Thieme

Hydroxychloroquine as a Preventive and Therapeutic Option in Preeclampsia – a Literature Review

Hydroxychloroquin als präventive und therapeutische Option bei Präeklampsie – eine Literaturübersicht

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ABSTRACT

Preeclampsia is one of the most feared complications of pregnancy and puerperium and represents a serious threat to mother and child. In addition, a history of preeclampsia increases the risk of future cardiovascular events. New diagnostic and therapeutic approaches are needed. New therapeutic options are currently being discussed, one of which is the administration of hydroxychloroquine. It is an antimalarial drug which is also used to treat rheumatological disease and its use in pregnancy is considered safe. A reduced incidence of preeclampsia in patients with selected rheumatological disorders after administration of hydroxychloroquine has already been shown; however, the case numbers are very low. Neither the full pathogenesis of preeclampsia nor the exact modes of action of hydroxychloroquine have been completely elucidated, but there are several common features which make hydroxychloroquine a promising option for the prevention and treatment of preeclampsia. Further research, especially prospective, randomized controlled trials, is needed to prove its efficacy. This review discusses the pathogenesis of preeclampsia and gives an overview of new options for its prevention and treatment, including the administration of hydroxychloroquine in pregnancy.

ZUSAMMENFASSUNG

Die Präeklampsie zählt zu den am meisten gefürchteten Schwangerschafts- und Wochenbettkomplikationen und stellt eine ernste Gefahr für Mutter und Kind dar. Hinzu kommt noch, dass eine vorherige Präeklampsie das Risiko für künftige kardiovaskuläre Ereignisse erhöht. Neue diagnostische und therapeutische Konzepte werden benötigt. Einige neue therapeutische Optionen werden inzwischen diskutiert, darunter die Gabe von Hydroxychloroquin. Hydroxychloroquin ist ein Antimalariamittel, das auch zur Behandlung von rheumatologischen Erkrankungen eingesetzt wird, und der Einsatz dieses Medikaments während der Schwangerschaft gilt als sicher. Bei Patientinnen mit spezifischen rheumatologischen Erkrankungen, die mit Hydroxychloroquin behandelt wurden, reduzierte sich die Häufigkeit von Präeklampsie, aber die Fallzahlen waren sehr niedrig. Weder die komplette Pathogenese von Präeklampsie noch die präzise Wirkungsweise von Hydroxychloroquin sind bislang gänzlich geklärt, aber es gibt mehrere Gemeinsamkeiten, die darauf hindeuten, dass Hydroxychloroquin eine vielsprechende Möglichkeit zur Prävention und Behandlung von Präeklampsie darstellen könnte. Es werden weitere Untersuchungen, insbesondere prospektive, randomisierte kontrollierte Studien, benötigt, um die Wirksam-

keit von Hydroxychloroquin zu belegen. In dieser Übersichtsarbeit wird die Pathogenese von Präeklampsie diskutiert, und es wird ein Überblick der neuesten Optionen bei der Prävention und Behandlung von Präeklampsie einschließlich der Hydroxychloroquin-Gabe während der Schwangerschaft vermittelt.

Abbreviations

aPL	antiphospholipid antibodies
APS	antiphospholipid syndrome
ASA	acetylsalicylic acid
eNOS	endothelial NO synthase
EOP	early onset preeclampsia
HCQ	hydroxychloroquine
IFNα/γ	interferon α/γ
ICAM-1	intracellular adhesion molecule-1
IL1/2/6/10	interleukin 1/2/6/10
IUGR	intrauterine growth restriction
LOP	late onset preeclampsia
NO	nitric oxide
PlGF	placental growth factor
sEng	soluble endoglin
sFLT-1	soluble fms-like tyrosine kinase-1
SLE	systemic lupus erythematosus
TGFβ	transforming growth factor-β
TLR	Toll-like receptor
TNFα	tumor necrosis factor α
VCAM-1	vascular cell adhesion molecule-1
VEGF	vascular endothelial growth factor

Background

Preeclampsia is one of the most feared complications of pregnancy and puerperium and represents a serious threat to mother and child. With an incidence of 2 %, it is a common disease and the cause of over 70 000 maternal deaths annually worldwide [1, 2].

