key role in cytotoxic immune responses. Overactivity of the Th1 system may play a role in the development of certain autoimmune diseases [2]. The Th2 subgroup express cytokines such as IL-4, IL-5 and IL-13 and are involved with humoral (antibody) responses and protection against some parasites. Overactivity of the Th2 system is thought to be implicated in the pathogenesis of allergies and atopy [3].

During normal pregnancy, there is a physiological shift in the maternal T-cell response towards a Th2 state. This finding was initially reported in several studies using mouse models of pregnancy and later confirmed in human studies [4].

In addition, a subset of CD4 T-cells, known as T-reg cells, are important regulators of the maternal immune response and tolerance to the fetus [5]. These cells produce IL10 and TGFβ, thereby suppressing local immunity [6]. During pregnancy, the population of T-reg cells increases [7]. However, when exposed to inflammatory stimuli (such as influenza or listeria), T-reg cells can rapidly differentiate into an additional class known as Th17 cells, which are highly inflammatory and associated with preterm labour and infection-related miscarriage [5]. In mouse models of pregnancy, T-reg depletion results in rejection of the fetus [8]. Women with recurrent miscarriage [7] or pre-eclampsia [9, 10] have lower numbers of decidual and circulating T-reg cells, compared to healthy human pregnant controls.

The changes in the innate and adaptive immune systems are driven by a number of cytokine and endocrine factors. Prostaglandin E (PGE2) and TGFβ enhance the proliferation and function of T-reg cells [11]. High levels of progesterone and oestrogen during pregnancy modulate the immune response by suppressing Th1 and Th17 responses and promoting Th2 and T-reg responses [12, 13].

As previously described, the first stage of pregnancy is pro-inflammatory, allowing implantation and placentation, as well as protection against infection during this crucial period. The subsequent shift towards an immunologically tolerant, anti-inflammatory Th2-predominant state allows rapid growth and development of the fetus in the second trimester of pregnancy [14].

Finally, in the third trimester, there is a return to a more pro-inflammatory state. An influx of immune cells into the myometrium and increased production of pro-inflammatory cytokines culminate in contraction of the uterus and delivery of the baby [14, 15]. This may be one of the reasons maternal infection is associated with preterm labour; amniotic fluid TNFα and IL-1 levels are significantly increased in women with preterm labour and infection [15].

### 15.2 Clinical Implications of the Altered Immune Response in Pregnancy

In addition to enabling implantation, tolerance, growth and delivery of the fetus, the physiological changes occurring in the immune system during pregnancy have significant clinical implications related to infection and autoimmune disease.

#### 15.2.1 Response to Infection

Pregnant women do not appear to have increased susceptibility to most infections (although there are a few notable exceptions including listeria and falciparum malaria—discussed below) [16]. However, with certain infections, there is an increased risk of severe disease resulting in a higher rate of mortality and morbidity than the general population [16]. In some (but not all) cases, this is related to the altered systemic immune status of the mother.

Influenza is an important cause of maternal morbidity and mortality. The 2009 H1N1 pandemic strain was particularly virulent, and pregnant women were at much higher risk of developing severe, complicated infections and respiratory failure. In the USA, there were 280 intensive care unit admissions and 56 deaths
among the 788 reported cases of influenza in pregnant women in the first 8 months of the pandemic. Initial data do not suggest that pregnant women are more susceptible to infection with SARS-CoV-2 (the coronavirus responsible for the COVID-19 pandemic), although severe disease leading to hospital admission is more common in the third trimester. Women over the age of 35 and those with obesity, hypertension and diabetes are at increased risk. In a nationwide study in the UK, 9% of pregnant women admitted required respiratory support, which is similar to the non-pregnant population [17, 18].

The reasons for this increased severity in pregnancy are not completely understood. The Th2-predominant T-cell profile may reduce viral clearance [19]. Animal models suggest that when the host is infected with influenza virus, the altered immunological state of pregnancy is associated with higher levels of pro-inflammatory mediators (IL-6, IL-1α, G-CSF and COX-2) in the lung tissue [20].

Hepatitis E usually causes a mild self-limiting illness in the nonpregnant population. However, it can cause severe disease in pregnancy, with a significant proportion progressing to fulminant hepatitis with a mortality rate varying from 30 to 100% [21]. The mechanisms are still unclear but may involve the human transcription factor NF-κB, which plays a key role in regulating the immune response to infection [22]. NF-κB is downregulated during normal pregnancy [23]. Animal experiments in mice studying the p65 component of NF-κB have shown its important role in liver development and regeneration and that mice lacking p65 develop liver degeneration due to widespread apoptosis [21]. This led to human studies, which have found that the activity of the p65 component of NF-κB was greatly diminished in peripheral blood mononuclear cells and post-mortem liver biopsy specimens in pregnant women (compared to the nonpregnant population) with fulminant hepatic failure (FHF) [24]. This suggests that the absence or reduced activity of NF-κB p65 is associated with severe liver damage in pregnant women that develop FHF.

Falciparum malaria may cause particularly severe disease in pregnancy because the parasites sequester in the placenta, causing inflammation and necrosis. Pregnant women are also more susceptible to hypoglycaemia [25, 26]. Acute infection appears to be more frequent in pregnant women [27]. Various explanations have been put forward, such as increased attractiveness to mosquitos [28] and impaired ability to limit parasite replication [27].

Acquired immunity against malaria is also diminished in women during their first pregnancy; they are susceptible to severe P. falciparum disease due to placental malaria causing a lack of immunity to placenta-specific cytoadherence proteins [29]. In subsequent pregnancies, immunity against placental-adherent strains may develop, reducing the risk of adverse effects of malaria on the mother and fetus.

