



The implications of autoimmunity and pregnancy

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A B S T R A C T

There are multiple epidemiological studies that document the potential adverse affects of autoimmunity on nearly every aspect of reproduction, even in the absence of clinically manifest autoimmune disease. Two decades ago, it was suggested that women with autoimmune diseases avoid pregnancy due to inordinate risks to the mother and the child. In contrast, newer epidemiological data demonstrated that advances in the treatment of autoimmune diseases and the management of pregnant women with these diseases have similarly improved the prognosis for mother and child. In particular, if pregnancy is planned during periods of inactive or stable disease, the result often is giving birth to healthy full-term babies without increased risks of pregnancy complications. Nonetheless, pregnancies in most autoimmune diseases are still classified as high risk because of the potential for major complications. These complications include disease exacerbations during gestation and increased perinatal mortality and morbidity in most autoimmune diseases, whereas fetal mortality is characteristic of the anti-phospholipid syndrome (APS). In this review, we will discuss these topics, including issues of hormones, along with potential long-term effects of the microchimerism phenomenon. With respect to pregnancy and autoimmune diseases, epidemiological studies have attempted to address the following questions: 1) Is it safe for the mother to become pregnant or are there acute or chronic effects of pregnancy on the course of the disease? 2) Does the disease alter the course and/or the outcome of a pregnancy and thereby represent an inordinate risk for the fetus and infant? And do new therapeutic and management approaches improve the pregnancy outcomes in women with autoimmune diseases? 3) Does passage of maternal autoantibodies represent a risk to the child? 4) Do pregnancy, parity, or other factors influencing hormonal status explain the female predominance of many autoimmune diseases, and is the pregnancy effect related to microchimerism? Answering these questions has taken on additional importance in recent decades as women in western countries now frequently choose to delay pregnancies and have some or all of their pregnancies after disease onset. In this paper, we primarily focus on APS, systemic lupus erythematosus (SLE), multiple sclerosis (MS), rheumatoid arthritis (RA), and type 1 diabetes (T1D).

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1. Introduction

It is increasingly recognized that autoimmunity even in the absence of clinically manifest autoimmune disease can affect every aspect of pregnancy, beginning with fertilization, and can contribute to maternal complications and adverse fetal outcomes. By examining associations between specific autoantibodies and pregnancy-related processes, epidemiology has an important role in identifying potentially pathogenic autoantibodies (and ruling out the involvement of others). Most autoimmune diseases occur much more frequently in women than in men, with female:male ratios ranging from ~2:1 in MS and ~3:1 in RA to ~10:1 in systemic

lupus erythematosus SLE, 12:1 in APS, and possibly even higher (up to 16:1) in primary biliary cirrhosis (PBC). This suggests the possibility that sex hormones influence the development of autoimmunity. Dramatic changes in the levels of estrogens and progesterone, but also cortisol, norepinephrine, and dehydroepiandrosterone, occur during pregnancy. At the same time, and partially under the influence of these hormones, there are profound immunological changes throughout pregnancy and during the post-partum period. These immunological changes are required in order to accommodate the semiallogeneic fetus and include immunosuppressive and immunoregulatory processes. Whereas a Th1-dominated milieu is required for successful implantation and the subsequent vascular and tissue remodeling of the uterus, later gestation is mainly a Th2-dominated state.

Both the hormonal and immunological changes have marked effects on the course of autoimmune disease, and the nature of the

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disease determines whether these effects are detrimental or beneficial. In turn, the disease course during gestation and the underlying immunological and possibly hormonal abnormalities of the disease may affect the course and outcome of the pregnancy.

2. Autoimmunity and fertility, pregnancy complications, and adverse fetal outcomes

A large variety of autoantibodies have been investigated for their potential association with unexplained infertility – often with inconclusive results [1]. For example, there is little evidence in support for a role of autoimmunity in isolated premature ovarian failure, one of the major causes of female infertility. Of note, fertility does not appear to be impaired in most autoimmune diseases, except in women treated with cytotoxic agents, particularly cyclophosphamide, or high-dose corticosteroids, or suffering from renal insufficiency. This even holds for women with SLE, a disease characterized by high prevalence rates of some of the autoantibodies that have been implicated in infertility (e.g. anti-dsDNA and anti-nuclear antibodies in ~90% and anti-phospholipid antibodies (aPL) in 20–60% of patients, respectively). There is considerable evidence, however, that autoimmunity plays a major role in premature ovarian failure associated with endocrine autoimmune diseases, such as thyroid disease or Addison's disease [1,2].

A considerable variety of non-organ-specific autoantibodies also have been implicated in pregnancy losses, although the results for many of them are contradictory [3]. Notable exceptions are aPL and anti-thyroid antibodies. As will be discussed in more detail below, recurrent spontaneous abortions are one of the diagnostic criteria of the APS. Even in the absence of APS, the association between aPL and fetal loss is well documented, though it is not observed in all investigations. Numerous studies from the US, various European regions, some Asian countries and Brazil have investigated the association between thyroid autoimmunity and miscarriage. The vast majority of these studies indicates that the presence of thyroid autoantibodies even in the absence of clinical or subclinical thyroid dysfunction increases the risk of miscarriage, particularly of pregnancy losses occurring in the first trimester. There appears to be considerable geographic variation in the prevalence of thyroid autoantibodies. Nonetheless, there is no discernible pattern in the geographic distribution of studies that did not find a significant association. A meta-analysis yielded a total odds ratio of 2.73 (CI 2.2–3.40) for eight case-control studies, and of 2.30 (CI 1.80–2.95) for 10 prospective cohort studies [4]. Interestingly, higher autoantibody titers do not confer an increased risk of miscarriage or spontaneous abortion. Whether the observed association reflects a causal relationship remains to be determined. It is also possible that the presence of thyroid autoimmunity is an epiphenomenon or marker for an underlying more general activation of the immune system, is an indicator of subtle thyroid hormone deficiency, or reflects the significantly higher age of women with thyroid antibodies, age being an independent risk factor for miscarriage.

One of the most severe complications of pregnancy is preeclampsia, which affects 1–5% of pregnancies worldwide in otherwise healthy women, the frequency being much higher in a variety of autoimmune diseases, e.g. APS, T1D, SLE, systemic sclerosis, RA, and other connective tissue diseases. Several autoantibodies have been investigated for their association with preeclampsia, but the strongest evidence exists for aPL, although evidence in women without autoimmune diseases is inconsistent [5,6]. In addition, much recent interest has focused on autoantibodies that stimulate the angiotensin II type 1 (AT1) receptor [7]. Several lines of evidence suggest a pathological role for these autoantibodies in preeclampsia: 1) their ability to activate the AT1 receptor on a variety of cell types has been shown to result in

biological responses that are known to participate in the vascular and placental abnormalities characteristic of preeclampsia; 2) they induce clinical features of preeclampsia when transferred into pregnant mice; and 3) they are found with high frequency (70–90%) in women with preeclampsia and are detectable before the onset of this condition and remain detectable post-partum in some women [8]. Unfortunately, all available prevalence data come from German women, although anti-AT1 antibodies also have been detected in women from the US and the UK [9]. There are also several arguments against a causal role of these antibodies in the development of preeclampsia: 1) their titers do not correlate with confirmed markers of preeclampsia; and 2) they are not specific to this condition. These findings suggest that they are markers for this pregnancy complication rather than being causally involved in it. Nonetheless, it remains possible that they have a pathological role if combined with some other factor(s).

