Pregnancy and Biologic DMARDs
By Stephanie Ensworth, MD, FRCPC, ABIM

Not all clinically significant questions have been definitively answered by randomized double-blind placebo-controlled trials. The Hallway Consult by-line in the Journal of the Canadian Rheumatology Association will seek a consensus answer from rheumatologic experts for your difficult questions.

Please forward questions for future issues to: Mandiw@sta.ca.

Response:
There is very limited available data regarding the subcutaneously administered biologic anti-TNFs and pregnancy (significantly more limited for adalimumab than etanercept as use of etanercept to treat rheumatoid arthritis [RA] was approved by the FDA five years before adalimumab). The FDA has classified these biologics as pregnancy risk category B which means that no adverse pregnancy effects have been observed in animal studies but there have been insufficient controlled human studies. Case reports and case series have reported exposure of pregnant RA patients to etanercept and adalimumab without increased risk of adverse pregnancy outcomes compared with the general population. More of this literature looks at exposure to the biologics early in pregnancy and there is less data after first trimester exposure.

International experts on rheumatic diseases in pregnancy differ in their opinions ranging from: “until more data are available, no final conclusions can be drawn regarding the safety of anti-TNF therapy before, during, or, immediately after pregnancy;” “the available data are reassuring but are insufficient to endorse TNF alpha inhibitor therapy…during pregnancy;” “anti-TNF therapy should not necessarily always be avoided during pregnancy.” The drug manufacturers recommend that etanercept be stopped at least two weeks prior and adalimumab be stopped five months prior to planned conception but these recommendations are often based on legal rather than medical considerations. Isolated case reports of congenital anomalies associated with exposure of mainly etanercept but also adalimumab have been published and reported to the FDA. Exposure has ranged from early in pregnancy alone to high dose (etanercept 50 mg twice weekly) throughout pregnancy. It is unclear whether there is a causal relationship between these congenital defects and exposure to these biologics in pregnancy. As there does not appear to be, at least, a large excess risk, the use of these biologic agents prior to and during pregnancy needs to be considered cautiously, at the lowest dosage, on an individual risk-benefit analysis for each patient which must be fully discussed with the patient well prior to discontinuation of contraception.

In this particular case, I would not recommend discontinuation of this patient’s biologic therapy while attempting conception. Conception could take up to one year or longer during which time her RA needs to remain under control. As there is more literature on etanercept in pregnancy compared to adalimumab and as etanercept has a shorter terminal half-life (four to five days) compared to adalimumab (14 days), if the “subcutaneously administered anti-TNF biologic” that this patient is currently receiving is adalimumab, I might consider changing to etanercept. As her RA is reportedly currently “in remission,” I would attempt a trial of a reduced dosage of etanercept, perhaps 25 mg sc weekly, and observe if RA disease control can be maintained. The patient should be

Case History:
Ms. Jordan, a 28 year old G1P1 patient with RA, is contemplating a second pregnancy. Her RA began four years ago, eight weeks after delivering her first child. After failure to respond to methotrexate, sulfasalazine and hydroxychloroquine she went into a remission for the past two years on a subcutaneously administered biologic anti-TNF. She takes no other medications.

Should she discontinue the biologic therapy before attempting conception and if so for how long? Can biologics be used during pregnancy? If her RA flares post-partum, will she have to stop breast feeding to restart the biologic?
educated and monitored carefully so that pregnancy can be diagnosed as early as possible. If the patient’s RA remains in remission on the biologic until diagnosis of pregnancy, I would stop the biologic immediately at diagnosis of pregnancy, thereby minimizing exposure of the embryo to the biologic.

As RA disease activity significantly improves during pregnancy in 70% of patients, this patient has a good chance of completing pregnancy without treatment.

The best predictor of pregnancy and post-partum outcomes of a particular patient’s rheumatic disease, is past obstetrical history. As Ms. Jordan’s RA began at eight weeks post-partum, and, because about as many RA patients who improve during pregnancy also flare post-partum, this patient is at very high risk to flare post-partum. She needs to be functional. A post-partum RA flare will be poorly tolerated. I would restart biologic therapy post-partum, as soon as the patient has healed from delivery.

Little is known about biologic therapy and breastfeeding. Thus, I would recommend that this patient not breast-feed. Prior to discontinuation of contraception, I would advise the patient that, in my opinion, it would be better for her, her new infant and her family that she not breast-feed and that she resume her biologic therapy soon after delivery in effort to avoid a post-partum RA flare.

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REFERENCES: