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Global comment on the use of hydroxychloroquine during the periconception period and pregnancy in women with autoimmune diseases

We would like to express our united concerns about the February, 2023 recommendation by the European Medicines Agency to update the background section of the summary of product characteristics and the patient information leaflet for the use of hydroxychloroquine in pregnancy.[1]

Previously, the background information on hydroxychloroquine use in pregnancy referenced data in "300–1000 prospective pregnancies from observational studies, as well as a meta-analysis of pregnancy exposure (mainly in women with autoimmune disease)", at doses ranging from 200 mg to 400 mg, "which did not show a statistically significant increase of congenital malformations or feto/neonatal toxicity related to hydroxychloroquine use in pregnancy."[2] This section will be replaced by text citing only one study by Huybrechts and colleagues[3] reporting findings of a small increased risk of congenital malformations with the use of high-dose hydroxychloroquine during pregnancy.

The updated patient leaflet will now state: "[Hydroxychloroquine] may be associated with a small increased risk of major malformations and should not be used during pregnancy unless your doctor considers the benefits outweigh the risks."[2]

The current summary of product characteristics recommendation remains unchanged: "Hydroxychloroquine should be avoided in pregnancy except when, in the judgment of the physician, the individual potential benefits outweigh the potential hazards. If treatment with hydroxychloroquine is necessary during pregnancy, the lowest effective dose should be used."[2]

The 2021 study by Huybrechts and colleagues[3] was based upon US health-insurance data comparing 2045 pregnancies exposed to hydroxychloroquine (all indications) during the first trimester with 3198589 unexposed pregnancies in the general population. The study found a risk of malformations of 54·8 per 1000 children exposed to hydroxychloroquine and 35·3 per 1000 children not exposed to hydroxychloroquine, corresponding to an unadjusted relative risk (RR) of 1·51 (95% CI 1·27–1·81). When adjusting for potential confounders, there remained overall a significant RR of 1·26 (1·04–1·54), although significance was lost (RR 0·95, 0·60–1·50) for patients treated with doses lower than 400 mg per day. Importantly, no comparison was made between hydroxychloroquine exposure at usual rheumatology dosing of up to 400 mg per day and atypical dosing of more than 400 mg per day.[3]

Our concerns relate to several aspects. First, removing previous evidence including observational data and a meta-analysis from a background section for any

recommendation and replacing it with a single study is not usual practice. All scientific evidence supporting the safety or harms of a medication should be systematically reviewed and presented. The British Society of Rheumatology (BSR),[4] European Alliance of Associations for Rheumatology,[5,6] and American College of Rheumatology[7] have published their guidance on the use of drugs in pregnancy on the basis of systematic literature reviews, summarising all available data on the safety of hydroxychloroquine in pregnancy. All three documents concluded that hydroxychloroquine is compatible with the periconception period, during pregnancy and breastfeeding. Notably, Huybrechts and colleagues[2] study was scrutinised in the BSR guideline published in November, 2022, and was incorporated into their related recommendation specifying a dose ceiling of 400 mg per day regardless of weight, if required to treat rheumatic disease.[4] In the systematic literature review underpinning the 2022 BSR guidance,[4] the findings that hydroxychloroquine showed no statistically significant difference in outcomes (including congenital malformations) were consistent across all other studies.

Second, the data from Huybrechts and colleagues[3] showing a small increase in risk of malformations with hydroxychloroquine at doses of 400 mg per day or higher did not display a consistent pattern of malformations apart from a slight over-representation of oral clefts (without specifying their exact nature, being labial, palatal or labiopalatal) or unspecified urinary abnormalities, without any information on familial malformations for these two groups of anomalies and based on very small numbers with wide CIs. This information might be relevant when communicating to those women whose hydroxychloroquine recommended dose of 5 mg/kg per day yields an amount higher than 400 mg per day. In these cases, physician–patient shared decision making would probably conclude that the need for keeping maternal disease under control likely outweighs a possible slight increase in the risk of malformations; however, each case should be individually managed as maternal disease can be different and risk perception might widely vary across people.