There are also indications that autoantibodies can affect pregnancy outcomes. Once again, the most convincing evidence exists for associations between aPL or thyroid autoimmunity and preterm delivery [10]. In addition thyroid autoantibodies have been implicated in lower birth weight and in perinatal mortality. Numerous other associations have been suggested but the data are as yet inconclusive.

3. Autoimmune diseases and pregnancy

3.1. Anti-phospholipid syndrome

APS is characterized by thrombosis or pregnancy complications in the presence of aPL. The Sapporo preliminary classification criteria for APS published in 1999 as well as the revised Sydney criteria from 2006 require the presence of at least one clinical criterion, either vascular thrombosis or pregnancy morbidity, in combination with at least one laboratory criterion [11]. The laboratory criteria are a) positivity for lupus anticoagulant (LAC), b) medium or high titer anticardiolipin (aCL) of the IgG and/or IgM isotype, and c) positivity for anti- β 2-glycoprotein 1 (anti- β 2GPI) of the IgG and/or IgM isotype, the latter were added as part of the Sydney revisions. APS is called primary when it occurs in the absence of other autoimmune diseases and is still commonly referred to as secondary if it is present in conjunction with other autoimmune diseases, primarily SLE, but also SS, RA, SSc, systemic vasculitis and dermatomyositis. (For simplicity, we will refer to this subgroup as APS/SLE). The revised Sydney classification criteria discourage the use of the term “secondary” because it is unclear whether SLE or other connective tissue diseases provide a setting for the development of APS or whether they each represent independent disease entities coinciding in the same individual.

Information on the incidence, prevalence and demographics of APS are rare, but data from a recent European multicenter study of 1000 APS patients (the Euro-Phospholipid Project) and a Spanish and a Latin American cohort of 100 patients each indicate that APS occurs slightly more frequently in the absence than in the presence of other autoimmune diseases [12–14]. More specifically, between 53 and 62% of patients were found to have primary APS (pAPS), while 38–41% had APS associated with SLE or lupus-like syndrome (fulfilling only 2–3 ACR criteria for SLE), the remainder being divided between other connective tissue diseases. Like most autoimmune diseases, APS is more common in women than in men, the overall female to male ratio being 5 or 6:1 in the European cohorts, but 13:1 in Latin American patients. Interestingly, the female:male ratio for pAPS was 3.5:1 in Europe, but 12:1 in Latin America [12,15]. Mean age of onset was between 28 and 36 years for the various European and Latin American cohorts, with a vast majority of cases reported to occur between the ages of 15 and 50 years [12].

This indicates that women in their childbearing years are frequently affected.

3.1.1. Pregnancy morbidity

The specific pregnancy morbidity criteria for APS are a) one or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation; b) one or more premature births of a morphologically normal neonate before the 34th week of gestation because of either eclampsia or severe preeclampsia or placental insufficiency; or c) three or more unexplained consecutive spontaneous abortions before the 10th week of gestation in the absence of anatomic, hormonal or chromosomal causes. This highlights one of the major differences between APS and other autoimmune diseases: whereas other autoimmune diseases may affect the course of pregnancy, pregnancy morbidity is a manifestation and a defining feature of APS. While late fetal loss is considered to be more characteristic of APS, recurrent early fetal loss is more common.

Before the advent of treatment, the prognosis for pregnancies in APS patients was dismal, with only 10% or less of all pregnancies resulting in live births [16,17], although others have reported somewhat better outcomes. It has become common practice to treat pregnant APS patients or SLE patients with aPL even in the absence of clinical manifestations of APS with low-dose aspirin alone or in combination with heparin, but considerable controversy remains as to the most appropriate approach [18]. Since the introduction of such preventive regimens, the pregnancy outcome among women with APS has improved dramatically. This is partially reflected in the data from the Euro-Phospholipid cohort, where the live birth rate was 47.7% in 590 women who had been pregnant [12]. As summarized in Table 1, the live birth rate in Latin American women was very similar, even though the study period was considerably later [14,15]. Interestingly, however, there were significant differences in the distribution of fetal losses. Mexican, Ecuadorian, and Colombian women with APS experienced early pregnancy loss significantly more often than their European counterparts, whereas their late pregnancy loss rate was lower, the latter reaching statistical significance only in patients with pAPS [14,15]. During a further 5 years of follow-up, the live birth rate in the European cohort improved significantly to 76.2%, with early and late pregnancy losses occurring in 17.1% and 6.7% of pregnancies, respectively [19]. This is consistent with numerous other studies showing success rates of 70–80% in pregnancies of women with APS who receive aspirin alone or in combination with heparin or other preventive regimens.

While the pregnancy outcome has improved significantly in recent years, the complication rates remain high. Typical complications in women with APS are preeclampsia/eclampsia, intra-uterine growth restriction (IUGR), premature rupture of membrane, Cesarean delivery and premature delivery, the latter being primarily due to preeclampsia/eclampsia or placental insufficiency. Overall, the reported rates of preeclampsia range between 0 and 51% and those for preterm delivery between 32 and 65% [20]. The Euro-Phospholipid study revealed preeclampsia in 9.5%, eclampsia

in 4.4%, premature rupture of membranes in 2.0%, and post-partum cardiopulmonary syndrome in 0.5% of pregnancies [12]. A substantial number of babies is born small for gestational age (SGA). As summarized in Table 1, the rates for hypertensive disorders and premature delivery were similar in the South American cohorts. Premature delivery was seen in 10.6% of the European pregnancies, but this figure rose to 35% in the pregnancies that occurred during follow-up, [19]. In addition, IUGR occurred in 13.7% of pregnancies. An analysis of nationwide obstetric hospitalization data in the USA similarly showed that women with APS had a significantly increased frequency of hypertensive disorders (13.0%), IUGR (5.1%), premature rupture of membranes (1.8%) and cesarean delivery (44.6%) compared to the general obstetric population [21]. Women with APS were significantly older, but even after adjusting for age, their risk of these pregnancy complications remained significantly elevated. There are indications that the complication rates, particularly for preterm delivery, giving birth to an SGA baby and preeclampsia, are higher in women who have thrombotic manifestations of APS [22].

3.1.2. Possible effects of pregnancy morbidity on the disease course

From the limited available data, it is difficult to determine whether recurrent pregnancy loss represents a risk factor for subsequent thrombosis in APS patients. One of the few prospective studies examining this issue used a definition of ≥ 2 miscarriages as recurrent pregnancy loss and compared patients with aPL with or without clinical manifestations of APS [23]. In this investigation, miscarriages were not significantly associated with the subsequent occurrence of thrombosis, whereas a history of vascular disease constituted a risk factor for subsequent miscarriages. This is consistent with other observations, including the finding from the Euro-Phospholipid cohort, where only 2.5% of women with exclusively obstetric APS manifestations at study begin developed a thrombotic event during 5 years of follow-up [19,24]. These findings are in marked contrast to the results of a retrospective analysis of data from three tertiary referral centers in the USA on 65 patients whose only clinical manifestation for the diagnosis of APS was recurrent pregnancy loss [25]. This subgroup of APS patients was found to be at high risk of subsequent thrombosis, particularly when not continuously treated with low-dose aspirin for the prevention of thrombotic events. Specifically, the non-aspirin-treated group of 34 patients had 20 events, including 7 venous thromboses, 5 strokes, and 5 transient ischemic attacks, during a mean follow-up of ~ 8 years, resulting in an event rate of 7.4/100 patient-years, whereas the aspirin-treated group had an event rate of 1.3/100 patient-years. Mean duration from initial pregnancy loss to clinical event was 4.2 years. Of note, pregnancy and the post-partum period may also represent a time of particular susceptibility to catastrophic APS (for more details, the reader is referred to [26,27]).

