The safety of atovaquone-proguanil for the prevention and treatment of malaria in pregnancy: A systematic review

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Author Contributions

EB wrote the protocol with input from NA, JG and KT. EB developed the search terms. KT and NA will review all abstracts independently. JG will serve as the tiebreaker. Two reviewers will abstract all data independently. JG and KT will conduct the data analysis. JG and KT will write the manuscript.

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INTRODUCTION

Rationale:

Malaria infection during pregnancy is associated with increased risk of complications for both mother and fetus.[1] This risk is elevated among individuals without previous exposure to malaria, such as travelers.[2] Pregnant women are advised to avoid or delay travel to malaria-endemic regions. If avoiding travel is not feasible, pregnant women should take measures to avoid mosquito bites and also use an effective regimen of chemoprophylaxis.[3]

However, chemoprophylaxis options for pregnant women are very limited. Currently, chloroquine and mefloquine are the drugs recommended for prophylactic use during pregnancy. Due to significant chloroquine resistance among *Plasmodium falciparum* parasites, use of chloroquine prophylaxis is restricted to just a few limited geographic areas, thus in most cases, mefloquine is the only available option for chemoprophylaxis during pregnancy. In some parts of South-East Asia, *P. falciparum* is also resistant to mefloquine, leaving pregnant women with no prophylaxis alternative.[3] Doxycycline, which is recommended in non-pregnant travelers, is contraindicated in pregnancy due to demonstrated teratogenicity, with detrimental effects to the teeth and bones of the fetus.[4] Primaquine is also contraindicated, due to the possibility of hemolytic anemia if the fetus has glucose-6-phosphate dehydrogenase deficiency.[5]

Atovaquone-proguanil (Malarone®) is a drug combination that is effective for malaria prophylaxis and treatment, even in regions with high rates of resistance to other anti-malarials.[6] Despite its efficacy, atovaquone-proguanil is not currently recommended for use by pregnant women due to insufficient data on the safety of its use in pregnancy.[3] Proguanil alone has a long history of clinical use in pregnancy for the prevention and treatment of malaria, although it is still categorized as Pregnancy Category C by the US Food and Drug Administration (FDA), given that there are no adequate controlled studies of its use in pregnant women[7,8,9,10,13]. Unfortunately, proguanil is less effective alone than when used in combination with atovaquone for the treatment of malaria.[7] Atovaquone has been used alone for the treatment of toxoplasmosis, and in combination with azithromycin for the treatment of babesiosis, but does not have approval for use in pregnant women for these indications either.[11,12]

Animal studies suggest that atovaquone-proguanil does not have teratogenic effects at concentrations corresponding to the estimated human exposure during treatment of malaria. Adverse fetal effects, which consisted of decreased fetal body lengths as well as increased early resorptions and post-implantation losses, were observed in rabbits only in the presence of maternal toxicity, which occurred at 1.3 times the estimated human exposure[13]. Human data on the use of atovaquone-proguanil in pregnancy remains limited, and the FDA[14] classifies malarone as pregnancy class C, indicating that insufficient adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

The limited data available from human studies of atovaquone-proguanil in pregnancy have not demonstrated an increased risk of adverse birth outcomes. A small prospective study carried out in an area of Thailand with high rates of resistant malaria enrolled 24 pregnant women with acute malaria who had failed a 7-day course of quinine. The participants in the study were given a combination of artesunate and atovaquone-proguanil; the participants' infants had similar birthweights to the general population in the area, and none of the infants born had any birth defects.[15] Another study in Thailand and Zambia treated twenty-six women in their third trimester with atovaquone-proguanil for acute uncomplicated *Plasmodium falciparum* malaria demonstrated no serious adverse effects, including no stillbirths, spontaneous abortions or birth defects.[16] Finally, a Danish registry-based study of a cohort of 570,877 live births investigated atovaquone-proguanil exposure in early pregnancy and found no significant association between exposure to atovaquone-proguanil between 3 and 8 weeks after conception and any major birth defects.[2]

Given that serious adverse birth outcomes and birth defects are rare, these individual studies do not offer the sample sizes needed to effectively assess safety outcomes. To improve researchers' ability to evaluate the safety of a drug for use in pregnancy, data from appropriate studies may be pooled together to increase the sample size. In order to better assess the safety profile of atovaquone-proguanil use in pregnancy, we will conduct a systematic review and, if possible, a meta-analysis of studies of atovaquone-proguanil exposures during pregnancy.

