Pregnancy and rheumatoid arthritis

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- Whether pregnancy is a risk factor for the development of new-onset RA remains an open question. At one point in time the onset of RA during pregnancy or immediately after was so commonly observed that it was postulated pregnancy could be regarded as an etiological factor.

- A large population-based Swedish study showed that parity was associated with an increased risk of sero-negative RA-- specifically anti-citrullinated peptide antigens (ACPA) negative -- in women of reproductive age.
- Parity and the postpartum period were not associated with ACPA-positive RA.

- In contrast, several studies have shown a significantly decreased risk of RA in women who have ever been pregnant compared to nulliparous women, both demonstrating the strongest RA risk reduction among those who were younger at the time of pregnancy.
- Other population-based cohort studies, have not detected an association between parity and subsequent risk of RA.

- Despite these mixed findings, women of childbearing age with RA face many challenges from fertility and preconception counseling, to birth outcomes and control of disease activity extending throughout the postpartum period.

Fertility

- Several studies have revealed that women with RA have fewer children than healthy controls and experience difficulties in conceiving, indicated by a higher rates of fertility treatment and longer time to conception (> 12 months) than those without RA.

- Factors associated with increased time to pregnancy (TTP) include age, nulliparity, Disease Activity Score in 28 joints (DAS28), preconception use of non-steroidal anti-inflammatory drugs (NSAIDs) and prednisone use of doses >7.5 mg daily.
- Smoking, disease duration, rheumatoid factor, anti-citrullinated protein antibodies, past methotrexate use, and preconception sulfasalazine use did not prolong TTP.
- The role of decreased sexual desire due to high levels of fatigue, mental distress and functional limitations due to pain have also been shown to be a factor in the smaller family size of patients with RA.

- There are many proposed physiological factors that may be responsible for impaired fertility in this population of women. These include RA induced alterations of cytokines including interleukin-1 (IL-1), IL-6, IL-11, epidermal growth factor, transforming growth factor- beta and tumor necrosis factor which are critical players in embryonic implantation.
- Other factors include aberrant functioning of T- cells where inadequate numbers of Treg cells or their functional deficiency are linked with infertility.

- Chronic NSAID use has been associated with anovulation and subfertility.
- By interfering with the synthesis of prostaglandins, NSAIDs may interfere with the release of the mature ovum, leading to an ovulation failure.
- NSAID use may also disrupt blastocyte implantation. A reversible effect has been observed, where successful conception has been achieved shortly after withdrawal of NSAIDs in those with severe rheumatoid arthritis.

- Glucocorticoids, such as prednisone, have multiple effects on fertility and thus should be minimized in RA patients looking to conceive.
- Glucocorticoids transiently suppress the hypothalamic-pituitary-ovarian axis, and have a direct effect on ovarian physiology and periconceptual uterine growth and proliferation.

- When examining serum levels of anti-Müllerian hormone (AMH), a reliable endocrine marker for ovarian reserve, studies have found that AMH levels are significantly lower in RA patients compared with those in healthy controls, with AMH levels lower in ACPA-positive patients than seronegative patients.
- Importantly however, AMH levels showed no significant association with TTP or self reported fertility. These findings support the multi-factorial nature of infertility in RA, outside of AMH level.

Preconception counseling

- Disease activity before conception is an important factor that influences disease course during pregnancy in patients with RA as quiescent disease often remains stable throughout pregnancy.
- In light of this, the mainstay of preconception counseling is based on optimization of disease control prior to and through pregnancy with safe medication use and appropriate washout time of teratogenic medications prior to conception.

- If medication adjustments are needed in advance of pregnancy, a 6-month period is ideally advisable in order to establish whether disease stability can be maintained in the setting of new treatment regimens. Treatment strategies should also take into account the negative effects of NSAIDs and medium/high dose prednisone and their effect on fertility independent of disease activity as required for flares.
- Patients should be co-managed by a rheumatologist and obstetrician.

Disease activity during pregnancy

- A commonly held notion is that the majority of RA patients experience spontaneous remission during pregnancy, and a tendency toward postpartum flare within 3–4 months.
- Newer data from RA patients using objective assessments of disease activity, has provided a more complete picture of disease activity during and after pregnancy.

- One of the first prospective studies using the modified DAS28-CRP activity measure found that indeed mean disease activity scores declined during pregnancy despite reduced rates of medication use compared to before conception, which demonstrates the beneficial effect of pregnancy itself.

