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### Disclosure of interest

The authors declare that they have no competing interest.

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## Chloroquine and hydroxychloroquine during pregnancy: What do we know?

*Keywords* Hydroxychloroquine; Chloroquine; Covid-19; Pregnancy

Chloroquine and hydroxychloroquine are currently highly broadcasted as medications for severe Covid-19 infection although, to date, the efficiency data are very limited.

What do we know about the safety of these medications in pregnant women?

Chloroquine and hydroxychloroquine cross the placenta.

The volume of distribution of these medications is very high and potentially worrying for pregnant women and their half-lives are long; 10 to 30 days for chloroquine and 30 to 60 days for hydroxychloroquine, which leads to prolonged exposure after stopping these drugs. Thus, a woman who takes and stops one of these drugs before pregnancy can therefore be exposed during the upcoming pregnancy.

More data on safety during pregnancy are available about chloroquine, an old medication widely used in the general population as antimalarial than about hydroxychloroquine which is currently indicated for some autoimmune diseases such as lupus or rheumatoid arthritis.

First, experimental studies (in mice and monkeys) have shown that chloroquine could accumulate in the eyes, ears and adrenals. At very high doses (>250 mg/kg), microphthalmia and anophthalmia have been reported in rats. More recently, in ''in vitro'' and ''in vivo'' experiments, chloroquine caused genetic mutations and chromosomal damage (summary of product characteristics of Nivaquine®).

In humans, three studies on 169, 130 and 774 [1—3] women exposed to chloroquine during the 1st trimester of their pregnancy did not suggest an increase in the risks of congenital anomalies, in utero death or low birth weight.

Regarding hydroxychloroquine, two meta-analysis including 8 and 6 studies were published in 2015 and 2018 [4,5]. Their conclusion are rather reassuring about the risks of teratogenicity, termination of pregnancy and prematurity. However, according to the authors, these data should be interpreted with caution because the studies included in these meta-analyses, only small numbers of pregnant women (9 to 383 pregnant women) and were often observational [6].

Due to already described animal observations and rare but severe ocular adverse effects of both chloroquine and hydroxychloroquine in treated patients (retinal damage, sometimes irreversible, after several years of exposure), several case-studies have focused on the potential risk of prenatal exposure to chloroquine and hydroxychloroquine on eye development. Two cases of retinal degeneration

after in utero exposure to chloroquine were published in 1969 [7] and 1 case of ocular abnormality in 2011 [8] in a child exposed prenatally to methotrexate and chloroquine. Two reviews of 12 and 9 studies [7,9] including respectively 588 and 246 children did not highlight an increased risk of eye abnormalities in children exposed in utero to the two medications of interest. However, the authors of the reviews underlined the insufficiency of data, the presence of numerous biases and the need to follow up the children over a longer period. The ocular toxicity of these 2 drugs is dependent on the ''dose'' and the ''duration of use'' [10]. Considering the half-lives of these drugs, one cannot exclude, in case of a long exposure, their accumulation, favouring adverse effects on the retina.

In conclusion, clinical data on chloroquine and hydroxychloroquine in pregnant women are rather reassuring when used in the indications of their marketing authorization. Some data exist with chloroquine when it is used against malaria. In other situations (other dosages, other durations of treatment, other indications), their benefit/risk balance is not established yet. These drugs can induce adverse effects, on the eyes (and a rare risk for the foetus cannot be entirely ruled out), but also on the heart rhythm (they are quinidine derivatives) that must increase our vigilance. In addition, chloroquine and potentially hydroxychloroquine are genotoxic.

The use of these medications in pregnant women should therefore only be considered if the benefit of their use clearly justifies it.

Given the half-lives of these drugs, it should also be remembered that a woman who took one of these 2 drugs will remain exposed up to 210 days for chloroquine and 420 days for hydroxychloroquine after stopping their intake. Thus, a woman who takes and stops one of these drugs before pregnancy can therefore be exposed during the upcoming pregnancy.

In the case of exposure during pregnancy, as a precaution, careful ultrasound monitoring, increased vigilance at birth (especially in case of prematurity) and ophthalmological monitoring of the child should be recommended.

### Disclosure of interest

The authors declare that they have no competing interest

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## Adverse drug reactions of hydroxychloroquine: Analysis of French pre-pandemic SARS-CoV2 pharmacovigilance data

*Keywords* Hydroxychloroquine; Pharmacovigilance; Adverse reaction

### Abbreviations

| | |
|---|---|
| ADRs | adverse drug reactions |
| HCQ | hydroxychloroquine |
| SL | systemic lupus |
| WHO | World Health Organization |

### Introduction

Hydroxychloroquine (HCQ) is a 4-aminoquinoline derivative indicated in systemic lupus (SL), lucites and rheumatoid arthritis [1]. Its main adverse drug reactions (ADRs) described in the summary of product characteristics are ocular damage, particularly retinopathy during long-term exposure with high doses, cardiac damage with QT