Certain other infections are notable for the higher rate of mortality and morbidity in pregnancy but probably for reasons unrelated to the altered systemic immune status of the mother. Listeria monocytogenes has a particular predilection for the placenta and fetus; therefore, invasive listeriosis is much more common in pregnant women, but this is likely to be because the nonpregnant population lack the placental entry point for infection [16].

Rubella, CMV and parvovirus B19 are significant in pregnancy due to the deleterious effects on the fetus rather than because of increased susceptibility or the maternal immune response in pregnancy. Maternal infection is usually subclinical or mildly symptomatic [25, 30].

Maternal HIV infection has major implications around mother-to-child transmission [31], but pregnancy does not affect disease progression [25, 32].

15.2.2 Autoimmune Disease

Around 10–25% of the general population of patients with autoimmune diseases presenting to emergency departments require hospital admission [33], and up to 30% of these patients require intensive care admission [34]. Mortality ranges from 17 to 55% in case series from the general population of patients with autoimmune diseases admitted to the intensive care unit [35].
More than two-thirds of maternal deaths in industrialised countries occur in women known to have medical comorbidities [36], and autoimmune diseases contribute directly and indirectly to these deaths [37]. It is therefore unsurprising that autoimmune diseases are frequent causes of morbidity during pregnancy. Pregnant women with autoimmune diseases have higher rates of obstetric and non-obstetric complications (e.g. pre-eclampsia, thromboembolism, infection), poor pregnancy outcomes (i.e. fetal growth restriction, preterm delivery,) as well as pregnancy loss (Fig. 15.1). Good disease control improves not only maternal but also pregnancy outcomes [38].

The altered immune state of pregnancy has an effect on the activity of several autoimmune diseases, which is summarised in Fig. 15.2. The shift from a Th1- to a Th2-predominant state is relevant here. Hormonal changes contribute significantly to this; high levels of circulating oestrogen (as seen in pregnancy) have been shown to modulate the cytokine profile and suppress disease activity in experimental models of rheumatoid arthritis [39] and multiple sclerosis [40].

In humans, diseases that are driven by a Th1 response, including rheumatoid arthritis [41, 42], multiple sclerosis [43], psoriasis [44] and Graves’ disease [45], tend to improve during pregnancy [13]. However, they may flare postpartum, possibly due to a rapid fall in oestrogen levels in this period, resulting in a diminished Th2 response and consequently tipping the balance back in favour of a Th1 response [13].

In contrast, diseases that are driven by a Th2 response, including atopic eczema, SLE and systemic sclerosis, have a higher rate of flaring during pregnancy compared to the nonpregnant population [13, 44]. Active flares of autoimmune

| Th1-type autoimmune disease | Influence of pregnancy on disease |
|-----------------------------|----------------------------------|
| Rheumatoid Arthritis        | Tends to improve                 |
| Psoriasis                   |                                  |
| Multiple Sclerosis          |                                  |
| Graves Disease              |                                  |

| Th2-type autoimmune disease | Influence of pregnancy on disease |
|-----------------------------|----------------------------------|
| Systemic Lupus Erythematosus| Higher rate of disease flare     |
| Systemic Sclerosis          |                                  |
| Atopic Dermatitis (Eczema)  |                                  |
disease should be treated aggressively to minimise adverse consequences for both mother and fetus.

Corticosteroids are usually the first-line treatment and can be used at any stage of pregnancy if clinically indicated. Dosing varies according to patient condition and should generally adhere to that administered to nonpregnant patients (see some details under subheadings). As with non-pregnant patients, steroids should be given at the lowest possible dose to control disease activity, but high doses should not be withheld if clinically indicated. Prednisolone and methylprednisolone are extensively metabolised by the placenta, and the fetal exposure is less than 10% of the maternal dose. Several large studies have not found any significant adverse effect on the fetus (major malformations, prematurity, low birthweight) attributable to these drugs [46]. However, treatment with these drugs has been associated with an increased maternal risk of gestational hypertension and diabetes.

There are also good safety data [47] in pregnancy for disease-modifying drugs, such as hydroxychloroquine, sulfasalazine, mesalazine and azathioprine, and the calcineurin inhibitors ciclosporin and tacrolimus. Non-steroidal anti-inflammatory drugs (NSAIDS) may also be used in the first and second trimesters [47, 48].

The newest class of immunomodulatory treatment is the “biologic” agents. These are monoclonal antibodies against specific targets involved in the disease process. There is now good evidence that infliximab, adalimumab, etanercept and certolizumab do not have any significant associations with a particular pattern of congenital malformations or adverse pregnancy outcomes. The use of these drugs in pregnancy is discussed further below in the section about antibodies and the placental barrier.

Intravenous immunoglobulin (IVIg) and therapeutic plasma exchange (TPE) can both be used in pregnancy [49–51] and should not be withheld if clinically indicated. It is important to note that IVIg and TPE are associated with risks of thromboembolism and fluid shifts in all patients, in particular those already at increased risk, such as critically ill and/or pregnant patients. The indications for these treatments would be the same as for nonpregnant patients. The aims of IVIg and TPE would vary slightly depending on the disease indication for treatment. For example, in GBS [52], there may be amelioration of disease and improved/faster recovery (see below). These treatments will be selected in addition to other supportive therapies such medications, physiotherapy, time and patience. A similar treatment principle would apply to conditions like immune thrombocytopenia purpura (Chap. 5) and myasthenia gravis (Chap. 26).