Research Question: Are subjects exposed to atovaquone-proguanil during pregnancy at increased risk of adverse events?

Primary Objectives: To summarize any available data on adverse events to the fetus that occur secondary to the use of atovaquone-proguanil, atovaquone, or proguanil in pregnancy for prevention or treatment of malaria or other parasitic diseases.

Secondary Objective(s): To summarize any available data on adverse events to the mother that occur secondary to the use of atovaquone-proguanil, atovaquone, or proguanil in pregnancy for prevention or treatment of malaria or other parasitic diseases.

METHODS

Eligibility Criteria

Due to the limited number of randomized-controlled trials of atovaquone-proguanil use during pregnancy, we will include all studies in which pregnant subjects were exposed to the combination atovaquone-proguanil, or to atovaquone or proguanil either as monotherapy or in combination with other drugs, including cohort studies, case-control studies and case series. Our search will include any animal or human subject exposed to atovaquone-proguanil, atovaquone, or proguanil during pregnancy, whether administered for prophylaxis or treatment. Among human subjects, we will include pregnant women from all geographic locations. For details of our eligibility criteria, see the PICOTS framework.

PICOTS Framework:

Components	Characteristics
Population	**Primary** Human and animal pregnant subjects exposed to atovaquone-proguanil during pregnancy -Subgroup analyses: • Animal subjects • Human subjects • Geography (women residing in malaria-endemic regions versus foreign travelers to those regions) • Timing of exposure • Indication for use (treatment or prophylaxis)
Intervention	**Primary** Exposure to atovaquone-proguanil for treatment or prevention of malaria during pregnancy **Secondary** Exposure to either atovaquone or proguanil for treatment or prevention of parasitic diseases during pregnancy

Control	• Pregnant women exposed to mefloquine for prophylaxis or treatment of malaria
Outcomes	Serious Adverse Events including but not limited to: • Adverse pregnancy outcomes (eg: stillbirth, miscarriage, congenital anomalies, small for gestational age, preterm birth) • Neonatal death • Maternal Death • Any event leading to hospitalization • Maternal adverse reactions
Timing	No time limits will be placed on the search
Setting	**Primary** Any study in which the population of interest was exposed to atovaquone-proguanil during pregnancy. **Secondary** Any study in which the population of interest was exposed to atovaquone or proguanil during pregnancy. Limit languages to English, French or Spanish

We will conduct our search, analyses, and reporting in adherence to the PRISMA guidelines for systematic reviews and meta-analyses.[17] An electronic literature search applying the PICOTS framework will be conducted using the following clinical databases: PubMed, MEDLINE, EMBASE, Web of Science, Scopus, CINAHL Plus, the Cochrane Library databases, WHO Global Health Library and the Malaria in Pregnancy Consortium (MiPc) Library. A multi-concept Boolean search strategy will be applied using keywords and MeSH terms. We will additionally search 'gray literature' databases, conference abstracts, manually review reference lists of selected publications as well as records recommended by contacting experts. The search strategy will be optimized for each database searched. We will merge citations from all individual databases into one citation software file, EndNote. Duplicates will be removed and the last date of the search documented.

PubMed Search Strategy:
Search Date May 17, 2016

	Framework	Search terms	Number of Articles
P	**Population**	Pregnant OR pregnancy OR maternal OR maternity OR gravid OR gravidity	

I	**Intervention**	AND malarone OR “atovaquone-proguanil” OR atovaquone OR proguanil	
C	**Control**	AND Mefloquine OR Lariam	
O	**Outcome**	-	
T	**Timing**	-	
S	**Setting**	AND (English OR French OR Spanish)	
			P+I+C+O+T+S: 275

Data Management

Two independent reviewers will screen titles of all citations found from the search strategy outlined above. The second screen will consist of any studies selected by either one these reviewers. In the second screen, two independent reviewers will screen abstracts and full texts and agree on final study eligibility. Any disagreements on citations will be resolved by consensus or by contacting a third reviewer who will serve as the tie-breaker. Articles considered eligible after full-text review by the two independent reviewers will be included in the final set of studies used for final analysis while those deemed ineligible will be excluded from the final analysis. A log will be kept of all studies excluded and reasons for exclusion after the first and second screen. The two reviewers will independently extract data using a standardized data extraction form, the data compared and any discrepancies will be resolved by consensus. The abstracted data will be entered into a database for analysis.