Lastly, removal of all previous data from the background section and not including even more recent data gives a biased presentation of existing information. In fact, the most recent evidence from May, 2021, and April, 2022, published after the study by Huybrechts and colleagues,[2] does not support their findings. Data from a Danish population register of 1 240 875 pregnancies including 1487 pregnancies treated with antimalarials (1184 chloroquine and 303 hydroxychloroquine) showed that in 983 pregnancies with first trimester exposure there was no increased risk of major congenital malformations compared with unexposed matched pregnancies (odds ratio [OR] prevalence 0·94, 95% CI 0·59–1·52).[8] In addition, the MotherToBaby Organization of Teratology Information Specialists Autoimmune Diseases in Pregnancy Study of 837 women (279 treated with hydroxychloroquine and 558 non-exposed, of whom 279 were disease matched and 279 healthy controls) found no evidence of an increased risk of structural birth defects.[9] This carefully designed prospective study showed that in women with live births, birth defects occurred in 20 (8·6%) of 232 women with hydroxychloroquine exposure in the first trimester, compared with 19 (7·4%) of 256 disease-matched unexposed controls (adjusted OR 1·18, 0·61–2·26) and 13 (5·4%) of 239 healthy controls (0·76, 0·28–2·05). Risks did not differ in women who were receiving a hydroxychloroquine dose of 400 mg per day or higher.[9] Furthermore, a 2023 systematic review, which included four cohort studies aiming to assess hydroxychloroquine use in the setting of pre-eclampsia, did not find an association between hydroxychloroquine use and congenital malformations.[10]

Our unease relates to the update of the background section and the amendment of the patient leaflet, which now states there is a small increased risk of major malformations as outlined. We are concerned that this update might cause direct and indirect harm to patients and their babies.

Direct harm might be caused to patients who would benefit from immunomodulation during pregnancy if the absence of complete published evidence in the summary of product characteristics leads physicians to be more hesitant in prescribing, and their patients less willing to take hydroxychloroquine during the periconception period and pregnancy. In addition, pharmacists might advise women to stop hydroxychloroquine treatment. Stopping hydroxychloroquine might lead to worsening of symptoms or disease flares, and active inflammatory disease has been widely associated with pregnancy complications such as miscarriage, intrauterine death, placental insufficiency, fetal growth restriction, pre-eclampsia, and preterm birth.[11]

These proposed statements might also cause indirect harm to patients. If the patient leaflet update describes potential adverse effects of medication on the fetus, patients might experience emotional distress or anxiety about negative consequences to their unborn child, yet be unaware of the risk of poorly controlled disease if the medication is stopped.

We therefore advocate using a more scientifically accurate statement in the background section of the hydroxychloroquine summary of product characteristics. For instance, the study by Huybrechts and colleagues[2] could be cited as "According to one US population-based study, offspring of mothers exposed to hydroxychloroquine during pregnancy could have a slightly higher risk of birth defects. This slight excess risk was not associated with the duration of exposure, not found for doses of hydroxychloroquine lower than 400 mg per day, and no specific pattern of malformations was identified."

In times of unmonitored and unverified sources of information, such as social media and artificial intelligence tools, we believe that regulators and other public domains have an increasingly important role and responsibility

Panel: **Use of hydroxychloroquine in the periconception period and pregnancy: what can I tell my patients?**

What can I tell my patients when discussing the February, 2023, European Medical Agency update in the background information of the summary of product characteristics and updated patient leaflet on the use of hydroxychloroquine during pregnancy with regard to malformations?

Why is there interest in hydroxychloroquine and malformations after decades of use during pregnancy in autoimmune diseases?

No safety signals specifically regarding hydroxychloroquine-induced malformations constituted background to the study by Huybrechts and colleagues.[3] The study was prompted by the initial suggestion that hydroxychloroquine was a useful drug for treating COVID-19 and the researchers looked at information from US health insurance to compare pregnant women who took hydroxychloroquine during the first few months of pregnancy (2045 women) with pregnant women who did not take hydroxychloroquine (3 198 589 women) in the period 2003–15.

The dose of hydroxychloroquine matters: no concerns with doses lower than 400 mg per day.

