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

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We would like to express our united concerns about the recent recommendation by the European Medicines Agency (EMA) to update the background section of the summary of product characteristics (SmPC) and the patient information leaflet for the use of hydroxychloroquine (HCQ) in pregnancy [1].

Previously, the background information on HCQ 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 to 400 mg, "*which did not show a statistically significant increase of congenital malformations or feto/neonatal toxicity related to HCQ use in pregnancy."*
This section will be replaced by text citing only one study by Huybrechts et al. reporting findings of a small increased risk of congenital malformations with the use of high-dose HCQ during pregnancy[2].
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*."
The current SmPC 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*."[3]

The 2021 study by Huybrechts et al. is based upon US health insurance data comparing 2045 pregnancies exposed to HCQ (all indications) during the 1st trimester with 3,198,589 unexposed pregnancies in the general population[2]. It found a risk of malformations of 54.8 per 1000 children exposed to HCQ and 35.3 per 1000 children not exposed to HCQ, 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 (95% CI: 1.04-1.54), although significance was lost - RR 0.95 (95% CI: 0.60-1.50) - for patients treated with doses < 400 mg/day.
Importantly, no comparison was made between HCQ exposure at usual rheumatology dosing of up to 400 mg/day and atypical dosing of > 400mg/day[2].

Our concerns relate to several aspects:

Firstly, 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 the risk of a medication should be systematically reviewed and presented. The BSR[4], EULAR[5,6] and ACR[7] have published their guidance on the use of drugs in pregnancy based on systematic literature reviews, summarizing all available data on the safety of HCQ in pregnancy. All three documents concluded that HCQ is compatible in the periconception period, during pregnancy and breastfeeding. Notably, the Huybrechts et al. study was scrutinized in the BSR guideline published in November 2022 and incorporated into their related recommendation specifying a dose ceiling of 400 mg/day regardless of weight, if required to treat rheumatic disease[4]. In the systematic literature review underpinning the BSR 2022 guidance[4] the findings for HCQ of no statistically significant difference in outcomes (including congenital malformations) were consistent across all other studies.

Secondly, the data from Huybrechts el al. showing a small increase in risk of malformations with HCQ at doses ≥ 400 mg/day did not display a consistent pattern of malformations apart from a slight over-representation of oral clefts (without specifying their exact nature: labial, palatal or labio-palatal) or unspecified urinary abnormalities, without any information on familial malformations for these two groups of anomalies and based on very small numbers with wide confidence intervals. This information may be relevant when communicating to those women whose HCQ recommended dose of 5 mg/kg/day yields an amount higher than 400 mg/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 may 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, published after the Huybrechts et al. study, does not support their findings. Data from a recent Danish population register of 1,240,875 pregnancies including 1,487 pregnancies treated with antimalarials (1184 chloroquine and 303 HCQ) showed that in 983 pregnancies with 1st 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 HCQ 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 HCQ exposure in the first trimester, compared to 19 (7.4%) of 256 disease-matched unexposed controls (OR 1.18, 95% CI 0.61–2.26) and 13 (5.4%) of 239 healthy controls (adjusted OR 0.76, 95% CI 0.28–2.05). Risks did not differ in women who were receiving an HCQ dose of ≥ 400 mg/day[9]. Furthermore, a recent systematic review, including four cohort studies aiming to assess HCQ use in the setting of pre-eclampsia, did not find an association between HCQ 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 a *small increased risk of major malformations* as outlined above. We are concerned that this may cause direct and indirect harm to patients and their babies.

Direct harm may be caused to patients who would benefit from immunomodulation during pregnancy if the absence of complete published evidence in the SmPC leads physicians to be more hesitant in prescribing, and their patients less willing to take HCQ during the periconception period and pregnancy. In addition, pharmacists may advise women to stop HCQ treatment. Stopping HCQ may 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, preeclampsia and preterm birth [11] .

These proposed statements may also cause indirect harm to our patients. If the patient leaflet update describes potential adverse effects of medication on the fetus, patients may 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 HCQ SmPC. For instance, the Huybrechts et al. study could be cited as: “According to one U.S. 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 <400 mg/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 to show complete, accurate and balanced information about the safety as well as 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. **Box 1** shows communication suggestions about the use of HCQ in pregnancy.

How do we go from here? Inspired by pediatric oncology, a field in which the EMA in May 2023 has started a pilot project enabling scientists’ participation in medicine regulation[12], we believe that experts in the field of reproductive healthcare in rheumatology also can provide valuable input to contextualize any safety signals within the frame of the risk-benefit ratio, which is the pillar of shared decision making.

1323 words.

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Box 1: Use of HCQ in the periconception period and pregnancy: What can I tell my patients?

Abbreviations: aPL: antiphospholipid antibodies; APS: Antiphospholipid Syndrome; CHB: Congenital Heart Block; HCQ: hydroxychloroquine; obAPS: obstetric APS; SLE: Systemic Lupus Erythematosus; SmPC: summary of product characteristics

What can I tell my patients when discussing the recent EMA update in the background information of the SmPC and updated patient leaflet on use of HCQ during pregnancy with regard to malformations?	**Why is there interest in HCQ and malformations after decades of use during pregnancy in autoimmune diseases?** No safety signals specifically regarding HCQ-induced malformations constituted background to the study by Huybrechts et al. The study was prompted by the initial suggestion of HCQ being a useful drug for treating COVID-19 and the researchers looked at information from US health insurance to compare pregnant women who took HCQ during the first few months of pregnancy (2,045 women) with pregnant women who didn't take HCQ (3,198,589 women) in the period 2003-2015. **The dose of HCQ matters: no concerns with doses less than 400 mg per day.** The study by Huybrechts et al. found that babies whose mothers took HCQ had a higher chance of having birth defects (54.8 out of 1,000 babies) compared to babies whose moms didn't take HCQ (35.3 out of 1,000 babies). Following statistical calculations, where other factors which may influence the risk where taken into account, this risk was 1.26 higher for babies whose mothers took HCQ. However, when the HCQ dose was less than 400 mg per day, which is often used for treating rheumatic diseases, the risk wasn't significantly higher and no direct comparison was made between typical rheumatology dosing of ≤400mg/day and atypical dosing of >400mg/day. **Malformations displayed no pattern.** In the study by Huybrechts et al, oral and urinary defects were more frequent than other ones, but no pattern of malformations was identified. Why is this important? When the same type of birth defects occurs in many babies exposed during pregnancy to a certain drug, scientists get alerted to investigate whether the drug causes that peculiar 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 HCQ in pregnancy in view of their underlying autoimmune disease?[4]	**The multiple benefits of HCQ in SLE pregnancy.** HCQ keeps SLE 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 HCQ is recommended for improving both maternal and fetal outcomes. **Improving pregnancy outcome in patients with APS.** Experimental studies showed that HCQ can help to dampen aPL-mediated inflammation and to prevent blood clots from forming at the placental level. Observational studies described better pregnancy outcomes for pregnant patients with refractory obAPS who were on HCQ. Current studies are aiming at clarifying the utility of HCQ as first-line treatment in the management of obAPS. While It is too early to recommend the routine use of HCQ in obAPS, its use can be considered in selected cases. **Reduced risk of anti-Ro/SSA-associated Congenital Hear Block (CHB).** Fetuses/babies exposed to maternal anti-Ro/SSA autoantibodies may develop a heart condition called CHB. HCQ was shown to lower the chances of CHB recurrence in pregnant women who already experienced this complication. Future studies will show whether HCQ may be also considered as primary prophylaxis in women with anti-Ro/SSA autoantibodies.