Data Items:

For animal studies, we will abstract data on species, serum concentrations of drugs, duration of exposure, timing of exposure with regard to gestation, birth outcomes including birthweight and congenital abnormalities, and maternal toxicity. For human studies, we will abstract data on the study population including age, geographic location, parity, reason for exposure to drug (prevention vs treatment), trimester during which exposure occurred, dose of medication administered, duration of exposure, pregnancy outcomes including miscarriage (pregnancy loss before 28 weeks), stillbirth (pregnancy loss at or after 28 weeks), preterm births (<37 weeks), birth weight, congenital anomalies, and any maternal adverse events reported. Congenital anomalies will be grouped into major (incompatible with life or requiring medical/surgical intervention), or minor (deviations from what is considered normal and do not have obvious medical, surgical, or cosmetic consequences) anomalies.[21]

Quality Assessment:

We will assess the quality of the clinical trials using The Cochrane Collaboration’s tool for assessing risk of bias.[18] The domains that will be evaluated are: selection, performance,

detection, attrition and reporting. We will assess the quality of observational studies using the Newcastle Ottawa Scale that evaluates non-randomized studies for selection bias, comparability, and assessment of outcomes.[19]

Data Analysis:

We will provide a descriptive summary of the literature that exists on use exposure during pregnancy to atovaquone-proguanil, atovaquone, and proguanil. This descriptive analysis will include information on the study year and location, study design, study population, as well as maternal adverse events and pregnancy outcomes reported by the study.

If sufficient data is available, we will conduct meta-analyses to generate pooled estimates of event rates and odds ratios with 95% confidence intervals. This analysis will stratify results by study type, population, geographic location, trimester of exposure, and indication for use (prophylaxis vs treatment). We will conduct sensitivity analyses to assess the influence of study quality on the results. We will assess publication bias through funnel plots. A two-tailed test p-value of < 0.05 will be considered statistically significant.

Title Review Criteria:

For title review, references will be included if they:

- Include information on atovaquone-proguanil, atovaquone, proguanil or mefloquine use during pregnancy in animal or human subjects
- Are randomized controlled trials, cohort studies, case-control studies, animal studies or case reports/case series.
- If it cannot be determined from the title whether the reference meets the above two criteria, it will progress to the abstract review phase.

Data Abstraction Forms:

A. Screening abstract	Study screening ID (e.g. A0001): A_____
1	First Author: _____ Publication Year:_____
Eligibility Criteria 1: Abstract Review *(if any of items 2-5 below are "no", study is not eligible for full text review)*	
2	Abstract language is English, French or Spanish: ___Yes ___No
3	Study population includes pregnant humans or animals? ___Yes ___No ___Can't tell
4	Study population exposed to atovaquone-proguanil, atovaquone, proguanil and/or mefloquine during pregnancy? ___Yes ___No ___Can't tell
5	Reports on birth outcomes? ___Yes ___No ___Can't tell
Study Eligible? ___Yes ___Can't tell *Proceed to screening full article* ___No *STOP HERE*	
Eligibility Criteria 2: Full Text Review *(if no to any of the following, study not eligible)*	
5	Language is English, French or Spanish: ___Yes ___No
6	Study design: ___Cohort ___ Case-control ___Clinical trial ___Animal study ___Case report/case series
7	Study population exposed to AP, atovaquone, proguanil and/or mefloquine? ___Yes ___No
8	*If yes to item 7 above:* Please mark drug(s) study population was exposed to (mark all that apply): ____ Atovaquone-proguanil ____ Atovaquone ____ Proguanil ____ Mefloquine
9	*If yes to item 7 above:* Were study subjects (human or animal) pregnant during exposure to at least one of the drugs marked in item 8 above? ____Yes ____No
10	*If yes to item 9 above:* Reports on birth outcomes following maternal exposure to at least one of the drugs marked in item 8 above? ____Yes ____No
Study Eligible? ___Yes *Proceed to DATA EXTRACTION* ___No *STOP HERE (exclude from final analysis)*	
Form completed by:_____(initials) Date:_____	

