

9th International Conference on Reproduction, Pregnancy and Rheumatic Diseases

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San Diego, California

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MEETING NOTES

Objective:

This conference brings together experts in the field of pregnancy in rheumatic disease. Specifically, it brings together worldwide leaders in this field to share data, clinical experience, and areas of potential study, to help formulate treatment strategies and research ideas that will ultimately impact patient care. The target audience for this conference is rheumatologists, obstetricians, internal medicine, PCPs and nurses/nurse practitioners.

Presentations:

Rheumatoid Arthritis: Assessment of Background Risk in Pregnancy, Eliza Chakravarty, MD, MPH

- In the past, it was thought that 75% of pregnant women with rheumatic disease got better with pregnancy; however, it is now known that actual rates may not be as high with a recent study showing that only 25% of women went into remission, 20% had higher disease activity in the 3rd trimester and 50% had intermediate to higher disease activity.
- For the most part, the disease is generally more controlled when going into pregnancy
- Moms with active RA typically give birth to children with lower birthweight
- In Europe, the issue of low birthweight was studied to determine if it was due to the presence of rheumatic disease or due to prednisone use; it was noted higher disease activity is usually associated with smaller birthweight babies, and it was also noted that higher prednisone use is usually associated with earlier delivery (resulting in lower birthweight babies)
- For women with active RA, there is a higher risk of having a pre-term baby
- Pregnancy outcomes in women with RA include: harder time getting pregnant, progression erosion/damage to joints, risks of hospitalization and pre-eclampsia
- Management of RA in pregnancy includes such issues as: discontinuation of medications known for teratogenicity (methotrexate and leflunomide), using medications that are known to be compatible during pregnancy (Hydroxychloroquine, sulfasalazine, azathioprine)
- More information is becoming available regarding the safety of TNF inhibitors during pregnancy

Systemic Lupus Erythematosus: Assessment of Background Risk in Pregnancy, Bonnie L. Bermas, MD

- Various risk factors for flares during pregnancy were identified: level of the disease activity in the previous 6 months, prior lupus nephritis, prior hypertension, active serologies, and primigravida
- Various pregnancy complications can occur in mothers with SLE: pre-eclampsia, pregnancy induced hypertension, higher maternal mortality, increased rates of c-section,

increased rate of pre-term birth, low birth rate and SGA infants, some potential for long-term impact on children (need for further exploration).

The Nuts and Bolts of the FDA Label Change, Melissa S. Tassinari, PhD, DABT

- The Food and Drug Administration recently changed the Pregnancy and Lactation Labelling Rules (PLLR) – drugs approved after 2001 will be required to use the new labelling format (older drugs will simply remove the lettering)
- Previous labelling used the association of “letters” – this proved confusing for consumers, as letter were associated grades, with “A” being the best, “B” being second best, etc.
- New labelling will have clear statements on the label
 - Will include a telephone number or website to join the pregnancy exposure registry
 - Will include a risk summary
 - Will include information on lactation, as well as statements for both females and males of reproductive age

How to Interpret Animal Data in the Label, Stephen Harris, PhD

- More pharmaceutical drug testing is being done to test the safety using animals, including younger animals
- It is important to assess the potential effects of a compound on the reproduction/development in animals in order to characterize potential risks for women and men of reproductive age prior to and after birth
- Successful characteristics of animal models used for developmental and reproductive toxicity studies are validity, sensitivity, reproducibility, and practicability

How to Interpret Lactation Data in the Label, Jason Sauberman, PharmD

- Many agents are already existent in breastmilk: immunoglobulins, IL-1RA, TNF α receptors, IL-10, Interferon γ (not α or β), Cortisol
- Challenge is how to measure biologics in milk when they are already present?
- Drugs do not typically stay in the milk, and exposure can be minimized by managing doses versus breastfeeding times
- Potential sources for information on drugs during lactation:
 - LactMed (toxnet.nlm.nih.gov/newtoxnet/lactmed.htm)
 - Medication and Mother’s Milk (www.medsmilk.com and www.infantrisk.com)
 - Reprotox (free for trainees) (www.reprotox.org)
 - Drugs in pregnancy and lactation (www.lww.com)
 - AAP 2013 (recommend LactMed)
 - Mother to Baby (formerly OTIS) (www.mothersbaby.org) – advice by phone, email, live chat from teratology counsellors
- List of medications & breastfeeding

