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The management of rheumatic diseases in pregnancy

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Abstract

Pregnancy can create a challenge for physicians caring for women with rheumatic diseases. For many women with rheumatoid arthritis (RA), pregnancy can provide a reprieve from long-term joint pain and inflammation, but others will not experience remission and will continue to need medication. Systemic lupus erythematosus (SLE) may remain quiet in some women, but in others may become more aggressive during pregnancy, putting both mother and foetus at risk. Women with limited scleroderma can do remarkably well, but scleroderma renal crises can be difficult to manage. A third of pregnancies in women with antiphospholipid syndrome (APS) may be refractory to our best therapy. In general, active inflammation from rheumatic diseases poses a stronger threat to the well-being of both mother and foetus than many immunosuppressant medications. Therefore, continued immunosuppression with the least risky medications will allow for the most optimal pregnancy outcomes.

As treatment for rheumatic diseases improves, more women with these illnesses are willing and able to start a family. This adds complexity to our treatment of young women with lupus, rheumatoid arthritis (RA), and other diseases. We must now address contraception, pregnancy planning, and medication risks early with our patients in order to optimize pregnancy success.

Fertility and contraception

In general, rheumatic disease does not appear to impair fertility. Comparisons of the total number of pregnancies and living children between women with and without systemic lupus erythematosus (SLE) demonstrate this point (1). Even during times of severe SLE activity, women with SLE are able to conceive. A survey of 214 patients with scleroderma, 167 patients with RA, and 105 normal controls found that 2–5% of patients in each group had difficulty conceiving and 12–15% of patients had a 1-year delay in conception (2). Although the total number of pregnancies in women with RA may be slightly lower than in the general public, this seems to be more closely tied to personal choice than infertility (3). For this reason, discussions of birth control are particularly important. Women taking teratogenic medications, in particular cyclophosphamide, methotrexate, leflunomide, and mycophenolate mofetil, require effective contraception to prevent pregnancy.

Women with rheumatic disease can use most forms of birth control without major concerns about side-effects. In particular, the intrauterine device (IUD) and progesterone-only methods (either Depo-Provera® subcutaneously every 3 months or the Implanon® implant every 3 years) are effective long-term contraception. Two randomized placebo-controlled trials demonstrated that women with stable, mild SLE can take oestrogen-containing oral

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contraceptives without increasing SLE activity (4, 5). These studies, however, did not include women with moderate to severe disease and exogenous oestrogen may increase the risk for thrombosis to an unacceptable level. Finally, all women should be aware of emergency contraception; progesterone-only pills taken within 72 h of unprotected intercourse are safe and effective.

RA and pregnancy

The majority of pregnancies in women with RA are without complication; the mother has a decrease in her arthritis pain and the baby is born healthy. Pregnancy outcomes are generally favourable for women with RA (6–11) (Table 1). The risk for preterm birth, however, does seem to be increased for women with RA. An ongoing prospective study of pregnancies found that one out of every four women with RA delivered early, compared to 1 in 10 women without RA (12). Pre-eclampsia and caesarean section rates have been shown to be higher in mothers with RA (7, 9). Having increased RA activity and using disease-modifying anti-rheumatic drugs (DMARDs) and steroid medications increases the risks for these complications (13).

Both clinical experience and the reports of over 500 patients in clinical studies demonstrate that RA activity decreases for many women. Studies show that an estimated 75% of women experienced improvement in their disease during pregnancy (range 54–86%) and 90% of women reported a relapse in disease within 3 months of delivery (14, 15). Two prospective studies have examined disease activity during pregnancy in the current era of expanded treatment options (16, 17). In the first, Barrett et al recruited 140 pregnant women [95 satisfied the American College of Rheumatology (ACR) criteria for RA and 45 women had definite synovitis observed by a physician] and followed them prospectively from the last trimester until 6 months postpartum (16). Retrospectively, 65% of the women reported that they had improvement in disease activity during pregnancy compared to pre-pregnancy. By the third trimester, 16% of women achieved remission, defined as using no anti-rheumatic drugs and having no swollen or painful joints. Ninety women (66%) reported worsening in joint swelling by 6 months postpartum, with the majority of deterioration occurring during the first month.