3.1.3. Antibodies in APS

The diagnosis of APS is first and foremost clinical. At the same time, it is crucially dependent on serological markers because of the

Table 1
Pregnancy morbidity in women with APS.

Country	Study period	No. of patients/ pregnancies	Early fetal loss	Late fetal loss	Live births	Preeclampsia/ eclampsia	Premature Births	Reference
Europe (13 countries)	1990–1999	590/1580	35.4	16.9	47.7	9.5/4.4	10.6	[12]
Europe (13 countries)	1999–2004	77/105	17.1	6.7	76.2		35.0	[19]
Mexico & Ecuador	2000–2005	66/266	49.6	5.6	44.7	7.6	16.8	[14]
Mexico, Ecuador, and Colombia – pAPS	2000–2006	77/266	54.1	1.1	44.7	1.5	3.0	[15]
Euro-Phospholipid – pAPS	1990–1999	307/928	44.4	16.6	39.0	4.0	4.3	[15]

high prevalence of thrombosis and pregnancy complications in the generally population. The classical aPL, LA and aCL, remain the major serological markers of APS. These antibodies were originally thought to bind directly to negatively charged membrane phospholipids. It has since become recognized that aPL constitute a heterogeneous group of antibodies that recognize negatively charged phospholipids, phospholipid-binding plasma proteins or complexes of the two. It is now widely accepted that the major target antigen of aCL and many LA is β 2-glycoprotein I (β 2GPI). Other plasma proteins that are targets of the humoral response in APS include prothrombin, annexin V, and proteins C, protein S, and Z. In addition, a long list of other autoantibodies have been identified in APS patients [28]. It should be pointed out that, despite efforts to standardize assays for LA, aCL and anti- β 2GPI, inter-assay and inter-laboratory agreement remains rather poor due to calibration and other methodological issues, but mainly because the cut-off values for positivity vary widely.

The inclusion of anti- β 2GPI antibodies among the laboratory criteria for the classification of APS did not find unanimous support, and their utility in comparison to LA or aCL remains controversial. However, β 2GPI is a potent natural anticoagulant and this activity appears to be abrogated by anti- β 2GPI antibodies. Therefore, enhanced uteroplacental thrombosis could be one mechanism by which these antibodies affect pregnancy outcome. In addition, β 2GPI is expressed by the trophoblast starting at 7 weeks of gestation, and anti- β 2GPI antibodies have been shown to be capable of binding to trophoblast cells in vitro. Furthermore, these antibodies have been implicated in abnormal trophoblast proliferation and placentation, and inflammatory mechanisms may play a role in these processes [29,30]. Together, these findings suggest a pathogenic role for these autoantibodies in the obstetric manifestations of APS. This has prompted numerous investigations of the possible association between anti- β 2GPI antibodies and pregnancy morbidity, with highly varying results. In a group of Viennese women who were persistently positive for LA, anti- β 2GPI antibodies were significantly associated with pregnancy loss [24]. This is consistent with earlier findings from Argentine women whose APS was diagnosed because of recurrent fetal loss and who were compared with parous women who were also positive for aCL and/or LA, but had no history of reproductive problems [31]. A significantly higher frequency of IgM anti- β 2GPI distinguished the women with a history of recurrent fetal from those without reproductive failure. In addition, the subgroup with late pregnancy loss showed higher levels of IgM aCL as well as IgM and IgG anti- β 2GPI. The same group of researchers found IgM anti- β 2GPI to be significantly associated with fetal loss in a group of aPL-positive patients with various clinical manifestations of this syndrome [32]. In contrast, others reported that the IgG isotype of anti- β 2GPI was associated with fetal loss in patients with either pAPS or APS/SLE, whereas IgM was not [33]. In a study from the UK, women who were persistently positive for aPL and had experienced recurrent fetal loss had a similar frequency of anti- β 2GPI as women with recurrent fetal loss who were persistently negative for aPL or healthy controls [34]. Similarly conflicting results have been obtained in investigations of SLE patients with or without APS or aPL. In Colombian and Spanish SLE patients, IgG anti- β 2GPI, but not IgM, correlated with a history of fetal loss [35], and a very strong association between IgG anti- β 2GPI (IgM was not investigated) has also been reported from Thailand [36]. In contrast, others did not detect any significant association in a large US cohort [37], and smaller cohorts from India or Japan [38,39].

The results of a recent meta-analysis do not support a role for anti- β 2GPI (IgM or IgG) in recurrent pregnancy loss in women without autoimmune diseases [40] and this is consistent with more recent studies from Italy, the Czech Republic, Israel and Tunisia

[41–44]. However, there are data suggesting that anti- β 2GPI of the IgA isotype is significantly associated with ≥ 3 pregnancy losses at less than 10 weeks of gestation or unexplained fetal death at >10 weeks of gestation [45]. Both the frequency and the levels of IgA anti- β 2GPI were found to be higher in these women compared to normal parous women. In another study, however, IgA anti- β 2GPI was not associated with recurrent pregnancy loss [42]. In Tunisian women, positivity for anti- β 2GPI did not correlate with recurrent pregnancy loss overall, but the IgM isotype showed a significant association with early pregnancy loss, while IgG was associated with late pregnancy loss [46,47]. In addition, the results of a large prospective trial in women with 510 healthy pregnant women indicated that anti- β 2GPI antibodies were significantly associated with preeclampsia/eclampsia even in the absence of LA or aCL [5].

Of note, the Sidney criteria now recognize that multiple positivity for aPL confers a risk factor for more severe manifestations of APS [11]. In a group of 53 Italian women with APS and positive for aCL and anti- β 2GPI, additional positivity for LA (triple positivity) was significantly associated with late pregnancy loss [48]. Triple positivity also correlated with the presence of thromboembolic events, and the combination of such an event and triple positivity was found to be an independent predictor of another unsuccessful pregnancy during a mean duration of follow-up of 6.3 years. Similar findings were reported in another study from the same center, which included 79 APS patients with 97 pregnancies [49]. Patients with triple positivity were found to have a significantly higher rate of pregnancy loss compared to women with double positivity (aCL and anti- β 2GPI without LA). Although it was also higher compared to single positive patients, the difference did not reach statistical significance.

It is currently impossible to determine to what extent ethnic differences contribute to these discrepancies. Too many other factors make direct comparison between these studies impossible. These include differences in patient selection, the definition of recurrent pregnancy loss, assay methods for detecting anti- β 2GPI and the cut-off values used for determining positivity. Of note, a group of European researchers recently provided rather convincing evidence that the most relevant anti- β 2GPI antibodies are those recognizing domain I of this protein [50]. Using sera from 200 women from nine tertiary rheumatology centers in Europe, it was shown that this subset of anti- β 2GPI antibodies correlated significantly with two of the three obstetric criteria of APS, namely fetal death beyond the 10th week of gestation and a history of premature birth(s) before the 34th week of gestation due to preeclampsia or placental insufficiency. When using an assay that detects antibodies against the complete β 2GPI protein, these researchers did not observe a significant association with any obstetric APS criteria. Whether this domain dependence provides an explanation for some of the observed discrepancies remains to be established.

