REPORT

Treating rheumatic diseases in pregnancy: dos and don'ts

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This paper presents a critical appraisal of the current evidence and recommendations regarding the use of pharmaceuticals and biologicals in pregnancy. Clinical experience is often at variance with published recommendations as studies have not taken into account the differences in physiology in the various stages of gestation and between animal and human pregnancies. Physicians should bear in mind that pregnancy causes disruption in several organ systems; the effects of an intervention may depend on the stage of gestation; and some effects of interventions in pregnancy may not manifest until adulthood.

Although much has been written about rheumatic disease and pregnancy, and about medications in pregnancy, little information is available about the interaction of disease, drugs, and pregnancy, and even less about different concerns at different stages of pregnancy. Most studies consider pregnancy to be a dichotomous event (one is pregnant or one is not) and outcome as a dichotomous event (a healthy baby is born or is not). However, a woman's biology varies considerably between conception and the first year postpartum, and fetal outcome is measured not only at birth but also into adulthood. This paper examines some of the issues of biology of pregnancy, fertility and assisted reproduction, pharmaceuticals and biologicals in pregnancy, and some of the biology of biologicals in pregnancy. The author draws extensively on work by Monika Østensen, Angela Tincani, and Jane Salmon.

BIOLOGY OF PREGNANCY

Pregnancy consists of a series of tightly regulated steps (box 1). At the cell and organ level, many different identified cytokine and intracellular regulatory mechanisms are active at each step. At the whole body level of the mother, extensive endocrine modulation; growth and development of other organs (breasts, uterus); restructuring of the musculoskeletal system (loosening of ligaments); brain adaptation (oxytocin leading to expansion of maternal bonding responses); and changes in fluid volume, circulating blood elements, coagulation factors, and renal filtration occur, and may be affected by administered agents. Available studies of the pharmacobiology and disease related pathology of human pregnancy have considered none of these issues.

With regard to the readout of pregnancy outcome, animal pregnancies differ considerably from human in placental physiology, in maturation status of the fetus at delivery, in the fact of litters versus singlet pregnancies, and many other features. Furthermore, growth and development of the child remains an important outcome variable that, pragmatically, is very difficult to study. The occurrence of vaginal sarcoma in teenaged and young adult women whose mothers used diethylstilbestrol during the relevant pregnancy is compelling evidence of potential long term effects of treatment during pregnancy,¹ paralleled in rheumatology by discovery of

(treatment unrelated?) verbal processing disorders in male children of lupus patients as they entered their school years.² Thus, animal models are crude measures on which to judge

Box 1: A minimal list of biological steps necessary to achieve a normal pregnancy

- Conception
 - Sperm development
 - Sperm maturation
 - Ovum development
 - Ovulation
 - Delivery of sperm to ovum
 - Sperm attachment
 - Penetration
 - Fertilisation
- Embryogenesis
 - Sex commitment
 - X-inactivation
 - Imprinting
 - Implantation
 - Organisation of fetus
- Placental and fetal development
 - Vascular invasion
 - Rapid growth
 - Uterine growth
 - Remodelling of placenta
- Maternal–fetal communication
 - Access to maternal proteins and vice versa
 - Access to maternal cells and vice versa
 - Establishment of vascular/immune boundary
 - Regulation of maternal and fetal hormones ovary/placenta
- Labour and delivery
 - Placental senescence
 - Initiation of labour
 - Labour and delivery
 - Initial function of fetus

Each step is characterised by identified regulatory and maturation steps which, if interrupted, may result in failure or pathological pregnancy.

safety or efficacy of a treatment offered during pregnancy, and the disease as well as the treatment may affect outcome. Despite all these potential complications, pregnancy outcomes are often good.

FERTILITY AND ASSISTED REPRODUCTION

The Fourth International Conference on Sex Hormones, Pregnancy and the Rheumatic Diseases, held in Stresa, Italy in September 2004 reviewed what is known about pharmacology in issues of fertility and pregnancy and rheumatic diseases.³ Conclusions drawn at that meeting include:

- Regarding fertility, among small molecules, non-steroidal anti-inflammatory drugs interfere with follicle development and fallopian tube cilia function, and thus can diminish apparent fertility to a relatively small degree.
- Sulfasalazine impairs male fertility.
- Among immunosuppressives, methotrexate and cyclophosphamide impair male sperm production, and cyclophosphamide is lethal to developing ova; azathioprine and 6-mercaptopurine and ciclosporin do not appear to impair fertility.
- The effects of mycophenolate are not well known.
- Infliximab is the only biological for which information is available, and it does not appear to impair fertility.