Methotrexate, mycophenolate mofetil, leflunomide and cyclophosphamide are teratogenic and should be avoided during pregnancy if possible. It is therefore important to address the use of these drugs in pre-pregnancy counselling and to aim for optimal disease control with an alternative drug prior to conception. However, the successful use of cyclophosphamide (500 mg IV pulsed dose every 2 weeks for 6 doses) in the second and third trimesters has been reported in the treatment of refractory life-threatening SLE and rapidly progressive interstitial lung disease [53]. This is a challenging scenario, and such decisions should only be reached after a detailed and frank discussion between the intensivist, treating physician, obstetrician and patient and/or her family (if she is unable to provide input). In the context of critical illness with a risk of death (or serious/permanent disability or organ damage), with no other effective treatment options, the conclusions of such discussions might be to use cyclophosphamide to prioritise maternal health while accepting the significant risk of fetal harm or loss. Of note, there are also data describing safe use of cyclophosphamide as part of chemotherapy regimens to treat breast cancer [54] and lymphomas [55] in pregnancy after 12 weeks gestation (Fig. 15.3).

15.2.2.1 SLE and Pregnancy

Systemic lupus erythematosus (SLE) is an idiopathic autoimmune condition which has multi-organ involvement. The disease process is incompletely understood, involving immune complex deposition resulting in widespread inflammation. There is polyclonal B-cell activa-
tion and antinuclear antibody production. There are also complement deficiencies and impaired T-cell regulation, which leads to a diminished ability to clear these immune complexes [56].

SLE is particularly prone to flaring during pregnancy. As many as 60% of women with pre-existing SLE experience a flare during or soon after pregnancy, compared with 40% of nonpregnant women over the same period [57]. The risk of flaring during pregnancy is highest for women with active disease at the time of conception, particularly if they have lupus nephritis [58]. SLE disease activity varies by organ system. Musculoskeletal flares are less common, while renal and hematologic flares are more common [59]. Severe morbidity requiring critical care may result from flares of lupus nephritis, interstitial lung disease, cardiovascular disease, neuropsychiatric lupus, thrombosis, thrombocytopenia or opportunistic infections.

Treatment of acute severe flares involves high-dose corticosteroids (e.g. pulsed IV methylprednisolone 500–1000 mg/day for 3 days followed by prednisolone 0.25–0.5 mg/kg/day) [60, 61].

| Drug / Treatment | Safety in pregnancy | Comments |
|------------------|---------------------|----------|
| Non-steroidal anti-inflammatory drugs (NSAIDs) | Acceptable for short-term use up to 28 weeks gestation. | Avoid use in third trimester. |
| Corticosteroids (prednisolone/methylprednisolone) | Can be used throughout pregnancy if clinically indicated. Not associated with any increased risk of congenital malformations, although there is an increased risk of diabetes and hypertension in the mother. | Fluorinated corticosteroids (e.g. dexamethasone and beclomethasone) are less metabolised by the placenta and should be avoided unless treating a fetal problem. |
| Hydroxychloroquine | Can be used throughout pregnancy if clinically indicated. Not associated with any increased risk of congenital malformations. | |
| Sulfalazine, mesalazine | Can be used throughout pregnancy if clinically indicated. Not associated with any increased risk of congenital malformations. | Women taking sulfasalazine during pregnancy should also receive folate supplementation of at least 2mg/day. |
| Azathioprine | Can be used throughout pregnancy if clinically indicated. Not associated with any increased risk of congenital malformations. | |
| Ciclosporin, tacrolimus | Can be used throughout pregnancy if clinically indicated. Not associated with any increased risk of congenital malformations. | May require higher doses during pregnancy to maintain levels within therapeutic range. |
| Infliximab | No evidence of a teratogenic effect—can be used in first trimester if clinically indicated. | If possible, stop at 20 weeks gestation. |
| Adalimumab | No evidence of a teratogenic effect—can be used in first trimester if clinically indicated. | If possible, stop at 28 weeks gestation. |
| Etanercept | No evidence of a teratogenic effect—can be used in first trimester if clinically indicated. | If possible, stop at 28 weeks gestation. |
| Certolizumab pegol | Limited evidence, but early data suggest compatibility with all three trimesters of pregnancy and do not show any evidence of a teratogenic effect. | |
| Rituximab, golimumab, abatacept, tocilizumab, belimumab, anakinra. | Limited data, although registry and observational data suggest that unintentional exposure to these drugs in the first trimester is unlikely to be harmful. | Data too limited to make any recommendation for use in pregnancy. |
| Intravenous Immunoglobulin (IVig) | Can be used throughout pregnancy if clinically indicated. | |
| Therapeutic Plasma Exchange (TPE) | Can be used throughout pregnancy if clinically indicated. | |
| Methotrexate | Teratogenic. Avoid during pregnancy. | These drugs should be withdrawn before a planned pregnancy. |
| Mycophenolate mofetil (MMF) | | |
| Leflunomide | | |
| Cyclophosphamide | | |

**Fig. 15.3** Safety of immunomodulatory and immunosuppressive therapies in pregnancy
Identifying SLE flares may be more challenging during pregnancy, as some of the symptoms and signs may overlap with normal pregnancy (e.g. lethargy, facial flushing, oedema, mild anaemia and thrombocytopenia) [62]. Good clinical judgement and specific laboratory tests such as declining serum complement levels and/or rising anti-dsDNA antibody titres may aid diagnosis of a lupus flare during pregnancy.

One of the biggest challenges is the differentiation between pre-eclampsia and a lupus nephritis flare. Both conditions may present with hypertension, proteinuria and deteriorating renal function. Here again, falling complement levels and rising anti-dsDNA antibody titres make lupus nephritis more likely, as does the detection of an active urinary sediment. A history of lupus nephritis also increases the likelihood of a renal flare in pregnancy, although lupus nephritis may present for the first time during pregnancy [56].