Drug	Milk transfer data	Comment
Green	AZA, colchicine, CSA, FK-506, NSAIDS, HCQ, prednisone, SSZ	Minimal-low exposure Long hx of safe use
	Warfarin, LMWH, ASA-low dose	Minimal to no exposure
Light Green	Biologic DMARDs	Certolizumab, Infliximab, Etanercept, Adalimumab;
		Breastfeeding safety individualized based

		“Insignificant” exposure.	on pregnancy exposure, TDM, infant immune status.
Yellow	Allpurinol, MTX, MMF	Low or likely low	Perform TDM, CBC
Red	Cyclophosphamide, leflunomide, Tofacitinib	None, but PK and chemical properties indicate very likely	Orally bioavailable Severe toxicities

PROMISSE Study, Jane E. Salmon, MD

- Looked at patients with lupus (9:1 Female:Male)
- Noted increased risk of complications: hypertension, pre-eclampsia, others

The Impact of Maternal Rheumatic Disease and the Long-Term Health of Offspring, Evelyne Vinet, MD, FRCPC

- Review of potential long-term outcomes on children born of mothers with rheumatic disease, including: autism, congenital heart disease, rheumatic and non-rheumatic autoimmune disease
- Conclusions were:
 - LSE offspring have a potentially increased risk of autism spectrum disorders, congenital heart defects and non-rheumatic autoimmune diseases (greater risk, but **overall effect is low**)
 - Rationale might extend to other rheumatic diseases, such as RA
 - Need to understand more on the potential role of disease-related factors, such as in utero drug exposure, maternal autoantibodies and cytokines

Abstract: Parental Rheumatoid Arthritis and Long-term Child Morbidity. A Nationwide Cohort Study, Ane Lilleøre Rom, Chun Sen Wu, Jørn Olsen, Damini Jawaheer, Merete Lund Hetland, Bent Ottesen, Lina Steinrud Mørch

- Results of the study showed the impact of parental arthritis and the impact on long-term child morbidity
 - Maternal RA was associated with an increased risk in morbidity (paternal RA did not)
 - Potential risks associated with JIA (3x), diabetes (30%) and asthma (20%)

Abstract: Parental Rheumatoid Arthritis and Childhood Epilepsy. A Nationwide Cohort Study, Ane Lilleøre Rom, Chun Sen Wu, Jørn Olsen, Damini Jawaheer, Merete Lund Hetland, Jakob Christensen, Bent Ottesen, Lina Steinrud Mørch

- Study showed that there was a greater risk of early and late childhood epilepsy with maternal RA, but not paternal RA
- Exposure to maternal clinical RA was associated with a higher risk of early childhood epilepsy than pre-clinical RA

The Behavioral and Emotional Health of the Offspring of Women with Rheumatic Disease, Wendy Marder, MD

- Intelligence tests are normal
- Increase in developmental/neurocognitive delays among offspring of mothers with connective tissue diseases (CTDs)
- Highest risk seem to be among pregnancies associated with antibody mediated diseases (SLE, APS)

- Children that are diagnosed can be provided with tools and support needed for success – advice for patients is to ensure their child is meeting key developmental milestones

Takayasu's Arteritis: Management of Peripartum Risks, Lindsay Forbess, MD

- Not much literature or research exists
- Complications (hypertension, pre-eclampsia, low birth weight, intrauterine growth restrictions, premature delivery) are 3x higher if the disease is active during pregnancy
- Pregnancy can be considered if the disease has been quiescent for 6 months, and if medications can be used in pregnancy; pregnancy should not be considered if there is extensive retinal vasculitis, extensive disease, renal insufficiency, aortic aneurysm and valvular disease
- Management of TA and pregnancy requires:
 - Multidisciplinary team approach
 - Management of hypertension aggressively and early
 - Management of the disease relapse
 - Consideration of aspirin (or low molecular weight heparin)
- Many patients with TA can have successful pregnancies; TA does not tend to flare during pregnancy