Data for antibodies to other phospholipid-binding proteins that are not included among the laboratory criteria for the classification of APS are equally inconsistent. While some studies identify anti-prothrombin antibodies as a strong risk factor for early pregnancy loss in APS patients [39,43], others do not detect a significant association in APS or SLE patients [31,32,51] or women with recurrent miscarriages in Italian women [41]. Anti-annexin V antibodies have been found to be significantly associated with recurrent miscarriage in studies from such geographically diverse areas as Italy, Tunisia, and Japan [39,41,44,46,52], but this is not a consistent finding either [34,53]. Finally, the results from a large Czech study indicate that antibodies against various negatively charged phospholipids, in particular phosphatidylinositol and phosphatidylserine, were significantly more frequent in women with ≥ 3 miscarriages or repeated in vitro fertilization failure [42].

3.1.4. Prevalence, isotype distribution, and clinical associations of aPL in different populations

The prevalence of LAC and aCL in the general population shows considerable geographic variation, ranging between of 0.3% and ~4% for LAC in subjects from the USA, Canada, various European and some Arab countries. Interestingly, a much higher prevalence (7%) was recently reported from healthy parous Tunisian women [44]. The corresponding figures for aCL are 1–4% for IgG, 0.5–5% IgM, and 2–5% for IgG/IgM combined. In patients with APS or SLE, there are at least equally pronounced geographical or ethnic differences in the prevalence and isotype distribution of aPL, and these are accompanied by differences in their clinical associations. The frequency of aCL positivity in SLE patients of European descent generally ranges between 25% and 40%, but appears to be significantly lower in Asian cohorts [54], while markedly higher rates (>70%) have been reported in patients from several Arab countries [55,56], though not in others [57,58]. Whereas earlier data from India indicated a similarly low prevalence of aCL as observed in other Asian cohorts, a more recent analysis reported detection of aCL in of 51% in Indian SLE patients [38]. Although all were positive for IgG either alone or in combination with other isotypes, only the presence of seizures was associated with aCL (or anti- β 2GPI) positivity, whereas venous thrombosis was rare in this population, and neither thrombosis nor recurrent pregnancy loss showed an association with either of these antibodies [38]. A significantly lower prevalence of any aPL (LAC or aCL) has also been reported for Chinese SLE patients compared to non-Chinese patients from the USA (African American of European ancestry), and this correlated with a markedly lower frequency of venous thrombosis [59].

Positivity for aCL and/or LA is a criterion for the diagnosis of APS, and isolated anti- β 2GPI positivity is relatively rare. Consequently, the prevalence of the classical aPL is high among APS patients. Among the 1000 participants of the Euro-Phospholipid Project, more patients had aCL (87.9%) than LA (53.6%) [12]. Two studies from Latin America used the same protocol for the assessment of clinical and laboratory characteristics as the Euro-Phospholipid Project, allowing direct comparison of the results. These showed that mestizo APS patients from Mexico and Ecuador had a very similar frequency of aCL positivity overall (88.1%), but a significantly lower proportion of patients was positive for the IgG isotype of aCL alone (22% versus 43.6%) [14]. In addition, significantly fewer mestizo patients had LA (38.5% versus 53.6%). Interestingly, a comparison between patients with pAPS from Mexico, Ecuador, and Colombia with pAPS patients from the Euro-Phospholipid Project did not reveal any significant differences in the frequency and isotype distribution of aPL, except that aCL of the IgM isotype was less prevalent among Europeans compared to Latin Americans [15]. This was not observed in a direct comparison of Colombian and Spanish SLE patients [35]. However, the Colombian and Spanish patient groups differed in the frequency and isotype distribution of anti- β 2GPI antibodies, with IgG being the major isotype in Colombians and IgM predominating in Spaniards. Notably, both IgG aCL and IgG anti- β 2GPI were associated with thrombosis and fetal loss in Colombian as well as Spanish SLE patients; however they were additionally associated with livedo reticularis among Spaniards, but with thrombocytopenia in Colombians. There are numerous indications that IgA is the most frequent isotype of aCL and anti- β 2GPI antibodies in African American as well as South African APS and SLE patients [37,51,60,61]. Although generally aCL and/or anti- β 2GPI of the IgG isotype are most strongly implicated in the clinical manifestations of APS, in two of these studies IgA aCL was found to be associated with thrombosis, but not with recurrent pregnancy loss in African American patients [61], and with any clinical APS manifestation in South African patients [51]. Unfortunately, aCL, LA, or anti- β 2GPI of the IgA isotype are not routinely

measured, and other data on their association with clinical manifestations are limited and controversial.

It is obvious that ethnic differences in the prevalence and isotype distribution could account for some of the disparities seen in the rates of pregnancy complications reported in cohorts from different geographical areas and for some of the discrepant results obtained in investigations of the clinical association of various aPL. Unfortunately, the patient selection criteria and the assay techniques used are too variable to allow determination of the extent to which ethnic differences may play a role.

3.1.4.1. Systemic lupus erythematosus. SLE is a systemic autoimmune disease that affects primarily women in their childbearing years, the female:male ratio being ~10:1. The presence of SLE was long thought to be a contraindication to pregnancy since early studies indicated that the disease represented a high risk of detrimental outcomes to both the mother and the fetus. With the advent of more effective therapeutic regimens, the outlook has improved considerably in recent decades. Only women with SLE who have pulmonary hypertension and renal failure are still strongly advised not to become pregnant because of the high risk of mortality to both the mother and child. Actually the effect of pregnancy on disease activity has long been and remains a matter of debate. The proportion of women experiencing flares during pregnancy varies enormously between studies, ranging from 2% in Indian and 4% in a Portuguese SLE patients to 85% in a Brazilian cohort that included almost 40% of patients with probable or possible SLE (see also Table 2). Relatively few studies compared the flare frequency during pregnancy and post-partum to that of the pre- or post-pregnancy period or to that in a control group of non-pregnant SLE patients. The results are quite variable, with prospectively gathered data from a US cohort (the Hopkins lupus cohort) indicating that flare frequency increases during pregnancy regardless of whether patients serve as their own controls or are compared to a control group of non-pregnant patients with SLE [62]. Similar results have been reported from a Spanish cohort [63]. In contrast, disease exacerbations occurred with similar frequency in pregnant (13.5%) and non-pregnant Greek SLE (22%) patients [64]. A major cause of these discrepancies is likely to be the lack of a standardized definition of flare.

There is considerable variability in the types and frequencies of pregnancy complications that have been reported in SLE in the literature. In addition, direct comparisons with healthy controls are rarely included. Notable exceptions are two analyses of nationwide obstetric hospitalization data in the US. These studies demonstrate that women with SLE were significantly older than controls but, even after adjusting for age, were at increased risk of hypertensive disorders including preeclampsia, cesarean delivery, preterm delivery and IUGR compared to the general obstetric population [21,65]. Other fetal outcomes could not be assessed in these studies. In addition, SLE was associated with a markedly elevated risk of infection, thrombosis and thrombocytopenia and, most notably, an almost 18-fold higher risk of maternal mortality. These results agree with other investigations, which in addition indicate that pregnant SLE patients have a significantly increased frequency of fetal loss, including spontaneous abortions, miscarriages, and stillbirths (see also Table 3). Their infants more often have low birth weight (LBW), and neonatal mortality is increased. Furthermore, SLE patients frequently (25–65%) harbor anti-SSA/SSB antibodies, which are tightly associated with the risk of neonatal lupus syndrome, one of several examples of the detrimental effects that can result from transplacental passage of maternal autoantibodies (discussed in more detail below). Of particular note, some of the pregnancy complications and adverse fetal outcomes are already seen in women who only later are diagnosed with SLE [66].