Despite these distinguishing features, the only investigation that can definitively distinguish pre-eclampsia from lupus nephritis is renal biopsy. This is not usually performed during pregnancy due to the risk of bleeding complications. It may occasionally be indicated in the first or second trimester if it is felt that the result is likely to alter management, for example, if appropriate treatment with immunosuppressive agents may allow prolongation of the pregnancy (see Chap. 31) [56]. If pre-eclampsia and lupus flare cannot be differentiated beyond 24–28 weeks gestation (when the fetus is viable) and maternal health is significantly compromised, then multidisciplinary discussion should be undertaken regarding early delivery. Delivery will both cure the pre-eclampsia and enable renal biopsy to guide immunosuppressive therapy if lupus nephritis is confirmed.

Guillain-Barre syndrome (GBS) is an acute immune-mediated polyneuropathy (Box 15.1). It presents as an acute, monophasic paralysing illness, usually provoked by a preceding infection. Although the condition has been reported in pregnancy [63], it is a rare condition, and there are insufficient data to make recommendations other than to manage the condition in the same way as in the nonpregnant patient. Respiratory failure is common (17–30%) [64] and is the usual reason for admission to the intensive care unit. Forced vital capacity (FVC) of less than 20 mL/kg is the widely accepted threshold to consider invasive ventilation. FVC does not change significantly in pregnancy [65], so a low FVC measurement should be attributed to genuine neuromuscular weakness rather than to the pregnancy. Indeed, the increased oxygen and ventilatory demands and the decreased lung compliance in pregnancy may result in more rapid exhaustion, decompensation and respiratory embarrassment. These patients must be closely observed for any early signs of respiratory muscle weakness, with a low threshold to admit to the high dependency or intensive care unit.

Box 15.1 IVIg and Plasma Exchange in Pregnancy: A Case-Based Example

A 33-year-old female attends the antenatal unit at 21 weeks gestation, with a 5-day history of progressive weakness. She is struggling to walk and reports that she is more breathless than usual. She was previously fit and well, although she did report a diarrhoeal illness a few weeks prior to this presentation. She has been assessed by the neurology team, who have concluded that she has Guillain-Barre syndrome. A critical care opinion has been requested, as she is slightly dyspnoeic, although she is able to communicate in full sentences. The patient is very concerned about the safety and availability of treatment options for her condition, given that she is pregnant.

In this case, the patient was observed on the critical care unit but fortunately did not deteriorate to the point of needing invasive ventilation. She responded well to IVIg, was discharged from the ICU after 5 days and made a full recovery over the following 8 weeks. She delivered a healthy baby by spontaneous vaginal delivery at 39 weeks.
Treatment of pregnant women with GBS is the same as that in nonpregnant patients. There is clear evidence that IVIg and plasma exchange (one or the other, not both in combination) is of benefit in GBS [52, 66]. Corticosteroids are ineffective and may even delay recovery [67].

Both plasma exchange and IVIg can be used in pregnancy. Trials have demonstrated that plasma exchange is associated with reduced duration of mechanical ventilation, reduced time to motor recovery and reduced time to walking without assistance [52]. If plasma exchange is used, care must be taken to avoid hypovolaemia or fluid overload. There may be a transient prolongation of prothrombin and activated partial thromboplastin times due to removal of clotting factors. Although significant bleeding is uncommon, this effect can be avoided by using plasma rather than albumin as the replacement fluid [68].

IVIg is equally as efficacious as plasma exchange and is often used as first-line therapy due to its relative ease of use. A suggested dosing regimen for IVIg is 0.4 g/kg/day for 5 days [69]. IVIg therapy is associated with an increased risk of thromboembolic events, particularly in patients with additional thrombotic risk factors [70]. Pregnancy is a pro-thrombotic state, and immobile patients in the critical care unit are at particularly high risk of venous thromboembolism. Adequate thromboprophylaxis (usually with low molecular weight heparin) is therefore essential.

### 15.3 Antibodies and the Placental Barrier

An important function of the placenta is to form a selective barrier between the maternal and fetal circulation. Most low molecular weight compounds (<500 Da) can move across the placenta by passive diffusion. Certain ions and amino acids are also actively transported. In contrast, high molecular weight compounds do not usually traverse the placenta, but an important exception is immunoglobulin G (IgG), which has a molecular mass of approximately 160kDa. Of the five antibody classes, IgG is the only class that crosses the placenta in significant quantities, although it is only transferred in significant quantities after 16 weeks gestation [71]. This is clinically relevant for three main reasons:

- Neonatal “passive” immunity to infection
- Effects of autoantibodies on the fetus/neonate
- Implications for use of “biologic” drugs

#### 15.3.1 Neonatal “Passive” Immunity to Infection

The neonatal immune system is immature and unable to mount an adequate adaptive immune response when exposed to pathogens during or soon after birth. Placental transfer of maternal IgG antibodies therefore plays an important role in protecting the neonate against infection during the initial weeks and months of life. For example, if the mother has circulating antibodies to pathogens such as varicella zoster virus, herpes simplex virus, or measles (due to prior vaccination or exposure to the pathogen), then these antibodies are detectable in the neonate too. This “passive” immunisation confers a degree of protection against these infections. This physiological process can be and often is exploited by vaccinating the mother during pregnancy for specific diseases (e.g. pertussis) [72, 73]. Similarly, IVIg has been used extensively in pregnancy without adverse effect on the fetus. It does cross the placenta (as it is IgG) but there is no association with harm. Indeed, IVIg is actually used to treat neonatal sepsis.

