PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Hydroxychloroquine for Prevention of Recurrent Miscarriage: Study Protocol for a Multicenter Randomized Placebo Controlled Trial BaBy hydroxychloroQuine (BBQ) study
AUTHORS	Pasquier, Elisabeth; de Saint-martin, Luc; marhic, Gisèle; Chauleur, Celine; Bohec, Caroline; Bretelle, Florence; Lejeune-Saada, Véronique; Hannigsberg, Jacob; Plu-bureau, Geneviève; Cogulet, Virginie; Merviel, Philippe; Mottier, Dominique

VERSION 1 – REVIEW

REVIEWER	M.A. Oudijk Amsterdam UMC, University of Amsterdam, The Netherlands
REVIEW RETURNED	19-Aug-2018

GENERAL COMMENTS	Well written straight forward RCT. I would encourage the authors to include additional secondary outcomes, such as PTB at different GA, for instance < 32 and < 37 weeks, PIH/PE/IUGR, side effects etc.

REVIEWER	Sohinee Bhattacharya University of Aberdeen
REVIEW RETURNED	15-Oct-2018

GENERAL COMMENTS	Many thanks for asking me to review this interesting trial protocol for hydroxychloroquine in recurrent miscarriage. The trial is well thought through and there are some minor details missing that the investigators may wish to consider. 1. The strategy for recruitment of participants could be better described - will the women be approached at RM clinics or general practice or from the community? 2. Details of recruiting centres should be provided. 3. The clinical trials unit(s) involved and funding source should be made explicit at the start. 4. Inclusion criteria: Consider relaxing the inclusion criteria to include women with fewer than 3 miscarriages or non-consecutive miscarriages as many of the previous RM trials have had to do this to make the sample size. 5. What will happen to women who have had late miscarriage or fertility treatment? Will they be excluded? 6. Exclusion criteria: What is the rationale for excluding women above 37 years of age? Or previous exposure to chloroquine > 4 years? What is meant by impossible follow up? 7. As chloroquine intake is often associated with nausea and vomiting this data should at least be collected as a secondary outcome as this can reduce compliance. 8. Please explain (153=34%) in line 31, Introduction page.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 Comments for the Author...
Well written straight forward RCT. I would encourage the authors to include additional secondary outcomes such as PTB at different GA, for instance <32 and <37 weeks, PIH/PE/IUGR, side effects etc…

Thank you for your suggestions. These variables will be collected according to the planned secondary endpoints referred as the occurrence of “placental vascular disease” and “premature delivery” on page 16 of the revised manuscript. Possible side effects for child are included in the last secondary endpoint “…Concerning the child: gestational age and weight at birth, survival at 28 days, safety data at 6 months of life, congenital abnormality” on page 16. Items concerning woman side effects are collected (at least monthly) and comparatively analyzed by the IDSMB. We agree that woman side effects should be added as a formal additional end point.

Reviewer 2 Comments for the Author...
Many thanks for asking me to review this interesting trial protocol for hydrychloroquine in recurrent miscarriage. The trial is well thought through and there are some minor details missing that the investigators may wish to consider.
1. The strategy for recruitment of participants could be better described. Will the women be approached at RM clinics or general practice or from the community?

Women will be approached by either Community and Institutional gynecologists or internal medicine practitioners, or by RM clinics or even by a general practitioner in order to obtain the most exhaustive recruitment which is supported by the research network of PREFIX study (Blood 2015).14 Thus, all obstetricians and internal medicine practitioners working in each participating centre’s catchment area have been informed and trained on BBQ study. They have been asked to refer potentially eligible women to the unit participating in the study for screening. Information on the study is currently being provided at medical meetings, by emails and letters sent to medical practitioners. In each centre, patient recruitment is ensured by already in place settings such as specific RM consultations or other OBS/GYN patient management units. In addition to this recruitment approach, poster information in consultation waiting rooms is being used to reach-out to more patients. In the initial submitted manuscript we just stated on page 11: “Those women are followed-up by their gynecologist or general practitioner who refers them to one of the RM specialized unit participating in the study for screening.” In the comprehensive version of study protocol, additional details are provided on pages 48 “Modalités de recrutement” section and on page 70 “Faisabilité” section. In the revised manuscript we added information as suggested on page 11-12, lines 212-219:”Through medical meetings, emails and letters, all obstetricians and internal medicine practitioners working in each participating centre’s catchment area have been informed and trained on BBQ study. All of those are asked to refer potentially eligible women to the unit participating in the study for screening. In each centre, patient recruitment is ensured by already in place settings such as specific RM consultations or other OBS/GYN patient management units. In addition to this recruitment approach, poster information in consultation waiting rooms is being used to reach-out to more patients.”