In the second study, de Man et al prospectively followed 84 women with RA according to the ACR criteria and measured the Disease Activity Score in 28 joints (DAS28) and medication use pre-pregnancy (if possible), during each trimester, and at weeks 6, 12, and 26 post-partum (17). The percentage of women with moderate RA during pregnancy decreased from 70% before pregnancy to approximately 40% during pregnancy. During the third trimester, 27% of women were in complete remission (DAS28 < 2.6) and had a significant decrease in medication use. The largest decrease in DAS28 was seen among women with the most active disease. Post-partum, 40% of women had increased disease activity but only 4% had a severe flare. The majority of women restarted DMARD therapy in the first 6 weeks after delivery.

The data and patient reports support a decrease in RA activity with pregnancy, but how does pregnancy suppress disease activity? The answer remains a mystery; however, the key may be regulatory T cells (Tregs). RA activity is partially driven by the T-cell production of tumour necrosis factor (TNF)α and interferon (IFN)-γ left unchecked by poorly functioning Tregs (18, 19). During pregnancy and particularly in the second trimester, Tregs increase in both number and suppressive activity (20, 21). In women with RA, this rise in Tregs leads to an increase in the anti-inflammatory interleukin (IL)-10 and a decline in TNFα and IFN-γ production, coinciding with the reduction in clinical RA symptoms (20). Maternal tolerance seems to be stronger when the mother and foetus are more genetically different. A study

published in 1993 showed that 75% of women with RA improved during pregnancy when the mother and foetus were human leucocyte antigen (HLA) mismatched but only 25% improved when the foetus had a very similar HLA pattern to the mother (22).

Ankylosing spondylitis (AS)

Compared to pregnant women with RA, women with AS generally experience unchanged or increased disease activity including increased morning stiffness, spinal tenderness, pain at night, and need for non-steroidal medications during pregnancy (23–27). Of the 20% of woman in one study who had a marked improvement in their symptoms, all had AS associated with small joint disease, psoriasis, or ulcerative colitis (27). Postpartum flares are also common, especially during the first 3 months after delivery. The postpartum flare is independent of level of disease activity during pregnancy, period of lactation, or the return of menses. Disease activity during the year following delivery seems to return to the same level as before conception (24). There appears to be no increase in frequency of miscarriage, premature labour, or delivery complications in this population of women (25).

Of note, women with AS experience a similar increase in Tregs during pregnancy as women with RA. However, Tregs in pregnant woman with AS secrete less IL-10 and have lower suppression of INF-γ and TNFα secretion by effector T cells (28). This may account for the difference in disease activity experienced during pregnancy among women with AS and RA.

SLE

Although the majority of women with SLE will have no or mild disease activity during pregnancy, a small but significant proportion will have more severe disease. The risk for severe disease during pregnancy is increased in women with active SLE in the 6 months prior to conception, in those with repeated flares in the years prior to conception, and in those who discontinue needed medications due to pregnancy (29, 30). For women with quiescent SLE in the 6 months prior to conception, less than 10% will have moderate to severe SLE during pregnancy (29). In my clinical experience, I find many women with relatively quiet SLE prior to pregnancy comment on how good they feel during pregnancy; it seems that, for some women, pregnancy may in fact ameliorate the arthritis, rashes, and fatigue of mild SLE activity. Almost 60% of women with increased SLE activity prior to conception continue to have SLE activity in pregnancy (29).

Whether SLE is active or not, women with SLE are at increased risk for medical complications in pregnancy. Pregnancy itself is a hypercoagulable state, increasing the risk of thrombosis two- to threefold (31). For a non-pregnant woman with SLE without APS, the risk of thrombosis is estimated at 3/100 patient years (32). Therefore, 5–10 of every 100 pregnant women with SLE can be expected to develop a thrombosis during pregnancy; these can include deep vein thromboses, pulmonary embolisms, strokes, or heart attacks. The risk for thrombosis extends for 6 weeks following delivery.

The maternal mortality rate for women with SLE is an estimated 20-fold higher than for average women (33). The rate of maternal mortality with SLE is 325/100 000 pregnancies. When compared to the annual death rate for women with SLE (estimated at 1000/100 000 patient years), it appears that pregnancy probably does not increase the risk of death for a women with SLE (34). There are particular women, however, who may be at higher risk for death. These include women with prior arterial thrombosis, a weakened heart from myocarditis, prior myocardial infarction or valve disease, uncontrolled hypertension, pulmonary hypertension, or a prior severe SLE flare during pregnancy.