#### 15.3.2 Direct Effects of Autoantibodies on the Fetus/Neonate

Certain autoimmune conditions are associated with autoantibodies that may have a direct adverse effect on the fetus. Patients with these conditions, for a variety of reasons, often require critical care admission; it is therefore vital that intensive care physicians are aware of the potential immunological complications specific to pregnancy.
Anti-Ro/SSA antibodies may be present in mothers with Sjogren’s syndrome, SLE or rheumatoid arthritis [74]. Women with these autoimmune conditions should be screened for the presence of these antibodies in order to inform the treating neonatologist following delivery. These antibodies cross the placenta and are associated with fetal cardiac abnormalities and transient neonatal cutaneous lupus [75]. The risk of congenital heart block is 1–5%, and there is also a risk of myocardial inflammation, endocardial fibroelastosis or atrioventricular (AV) valve apparatus dysfunction [76]. The risk is particularly high if a previous fetus has been affected.

Several other autoimmune disease-associated IgG antibodies can cross the placenta to cause harm to the fetus. These are summarised in Fig. 15.4. However, it is important to note that the presence/titres of these antibodies don’t necessarily correlate with the degree of pathology.

### 15.3.3 Implications for Use of “Biologic” Drugs

Most “biologic” drugs are monoclonal derivatives of IgG and therefore cross the placenta.

Infliximab and adalimumab are monoclonal antibodies against TNFα. Etanercept is a fusion molecule comprising of a soluble TNFα receptor and the Fc-fragment of IgG1. These drugs can be initiated or continued during pregnancy if clinically indicated. In the intensive care setting, they are likely to be used in combination with corticosteroids to treat acute flares or de novo inflammatory disease. In mothers treated with these drugs, fetal exposure is minimal in the first trimester, and there is no evidence of a teratogenic effect [48, 77]. However, from 16 weeks gestation onwards, the antibody molecules are actively transported across the placenta and, by the third trimester, can result in higher drug levels in the fetus/neonate than in the mother.

To minimise neonatal levels at birth, these drugs are often discontinued in the second trimester (by 20 weeks for infliximab and 28 weeks for adalimumab or etanercept). However, if the drug is required to control active maternal inflammatory disease, it is acceptable to continue treatment throughout pregnancy. Moreover, while there have been theoretical concerns about neonatal immune suppression, data from the PIANO registry [77] are reassuring: third trimester anti-TNFα use had no effect on infant growth, development or immune development in the first year of life, and a systematic review [78] found no increased risk of infections up to 1 year of age. The British Society of Rheumatologists and European League Against Rheumatism have recently issued detailed guidance [47, 48] on this topic. All of these drugs may be detectable in breast milk at very low levels, but they are very poorly absorbed via the oral route, so breastfeeding is considered safe [48].

There are a number of newer anti-TNFα drugs, some of which have been modified to alter the pharmacokinetic profile. Certolizumab pegol is a monoclonal antigen-binding fragment (Fab) of an anti-TNFα antibody (lacking the Fc region) that has been conjugated with polyethylene glycol. It has low rates of placentental transfer, and early data suggest that it is compatible with all three trimesters of pregnancy. Safety data are limited for rituximab, golimumab, abatacept, tocilizumab, belimumab and anakinra, although registry and observational data suggest that unintentional fetal exposure to these drugs in the first trimester is unlikely to be harmful [48].

### 15.4 Conclusion

The immunological changes in pregnancy are complex. There are pro-inflammatory changes as well as increased immune tolerance, with a shift from a Th1- towards a Th2-predominant immunological profile. Certain infections, such as influenza, hepatitis E and falciparum malaria, tend to cause more severe disease in pregnancy, with higher morbidity and mortality. Pregnancy also influences the activity of autoimmune diseases, which are relatively common in women of childbearing age. Severe flares of autoimmune disease often require critical care admission for observation and treatment. Identifying autoimmune flares may be more challenging during pregnancy, as
| Autoimmune disease                                                                 | Autoantibodies                                                                 | Potential effect of antibodies on fetus/neonate                                                                 | Management                                                                 | Comments                                                                 |
|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Sjogrens Syndrome, SLE, Rheumatoid arthritis, other connective tissue diseases     | Anti-Ro/SSA                                                                   | Complete heart block and other cardiac pathologies (see main text). Transient neonatal cutaneous lupus          | Mother: Hydroxychloroquine Fetus: surveillance                             | A history of connective tissue disease should prompt antibody screening, even if the mother is asymptomatic. |
| Graves Disease                                                                    | TSH Receptor stimulating antibodies                                            | Thyrotoxicosis, goitre                                                                                            | Mother and/or neonate: Anti-thyroid drugs (Propylthiouracil or carbimazole). | A history of Graves disease should prompt antibody screening, even if the mother is euthyroid. |
| Pemphigoid gestationis (severe but rare pregnancy-specific dermatosis)           | Antibodies to Bullous Pemhigoid Antigen 2                                     | Bullous skin eruption (in 10%; usually mild and transient).                                                     | Mother: Corticosteroids, immunosuppression.                                |                                                                          |
| Pemphigus Vulgaris                                                                | Antibodies to Desmoglein 3 or 1                                                | Neonatal pemphigus                                                                                               | Mother: Corticosteroids, immunosuppression, therapeutic plasma exchange.   |                                                                          |
| Myasthenia Gravis                                                                  | Anti-AChR (90%) Anti-MuSK (10%)                                                 | Transient neonatal myasthenia gravis; floppy baby, difficulty breathing, respiratory compromise. Becomes apparent in first 2 days after birth and usually resolves within 2 months. | Mother and/or neonate: Acetylcholinesterase inhibitor drugs Mother: Corticosteroids, immunosuppression, IVIg, therapeutic plasma exchange. |                                                                          |
|                                                                                   | High titres of antibodies to fetal \( \gamma \) subunit of AChR               | Arthrogryposis; contractures and impaired swallowing; often fatal. Milder cases may survive with persistent myopathy. |                                                                          |                                                                          |
| Immune thrombocytopenic purpura (ITP)                                             | Anti-platelet antibodies (testing not readily available, and not required to make diagnosis) | Neonatal thrombocytopenia. There is a small risk of fetal/neonatal intracranial haemorrhage. | Mother and/or neonate: IVIg Mother: Corticosteroids, immunosuppression. | Neonatal platelet count reaches lowest point 2-5 days after birth in affected infants and most haemorrhages occur 24-48h after delivery. There is no evidence that caesarean section reduces the risk of intracranial haemorrhage. |