According to the AWMF guideline [3], it is defined by hypertension (blood pressure ≥ 140/90 mmHg) and significant proteinuria in or after the 20th week of gestation or onset of another organic disorder (renal, liver, neurological, pulmonary or placental dysfunction or thrombocytopenia). Other definitions differ slightly. The number of severe complications of pregnancy such as eclampsia has been successfully reduced in recent years [2]. This can be attributed to an improved understanding of the complex pathogenesis of this disease and to new diagnostic approaches. Many institutions are now able to routinely determine the ratio of soluble fms-like tyrosine kinase-1 (sFlt-1) to placental growth factor (PlGF). This ratio indicates the relation of anti-angiogenic to pro-angiogenic factors and has evolved into a useful tool, with elevated values corroborating the diagnosis of preeclampsia. When the ratio is less than 38, onset of preeclampsia in the coming week is deemed very unlikely [5].

Another parameter to evaluate the risk of developing preeclampsia, is the sonographically determined pulsatility index of the uterine artery. It has been found to have a high positive predictive value for early onset preeclampsia (EOP) [6]. However, predicting preeclampsia remains complex, and several aspects need to be taken into consideration, including prior history of clinical symptoms, individual risk factors, mean arterial blood pressure, urine analysis, laboratory values, fetal parameters such as estimated birth weight, and Doppler values.

Risk Factors and Preventive Therapeutic Options

Risk factors for preeclampsia include rheumatological disorders, autoimmune diseases, antiphospholipid syndrome (APS), pre-existing diabetes mellitus or kidney disease, pre-existing hypertension or a history of preeclampsia [7, 8]. For an overview of general and pregnancy-associated risk factor, see also ▶ **Table 1**. These risk factors must always be evaluated in early pregnancy, as close supervision during pregnancy and preventive administration of medication may be indicated. It is recommended to start oral administration of low-dose acetylsalicylic acid (ASA) before the 16th week of gestation and to continue until the 34th to 36th week of gestation if one or more risk factors are present. A significant reduction in the incidence of preeclampsia by more than 10 % was achieved when administration of ASA was started before 16 weeks of gestation; the incidence of severe preeclampsia decreased by more than 14 % [9, 10]. The impact on preterm pre-

▶ **Table 1** Risk factors for preeclampsia, modified from Armaly et al. and Bartsch et. al. and the Guideline for Hypertensive Pregnancy Disorders of the German Society of Gynecology and Obstetrics [3, 7, 8].

	Relative risk (RR)
General risk factors	
▪ Autoimmune diseases	2.5
▪ Antiphospholipid syndrome (APS)	2.8–9.7
▪ Pre-existing diabetes mellitus	3.5–3.7
▪ Kidney disease	1.8–7.8
▪ Pre-existing hypertension	1.5–5.1
▪ Ethnicity (Afro-American)	2
▪ Obesity	2.5–2.9
▪ Maternal age (over 40 years)	1.5–2
Pregnancy-associated risk factors	
▪ History of preeclampsia	7–8.4
▪ Nulliparous	2.1–5.4
▪ Family history of preeclampsia	2.3–2.6
▪ Gestational diabetes	
▪ In vitro fertilization	
▪ Twin or multiple pregnancy	2.8–3.5
▪ Chromosomal or fetal disorders	

eclampsia appears to be even greater, with a reported reduction rate of 62 % [11].

The exact mode of action of low-dose ASA in preeclampsia is not completely understood. There is evidence suggesting it has a pro-angiogenic effect via inhibition of thromboxane rather than prostacyclin synthesis and release of sFlt-1, resulting in decreased vasoconstriction, platelet activity and the promotion of remodeling of spiral arteries [9, 12].