Table 2

Flare frequency and pregnancy complications in SLE patients (percentage of patients affected).

Country	Study period	No. of patients/ pregnancies	Flares during pregnancy	Flare up to 1 year after	Preeclampsia	Hypertensive complications	Cesarean	Reference
Portugal	1993–2007	107/136	4.0			14	45.0	[111]
Portugal	1993–2007	43/51	21	2 puerperium, 8 later				[112]
USA	2002	~4425				23.2	39.4	[21]
USA	2000–2003	~13,555			22.5		36.6	[65]
Spain	1985–1996	46/60	28.3		7.5	18.9	26.4	[113]
Spain	1986–1999	60/103	33		3.3	8		[63]
Greece	1982–1997	47/59	13.5					[64]
France	1982–1995	38/62					18.8	[114]
UK	~1989–1994	90/108	40	24				[115]
Argentina	1986–2004	61/72	19.4	4.1 puerperium	11	20.8	63.6	[116]
Brazil (juvenile SLE)		24/28	8				26	Silva [117]
Brazil 62% ACR	1995–2002	67/76	85.3		11.8	26.3	68.6	[118]
India		17/33	27		3.7			[119]
India	1989–2002	31/52	2	4				[120]
Taiwan	2000–2005	17/24	0	19.2	12.5			[121]
Malaysia	2006–2007	16/17	35.3		23		50	[122]
South Africa	1992–2002	31/47	13		33.3	5.6		[123]

A variety of risk factors for these pregnancy complications and adverse pregnancy outcomes have been identified. Disease activity, particularly at the time of conception and during early pregnancy, is consistently associated with preterm delivery and possibly IUGR. Active nephritis shows a strong association with fetal loss, whereas a majority of investigations indicate that a past history of lupus nephritis does not constitute a significant risk factor for adverse pregnancy outcomes. Hypertension at conception or during pregnancy increases the risk of preterm delivery and possibly IUGR and fetal loss. Although the association of aPL and particularly APS with fetal loss is well established, such an association is seen in some, but not all, studies of pregnant SLE patients. This may be partly due to differences in the approaches used in treating pregnant women with aPL and APS. As discussed above, APS is also related to preeclampsia, placental insufficiency, prematurity and giving birth to LBW or SGA babies. There are indications that the combination of APS and SLE results in a higher frequency of these complications than APS alone, suggesting that other disease-related factors contribute. Other associations that are not as consistently examined or observed include hypocomplementemia with spontaneous abortions and stillbirths, proteinuria at conception with prematurity, and corticosteroids with IUGR. The latter may be an indicator of active disease during

pregnancy requiring treatment with corticosteroids rather than an independent risk factor.

In addition, anti-SSA/SSB antibodies were found to be significantly associated with fetal loss in SLE patients from certain ethnic groups [67,68], whereas others saw an association only in non-SLE patients [69], did not detect any effect [70], or actually showed anti-SSA/SSB antibodies to be protective [71]. These discrepancies could simply reflect random variations in the absence of a true association. Another possibility is suggested by the finding that only recognition of specific epitopes by anti-SSA antibodies appears to cause congenital complete heart block. One could speculate that such specificities are also involved in fetal loss. If these specificities were more frequent in certain ethnic groups, this might explain why the associations between anti-SSA/SSB antibodies and fetal loss show such ethnic variation. Interestingly, the prevalence of anti-SSA/SSB antibodies varies considerably between ethnic groups, with 24–40% of European and Latin American SLE patients showing anti-SSA positivity, while rates up to 64% have been reported from certain Arab populations [56–58]. Unfortunately, data on pregnancy complications and outcomes are not yet available from these regions. Yet, such studies may provide important insights into the effects of these antibodies on the course and outcome of SLE pregnancies.

Table 3

Fetal and neonatal outcomes in SLE patients (percentage of patients affected).

Country	Study period	Live births	Neonatal death	Stillbirth	Spontaneous abortions	Preterm delivery	IUGR	LBW (<2500 g)	Reference
Portugal	1993–2007	92	0.8	0	5.9	25.0	14	20.0	[111]
Portugal	1993–2007	90	1	2	6	16			[112]
Spain	1985–1996	88.3	9.4	1.7	5	20.8	9.4	24.5	[113]
Spain	1984–1999	66		12	14	28	35		[63]
Greece	1982–1997	78	0	2	15	12.5			[64]
France	1982–1995	77		3	16	57	2		[114]
UK	~1989–1994	82			37	42	31		[115]
Argentina	1986–2004	85	5	8	7	46		39	[116]
Brazil	n.a.	75	5.6		21	11		5.6	[117]
Brazil (62% ACR)	1995–2002	82	6.5	3.9	7.8	50	(22.3 SGA)		[118]
India	n.a.	45			36	7.4	14.8		[119]
India	1989–2002	58.5	7.7	7.3	29.3	3.8			[120]
Taiwan	2000–2005	91.6				33.3	20.8		[121]
Honk Kong	1982–1996	88				16.2	17.5		[124]
Malaysia	2006–2007	82	0	0	0	12.5	31.3		[122]
South Africa	1992–2002	77		2	17	39	14		[123]

n.a. = not available.

3.1.4.2. Multiple sclerosis (MS). The incidence of MS varies by a factor of almost 20-fold between various regions of the world (e.g. 0.61/100,000 in Japan to 10.73 in Greece in some of the most recent studies), but appears to have increased worldwide in recent decades. There are indications, however, that the originally identified gradient of higher incidence with increasing latitude is diminishing. MS affects women approximately twice as frequently as men. The peak onset is during the 3rd and 4th decades of life, i.e., during the childbearing years. The disease is classified into relapsing-remitting, secondary progressive and primary progressive forms. More than 90% of the patients included in epidemiological studies on the interactions between MS and pregnancy have the relapsing-remitting course, while pregnancy in women with the primary progressive course is very rare. MS is one of the autoimmune diseases that improves during pregnancy, and a decrease in the relapse rate during pregnancy compared to the year preceding it has been seen very consistently in studies from various regions of the world, including Germany, Finland, Spain, other European countries, Iran, Brazil and Argentina (summarized in Table 4). The most significant decrease is always observed in the third trimester. Relapses during pregnancy generally are mild and do not require therapy. Unfortunately, the existent data provide little information on the course of MS during individual pregnancies, which seems to be quite variable [72]. There is also general agreement among all recent studies that the relapse rate increases significantly post-partum, mainly in the first 3 months after delivery, frequently exceeding the pre-pregnancy rate. In addition, post-partum relapses are severe in a substantial portion of patients. The overall data indicate that the course of MS during pregnancy is very homogeneous throughout the world, even if data from non-Caucasian women are still rare.