Fig. 15.4 Autoimmune disease-associated antibodies and the potential direct effects on the fetus during and after pregnancy
some features may overlap with normal pregnancy and/or pre-eclampsia. Some autoimmune diseases are associated with antibodies that cross the placenta, with potential to affect the fetus. Many immunosuppressive treatments can be used during pregnancy and should not be withheld, as uncontrolled maternal disease results in poorer outcomes for both mother and fetus. There is now good evidence that “biologic” anti-TNFα therapies can be used during pregnancy.

References

1. Mor G, Cardenas I. The immune system in pregnancy: a unique complexity. Am J Reprod Immunol. 2010;63(6):425–33.
2. Raphael I, Nalawade S, Eagar TN, Forsthuber TG. T cell subsets and their signature cytokines in autoimmune and inflammatory diseases. Cytokine. 2015;74(1):5–17.
3. Berker M, Frank LJ, Geßner AL, et al. Allergies—a T cells perspective in the era beyond the TH1/TH2 paradigm. Clin Immunol. 2017;174:73–83.
4. Marzi M, Vigano A, Trabattoni D, et al. Characterization of type 1 and type 2 cytokine production profile in physiologic and pathologic human pregnancy. Clin Exp Immunol. 1996;106(1):127–33.
5. Bonney EA. Immune regulation in pregnancy: a matter of perspective? Obstet Gynecol Clin North Am. 2016;43(4):679–98.
6. Aluvihare VR, Kallikourdis M, Betz AG. Regulatory T cells mediate maternal tolerance to the fetus. Nat Immunol. 2004;5(3):266–71.
7. Figureiredo AS, Schumacher A. The T helper type 17/regulatory T cell paradigm in pregnancy. Immunology. 2016;148(1):13–21.
8. Robertson SA, Moldenhauer LM. Immunological determinants of implantation success. Int J Dev Biol. 2014;58(2–4):205–17.
9. Sasaki Y, Darmochwal-Kolarz D, Suzuki D, et al. Proportion of peripheral blood and decidual CD4+(+)/CD25(bright) regulatory T cells in pre-eclampsia. Clin Exp Immunol. 2007;149(1):139–45.
10. Williams Z. Inducing tolerance to pregnancy. N Engl J Med. 2012;367(12):1159–61.
11. Baratelli F, Lin Y, Zhu L, et al. Prostaglandin E2 induces FOXP3 gene expression and T regulatory cell function in human CD4+ T cells. J Immunol. 2005;175(3):1483–90.
12. Khan D, Ansar AS. The immune system is a natural target for estrogen action: opposing effects of estrogen in two prototypical autoimmune diseases. Front Immunol. 2016;6:635.
13. Piccinini MP, Lombardelli L, Logiodice F, et al. How pregnancy can affect autoimmune diseases progression? Clin Mol Allergy. 2016;14:11.
14. Mor G. Inflammation and pregnancy: the role of toll-like receptors in trophoblast-immune interaction. Ann N Y Acad Sci. 2008;1127:121–8.
15. Romero R, Espinoza J, Kusanovic J, et al. The preterm parturition syndrome. BJOG. 2006;113(Suppl 3):17–42.
16. Kourtis AP, Read JS, Jamieson DJ. Pregnancy and infection. N Engl J Med. 2014;370(23):2211–8.
17. Knight, M et al. The UK Obstetric Surveillance System SARS-CoV-2 Infection in Pregnancy Collaborative Group. May 2020.
18. Siston AM, Rasmussen SA, Honein MA, et al. Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. JAMA. 2010;303(15):1517–25.
19. Raj RS, Bonney EA, Philippe M. Influenza, immune system, and pregnancy. Reprod Sci. 2014;21(12):1434–51.
20. Littauer EQ, Esser ES, Antao OQ, Vassilieva EV, Compans RW, Skountzou I. H1N1 influenza virus infection results in adverse pregnancy outcomes by disrupting tissue-specific hormonal regulation. PLoS Pathog. 2017;13(11):e1006757.
21. Navaneethan U, Mohajer MA, Shata MT. Hepatitis E and pregnancy—understanding the pathogenesis. Liver Int. 2008;28(9):1190–9.
22. Lawrence T. The nuclear factor NF-κB pathway in inflammation. Cold Spring Harb Perspect Biol. 2009;1(6):a001651.
23. McCracken SA, Drury CL, Lee HS, Morris JM. Pregnancy is associated with suppression of the nuclear factor kappaB/IκB activation pathway disrupting tissue-specific hormonal regulation. PLoS Pathog. 2017;13(11):e1006757.
24. Prusty BK, Hedau S, Singh A, Kar P, Das BC. Selective suppression of NF-κBp65 in hepatitis virus-infected pregnant women manifesting severe liver damage and high mortality. Mol Med. 2007;13:518–26.
25. Nelson-Piercy C. Handbook of obstetric medicine. 5th ed. Boca Raton: CRC Press; 2015.
26. The diagnosis and treatment of malaria in pregnancy. Royal College of Obstetricians and Gynaecologists Green–top Guideline No. 54b. 2010. https://www.rcog.org.uk/globalassets/documents/guidelines/gtg_54b.pdf. Accessed 13 Aug 2018.
27. Rogerson SJ, Mwapasa V, Meshnick SR. Malaria in pregnancy: linking immunity and pathogenesis to prevention. In: Breman JG, Aliillo MS, White NJ, editors. Defining and defeating the intolerable burden of malaria III: progress and perspectives: supplement to volume 77(6) of American Journal of Tropical Medicine and Hygiene. Northbrook: American Society of Tropical Medicine and Hygiene; 2007.
28. Lindsay S, Ansell J, Selman C, Cox V, Hamilton K, Walraven G. Effect of pregnancy on exposure to malaria mosquitoes. Lancet. 2000;355(9219):1972.
29. Maestre A, Carmona-Fonseca J. Immune responses during gestational malaria: a review of the current knowledge and future trend of a research. J Infect Dev Ctries. 2014;8(4):391–402.