Pathogenesis of Preeclampsia

Defining a therapeutic drug approach is challenging as long as the pathogenesis of preeclampsia is not fully understood. Most studies differentiate between early and late onset preeclampsia, with EOP usually defined as developing before 34 weeks of gestation, whereas late onset preeclampsia (LOP) evolves at or after 34 weeks of gestation [13]. The two types differ in several aspects. They appear to differ with regard to placentation as well as with regard to certain angiogenic and oxidative factors, but studies analyzing differences in the genesis of EOP and LOP are few and the results are inconsistent [13].

EOP is often described as originating from abnormal placentation [13], while LOP is associated with undetected or insufficiently controlled maternal risk factors, such as pre-existing diabetes mellitus or increased body mass index before pregnancy [14, 15]. Huppertz and colleagues, however, emphasize that maternal conditions also influence the release of placental factors and that placental development also seems to play a role in LOP [16]. A recent study by Valencia-Ortega et al. concluded that EOP is associated with a pro-inflammatory placental state, whereas LOP is linked to a systemic maternal inflammation. They stated that maternal endothelial dysfunction is one of the key components of both subtypes [17]. Outcomes are generally better in the more common LOP [13, 18]; however, when screening for preeclampsia, the detection rates for EOP are higher than those for LOP.

What EOP and LOP have in common is an imbalance in anti- and pro-angiogenic factors in favor of anti-angiogenic factors. High concentrations of circulating sFlt-1 and soluble endoglin (sEng) are found in preeclamptic women, whereas levels of pro-angiogenic factors such as PlGF and vascular endothelial growth factor (VEGF) are low [13, 19]. sFlt-1 binds VEGF to maternal endothelial cells and thus reduces its bioavailability. Recent studies have shown that sFlt-1 enhances the sensitivity of endothelial cells to pro-inflammatory cytokines rather than having a pro-inflammatory effect itself. The subsequent lack of available PlGF and VEGF results in lower endogenous production of prostacyclin (PGI2) and nitric oxide (NO) and consequently leads to the vasoconstriction of placental arteries, which is crucial for the development of preeclampsia [20].

The development of preeclampsia is a multifactorial process, and placentation represents another link in the chain. Abnormal placental development includes incomplete remodeling of the spiral arteries, decreased trophoblast invasion and altered vascular characteristics. This abnormal placentation appears to be more pronounced in EOP than in LOP. This leads to higher vascular resistance, which can cause hypertension and malperfusion. This is especially relevant for the uteroplacental unit. This condition of intermediate ischemia and subsequent hypoxia can lead to a state similar to that of reperfusion syndrome, with rising levels of oxidative stress, the development of toxic metabolites, and initiation of inflammatory reactions [7, 13, 14].

Together with the hypoxic status, the NADPH oxidase activation leads to the formation of reactive oxygen species, which in turn activate NFκB-controlled pathways, resulting in cell death by apoptosis [21 – 23]. Ischemia, NFκB activation and apoptosis are followed by the expression of Toll-like receptor (TLR) 7 and 9. This leads to the release of interferon α (IFNα) and the production of pro-inflammatory cytokines, such as interleukin 6 (IL6) and tumor necrosis factor α (TNFα). When TNFα and IL6 levels increase, sFlt-1 levels also increase [21, 24].

These changes as well as the NFκB-mediated apoptosis lead to endothelial dysfunction, one of the major steps in the pathogenesis of preeclampsia [22]. The high levels of oxidative stress and the production of reactive oxygen species further aggravate endothelial dysfunction.

As more pro-inflammatory cytokines are set free (and consequently, sFlt-1 levels increase), cell adhesion molecules, such as vascular cell adhesion molecule-1 (VCAM-1), intracellular adhesion molecule-1 (ICAM-1) and E-selectin, are increasingly expressed and apoptosis rates rise [13, 17, 21]. Renal endothelial dysfunction leads to maternal proteinuria, while the vasoconstrictive effect contributes to arterial hypertension [7] and presumably plays a role in the genesis of HELLP syndrome and eclampsia.