Pulmonary Hypertension: Management During and Following Pregnancy, Jess Mandel, MD

- In general, patients with pulmonary arterial hypertension should be counseled to avoid pregnancy as the risks are very high to the mother and the unborn child
- Patients who become pregnant should be closely followed during pregnancy
- Postpartum period is the highest risk period

The Management of Myositis in Pregnancy, Lisa Christopher-Stine, MD, MPH

- Very little literature is available (in 56 years, there are 88 pregnancies in 71 women documented)
- Well controlled myositis (6 months quiescent) is associated with normal fertility rates
- If the disease is active, fetal outcomes are worse, can be as high as 55% fetal loss
- Having myositis did not seem to worsen the prognosis for mothers and babies

Abstract: International Multicentric PROspective Study on PREgnancy in Systemic Sclerosis (IMPRESS 2): study design and preliminary data, Veronique Ramoni, Mauro Betelli, Yannick Allanore, Fabiola Atzeni, Marko Baresic, Fausta Beneventi, Silvia Bosello, Paola Caramaschi, Maurizio Cutolo, Sara De Carolis, Angelo De Cata, Guilherme de Jesus, Maria De Santis, Gianluca Erre, Paola Faggioli, Maria Favaro, Roberto Gerli, Maria Gerosa, Marcello Govoni, Eric Hachulla, Florenzo Iannone, Francesca Ingegnoli, Massimiliano Limonta, Marco Matucci – Cerinic, Marianna Meroni, Pier Luigi Meroni, Melissa Padovan, Giuseppe Paolazzi, Susanna Peccatori, Stefania Rampello, Valeria Ricciari, Edoardo Rosato, Felice Salsano, Alessandro Santaniello, Maria Scolack, Vanessa Smith, Mara Taraborelli, Angela Tincani, Guido Valentini, Madelon Vonk, Antonio Brucato

- Risks associated with pregnancies in mothers of systemic sclerosis include prematurity and intrauterine growth restrictions
- Pregnancy is not recommended if there is severe organ damage

MotherToBaby: New Data on TNF-Inhibitors in Pregnancy, Christina Chambers, PhD, MPH

- Has done research in various areas, including vaccines, asthma and asthma medications, RA, Crohns, psoriasis, AS, MS, lupus, etc.

- Study was undertaken to identify key points to consider for use of antirheumatic drugs before, during and after pregnancies

Results from the Euler Task Force: Non-TNF Biologicals, Monika Ostensen, MD

- Need to discontinue drugs during pregnancy that are known for teratogenicity (methotrexate, cyclophosphamide, MMF)
- For use of biologics during pregnancy, there is a need to consider the transfer through the placenta, which is dependent on various factors
- There is scarce data – until more data is available, it is suggested to use known drugs
- Where the disease is severe, and no risks have been identified to date, the benefit of using the drug may outweigh the risk

Abstract: Discontinuing TNF-inhibitor treatment at the positive pregnancy test and its effect on disease course and pregnancy outcome in patients with rheumatoid arthritis and spondyloarthritis, Stephanie van den Brandt, Astrid Zbinden, Dominique Baeten, Peter M Villiger, Monika Østensen, Frauke Förger

- Where there is a flare in RA, there may be a response to TNF inhibitor and glucocorticoids
- Where there is a flare in sPA, they may be a response only in part to TNF inhibitor, and not to glucocorticoids

Abstract: A self-reported RA disease activity measure, the RA Disease Activity Index (RADAI), strongly correlates with CDAI and DAS28-CRP3 during pregnancy, Sara K. Tedeschi, MD, Michelle Frits, Nancy Shadick, MD, MPH, Bonnie L. Bernas, MD