Ideally, prior to pregnancy a woman with SLE should have low lupus activity for at least 6 months and have medications adjusted. The benefits of maintaining low SLE activity in pregnancy is twofold: it improves the health of the mother and increases the chances of the delivery of a healthy baby. Increased SLE activity is a primary cause of preterm birth and pregnancy loss in this population. The risk for pregnancy loss is increased three- to fivefold if SLE is active or platelet counts are low in the first trimester (44% pregnancy loss with active SLE) (35). Women with active SLE are at twice the risk for a preterm birth (66% preterm birth with active SLE vs. 33% with inactive SLE) (29). Some of these deliveries may be induced to protect the health of the mother, but the majority are spontaneous preterm deliveries.

Pre-eclampsia, the combination of hypertension and proteinuria in the third trimester, is a dangerous pregnancy complication that is common in women with SLE. Studies estimate that up to one in four women with SLE will develop pre-eclampsia (10, 33). This risk is particularly high for women with pre-existing hypertension or a prior history of lupus nephritis (36). The risk for pre-eclampsia might be reduced with daily dosing of low-dose aspirin (LDA). Studies on non-SLE high-risk pregnancies show that aspirin can decrease the risk for pre-eclampsia by 20% and is a safe medication for both mother and baby (37). Studies of the effect of lupus on pregnancy outcomes (38–42) are summarized in Table 2 and studies of the effect of prior and current lupus nephritis on pregnancy outcomes (43–45) are presented in Table 3.

Scleroderma

Although scleroderma was once considered a strict contraindication for pregnancy, with careful timing of pregnancy and close monitoring, successful pregnancies can be achieved with good outcomes for both the mother and infant (2). Studies have shown no increase in miscarriage rate, with the exception of women with longstanding diffuse scleroderma [42% with long-standing diffuse scleroderma vs. 13% of all other subjects; relative risk (RR) 2.8, 95% confidence interval (CI) 1.23–6.37, $p < 0.05$] (46). Another study found the live birth rate was 84% for women with limited scleroderma, 77% for women with diffuse scleroderma, and 84% in a historical control group (46). An increased risk for premature births has been reported in case series and a recent prospective study (47–49). Low birth weight (< 2500 g at term) was also common (48–50).

Scleroderma disease activity does not change in pregnancy (46–48). In one study there seemed to be no change in 10-year cumulative survival between those women with scleroderma who became pregnant after diagnosis and those who did not (48). Raynaud's phenomenon may improve with pregnancy secondary to a physiological increase in cardiac output, while gastroesophageal reflux disease (GERD) worsens, especially during the latter part of pregnancy.

Scleroderma renal crisis is a feared complication during pregnancy. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers are life-saving treatments for scleroderma renal crisis, but carry significant risk for foetal anomalies (51). These risks occur late in pregnancy and include renal atresia, pulmonary hypoplasia, and foetal death (52). A prior episode of renal crisis is not a strict contraindication for future pregnancy, but it is recommended that a woman wait several years until her disease is stable before trying to conceive. A trial without ACE inhibitors prior to pregnancy is recommended to determine if blood pressure can be adequately controlled with alternative anti-hypertensive medications.

APS and pregnancy

APS is characterized by the presence of antiphospholipid antibodies (aPL) in the setting of either vascular thrombosis or pregnancy complication as defined in the classification criteria for APS (Table 4) (53). The pregnancy complications include repeated early pregnancy losses, a single late-term loss, or early severe pre-eclampsia. APS is the leading cause of miscarriage and infertility among patients with either hereditary or acquired thrombophilia (54). Additionally, patients with APS can have multiple pregnancy complications including foetal growth retardation, infertility, and maternal thrombosis. Untreated, pregnancy loss will occur in 45–90% of pregnancies with APS (55). Treatment, however, reduces the chance of pregnancy loss to less than 30% (56).