Placental ischemia leads to the production of sFlt-1, which antagonizes the pro-angiogenic effects of VEGF and PlGF [13, 25]. sEng is released, which blocks transforming growth factor-β (TGFβ), has a vasoconstrictive effect, and aggravates endothelial dysfunction. It also inactivates endothelial NO synthase (eNOS), which again leads to hypertension and reduces blood flow to the placenta and fetus [7, 25, 26].

In summary, the pathogenesis of preeclampsia is multifactorial, with many of the factors reinforcing each other and aggravating the manifestation of the disease.

New Therapeutic Options

While previous therapeutic strategies focused on controlling symptoms and limiting severe complications, new therapeutic options are targeting the pathogenesis of preeclampsia.

Several studies have shown that sildenafil, a phosphodiesterase type 5 inhibitor approved for the treatment of erectile dysfunction and pulmonary hypertension, may improve fetal and maternal outcomes in preeclampsia (by improving fetal birth weight and maternal blood pressure regulation) [27 – 29]. The drug was previously thought to be safe during pregnancy with no reports of severe adverse events [27]. However, a recent large placebo-controlled drug trial in the Netherlands treating intrauterine growth restriction (IUGR) by oral administration of sildenafil to mothers was discontinued, since no benefit was observed and potential adverse neonatal effects were noted [20, 30].

Another approach to treat preeclampsia is the attempt to adjust the imbalance between pro- and anti-angiogenic factors by either reducing anti-angiogenic factors or increasing pro-angio-

genic ones. The administration of human recombinant PlGF is one way of increasing pro-angiogenic factors in preeclamptic women. Spradley et al. reported that the administration of PlGF led to a reduction in placental ischemia-induced hypertension in women treated with PlGF without the occurrence of severe adverse events [31]. Another study also showed a decrease in hypertension when human recombinant PlGF was infused in a preeclamptic setting [7]. Apheresis, on the other hand, could potentially reduce anti-angiogenic factors such as sFlt-1. Thadhani and colleagues demonstrated that a reduction of sFlt-1 using apheresis was correlated with milder proteinuria in women with EOP and even appeared to prolong pregnancy without major adverse consequences for mother or child [32].

The better we understand the pathogenesis of preeclampsia, the wider the range of drugs with the potential to treat preeclampsia. There is evidence that both statins and metformin can decrease sFlt-1 concentrations and thus may be able to prevent or treat preeclampsia [33, 34].

Statins are inhibitors of 3-hydroxy-methylglutaryl coenzyme A reductase; the primary effect is a decrease in cardiovascular mortality by reducing serum cholesterol. However, statins also exert pleiotropic effects not linked to the cholesterol metabolism [35]. Their use during pregnancy is considered controversial, as they were formerly linked to a risk of congenital malformations in the first trimester, although recent studies have not confirmed these findings. The intake of statins by patients with hypercholesterolemia can typically be paused during pregnancy without substitution [36]. While statins were reported to reduce sFlt-1 in a preclinical setting, no final conclusion could be drawn in a clinical trial so far, due to the low case numbers. However, the impact appears to be lower than estimated [37, 38].

Metformin on the other hand is a biguanide; it reduces glucose synthesis in the liver and improves insulin sensitivity in muscle and adipose tissue. Indications for metformin administration are diabetes mellitus and polycystic ovary syndrome. In pregnancy, insulin is preferred to metformin for the treatment of diabetes as there is more experience with insulin, although there are no indications for higher fetal or maternal perinatal morbidity or mortality rates following metformin administration [25]. A study by Brownfoot et al. showed that metformin reduced endothelial dysfunction while increasing angiogenesis and might therefore be an effective option to prevent or treat preeclampsia [34]. In contrast, a Cochrane analysis comparing insulin with metformin as treatment options for pregnant women with diabetes mellitus type II found no differences with regard to the development of preeclampsia, although a reduction in the rates of pregnancy-induced hypertension, cesarean section, and fetal hypoglycemia was noted for metformin [39].