The effects of MS on the course and outcome of pregnancy have only rarely been examined. In a population-based study from the USA (Seattle, WA) that used obstetric hospitalization data for 1987–1996, 198 women with MS were no more likely than 1584 healthy women to have complications during pregnancy or delivery or to give birth to preterm or LBW infants [73]. In previous pregnancies, women with and without MS reported similar rates of fetal loss (spontaneous abortions and miscarriages). This is in keeping with several smaller studies indicating that MS does not significantly affect the course and outcome of pregnancies, although direct comparisons to the general population are frequently lacking. In contrast, in population-based studies from Norway, women with MS were at increased risk of cesarean delivery (though planned and not due to emergencies) and giving birth to SGA babies or with lower mean birth weight [74]. An increased risk of SGA babies and cesarean delivery was also detected in a population-based study from Taiwan [75]. In addition, Taiwanese MS patients were more likely to have preterm delivery.

There is general agreement that pregnancy does not appear to have negative effects on the long-term prognosis of MS. Indeed, a recent study from Iran indicates that disease progression slowed in the 5 years after childbirth, despite an increased flare rate

immediately post-partum [76]. In addition, the results of several investigations (from Sweden, Belgium, the Netherlands, and Denmark) suggests that pregnancy after disease onset is associated with less disability and a lower risk of changing from a relapsing-remitting to a chronic progressive course. It is possible that these findings are a reflection of the bias that could result if women who are less disabled by MS are both more likely to become pregnant and to have a better prognosis.

3.1.4.3. Rheumatoid arthritis (RA). The incidence of RA in women rises with increasing age, reaches a peak around 40–50 years of age and remains stable thereafter. As a result, while RA affects ~1% of the population, it is much less common in women between the ages of 16 and 45, with a study from the UK estimating the prevalence in this age group to be 1 or 2 per 1000. Overall, women are affected 2–3 times more frequently than men, but in women in their reproductive years the female:male ratio exceeds 4:1. There is some geographic variation in the incidence of RA, with North America and northern Europe having higher rates compared to southern Europe and developing countries.

According to a considerable number of both retrospective and prospective studies, dating mostly from the 1950s and 1960s, a majority (>70%) of women with RA reported considerable improvement or even remission of their disease activity during pregnancy, particularly during the third trimester. An almost equal proportion of women indicated that their disease flared post-partum. More recent large prospective studies from the UK and the Netherlands, using both subjective and objective measures of disease activity, confirmed the amelioration of RA during pregnancy and the increased disease activity post-partum [77,78]. They also indicated, however, that neither the improvement nor the relapse rate after childbirth was as substantial as suggested by earlier investigations. Specifically, remission during the third trimester was only seen in 16% of patients in one study (which included only 68% patients with definite RA) [77]. In the other study, which used a different definition of remission, the percentage of women in remission increased from ~11% before conception to 27% in the third trimester [78]. In addition, post-partum flares of mostly moderate severity occurred in only 39% of patients in this study. Of note, the pregnancy-associated decrement in disease activity was greatest in patients with high disease activity during the first trimester. This strongly suggests that, with the recent advances in therapy, more RA patients have little or no disease activity before pregnancy, leaving less room for improvement during gestation.

Contemporary reviews frequently leave the impression that the course and outcome of pregnancies in women with RA is not substantially different from that of the general population. This is, however, not quite correct, even though surprisingly limited data are available on the subject, and almost exclusively from the US and some European countries. There are three recent large population-based studies investigating the effects of RA on certain pregnancy complications and outcomes, two from the US [21,79] and one from Taiwan [80]. All three found women with RA to be at significantly

Table 4
Relapse rates (RR) before, during and after pregnancy in MS patients.

Country	Study period	N =	Pre-pregnancy RR	Pregnancy RRs (1st/2nd/3rd trimester)	Post-partum RR	Reference
Finland		42	1.0	0.5/n.a./0.2	1.5	[125]
12 European		227	0.7	0.5/0.6/0.2	1.2	[126]
Spain	n.a.	74/88	0.61	0.31	0.87	[127]
Argentina	n.a.	81/141	0.22	0.31/0.19/0.04	0.82	[128]
Argentina		46/86	1.3	0.7/0.6/0.1	1.2	[129]
Brazil	~2003–2008	47/49	1.37	0.29	0.86	[130]

n.a. = not available.

increased risk of cesarean delivery. Taiwanese women also faced a significantly higher risk of preeclampsia than the control group [80], and a similar tendency was apparent in both of the US studies. Taiwanese women with RA were at increased risk of delivering LBW and SGA infants, whereas the rate of prematurity was only non-significantly increased ($p = 0.077$) among patients compared to controls [80]. In contrast, the infants of women with RA in one of the US cohorts were significantly more likely to be born preterm [79]. The increased frequency of LBW was no longer significant after adjusting for gestational age, suggesting that prematurity accounted for most cases of LBW. Women with RA tended to have more infants who were SGA in one of the US studies or to suffer from IUGR in the other. These results largely recapitulate the findings of older and smaller studies that included, but rarely focused specifically on, women with RA. It has also been suggested that women with RA are more likely to have spontaneous abortions, but this has not been confirmed in several other studies. Unfortunately, there is very limited information on the rates of miscarriage, stillbirth or congenital abnormalities in patients with RA.

3.1.4.4. Type 1 diabetes (T1D). Worldwide incidence rates of T1D vary widely, ranging from 0.1/100,000 in China to 37/100,000 in Finland and Sardinia. Very high rates have also been reported from the US and Canada, several Scandinavian countries, as well as some Arab populations. Non-Scandinavian European countries generally have a high incidence, whereas the rates in Asian countries are generally low and those in sub-Saharan Africa low to intermediate.

T1D differs from many other autoimmune diseases in that its onset generally precedes (rather than coinciding with or occurring after) the childbearing years. Its sex distribution is about equal, at least in Europe, North America, and some North African countries, whereas a clear female predominance has been reported from various Chinese regions (with female:male ratios as high as 4:1). In addition, the diminished function of the organ targeted by the autoimmune reaction, rather than the immunological features or the activity of the disease, has a negative impact on the course and outcome of pregnancies.

Epidemiological studies have established that, compared to the general obstetric population, women with T1D face a significantly increased risk of maternal complications during pregnancy and delivery, including gestational hypertension, preeclampsia, and cesarean delivery. Maternal mortality is also markedly higher in some studies. In addition, the prevalence of adverse pregnancy outcomes, in particular pregnancy loss, perinatal mortality, congenital anomalies,

premature delivery, macrosomia (birth weight > 4000 g), respiratory distress syndrome, and neonatal hypoglycemia, is markedly elevated in women with T1D and their neonates. Epidemiological studies also have provided evidence that tighter glycemic control substantially reduces the malformation and perinatal mortality rates. Indeed, in selected populations with intensive management and care at specialized tertiary centers, the pregnancy outcomes of women with T1D were reported to approach those of the non-diabetic population. Large population-based and nationwide cohort studies indicate that pregnancy outcomes have improved substantially in recent decades [81]. Nonetheless, they also highlight that meeting the currently targeted values for “good” metabolic control does not yield results as set out by the St. Vincent’s declaration of 20 years ago, namely to achieve pregnancy outcomes similar to those seen in the healthy control population [82–84]. The risk of congenital malformations remains at least 2-fold and up to 6-fold higher, while the risk of perinatal mortality continues to be between 3.5 and 8.5-fold higher than in the general population [85], even in carefully planned and monitored pregnancies in women who mostly achieved good to excellent glycemic control [86].