- RADAI is shown to be a reliable patient reported disease activity measure, and strongly correlates to the DAS28-CRP3

The Risks and Benefits of Corticosteroids for Pregnancy and Offspring, Radboud J.E.M. Dolhain, MD, PhD

- In RA, one clear study demonstrated that prednisone >7.5mg daily impairs fertility
- Pregnancy outcomes
 - Common side effects of prednisone have more impact during pregnancy
 - Association of prednisone with shorter gestational age
 - No association with miscarriages or congenital malformations
- (Long-term) consequences for offspring
 - Low dose prednisone diffuses to fetus before week 10 of gestation, risk that it may also be crossing the placenta
 - While more research is required, there is a risk that even low dose prednisone may have long-term consequences

The Management of Lupus Nephritis in Pregnancy, Catherine Nelson-Piercy, MBBSMA, FRCP, FRCOG

- With lupus nephritis, there is increased risk of pre-eclampsia / FGR / preterm delivery – Pre-pregnancy counselling needs to include a discussion of associated risks, including prematurity and handicaps
 - Starting aspirin can help prevent pre-eclampsia
 - Pregnancies should be delayed 6 months after a renal flare
- Lists of drugs during pregnancy

YES – OK	NO – NOT OK
<ul style="list-style-type: none"> • Prednisone • Azathioprine 	<ul style="list-style-type: none"> • Mycophenolate mofetil • Rituximab

<ul style="list-style-type: none"> • Hydrochloroquine • IVIG • Tacrolimus • Low Molecular Weight Heparin (LMWH) 	<ul style="list-style-type: none"> • Cyclophosphamide • ACE Inhibitors • AT II receptor blockers • Statins
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- MMF – known teratogenic, causes jaw and ear malformations (for example)
 - Suggest stopping for 6 weeks to 3 months (long half life)
 - To ensure disease is stable before moving to AZA (AZA safe during breastfeeding)
- Tacrolimus use in lupus nephritis: allows the reduction/minimal steroid treatment when pregnant
 - Babies expel the excess TAC during breastfeeding

Preeclampsia in Rheumatic Disease: Pathogenesis, Predictors, and Possible Remedies, Catherine Nelson-Piercy, MBBSMA, FRCP, FRCOG

- Pre-eclampsia is a disease of the placenta, and not of the kidney or the liver
- Risk factors of pre-eclampsia include
 - Maternal preterm delivery / low birth weight
 - Obesity
 - Pre-existing medical conditions
 - Chronic hypertension
 - Diabetes mellitus
 - Antiphospholipid syndrome / SLE
 - Infertility
 - Renal disease
- Placental growth factor (PIGF) is a marker for pre-eclampsia
- Preventing pre-eclampsia – avoiding pregnancy, taking aspirin
- Pre-eclampsia and maternal placental syndrome should be viewed as a risk factor for subsequent cardiovascular morbidity and mortality in women with SLE

Abstract: Preterm delivery as a marker for accelerated cardiovascular events in parous women with SLE, May Ching Soh, Catherine Nelson-Piercy, Lesley McCowan, Magnus Westgren, Dharmindra Pasupathy

- Pre-term delivery (under 34 weeks) is a risk factor of 1.8x of future CVE for women with SLE

The Management of Refractory Obstetric APS, Roger A. Levy, MD, PhD

- Pre-conception and planning is critical
- Not much research/literature exists
- No additional benefit from IVIG or rituximab
- Potential future options include HCQ and maybe a TNF

The Effect of Maternal APS on Offspring, Cecilia Nalli, MD

- Long-term results show children have normal intelligence levels and normal neurological physical exams, while some minor disorders have been detected
- In children of mothers with APS, language delay was noted, and learning disabilities were at a higher rate than the general age-school population
- Maternal autoimmune profile does not seem related to an increased risk.

- Children born to patients with systemic autoimmune disease, in particular with antiphospholipid antibodies may need long-term follow-up focusing on milestones of neuropsychological development in order to detect and support any behavioural, neurological or cognitive issues as early as possible.