There are several proposed mechanisms for pregnancy loss from APS, including aPL interaction with platelet membrane phospholipids, inhibition of annexin-V, a cell surface protein that inhibits tissue factor, direct inhibition of protein S, and, most recently discovered, altered regulation of the complement cascade (54, 57). Recent insights into the pathophysiology of the disease highlight that not only thrombosis but also inflammation via the complement cascade plays an important role in poor pregnancy outcomes. Although it was previously thought that heparin was particularly helpful because of its anticoagulant properties, recent studies show that it also inhibits complement formation and deposition in decidual tissues in vitro (58).

There have been several trials evaluating different therapeutic regimens for women with APS. The most well-designed studies are in women with obstetric APS, defined as women with aPL and recurrent early pregnancy loss or at least one foetal loss, in the absence of SLE or previous thrombosis (see Table 5). The current recommendations, based on the best existing data and expert opinion, are:

- **i.** no treatment or treatment with LDA in patients with aPL but no history of thrombosis or pregnancy complication;
- **ii.** prophylactic dose of low molecular weight heparin (LMWH) with LDA in women with aPL and history of pregnancy complication;
- **iii.** full-dose LMWH and LDA in women with aPL and history of vascular thrombosis (62).

Given the increased risk of thrombosis in the post-partum period, treatment with anticoagulation for up to 6 weeks postpartum is also recommended for patients with APS (63). Although unfractionated heparin costs less than LMWH and has been used for anticoagulation in APS patients, LMWH is the recommended anticoagulant because of the decreased risk for osteoporosis, heparin-induced thrombocytopaenia, and bruising (64). Currently, there are no data to suggest that long-term anticoagulation following pregnancy with warfarin is indicated in APS patients with only obstetric complications, although there are some retrospective data that suggest aspirin provides protection against thrombosis (65).

Medications in pregnancy

The US Federal Drug Administration (FDA) has designated medications according to a pregnancy risk score. The assigned category can be misleading and is not always a good guide for discontinuing medications. The FDA is planning to eliminate the categories in favour of more data disclosure about pregnancy outcomes in the future. In the meantime, we have included the FDA pregnancy categories for general reference. According to the current FDA system, category A is assigned to drugs with extensive human safety data demonstrating no foetal risk. Category B includes drugs with reassuring animal studies and

little or no human data OR animal studies demonstrating risk but good human data showing no foetal risk. Category C includes drugs in which animal studies show risk and no human data are available to refute this concern. Category D includes drugs with some evidence of adverse reactions in the foetus, but in which the potential benefit of the drug to the mother may outweigh these foetal risks. Category X includes drugs in which there is documented foetal harm and the benefits to the mother do not outweigh the foetal risks.

Treatment algorithms for SLE in pregnancy and inflammatory arthritis in pregnancy are presented in Tables 6 and 7, respectively.

Corticosteroids

Corticosteroids are relatively safe in pregnancy and are the mainstay of rheumatic disease treatment during this time. Exogenous corticosteroid use during the first trimester may increase the risk of cleft lip/palate threefold, to an estimated 3/1000 babies (66). When treating the mother with a corticosteroid, prednisone and predniso-lone should be used because less than 10% of the dose of these drugs crosses the placenta. Fluorinated steroids, including dexamethasone and betamethasone, easily cross the placenta and should be reserved for treating the foetus (i.e. congenital heart block or to hasten lung maturity prior to a preterm birth). Babies exposed to ongoing dexamethasone or high-dose prednisone treatment in utero may have adrenal insufficiency at birth (67). Although it is optimal to keep daily prednisone to less than 20 mg/day, higher doses are acceptable if they are required to treat aggressive disease. In most situations, the inflammation caused by excessive autoimmune activity is more harmful to the pregnancy than high-dose steroids.

Disease-modifying medications

Hydroxychloroquine (HCQ; Category C)—HCQ can, and should, be continued throughout pregnancy. In more than 300 offspring with in utero HCQ exposure, there has been neither a specific pattern of anomalies nor an increase in congenital anomalies (30, 68). Infants exposed to HCQ in utero have normal electrocardiography (ECG) at birth and normal ophthalmic and auditory examinations after birth (68–70). In addition, HCQ has been shown to decrease the risk for SLE flares and the need for higher doses of corticosteroids (30).