2. Details of recruiting centres should be provided.

Thank you. A setting section has been added on page 11 of the revised manuscript.

“Study setting
Women are currently being enrolled in university hospitals (gynecology units: Besançon, Brest, Clermont Ferrand, Lille, Marseille, Nantes, Paris Cochin, Paris Bichat, Rennes, Saint-Etienne; internal

medicine units: Brest, Paris Saint-Antoine) or in general hospitals (gynecology units: Auch, Quimper, Mont de Marsan, Pau)."

3. The clinical trials unit(s) involved and funding source should be made explicit at the start.

We added the following sentence to the end of introduction section, on page 9 of the revised manuscript:" We therefore initiated a multicenter placebo-controlled trial sponsored by Brest University hospital and supported by a grant from the French Ministry of Health (PHRCN-17-0573)."

4. Inclusion criteria: Consider relaxing the inclusion criteria to include women with fewer than 3 miscarriages or non-consecutive miscarriages as many of the previous RM trials have had to do this to make the sample size.

Thank you for this suggestion. In case of difficulties to reach inclusion objectives, we would most likely relax our inclusion criteria.

5. What will happen to women who have had late miscarriage or fertility treatment? Will they be excluded?

Fertility treatment is not an exclusion criterion. If a woman did suffer 3 previous consecutive miscarriages in the first trimester of pregnancy, she may be included even in case of previous other additional adverse pregnancy events as a late miscarriage.

6. Exclusion criteria: What is the rationale for excluding women above 37 years of age? Or previous exposure to chloroquine>4 years? What is meant by impossible follow-up?

Thank you. An altered ovarian reserve could most likely play a role in underlying mechanisms of fetal loss in women 37 years old or older. Noteworthy, the known quantitative markers of ovarian reserve (follicle count, anti-müllerian hormone level…) are less accurate qualitative markers than the woman age. In the BBQ study, a woman can be included just until 38 years old and get pregnant after one year of treatment, i.e. just before 39 years old. Consequently, we have set at ≤ 37 years the upper limit in age for inclusion. We agree that this upper limit could perhaps be relaxed to ≤ 38 years old according to the current census of procreation age in France.

Given that the retinal deposits of hydroxychloroquine can occur after 5 years of exposure, requiring specialized ophthalmologic follow-up, we chose not to include women with a previous exposure (>4 years) to chloroquine (or hydroxychloroquine). Noteworthy, this would avoid an additional year of exposure (BBQ study duration) to HCQ in such women.
Impossible follow-up means that the woman cannot be contacted after inclusion by phone or writing; don't come to medical visits, most likely because of a change in life setting, e.g. moving to another town. This should be very rare thanks to the many centers participating in the study in France.

7. As chloroquine intake is often associated with nausea and vomiting, this data should at least be collected as a secondary outcome as this can reduce compliance.

Thank you for your suggestion. All digestive adverse events will be collected as a secondary outcome.

Please explain 153=3.4% in line 31, introduction page

Thank you for your comment. This is a typographic error corrected in the revised manuscript:
(15*15*15% = 0.34 %)

VERSION 2 – REVIEW

REVIEWER	Sohinee Bhattacharya University of Aberdeen United Kingdom
REVIEW RETURNED	03-Jan-2019

GENERAL COMMENTS	The authors have dealt well with the minor concerns raised by reviewers and editors. I would still argue that there is no need to set an upper age limit as inclusion criteria as if randomisation is adequate, women above the age limit should have the same chance of being included in the intervention arm as the control arm.

VERSION 2 – AUTHOR RESPONSE

Reviewer 2 Comments for the Author...

The authors have dealt well with the minor concerns raised by reviewers and editors. I would still argue that there is no need to set an upper age limit as inclusion criteria as if randomisation is adequate, women above the age limit should have the same chance of being included in the intervention arm as the control arm.

Thank you for this comment. We do agree with your suggested inclusion strategy (criterion) and have written a modification amendment to the initial protocol version accordingly. We hope for a favorable response from the ethics committee.