As a result, some investigators argue that even tighter glycemic control should be aimed for, especially after recent studies showed that fasting and postprandial glucose values in pregnancies of healthy women were significantly lower than the targets currently set for glycemic control in pregnant diabetic patients. Note, however, that many of the newer formulations of insulin that are designed to provide enhanced metabolic control frequently are not associated with significantly improved pregnancy outcomes. In addition, tighter metabolic control increases the risk of hypoglycemia, which has not been shown to adversely affect pregnancy outcomes, but does represent a significant risk to the mother. Others suggest that factors other than glycemic control may play a role in the increased risk of adverse pregnancy outcomes in T1D. There are considerable differences in the malformation and perinatal mortality rates in different ethnic groups and geographic locations (see also Table 5). Note that a direct comparison between studies is severely hampered by the use of different definitions for perinatal mortality (with some authors including neonatal death up to 28 days after birth, whereas others refer to the immediate neonatal period 7 days after birth only). In addition, the rates of detection and termination of pregnancies with congenital anomalies differ considerably between cohorts. Since such anomalies account for a large portion of neonatal deaths, the termination rate will considerably influence the perinatal mortality rate. Despite these limitations, a comparison of international results highlights

Table 5

Rates (in %) of perinatal mortality (PM), congenital malformations (CM), and other adverse fetal outcomes in T1D.

Country	Subgroups	n [total/type 1 (% type 1)]	Study period	PM	Still-birth	Neonatal death	Fetal loss	CM	Macrosomia (M)/LGA	Cesarean	First Author
UK	Caucasian	766/305 (39.8)	1990–2002	0.4		1.4	3.5	2.1	M 20/LGA 33	74	Chaudhry
	Afro-Caribbean	90/9 (10)		0		2.6	4.4	1.2	M18/LGA 33	43	
UK	Caucasian	312/172	1990–1998	4.7	3.6		9.1	9.4	LGA 37	62	Dunne
	Indo-Asian	128/12 (10)		0	0		13.5	9.3	LGA 25	40	
UK	Caucasian	60/60 (100)	1994–2002	0	0		6.7	3.8			Verheijen
	Asian	36/36 (100)		6.3	6.3		11	15.6			
South Africa		142/67 (47)	1993–1997	3.7			6	2 (all minor)	M 27	49	Daponte
South Africa		172/172 (100)	1992–2002	3.9	3.9	0	0	0.6	M 5.2	63	Huddle
The Netherlands		323	1999–2000	2.8	1.9	1.0	1.0	8.8	M 52.5	44.3	Evers
Norway	Caucasian	142/127 (89)	1992–1998	1.8				3.0	M 5.7	47.5	Valen
	Immigrants	43/12 (28)		2.0				1.0	M 13.0	37.0	
UK		1707/1707 (100)	2002–2003	3.2	2.58	0.96		4.8 major			MacIntosh
Scotland		273/273 (100)	1998–1999	3.2	1.9	0.93	14.7	6.0	M 55		Penney
France		289/289 (100)	2000–2001	6.6	1.4	0.3		4.5	M 17.3	58.9	Boulot
Denmark		1218/1218 (100)	1993–1999	3.1	2.1			5.0	M 8.0 (>4500 g)/LGA 62.5	18.1	Jensen

that diabetic women in some countries with less than optimal health care have very low rates of congenital malformation and macrosomia. Therefore, more extensive comparisons between ethnic groups with high and low malformation and perinatal mortality rates may help identify factors beyond glycemic control that influence pregnancy outcomes.

Maternal autoantibodies could be among these factors, yet surprisingly few investigations have addressed this issue. There are data suggesting that maternal insulin could be transferred across the placenta via maternal anti-insulin antibodies, thereby resulting in fetal hyperinsulinemia and contributing to macrosomia. Conversely, it could be hypothesized that maternal antibodies against glutamic acid decarboxylase or tyrosine phosphatase could reduce fetal insulin secretion and result in reduced birth weight. However, recent studies found no association between the presence of any of these autoantibodies in the mother or in cord blood with the infant's birth weight [87,88]. Nonetheless, the possibility remains that maternal autoantibodies are associated with poor pregnancy outcomes other than birth weight.

4. Neonatal disease caused by transplacental passage of maternal autoantibodies

In addition to causing pregnancy complications and adverse pregnancy outcomes, transplacental passage of maternal autoantibodies of the IgG isotype can result in a variety of neonatal diseases (summarized in Table 6) [89]. Among the best known of these is the neonatal lupus syndrome (NLS), which can manifest as cutaneous lesions resembling those of SLE (16–50%), life-threatening congenital complete heart block (CCHB, 1–2%), hematological (~26%) and hepatobiliary manifestations (9–24%). It is almost invariably associated (in 95% of cases) with maternal antibodies against Ro/SSA alone or in conjunction with anti-La/SSB. Anti-U1-RNP (ribonucleoprotein) antibodies are associated exclusively with the cutaneous manifestations of NLS. All of these antibodies are found primarily in women with SLE or Sjögren's syndrome (SS), but can also occur in women with other connective tissue diseases and in completely asymptomatic women. Interestingly, there are some suggestions that infants of mothers with SLE are more rarely affected by CCHB than those of mothers with SS or with undifferentiated connective tissue disease [90,91]. In contrast, there are indications that the presence of hypothyroidism increases the risk of CCHB, but not NLS overall, in infants of anti-SSA-positive mothers regardless of whether they have an underlying autoimmune disease or are asymptomatic [92].

Data on the incidence of NLS are rare. The prevalence of anti-SSA/SSB varies considerably in different ethnic groups, not only in SLE and SS patients, but also in the general population (with a prevalence of 2.6% reported from Japan and 0.4% in Brazil). Overall, ~1–2% of women are thought to have anti-SSA/SSB antibodies, and estimates of their risk of having a child affected by NLS range between 2% and 52% in prospective studies [90,91]. Only 1–2% will give birth to a child with CCHB. The large variation stems from differences in the thoroughness with which the various (and frequently asymptomatic) manifestations of NLS are determined and the length of follow-up since some of the NLS symptoms, including the cutaneous lesions, are not always obvious at birth. The risk that a second child is affected ranges between 15% and 20%. The fact that not all children of women with anti-SSA/SSB antibodies develop NLS indicates that other factors, probably including fetal ones, play a role.

Of particular note, a recent report on the long-term follow-up of 49 children with NLS indicated that definite autoimmune diseases were already present in 6 of 49 affected children (5 of them female) at a mean age of 14.8 years, but in none of the 45 unaffected siblings or the 53 unrelated controls [93]. Similarly, it has been reported that children and adolescents diagnosed with autoimmune thyroid disease had been exposed to maternal thyroid peroxidase antibodies in utero significantly more frequently than randomly selected control children [94]. This strongly suggests that, in addition to inheritance of susceptibility genes from an affected mother, transplacental exposure to maternal autoantibodies predisposes to the development of autoimmune diseases.

5. Parity, pregnancy, and the risk of developing autoimmune diseases

Parity or total number of pregnancies was not associated with the development of SLE in women from the USA or Sweden [95–97]. In contrast, a recent study from Denmark found that women with at least one live-born child were at decreased risk of developing SLE than nulliparous women and the risk was further decreased in women with 2 or more children [98]. Recurrent pregnancy losses, however, increased the risk of SLE. The results of studies examining the association between oral contraceptive use, hormone replacement therapy or other indicators of hormonal status (age at menarche and at menopause) and the development of SLE are equally contradictory. Several case-control studies from the USA and Finland, failed to detect significant associations [95,99,100]. In contrast, a slight increase in risk was seen in the

Table 6
Neonatal diseases caused by maternal autoantibodies [89].