Several authors have suggested the use of gonadotropin releasing hormone agonists for protection of fertility in women receiving cyclophosphamide. A single controlled study justifies this recommendation, but women who have used leuprolide will testify to the unpleasantness of its side effects.⁴

PHARMACEUTICALS AND BIOLOGICALS IN PREGNANCY

The US Food and Drug Administration (FDA) has established pregnancy categories for drugs. The definition of category B is:

“Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.”

Most biologicals have received this category assignment. The definition of category C is:

“Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant the use of the drug in pregnant women despite potential risks.”

Most pharmaceuticals have received this assignment.

Clinical experience often disagrees with FDA classifications. Table 1 outlines the conclusions of the Stresa conference regarding clinical *versus* FDA conclusions about various medicines that might be usable in pregnancy. A survey of practising rheumatologists found that almost all feel pregnancy is contraindicated in women taking methotrexate or leflunomide, but well under half find harm in the use of etanercept or infliximab.⁵ A retrospective voluntary report survey of 148 pregnant women using infliximab (primarily for Crohn's disease) found no increase in elective termination, miscarriage, or malformation compared with a general population control,⁶ and a more recent report of 10 pregnancies also found no problems.⁷ A British rheumatology register of 32 pregnant women with rheumatic disease who

were using any antitumour necrosis factor (anti-TNF) agent found 67% healthy infants, 23% first trimester miscarriages, and 10% elective terminations,⁸ and an American Organization of Teratology Information Services survey identified 29 persons taking etanercept and 4 infliximab. Compared with 74 disease and 49 non-disease controls, preterm delivery rates and birthweights were worse for disease (not for treatment); miscarriages and fetal malformations were like those of controls.⁹ Essentially no information is available for adalimumab or alefacept. Specialists in infertility are using these drugs off-label to enhance fertility, but they do not report their results in peer reviewed literature.

TNF α may play a role in regulating hormone synthesis, placental architecture, and embryo development. In the murine model of miscarriage induced by antiphospholipid antibody, inhibition of TNF α enhances fetal survival,¹⁰ as does complement inhibition,¹¹ suggesting possible future use of TNF α inhibitors (and/or complement inhibitors) to prevent recurrent fetal loss. Tests of these hypotheses are now under consideration for human pregnancy. This interesting new biology does not, at this time, justify an assumption that TNF α blockade is safe for rheumatic disease pregnancies, but, to date, adverse signals regarding these drugs, and all biologicals, have been few.

Two questions remain. Firstly, can biologicals be used to prevent recurrent pregnancy loss? The answer is a possible yes, depending on very narrow windows of efficacy and on the cause of threatened pregnancy failure. Secondly, are biologicals safe in pregnancy? It is important to keep in mind that:

- The portions of the immune system thought to be aberrant in rheumatic disease constitute only a small part of the biological systems likely to differ between pregnant and non-pregnant states and likely to be susceptible to inadvertent disruption by use of pharmaceuticals or agents.
- Timing of an intervention may be critical for both the fetus and the mother, since a four week pregnancy differs from an eight week pregnancy, both differ from a 16 week pregnancy, etc.

Table 1 A comparison of experiential beliefs about pregnancy risks of some agents used for treatment of rheumatic disease and Food and Drug Administration (FDA) classifications for the same agents

Drug	FDA class	Clinical assessment
Pharmaceuticals		
Non-steroidal anti-inflammatory drugs	C	Patent ductus arteriosus
Steroid	C	Prematurity
Hydroxychloroquine	C	–
Sulfasalazine	B	–
Immunosuppressives		
Azathioprine/6-MP	D	Possibly safe
Mycophenolate	C	Possibly not safe
Ciclosporin	C	Maternal renal
Methotrexate	X	Teratogenic
Cyclophosphamide	D	Teratogenic
Biologicals		
Tacrolimus	C	Possibly safe
Etanercept	B	–
Infliximab	B	Possibly safe
Adalimumab	B	Possibly safe
Rituximab	B	Possibly safe
Alefacept	B	–
Abatacept	–	–

–, no available information.

- Delivery of a high Apgar, 3000 g baby with 10 fingers and toes is not, by itself, an acceptable measure of success, as full knowledge of the effects of therapy, or of maternal illness, may not become apparent until that baby's adulthood.

Competing interests: none declared

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