Another potential treatment option is a class of proton pump inhibitors (PPI) considered safe in pregnancy and indicated for gastric reflux [40]. It has been shown that PPI can decrease sFlt-1 and endoglin secretion and therefore increase endothelial function and blood flow while reducing hypertension [40]. However, Cluver et al. found that the administration of esomeprazole did not prolong gestation in preeclamptic pregnancies and did not increase sFlt-1 concentrations in patients with EOP [41].

Another suggested therapeutic approach is the administration of antimalarials.

Administration of Hydroxychloroquine in Pregnancy

Hydroxychloroquine (HCQ) is an antimalarial drug which is also used to treat rheumatic diseases such as rheumatoid arthritis and systemic lupus erythematosus (SLE). It is derived from chloroquine and has been in use for over 60 years [42]. Its definite mechanism of action has yet to be elucidated but it appears to work through different pathways, inducing anti-inflammatory, anti-oxidant and anti-thrombotic effects [21]. Rare but feared side effects, especially when chloroquine is administered in high doses over the long term, include retinal toxicity and ototoxicity. Its use during pregnancy is deemed acceptable by most authors [43, 44].

The Embryotox database assesses the risks of HCQ in pregnancy as follows: in the first trimester, no reports of significant numbers of congenital malformations and a slightly higher abortion rate compared to healthy women taking no medication, which could also be due to primary maternal disease. In the 2nd and 3rd trimesters, current observations do not suggest any increased risk of fetotoxic effects. In summary, Embryotox concludes that therapy with HCQ could be initiated or continued during pregnancy and that it is highly recommended that patients with SLE continue taking HCQ [45].

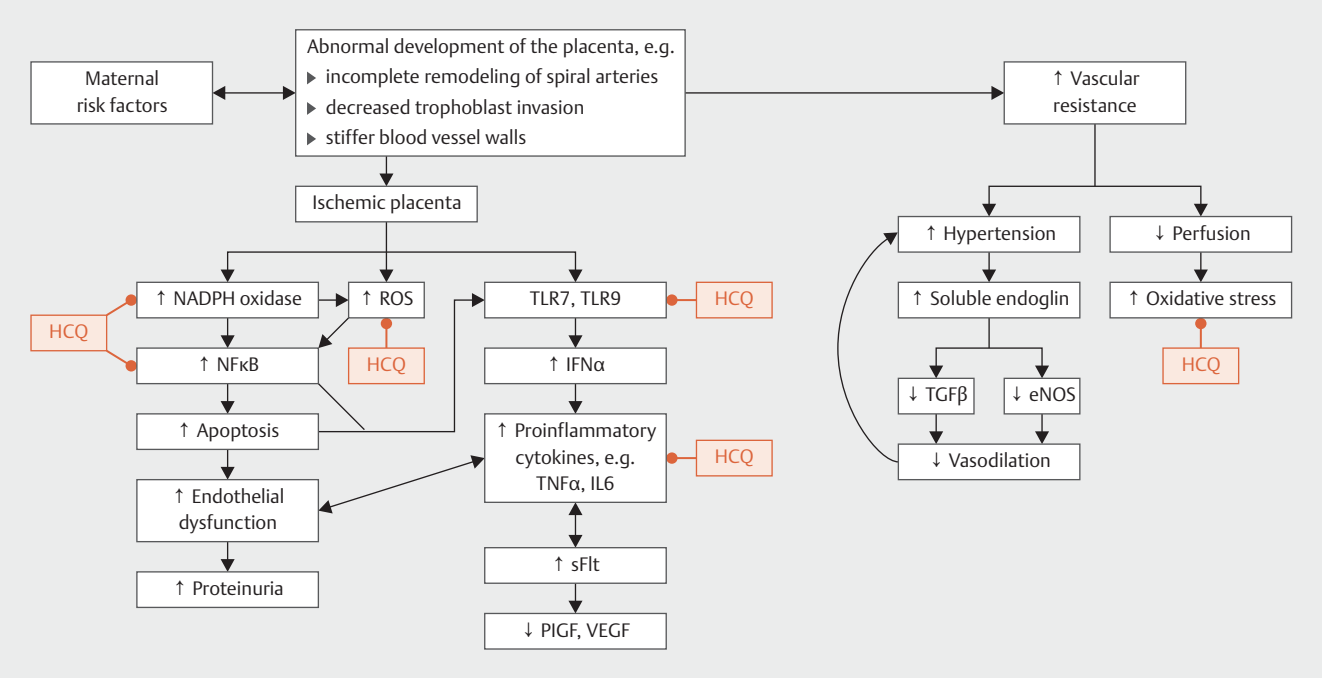
A review of more than 250 pregnant women with SLE treated with HCQ showed no signs of fetotoxicity and, in particular, no visual or auditory impairments [46]. Taken together, the administration of HCQ in pregnancy appears to be safe [43, 46–48], and some authors even highlight its potential to improve not only maternal but also fetal outcomes. Leroux and colleagues described a decreased rate of preterm births and IUGR in patients with SLE when taking HCQ during pregnancy [49].