<u>Data Extraction Forms</u>

	B. **Data Extraction: For all eligible studies *(Full Analysis)*** Study Screening ID (e.g. B001): B_____
1	Title: _____ First Author: _____ Publication Year: _____ Journal:_____ Volume:_____ Issue:_____ Pages: _____
2	 Country/Countries:_____
3	Study Design: ___Cohort ___ Case-control ___Clinical trial ___Case report/case series ___Animal study* ___Other(specify):_____
4	Study Start: Month_____ Year _____ ___Not Documented
5	Study End: Month_____ Year _____ ___Not Documented

Study Population
Species: ____Human ____Animal *specify species* _____

Inclusion Criteria (*write-in all inclusion criteria listed in the study):*

Exclusion Criteria (*write-in all exclusion criteria listed in the study)*:

For the following tables, fill in all boxes that are applicable. If not applicable to the study being reviewed, leave blank.

		Atovaquone-proguanil (AP)	Atovaquone	Proguanil	Mefloquine	Control
Number of subjects						
Age: *fill in row for mean or median as appropriate based on what study reports*	Mean					
	Median					
	Range (years)					
Parity *(For human studies only)*	Average parity					
	Range					

Exposures to Drugs During Pregnancy			AP	Atovaquone	Proguanil	Mefloquine	Control
Dose (*specify units)*							
Route							
Frequency *(specify units)*							
Serum levels *(specify units)*							
Duration of exposure *(specify units)*							
Timing of exposure	Human studies	Trimester 1					
		Trimester 2					
		Trimester 3					
	Animal studies: *Timing of exposure (days)*						
Reason for exposure	Prophylaxis for malaria						
	Treatment of malaria						
	Prophylaxis for other infection (*specify):* _____						

Infant Outcomes: Exposure at any time in pregnancy: *Fill in all boxes that are applicable. If not applicable, leave blank.*		**Atovaquone-Proguanil N(%)**	**Atovaquone N (%)**	**Proguanil N (%)**	**Mefloquine N (%)**	**Control N (%)**
Total exposed any time in pregnancy						
Any fetal/infant adverse event						
Stillbirth						
Miscarriage						
Early neonatal death (<7 days)						
Small for gestational age						
Preterm birth						
Major congenital anomalies *Write-in each major anomaly in boxes to the right. Include CTCAE Grade if reported.*	1.					
	2.					
	3.					
	4.					
	5.					
Minor congenital anomalies *Write-in each minor anomaly in boxes to the right. Include CTCAE grade if reported.*	1.					
	2.					
	3.					
	4.					
	5.					

Infant Outcomes: Exposure during 1st Trimester: *Fill in all boxes that are applicable. If not applicable, leave blank.*		**Atovaquone-Proguanil N(%)**	**Atovaquone N (%)**	**Proguanil N (%)**	**Mefloquine N (%)**	**Control N (%)**
Total exposed during 1st trimester						
Any fetal/infant adverse event						
Stillbirth						
Miscarriage						
Early neonatal death (<7 days)						
Small for gestational age						
Preterm birth						
Major congenital anomalies *Write-in each major anomaly in boxes to the right. Include CTCAE Grade if reported.*	1.					
	2.					
	3.					
	4.					
	5.					
Minor congenital anomalies *Write-in each minor anomaly in boxes to the right. Include CTCAE grade if reported.*	1.					
	2.					
	3.					
	4.					
	5.					