Methotrexate (MTX; Category X)—MTX, a dihydrofolate reductase inhibitor, is contraindicated during pregnancy and must be stopped 3 months prior to conception because of the risk of pregnancy loss and congenital abnormalities. A specific pattern of central nervous system, craniofacial, and skeletal defects can occur in a foetus exposed to chemotherapy doses of MTX (71). The risk of developing foetal abnormalities at rheumatological doses of MTX (5–25 mg weekly) is less clear. There have been several reports of increased rates of spontaneous abortion and major foetal anomalies, as well as successful pregnancies that result in a healthy infant (72–75). Folic acid should be continued throughout pregnancy for women who have taken MTX prior to pregnancy. MTX is excreted into breast milk and is therefore contraindicated in lactating women (76).

Leflunomide (LEF; Category X)—LEF, a dihydro-orotate dehydrogenase inhibitor that impairs pyrimidine synthesis, is also contraindicated in pregnancy (77). Animal studies show foetal anomalies at low doses (78). However, the Organization of Teratology Information Specialists (OTIS) followed 63 pregnancies in women with RA exposed to LEF and did not find an increase in miscarriage or foetal malformation compared to 108 pregnancies in woman with RA not exposed to LEF (12). The active metabolite of leflunomide can stay in the body for up to 2 years (79). It is therefore recommended that cholestyramine 8 g three times/day for 11 days be given to women who took LEF prior to

conception. Plasma levels less than 0.02 mg/L should be verified by two separate tests performed at least 14 days apart (product information, Arava® oral tablets, 2007). It is not known whether LEF is excreted into breast milk. For this reason it is contraindicated during lactation.

Sulfasalazine (SSZ; Category B, D at term)—SSZ, a folic acid antagonist, and its metabolite sulfapyridine cross the placenta (80). Animal studies in rats and rabbits have not shown foetal harm at doses six times the human dose (67). Much of the information on SSZ and pregnancy comes from the literature on inflammatory bowel disease (IBD). Observational studies of pregnant women with IBD taking SSZ have not shown a significant increase in birth defects (81, 82). There have been isolated reports of foetal anomalies including oral cleft, renal, and cardiac defects (83, 84). Folic acid should be continued throughout pregnancy. A small amount of SSZ is excreted into breast milk, but it is not thought to be at a level that would harm an infant. Although there is a theoretical risk that SSZ from breast milk could displace bilirubin, exacerbating jaundice, this has not been reported in human babies.

TNFα antagonists (Category B)—Etanercept, adalimumab, and infliximab are biological agents that inhibit TNFα, an inflammatory cytokine. Animal studies using etanercept in rats and rabbits at doses 60 to 100 times greater than the recommended human dose and an anti-TNFα monoclonal antibody similar to infliximab in mice have not shown adverse effects on pregnancy or foetal development (85, 86). For this reason, these medications have been classified as category B risk.

The risk in humans has not been sufficiently documented. Initial reports from over 300 pregnancies exposed to anti-TNFα therapy during the first trimester appeared reassuring. In the Infliximab Safety Database, two infants of mothers with Crohn's disease had congenital anomalies: one with tetrology of fallot and the other with intestional malrotation. The occurrence of these abnormalities was not felt to be different from that seen in the general population (87). A review of the FDA database of reported adverse events with etanercept, infliximab, and adalimumab from 1999 to 2005 revealed 61 congenital anomalies in 41 children born to mothers on anti-TNFα therapy. Congenital anomalies included heart defects (most common), cystic kidney, pulmonary malformations, teratoma, tracheal stenosis, hypospadias, trisomy 21, and hydrocele (88). This last report is difficult to interpret for several reasons, including the fact that the number of exposed pregnancies is unknown (only 1500 pregnancies would be required to have 41 infants with malformations in the general population) and there is significant report bias for the elective reporting programme used. The types of congenital anomalies reported in the FDA database are similar in distribution to those found in the general population. Although this report suggests that further surveillance is needed, it should not lead to cessation of essential therapy in women with severe RA.