- Data showed that 48% of patients who had at least moderate disease activity in the first trimester had an improvement in disease activity during pregnancy, with 25% of women experiencing RA remission during the 3rd trimester -- a substantial yet smaller proportion than previously expected.
- In patients with low disease activity in the first trimester disease activity was stable during pregnancy. In the postpartum period, disease activity increased, with deterioration in RA control in 39% of patients, noting a moderate or severe flare even in the context of increased medication use after delivery.
- A large, recent meta-analysis reviewing 10 studies showed similar findings; disease activity improved in 60% of patients with RA in pregnancy and flared in 46.7% postpartum.

- When predicting disease activity during pregnancy, seropositivity, defined as the positivity for or elevated level of rheumatoid factor or anti citrullinated antibodies, has been associated with active disease during pregnancy.
- Further analyses have shown that women with rheumatoid arthritis negative for anti-citrullinated antibodies and rheumatoid factor were more likely to improve during pregnancy, with a significantly higher percentage of women without autoantibodies (negative for anti-CCP and RF) improving compared with women positive for either or both autoantibodies.
- The occurrence of a flare postpartum was comparable between these groups.

Outcomes

- Newer results from the Nationwide Inpatient Sample from 2003-2011 which included approximately 42 millions deliveries corroborated previous findings; the maternal RA population had a significantly higher prevalence of

❖hypertensive diseases,

❖PROM,

❖antepartum hemorrhage,

❖preterm delivery,

❖IUGR and

❖cesarean delivery.

- Among the medications taken by RA patients during pregnancy -- including sulfasalazine, hydroxychloroquine and prednisone -- prednisone use has been linked to lower gestational age at birth.
- Deliveries have been shown to be, on average, 1 week earlier and more often occurring at < 37 weeks compared to RA patients not taking prednisone during pregnancy.
- Prednisone had an indirect negative effect on birth weight through shortening of the gestational age at delivery.

- The etiology of how increased disease activity causes lower birth weight is not yet certain.
- Proposed mechanisms include

❖vascular endothelial dysfunction causing maldevelopment of the placenta, and

❖dysregulated fetal:maternal cortisol levels driven by maternal chronic stress and/or the presence of high levels of proinflammatory cytokines.

Antirheumatic drugs during pregnancy and lactation

Table 1
Use of disease-modifying agents during pregnancy and lactation

Medication	Pregnancy	Lactation
Nonsteroidal anti-inflammatory drugs	May impair fertility	Low concentrations in breast milk
	Stop before 32 wk gestation (premature closure of ductus arteriosus)	Compatible with breastfeeding
Glucocorticoids	Nonfluorinated glucocorticoid (prednisone) metabolized by the placenta Compatible with pregnancy Use lowest dose for the shortest duration necessary	Compatible with breastfeeding
Methotrexate	Known teratogen	Can be detected in breast milk
	Discontinue 3 mo before pregnancy	
Leflunomide	Teratogenic in animal studies	Limited data on breastfeeding
	Small human studies show no increased risks Cholestyramine washout before pregnancy strongly recommended	Avoid use during breastfeeding
Sulfasalazine	Compatible with pregnancy at doses ≤2 g daily	Compatible with breastfeeding full-term infants
	Folate supplementation strongly recommended	Avoid use in premature or ill infants
Hydroxychloroquine	Compatible with pregnancy	Compatible with breastfeeding
Tumor necrosis factor inhibitors	Actively crosses placenta during second trimester Most studies found no increased risk of birth defects Low placental transfer of etanercept and certolizumab throughout pregnancy Postpone live vaccines in exposed infants for 6 mo	Compatible with breastfeeding
Other biologicals	Limited human data on pregnancy exposure Recommend avoiding during pregnancy	Limited data on breastfeeding Avoid use during breastfeeding

Table 2 A protocol for anti-natal monitoring the autoimmune rheumatic diseases patients during pregnancy

Clinical assessment	Measurements and investigations	Specific monitoring
Rheumatology clinic: 4–6 weekly, more frequent if the disease becomes active or flares	Standard: Each visit: blood pressure, body weight Full blood count, serum uric acid, liver functions, urea, creatinine, electrolyte levels, urinalysis SLE patients: protein/creatinine ratio, complement levels and dsDNA antibodies	Positive anti-Ro antibodies: foetal echocardiography, weekly from week 16–26 and biweekly thereafter, continuing till delivery
Obstetrician: monthly till week 20, then 2 weekly till week 28, and weekly thereafter	Ultrasound: -early pregnancy for gestational dating, -between week 16–20 to screen for foetal anomalies, −4 weekly thereafter to monitor growth	Preeclampsia: uterine artery Doppler study (week 20 and 4 weekly thereafter), foetal umbilical artery Doppler velocimetry (weekly from week 26 onwards)
	Foetal surveillance tests (FST): weekly starting form week 26	Intra-uterine growth retardation (IUGR): increase frequency of growth monitoring by ultrasound and FST

FST foetal surveillance tests, *IUGR* intra-uterine growth retardation