Comment on: High-risk pregnancy and the rheumatologist: reply

Sir, We thank Sonja Praprotnik for her interest in our paper and due diligence in reading the original publication [1, 2]. She raises a valid point that would benefit from further discussion [3].

In the article by Daniel et al. [2], there was no increased risk of fetal malformations in 119 women exposed to selective cyclooxygenase 2 (COX-2) inhibitors in the first trimester. While there were additional data on concomitant drugs prescribed in the first trimester, these data were not included in the multivariate logistic regression because the authors deemed that there was no increased risk. Similarly, these data were excluded from sensitivity analysis, in which individual classifications of malformations were further explored. In the category of musculoskeletal malformations, the absolute numbers affected were small (n = 5 in COX-2 selective inhibitor use) and confidence intervals very wide. A similar trend towards increased risk of musculoskeletal malformations was observed for indomethacin, for which again the absolute numbers prescribed concomitant drugs to manage their inflammatory disease, and it is probable that these drugs (e.g. MTX) could be contributing to the overall risk of musculoskeletal malformations seen in this group. MTX traditionally causes limb skeletal abnormalities (partial or absent ossification of bones, shortened limbs, syndactyly, absent digits and multiple cranial ossification abnormalities); hence, it is within the realms of possibility that these are in keeping with the musculoskeletal abnormalities described in the sensitivity analysis [4].

COX is responsible for the production of prostaglandins—COX-1 and COX-2. NSAIDs interrupt the conversion of COX to prostaglandins, and thereby non-selectively inhibiting both COX-1 and COX-2 production. COX-2 inhibitors discussed in our paper have a more streamlined effect on both maternal and fetal tissues. So, one could hypothesize that the dual blockade of COX-1 and COX-2 by NSAIDs would have a greater effect on the developing fetal organs than seen in COX-2 inhibition alone. This is very much evident in the use of COX-2 inhibitors for the treatment of preterm labour when oligohydramnios is less profound and preterm closure of the ductus arteriosus is delayed when compared with NSAID use [5, 6].

There is now good evidence for lack of teratogenicity with NSAIDs; this is despite early reports to the contrary and possible association with a variety of anomalies [7]. Drugs often require decades of use before they are accepted as safe in pregnancy, simply because pregnant women are excluded from most drug trials. We believe the data for the safety of COX-2 selective inhibitor use in pregnancy will be even slower to emerge, because many clinicians will be more inclined to swap pregnant women on COX-2 selective inhibitors to a NSAID with a more established safety profile. However, the strengths of COX-2 selective inhibitors may lie in their use beyond 32 weeks’ gestation for women who require intermittent NSAID use in pregnancy for the management of inflammatory pain.

Nevertheless, we agree with Dr Praprotnik that until further evidence is available, we should exercise caution in the use of COX-2 inhibitors in early pregnancy, hence our sentence “data for the safety of COX-2 inhibitors is emerging . . .”. In retrospect, the disclaimer was somewhat ambiguous, and we hope this reply better quantifies the risk of COX-2 selective inhibitor use in pregnancy.

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References