30. To M, Kidd M, Maxwell D. Prenatal diagnosis and management of fetal infections. Obstet Gynecologist. 2009;11:108–16.

31. de Ruiter A, Taylor GP, Clayden P, Dhar J, Gandhi K, Gilleece Y, Harding K, Hay P, Kennedy J, Low-Beer N, Lyall H, Palfreeman A, O’Shea S, Tookey P, Tosswill J, Welch S, Wilkins E. British HIV Association. British HIV Association guidelines for the management of HIV infection in pregnant women 2012 (2014 interim review). HIV Med. 2014;15 Suppl 4:1–77.

32. Sappenfield E, Jamieson DJ, Kourtis AP. Pregnancy and susceptibility to infectious diseases. Infect Dis Obstet Gynecol. 2013;2013:752852.

33. Ranzani OT, Battaini LC, Moraes CE, et al. Outcomes and organ dysfunctions of critically ill patients with systemic lupus erythematosus and other systemic rheumatic diseases. Braz J Med Biol Res. 2011;44(11):1184–93.

34. Janssen NM, Karnad DR, Guntupalli KK. Rheumatologic diseases in the intensive care unit: epidemiology, clinical approach, management, and outcome. Crit Care Clin. 2002;18(4):729–48.

35. Quintero OL, Rojas-Villarraga A, Mantilla RD, et al. Autoimmune diseases in the intensive care unit. An update. Autoimmun Rev. 2013;12:380–95.

36. Knight M, Nair M, Kenyon S, et al. (Eds.) on behalf of MBRACE-UK. Saving lives, improving mothers’ care—surveillance of maternal deaths in the UK 2012–14 and lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2009–14. Oxford: National Perinatal Epidemiology Unit, University of Oxford. 2016. https://www.npeu.ox.ac.uk/downloads/files/mbrrace-uk/reports/MBRACE-UK%20Maternal%20Report%202015.pdf. Accessed 13 Aug 2018.

37. Cooper GS, Stroehla BC. The epidemiology of autoimmune diseases. Autoimmun Rev. 2003;2:119–25.

38. Brouwer J, Hazes JM, Laven JS, Dolhain RJ. Fertility in women with rheumatoid arthritis: influence of disease activity and medication. Ann Rheum Dis. 2015;74(10):1836–41.

39. Engdahl C, Jochems C, Windahl SH, et al. Amelioration of collagen-induced arthritis and immune-associated bone loss through signaling via estrogen receptor α, and not estrogen receptor β or G protein–coupled receptor 30. Arthritis Rheum. 2010;62(2):524–33.

40. Lelu K, Laffont S, Delpy L, et al. Estrogen receptor α signaling in T lymphocytes is required for estradiol-mediated inhibition of Th1 and Th17 cell differentiation and protection against experimental autoimmune encephalomyelitis. J Immunol. 2011;187(5):2386–93.

41. de Jong PH, Dolhain RJ. Fertility, pregnancy, and lactation in rheumatoid arthritis. Rheum Dis Clin North Am. 2017;43(2):227–37.

42. de Man YA, Dolhain RJ, van de Geijn FE, et al. Disease activity of rheumatoid arthritis during pregnancy: results from a nationwide prospective study. Arthritis Rheum. 2008;59(9):1241–8.

43. Confavreux C, Hutchinson M, Hours MM, et al. Rate of pregnancy-related relapse in multiple sclerosis. Pregnancy in Multiple Sclerosis Group. N Engl J Med. 1998;339(5):285–91.

44. Vaughan Jones S, Ambros-Rudolph C, Nelson-Piercy C. Skin disease in pregnancy. BMJ. 2014;348:g3489.

45. Weetman AP. Immunity, thyroid function and pregnancy: molecular mechanisms. Nat Rev Endocrinol. 2010;6(6):311–8.

46. Hviid A, Mølgaard-Nielsen D. Corticosteroid use during pregnancy and risk of orofacial clefts. CMAJ. 2011;183(7):796–804.

47. Götestam Skorpen C, Hoeltzenbein M, Tincani A, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Ann Rheum Dis. 2016;75(5):795–810.

48. Flint J, Panchal S, Hurrell A, van de Venne M, Gayed M, Schreiber K, Arthanari S, Cunningham J, Flanders L, Moore L, Crossley A, Purushotham N, Desai A, Piper M, Nisar M, Khamashita M, Williams D, Gordon C, Giles I, BSR and BHPR Standards, Guidelines and Audit Working Group. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding—part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. Rheumatology (Oxford). 2016;55(9):1693–7.

49. Andreoli L, Bertssias GK, Agmon-Levin N, et al. EULAR recommendations for women’s health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or anti-phospholipid syndrome. Ann Rheum Dis. 2017;76(3):476–85.

50. Cox JL, Koepfell SA, Shunkwiler SM. Therapeutic plasma exchange and pregnancy: a case report and guidelines for performing plasma exchange in a pregnant patient. J Clin Apher. 2017;32(3):191–5.

51. Ahmed AR, Gürcan HM. Use of intravenous immunoglobulin therapy during pregnancy in patients with pemphigus vulgaris. J Eur Acad Dermatol Venereol. 2011;25(9):1073–9.

52. Chevret S, Hughes RAC, Annane D. Plasma exchange for Guillain-Barré syndrome. Cochrane Database Syst Rev. 2017;2:CD001798.

53. Nelson-Piercy C, Agarwal S, Lams B. Lesson of the month: selective use of cyclophosphamide in pregnancy for severe autoimmune respiratory disease. Thorax. 2016;71(7):667–8.

54. Amant F, Loibl S, Neven P, Van Calsteren K. Breast cancer in pregnancy. Lancet. 2012;379(9815):570–9.
213
55. Lee EJ, Ahn KH, Hong SC, Lee EH, Park Y, Kim BS. Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy for diffuse large B-cell lymphoma in pregnancy may be associated with preterm birth. Obstet Gynecol Sci. 2014;57(6):526–9.
56. Cauldwell M, Nelson-Piercy C. Maternal and fetal complications of systemic lupus erythematosus. Obstetrician Gynaecologist. 2012;14:167–74.
57. Khamashia MA. Systemic lupus erythematosus and pregnancy. Best Pract Res Clin Rheumatol. 2006;20(4):685–94.
58. Soh M, Nelson-Piercy C. High-risk pregnancy and the rheumatologist. Rheumatology (Oxford). 2015;54(4):572–87.
59. Petri M. The Hopkins Lupus Pregnancy Center: ten key issues in management. Rheum Dis Clin North Am. 2007;33(2):227–35.
60. Lateef A, Petri M. Systemic lupus erythematosus and pregnancy. Rheum Dis Clin North Am. 2017;43(2):215–26.
61. Bertsias GK, Tektonidou M, Amoura Z, et al. Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. Ann Rheum Dis. 2012;71(11):1771–82.
62. Lateef A, Petri M. Managing lupus patients during pregnancy. Best Pract Res Clin Rheumatol. 2013;27(3):435–47.
63. Brooks H, Christian AS, May AE. Pregnancy, anaesthesia and Guillain-Barré syndrome. Anaesthesia. 2000;55(9):894–8.
64. Hughes RAC, Wijdicks EFM, Benson E, et al. Supportive care for patients with Guillain-Barré syndrome. Arch Neurol. 2005;62(8):1194–8.
65. Bedson R, Riccoboni A. Physiology of pregnancy: clinical anaesthetic implications. Cont Educ Anaesth Crit Care Pain. 2014;14:69–72.
66. Hughes RAC, Swan AV, van Doorn PA. Intravenous immunoglobulin for Guillain-Barré syndrome. Cochrane Database Syst Rev. 2014;(9):CD002063.
67. Hughes RAC, Brassington R, Gunn A, van Doorn PA. Corticosteroids for Guillain-Barré syndrome. Cochrane Database Syst Rev. 2016;10:CD001446.
68. Kaplan AA, Fridey JL. Therapeutic apheresis (plasma exchange or cytapheresis): complications. In: Post TW, editor. UpToDate. Waltham: UpToDate; 2014. https://www.uptodate.com/contents/therapeutic-apheresis-plasma-exchange-or-cytapheresis-complications. Accessed 27 Apr 2018.
69. Donofrio PD, Berger A, Brannagan TH 3rd, Bromberg MB, Howard JF, Latov N, Quick A, Tandan R. Consensus statement: the use of intravenous immunoglobulin in the treatment of neuromuscular conditions report of the AAEM Ad Hoc Committee. Muscle Nerve. 2009;40(5):890–900.
70. Caress JB, Hobson-Webb L, Passmore LV, Finkbiner AP, Cartwright MS. Case-control study of thromboembolic events associated with IV immunoglobulin. J Neurol. 2009;256(3):339–42.
71. Palmeira P, Quinello C, Silveira-Lessa AL, et al. IgG placent transfer in healthy and pathological pregnancies. Clin Dev Immunol. 2012;2012:985646.
72. McMillan M, Clarke M, Parrella A, et al. Safety of tetanus, diphtheria, and pertussis vaccination during pregnancy: a systematic review. Obstet Gynecol. 2017;129(3):560–73.
73. Donegan K, King B, Bryan P. Safety of pertussis vaccination in pregnant women in UK: observational study. BMJ. 2014;349:g4219.
74. Martínez-Sánchez N, Pérez-Pinto S, Robles-Marhuenda A, Arnalich-Fernández F, Martín Cameán M, Hueso Zalvide E, Bartha JL. Obstetric and perinatal outcome in anti-Ro/SSA-positive pregnant women: a prospective cohort study. Immunol Res. 2017;65(2):487–94.
75. Donofrio MT, Moon-Grady AJ, Hornberger LK, et al. Diagnosis and treatment of fetal cardiac disease: a scientific statement from the American Heart Association. Circulation. 2014;129:2183–242.
76. Cuneo BF, Fruitman D, Benson DW, et al. Spontaneous rupture of atrioventricular valve tensor apparatus as late manifestation of anti-Ro/SSA antibody mediated cardiac disease. Am J Cardiol. 2011;107:761–6.
77. Mahadevan U, Martin C, Sandler R, et al. PIANO: a 1000 patient prospective registry of pregnancy outcomes in women with IBD exposed to immunomodulators and biologic therapy (abstr 865). Gastroenterology. 2012;142(suppl 1):S-149.
78. Nielsen OH, Loftus EV Jr, Jess T. Safety of TNF-alpha inhibitors during IBD pregnancy: a systematic review. BMC Med. 2013;11:174.