The study by Huybrechts and colleagues[3] found that babies whose mothers took hydroxychloroquine had a higher chance of having birth defects (54·8 per 1000 babies) compared with babies whose mothers did not take hydroxychloroquine (35·3 per 1000 babies). Following statistical calculations, in which other factors that might influence risk were taken into account, this risk was 1·26 higher for babies whose mothers took hydroxychloroquine. However, when the hydroxychloroquine dose was less than 400 mg per day, which is often used for treating rheumatic diseases, the risk was not significantly higher and no direct comparison was made between typical rheumatology dosing of 400 mg per day or lower and atypical dosing higher than 400 mg per day.

Malformations displayed no pattern.

In the study by Huybrechts and colleagues,[3] oral and urinary defects were more frequent than other types of defects, but no pattern of malformations was identified. Why is this important? When the same type of birth defects occurs in many babies exposed to a specific drug during pregnancy, scientists are alerted to investigate whether the drug causes that particular type of birth defect. If the type of birth defect is identified as being caused by a drug, initiatives are taken to prevent harm to the mother and baby.

What can I tell my patients when discussing the potential benefits of hydroxychloroquine in pregnancy in view of their underlying autoimmune disease?[4]

The benefits of hydroxychloroquine in women who have systemic lupus erythematosus and are pregnant.

Hydroxychloroquine keeps systemic lupus erythematosus quiescent and reduces the risk of flares, including organ involvement such as lupus nephritis. As active disease itself is a risk factor for pregnancy complications, the use of hydroxychloroquine is recommended for improving both maternal and fetal outcomes.

Improving pregnancy outcome in patients with antiphospholipid syndrome.

Experimental studies showed that hydroxychloroquine can help to dampen antiphospholipid antibody-mediated inflammation and to prevent blood clots from forming at the placental level. Observational studies described better pregnancy outcomes for pregnant patients with refractory obstetric antiphospholipid syndrome who were on hydroxychloroquine. Current studies are aiming to clarify the utility of hydroxychloroquine as first-line treatment in the management of obstetric antiphospholipid syndrome. Although it is too early to recommend the routine use of hydroxychloroquine in obstetric antiphospholipid syndrome, its use can be considered in selected cases.

Reduced risk of anti-Ro/SSA and anti-La/SSB-associated congenital heart block.

Fetuses and babies exposed to maternal anti-Ro/SSA and anti-La/SSB autoantibodies might develop a heart condition called congenital heart block. Hydroxychloroquine was shown to lower the chances of congenital heart block recurrence in pregnant women who already had this complication. Future studies will show whether hydroxychloroquine might also be considered as primary prophylaxis in women with anti-Ro/SSA and anti-La/SSB autoantibodies.

to show complete, accurate, and balanced information about the safety, risk, and benefit of medication use in pregnancy. This more balanced advice will help to reduce the harmful effects that arise from loss of disease control upon stopping a medication that, according to specialists, is considered to be compatible with use during the periconception period, pregnancy, and breastfeeding. We have provided suggestions for communication about the use of hydroxychloroquine in pregnancy (panel).

How do we proceed from here? Inspired by paediatric oncology, a field in which the European Medicines Agency started a pilot project in May, 2023, enabling scientist participation in medicine regulation,[12] we believe that experts in the field of reproductive health care in rheumatology can also provide valuable input to contextualise any safety signals within the context of the risk–benefit ratio, which is the pillar of shared decision making.

The idea for this collaborative global response was born at the inaugural meeting of the EULAR study group for Reproductive Health and Family Planning in Milan in June, 2023. We would like to thank Kirsten Frøhlich (Danish Centre for Expertise in Rheumatology (CeViG), Danish Hospital for Rheumatic Diseases, Sonderborg, Denmark) for her immense logistic support throughout the process of this work. CN-P reports consultancy fees from Sanofi Aventis and UCB; speakers fees from UCB, Sanofi and Otsuka; is a medical advisor (medical advisory board) for the pregnancy sickness support charity; and a patron of the Lauren Page Trust. RJEMD reports grants from Galapagos and UCB; speakers fees from Galapagos, Eli Lilly, Novartis, and UCB; support for attending meetings from UCB; and participation on advisory boards for Galapagos and UCB. 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