Our current practice is to allow women to conceive on these medications, but discontinue them once a pregnancy is discovered. If a woman has a significant flare of arthritis during pregnancy, we will consider restarting the anti-TNFα therapy. Transfer of infliximab has been documented in the third trimester; avoidance of these drugs near the time of delivery may diminish the risk for infection in the infant (89–91). Although there are only a few cases reported, it does not appear that anti-TNFα medications pass into the breast milk of women who are actively lactating; however, more research into this area would be helpful (92).

Azathioprine (Category D)—Azathioprine is relatively safe in pregnancy, despite the warning category from the FDA. Although there are some early reports of

immunosuppression in offspring, more recent studies have documented its relative safety. It is reported that the majority of azathioprine that crosses the placenta is in the inactive metabolite thiouric acid (93). Several case–control studies of pregnancies with and without azathioprine exposure found no significant increase in congenital abnormalities (93). In addition, there has been no identifiable pattern of congenital anomalies among these pregnancies (93).

Mycophenolate mofetil (MMF; Category D)—MMF has recently been found to pose a significant risk to pregnancy. In a registry of pregnancies following solid-organ transplantation, the pregnancy loss rate for those exposed to MMF was 42%, far higher than pregnancies in women without MMF use. Of the surviving pregnancies, 67% delivered preterm and 26% had congenital anomalies (3/4 included abnormalities of the ear) (94). With these high rates of pregnancy loss and anomalies, it is recommended that MMF is to be discontinued prior to conception. For patients maintained on MMF, with stable SLE who desire pregnancy, we recommend transitioning to azathioprine prior to conception.

Cyclophosphamide (Category X)—Cyclophosphamide is a well-known teratogen, particularly with first-trimester exposure. For women with breast cancer in pregnancy, it has been administered during the latter half of pregnancy without significant pregnancy loss or congenital anomalies (95). The use of cyclophosphamide in lupus pregnancy, however, has been less successful. There are three cases reported in the literature, one resulting in a live birth, and two ending with intrauterine foetal demise soon after the drug was administered (96, 97). Whether it is the medication or the severity of the lupus activity that triggered the use of the drug is unclear. It is important to avoid inadvertent conception during cyclophosphamide therapy by prescribing contraception and administering pregnancy tests throughout therapy.

Intravenous immunoglobulin (IVIg)—IVIg is an option for the treatment of SLE during pregnancy. It is thought to be relatively safe during pregnancy as the foetus is already exposed to maternal immunoglobulins during the latter half of pregnancy. IVIg can be effective therapy for moderate to severe SLE flares. It has been shown to diminish SLE activity and promote pregnancy success in a small cohort of 12 patients with SLE (98). Further validation of this finding is needed.

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Table 1

Pregnancy outcomes for women with rheumatoid arthritis.

Study	Year of publication	Study design	Population	Miscarriage	Low birthweight and/or prematurity	Caesarean section
Bowden et al (11)	2001	Prospective cohort	133 RA vs. 103 controls	NR	RA: 3.3 kg vs. non-RA: 3.5 kg (p =0.04)	NR
Chakravarty et al (10)	2006	Cross-sectional	1425 RA	NR	RA: 3.4% with IUGR vs. non-RA: 1.6% (p <0.001)	RA: 37.2% vs. non-RA: 26.5% (p <0.01)
de Man et al (13)	2006	Prospective cohort	75 RA vs. population controls	NR	No difference in birthweight with the exception of the severe RA group	NR
Reed et al (9)	2006	Case–control	243 RA vs. 2559 controls	No statistical difference	No difference in birthweight RA: odds of prematurity increased 78%	RA: odds increased 66%

IUGR, intrauterine growth restriction; NR, not reported.

Table 2

The effect of lupus on pregnancy outcomes.

Cohort	Number	Miscarriages and stillbirths n (%)	Preterm births n (%)	Low birthweight n (%)	Pre-eclampsia n (%)
Carmona 1999 (38)	60	8 (13)	11 (21)	5 (10)	4 (8)
Georgiou 2000 (39)	59	13 (22)	3 (6)	NR	NR
Cortes-Hernandez 2002 (40)	103	35 (34)	19 (28)	24 (35)	2 (3)
Clark 2003 (41)	88	15 (17)	28 (38)	NR	2 (2.7)
Clowse 2005 (29)	267	38 (14)	106 (46)	51 (22)	NR
Cavallasca 2008 (42)	72	11 (15)	28 (45)	24 (39)	8 (13)

NR, data not reported.