Neonatal disease	Maternal disease	Causative antibody	Proportion of antibody-positive pregnant women	% Affected neonates of antibody-positive mothers
Neonatal lupus syndrome	SLE, SS, RA, other connective tissue diseases, or asymptomatic	Anti-SSA/SSB	1–2%	Up to 52%
Neonatal autoimmune thrombocytopenia	Immune thrombocytopenic purpura	Anti-platelet	0.1%	10%
Neonatal autoimmune neutropenia	Autoimmune neutropenia	Anti-neutrophil	1:50,000	
Neonatal Graves' disease	Graves' disease	Anti-TSH ^a receptor	0.1–0.4%	1%
Autoimmune hemolytic anemia of infancy	Autoimmune hemolytic anemia	Anti-erythrocyte	1–2:100,000	Very rare
Pemphigus		Anti-desmoglein	1:50,000	10–40%
Myasthenia	Myasthenia gravis	Anti-acetylcholine receptor	1:10,000–2:10,000	10–20%
Hypothyroidism		Anti-thyroid	10–15%	0.32–0.56/100,000 ^b
Neonatal APS	Primary or secondary APS or asymptomatic	aPL	2%	30–37%

^a TSH thyroid-stimulating hormone receptor.

^b Of infants overall.

Nurses' Health Study cohorts (USA) [101], and UK case-control studies indicated an increased risk of SLE development with past and particularly current use of combined oral contraceptives and in some cases with postmenopausal hormone replacement therapy [96,102].

Consistent with the favorable effects of pregnancy on disease activity in MS, a prospective Swedish incidence cohort study showed that the onset of MS symptoms was significantly less likely to occur during gestation compared to the periods before and after pregnancy [103]. In addition, a significantly higher proportion of women with MS were nulliparous at disease onset than would have been expected from population data. This could suggest a protective role for pregnancy in the development of MS; however, it could also reflect that some health impairments already exist in women who later develop MS, since only healthy women are likely to become pregnant. Data from three large cohort studies and one case-control study (3 from the UK and 1 from the US) indicate that parity and oral contraceptive use do not significantly affect the risk of MS [104]. One of them provides some indication, however, that the risk of MS onset is temporarily increased during the first 6 months after childbirth; in addition, the current use of oral contraceptives may delay the onset of MS.

Although addressed in a large number of studies, it remains unclear whether there is an association between parity and risk of RA, with a number of older studies finding that nulliparity constitutes a risk factor for RA, whereas the prospective Nurses' Health study did not detect any association [105], nor did a large Finnish cohort study [106]. The Nurses' Health study found a strong trend towards decreasing RA risk with increasing duration of breastfeeding [105]. Therefore the protective effect of parity detected in some studies may have been confounded by breastfeeding. Similarly, a majority of studies show no significant association between oral contraceptive use and risk of RA onset, although some found a significant protective effect. In at least one study, the association was stronger in women who used the earlier OC preparations, suggesting that higher doses of estrogens and progestins provided stronger protection [107].

Pregnancy involves highly complex and dynamic interactions between hormonal and immunological factors. It seems possible, therefore, that it could have differential effects on the development of an autoimmune disease depending on its timing relative to the initiation or progression events that are likely to precede manifest disease. This might explain some of the discrepancies in these results. Because of their inconsistency, the currently available data do not provide convincing evidence that parity provides an explanation for the female predominance in SLE, MS, RA and other autoimmune diseases.

6. Microchimerism

Chimerism is defined as the persistence in an individual of DNA or cells from a genetically distinct individual. The term microchimerism refers to the presence of low levels of such donor cells. It had long been known that bidirectional trafficking of cells occurs during pregnancy, with maternal cells entering the fetal circulation and fetal cells passing into the maternal circulation. It was not until 1996/7, however, that chimeric cells were discovered to persist in the circulation of the host (fetal cells in the mother and maternal cells in the offspring) for several decades. This suggested the possibility that fetal microchimerism could account for the female predominance of certain autoimmune diseases. Specifically, it was hypothesized that fetal microchimerism could trigger a graft-versus-host-like response, thereby contributing to the pathogenesis of systemic sclerosis (SSc), an autoimmune diseases that has marked similarities with graft-versus-host disease (GVHD). When

testing this hypothesis, Nelson et al. [108] found significantly higher levels of fetal DNA, but a similar frequency of positivity, in women with SSc compared to healthy controls, both groups of women having given birth to at least one son. This and subsequent studies also suggested that HLA class II compatibility between mother and child contributed to the persistence of fetal microchimerism. This represents a further similarity to GVHD, where HLA relationship between donor and host is known to play an important role. Although similar results were obtained in several subsequent investigations, more recent data raise some doubts concerning the association between fetal microchimerism and SSc. In addition, several analyses found that nulliparous women were at increased risk of developing SSc compared to women who had ever been pregnant and that the risk decreased with increasing numbers of pregnancies.

Like SSc, PBC and SS, have clinical and immunological features resembling GVHD and are characterized by a high female predominance. Explorations of the possible role of fetal microchimerism in peripheral blood and salivary glands of patients with SS have yielded highly variable results. However, the limited data available indicate that the risk of developing the disease is increased in parous compared to nulliparous women. The great majority of studies of microchimerism in PBC have failed to demonstrate an association between PBC and fetal microchimerism in peripheral blood and liver tissue. Data on the association between parity and the development of PBC are conflicting, with one study reporting a significant positive association [109], whereas another population-based study did not find a significant relationship [110]. Similarly inconclusive results have been obtained in other autoimmune diseases.

In early studies, the fetal chimeric cells were identified as CD34+ or CD34+CD38+ hematopoietic stem cells capable of differentiating into immune competent cells. This along with the results of a limited number of studies suggested that chimeric cells could actively participate in alloimmune reactions. Since then, it has been recognized that both fetal and maternal chimeric cells show considerable plasticity and are capable of differentiation into a variety of tissue-specific somatic cell types. While this raises the possibility that they also could become targets of inflammatory reactions, there is growing evidence suggesting that both fetal and maternal chimeric cells participate in tissue repair processes.

Of note, there are some indications that in some women fetal cells from only one specific child persist, even though they have delivered several children. This suggests that specific maternal and/or fetal factors are required for the persistence of chimeric cells. It also seems possible that only specific chimeric cell types are pathological, whereas others participate in repair processes. As long as these questions have not been addressed in detail, the available data do not allow conclusions as to the role of microchimerism in the development of autoimmune diseases. They also do not support the hypothesis that fetal microchimerism accounts for the female predominance of these diseases.

7. Concluding remarks

Women with autoimmune diseases were long advised not to become pregnant or to have therapeutic abortions if they did – because of earlier case reports and series indicating poor outcomes for both the mother and the baby. Thanks to epidemiological studies it has become obvious that advances in treatment and careful and multidisciplinary management in the periconception period and throughout pregnancy, the outlook in essentially all autoimmune diseases has improved considerably. Particularly patients with stable disease at the time of conception frequently have uneventful pregnancies without disease exacerbation and

give birth to healthy full-term infants without an increased risk of complications.

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