HCQ and its Complex Mode of Action

Both HCQ and chloroquine are derived from 4-aminoquinoline. It is a weak base, water-soluble and can cross cell membranes. It is metabolized in the liver (CYP2C3 and CYP3A4 are responsible for over 80% of its metabolism) and excreted through the kidneys (60%) and in feces (8–25%) and is stored in lean tissue. Therefore, liver and/or kidney insufficiency could lead to an accumulation of the drug with subsequent toxic effects. Its volume of distribution of more than 40 000 L is large and the elimination half-life of 40 days rather long [50].

HCQ administration can have different effects: it has been reported to reduce edema, proteinuria, the risk of thrombosis and also appears to have anti-inflammatory, anti-oxidant, and anti-diabetic effects [43]. Currently, a variety of mechanisms of action have been postulated to try and explain these benefits. Many of the effects listed below have been observed especially or exclusively in patients with rheumatological disease.

Because of its characteristics, HCQ accumulates in lysosomes and inhibits lysosomal enzyme release and activity [43]. It inhibits the production and/or release of a number of prostaglandins and cytokines, including IL1, IL2, IL6, IL10, TNFα, and IFNγ. It decreases the activity of Toll-like receptors (TLR-3, TLR-7, TLR-9) and NADPH oxidase and also has an inhibitory effect on the mito-



▶ **Fig. 1** Overview of the current understanding of the pathogenesis of preeclampsia and the potential target points for therapy with hydroxychloroquine (HCQ) in preeclampsia. Not all interactions and mechanisms are displayed in this figure.

gen-activated protein kinase pathway which regulates the cell cycle and apoptosis. It inhibits platelet aggregation and reduces concentrations of soluble tissue factor. It affects the expression of major histocompatibility complex II and antigen presentation, seemingly inhibiting CD4 T cell stimulation while promoting CD8 T cell stimulation. Furthermore, it may also reduce the production of reactive oxygen species by affecting leukocytes [43, 50 – 52].

HCQ – a Promising Treatment for Preeclampsia

Although the exact pathogenesis of preeclampsia and the definite mechanisms of action of HCQ are not thoroughly understood, they share multiple common points where they could interact.

As described in detail above, oxidative stress and inflammatory processes leading to cellular dysfunction and/or apoptosis play a key role in the pathogenesis of preeclampsia. According to the currently available information, the beneficial effects of HCQ result from reversing these specific conditions. The relationships are shown in detail in ▶ **Fig. 1**. In summary, ischemic conditions exist in preeclampsia due to aberrant placentation and abnormal perfusion, leading to increased vascular resistance. These circumstances result in high blood pressure, poorer overall perfusion and NADPH oxidase activation, inducing further formation of reactive oxygen species in the mother. In addition, TLR are activated, and cytokines and prostaglandins are released, especially IFNα, IL6, TNFα and subsequently also sFlt-1.