Preterm birth and low birth weight percentage calculated based on total number of live births.

Scand J Rheumatol. Author manuscript; available in PMC 2013 July 26.

Table 3

The effect of prior and current lupus nephritis on pregnancy outcomes.

Cohort	Number	Miscarriages and stillbirths n (%)	Preterm births n (%)	Low birthweight n (%)	Pre-eclampsia n (%)
Rahman 2005 (43)					
Prior lupus nephritis	36	11 (30.5)	6 (22)	3 (11)	5 PIH
Current lupus nephritis	19	10 (52.6)	7 (70)	3 (30)	6 chronic HTN 4 severe PIH
Wagner 2009 (44)					
No lupus nephritis	47	4 (9)	9 (19)	2 (4)	NR
Quiet lupus nephritis	20	5 (25)	6 (30)	1 (5)	NR
Active lupus nephritis	23	8 (35)	12 (52)	1 (4)	NR
Imbasciati 2009 (45)					
Combined active and prior lupus nephritis	114	18 (16)	31 (32)	34 (35)	NR

PIH, pregnancy-induced hypertension; HTN, hypertension; NR; not reported.

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Table 4

2006 revised criteria for antiphospholipid antibody syndrome (APS) (53).

For a diagnosis of APS, a woman must have at least one clinical criteria *and* one laboratory criteriaClinical criteria

1. Vascular thrombosis
2. Pregnancy morbidity
   - **a.** One or more unexplained deaths of a morphologically normal foetus at or beyond the 10th week of gestation, with normal foetal morphology documented by ultrasound or by direct examination of the foetus
   - **b.** One or more premature births of a morphologically normal neonate before the 34th week of gestation because of:
     - Eclampsia or severe pre-eclampsia defined according to standard definitions OR
     - Recognized features of placental insufficiency
   - **c.** Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomical or hormonal abnormalities and paternal and maternal chromosomal causes excluded

Laboratory criteria

1. Lupus anticoagulant (LA) on two or more occasions at least 12 weeks apart
2. Anti-cardiolipin antibody (aCL) of IgG and/or IgM isotype, present in medium or high titre (i.e. > 40 GPL or MPL, or > the 99th percentile), on two or more occasions, at least 12 weeks apart
3. Anti-b2 glycoprotein-I antibody of IgG and/or IgM isotype (in titre > the 99th percentile), present on two or more occasions, at least 12 weeks apart

Table 5

Evidence for treatment of women with obstetric APS.

			Live birth rate (%)		
Reference	**Study type**	**Therapeutic regimen**	**Heparin + ASA**	**ASA alone**	**Preterm birth* (%)**
Kutteh (59)	Controlled, non-randomized	Heparin plus ASA vs. ASA alone	80	40	13
Rai (60)	Randomized	Heparin plus ASA vs. ASA alone	71	42	24
Farquharson (61)	Randomized	LMWH plus ASA vs. ASA alone	78	72	7

ASA, acetylsalicylic acid (aspirin); LMWH, low molecular weight heparin.

*No association was found between prematurity and therapeutic regimen in any study.

Table 6

Treatment algorithm for SLE in pregnancy.

SLE activity	Hydroxychloroquine	Prednisone dose	Other medication options
No SLE activity	Optional. Continue if taking prior to pregnancy	None	
Mild SLE activity	Yes	≤ 10 mg	
Moderate SLE activity	Yes	10–30 mg	Azathioprine IVIg
Severe SLE activity	Yes	Up to 1 mg/kg/day Pulse-dose prednisolone	Azathioprine IVIg Cyclophosphamide in the second/third trimester

Table 7

Treatment algorithm for inflammatory arthritis in pregnancy.

Degree of disease activity	Treatment
No activity	• None required
Mild activity	• Acetaminophen • Occasional NSAIDs in the second trimester • Low-dose prednisone (< 10 mg/day) • Hydroxychloroquine
Moderate activity	• Moderate-dose prednisone (10–20 mg/day) • Hydroxychloroquine • Sulfasalazine
Severe activity	• High-dose prednisone (20–60 mg/day) • Sulfasalazine • TNFα inhibitors

NSAID, non-steroidal anti-inflammatory drug.