Infant Outcomes: Exposure during 2nd Trimester: *Fill in all boxes that are applicable. If not applicable, leave blank.*		**Atovaquone-Proguanil N(%)**	**Atovaquone N (%)**	**Proguanil N (%)**	**Mefloquine N (%)**	**Control N (%)**
Total exposed during 2nd trimester						
Any fetal/infant adverse event						
Stillbirth						
Miscarriage						
Early neonatal death (<7 days)						
Small for gestational age						
Preterm birth						
Major congenital anomalies *Write-in each major anomaly in boxes to the right. Include CTCAE Grade if reported.*	1.					
	2.					
	3.					
	4.					
	5.					
Minor congenital anomalies *Write-in each minor anomaly in boxes to the right. Include CTCAE grade if reported.*	1.					
	2.					
	3.					
	4.					
	5.					

Infant Outcomes: Exposures during 3rd trimester: *Fill in all boxes that are applicable. If not applicable, leave blank.*		**Atovaquone-Proguanil N(%)**	**Atovaquone N (%)**	**Proguanil N (%)**	**Mefloquine N (%)**	**Control N (%)**
Total exposed during 3rd trimester						
Any fetal/infant adverse event						
Stillbirth						
Miscarriage						
Early neonatal death (<7 days)						
Small for gestational age						
Preterm birth						
Major congenital anomalies *Write-in each major anomaly in boxes to the right. Include CTCAE Grade if reported.*	1.					
	2.					
	3.					
	4.					
	5.					
Minor congenital anomalies *Write-in each minor anomaly in boxes to the right. Include CTCAE grade if reported.*	1.					
	2.					
	3.					
	4.					
	5.					

Maternal Outcomes: **Exposure at any time during pregnancy.** *Fill in all boxes that are applicable. If not applicable, leave blank.*		**Atovaquone-Proguanil N(%)**	**Atovaquone N (%)**	**Proguanil N (%)**	**Mefloquine N (%)**	**Control N (%)**
Any maternal adverse event at any time during pregnancy						
Specific maternal adverse events *Write-in each adverse event in boxes to the right. Include CTCAE Grade if reported.*	1.					
	2.					
	3.					
	4.					
	5.					
	6.					
	7.					
	8.					
	9.					
	10.					

Forms for the assessment of Trial Quality:

The Cochrane Collaboration's tool for assessing risk of bias.

Entry	Judgement of Risk	Support for Judgement
Random sequence generation (selection bias)		
Allocation concealment (selection bias)		
Blinding of participants and personnel (performance bias)		
Blinding of outcome assessment (detection bias)		
Incomplete outcome data addressed (attrition bias)		
Selective reporting (reporting bias)		

The Newcastle-Ottawa Scale for assessing the quality of nonrandomized studies in meta-analyses

CASE CONTROL STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition adequate?
   a) yes, with independent validation
   b) yes, eg record linkage or based on self reports
   c) no description

2) Representativeness of the cases
   a) consecutive or obviously representative series of cases
   b) potential for selection biases or not stated

3) Selection of Controls
   a) community controls
   b) hospital controls
   c) no description

4) Definition of Controls
   a) no history of disease (endpoint)
   b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis

a) study controls for _____ (Select the most important factor.) b) study controls for any additional factor (This criteria could be modified to indicate specific control for a second important factor.)

Exposure

1) Ascertainment of exposure

a) secure record (eg surgical records)

b) structured interview where blind to case/control status

c) interview not blinded to case/control status

d) written self report or medical record only

e) no description

2) Same method of ascertainment for cases and controls

a) yes

b) no

3) Non-Response rate

a) same rate for both groups

b) non respondents described

c) rate different and no designation

COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average _____ (describe) in the community
   b) somewhat representative of the average _____ in the community
   c) selected group of users eg nurses, volunteers
   d) no description of the derivation of the cohort

2) Selection of the non exposed cohort
   a) drawn from the same community as the exposed cohort
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure
   a) secure record (eg surgical records)
   b) structured interview
   c) written self report
   d) no description

4) Demonstration that outcome of interest was not present at start of study
   a) yes
   b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for _____ (select the most important factor)
   b) study controls for any additional factor (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome
   a) independent blind assessment
   b) record linkage
   c) self report
   d) no description

2) Was follow-up long enough for outcomes to occur
   a) yes (select an adequate follow up period for outcome of interest)
   b) no

3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost)
   c) follow up rate < ____% (select an adequate %) and no description of those lost
   d) no statement

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