Treatment with HCQ targets hypoxic and inflammatory conditions by inhibiting the production and release of specific cytokines and prostaglandins and decreasing NADPH oxidase activity and TLR activation; it may also reduce the production of reactive oxygen species.

Using HCQ to treat patients with a high risk for preeclampsia is currently of great interest because HCQ is considered a safe drug in pregnancy. Severe side effects are rare and usually preventable. The most feared complication is HCQ-induced retinopathy, which is dose-dependent and usually develops after years of HCQ administration. It can be prevented by regular ophthalmological monitoring and especially by careful, body weight-adjusted dosing of the drug [53].

Many authors have proposed HCQ as a promising adjuvant treatment for preeclampsia. Abd Rahman and colleagues emphasize the antioxidant effect of HCQ and suggest that the drug could reduce the consequences of oxidative stress in the placenta and maternal endothelium. They also point to its anti-inflammatory action and its positive effect on angiogenesis [21]. Other scientists have previously shown that HCQ can reduce clinical symptoms/manifestations of preeclampsia such as edema and proteinuria [43].

Several clinical studies have reported a positive effect of HCQ on the prevalence of preeclampsia. Sciascia et al. reported a reduction of placenta-mediated complications (preeclampsia, IUGR and placental abruption) and an increased rate of live births in patients with antiphospholipid antibodies after the administration of HCQ during pregnancy. No side effects of HCQ treatment were observed in this study [54]. Mekinian and colleagues compared pregnancy outcomes in patients with APS or asymptomatic carriers of antiphospholipid antibodies treated with HCQ to pregnancy outcomes in this cohort receiving conventional treatment

regime (ASA and heparin). They showed that pregnancy losses decreased from 81 to 19% following the addition of HCQ to conventional treatment. They were also able to show a decreased rate of preeclampsia and/or HELLP syndrome in the group receiving HCQ [55].

Schreiber and colleagues initiated the HYPATIA protocol, a randomized controlled trial of women with antiphospholipid antibodies, comparing HCQ versus placebo in addition to conventional treatment with regard to pregnancy outcomes [51]. Previous data from this research group has shown that pregnancy duration was longer and fetal losses after 10 weeks of gestation less frequent in patients with antiphospholipid antibodies receiving HCQ than in controls not treated with HCQ. Moreover, ischemic placental-mediated complications (preeclampsia, eclampsia, and fetal growth restriction) were less prevalent in the HCQ-treated compared to the control group (2 vs. 10.9%, $p = 0.05$) [54]. The HYPATIA trial started in 2018 and will last for a total of 36 months [51].

These findings are promising and suggest that HCQ may be a new option for patients with definite risk factors for preeclampsia and possibly for women with incipient preeclampsia prior to the onset of severe complications. It will be interesting to see whether sFlt-1 levels decrease during therapy with HCQ.

Conclusion

Although the pathogenesis of preeclampsia is not yet fully understood, many of its mechanisms have been decoded in recent years. Several of these mechanisms can be influenced by HCQ, and the rates of preeclampsia have been shown to be low in high-risk patients taking HCQ for maternal rheumatological disease. In light of these promising findings, the first prospective and randomized intervention trials have been initiated, as low-dose ASA is currently the only preventive medication recommended for patients with an elevated risk of preeclampsia.

Given the long-term complications associated with preeclampsia for both mother and child, HCQ may turn out to be an additional medication which could further reduce the incidence of preeclampsia. Research is increasingly focused on the use of HCQ as a therapeutic option, especially to treat patients with EOP. Further research is needed to prove the efficacy of HCQ as means of preventing and treating preeclampsia, and more results on this topic can be expected in future.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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Correction

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The name of an author was corrected. The correct name is: Kathrin Oelmeier de Murcia.