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# Safety of atovaquone-proguanil during pregnancy

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## Abstract

**Background:** Malaria during pregnancy increases the risk of maternal and foetal complications. There are very limited options for prophylaxis in pregnant travellers. Atovaquone-Proguanil (AP or Malarone®) is an effective and well-tolerated antimalarial medication, but is not recommended for use in pregnancy due to limited data on safety. Passively reported adverse event data may provide additional information on the safety of AP during pregnancy.

**Methods:** We analysed adverse event data on pregnancy and birth outcomes following accidental exposures to AP during pregnancy, which were passively reported to GlaxoSmithKline LLC (GSK) between 13 May 1997 and 15 August 2017. Birth outcomes of interest included live birth, miscarriage, and stillbirth. Adverse outcomes of interest were defined as any of the following: small for gestational age (SGA), low birth weight (LBW, <2500 gm), congenital anomalies, and a composite 'poor live birth outcome,' including preterm birth (PTB), LBW or SGA.

**Results:** Among 198 women who received AP during pregnancy or breastfeeding, 96.5% occurred in women taking malaria prophylaxis, and 79.8% of exposures occurred in the first trimester. Among 195 with available birth outcome data, 18.5% resulted in miscarriage and 11.8% were elective terminations. Available adverse outcomes included SGA in3.5% (3/85), LBW in 7.0% of infants (6/86), and the composite 'poor live birth outcome' in 13.7% (14/102). Congenital anomalies were reported in 30/124 (24.2%), with no specific pattern to suggest an effect related to AP.

**Conclusions:** These data provide a description of outcomes in the pregnancies reported to this dataset, and it should be noted that there is likely a bias towards reporting cases resulting in poor outcomes. While there was no specific signal to suggest a teratogenic effect of AP, AP data during

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Author contributions

JRG and KRT conceived the study and obtained the data. RCM transcribed the data into the database and JRG reviewed for accuracy. RCM and JRG analysed the data. RCM and JRG drafted the manuscript. All authors reviewed and provided input into the final manuscript, and all authors approved the submission. All authors had full access to the data and analysis. JRG and KRT accept full responsibility for the content.

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pregnancy were too limited to determine AP's safety with confidence. As inadvertent exposures are not infrequent, better data are needed.

**Keywords**

Atovaquone; proguanil; malaria; pregnancy; safety

## Background

Malaria during pregnancy increases the risk of maternal and foetal complications.[1] Pregnant women living in non-endemic settings are advised to avoid or delay travel to malaria-endemic regions, and to use antimalarial prophylaxis if they must travel.[2] The only options for malaria chemoprophylaxis in pregnant women are chloroquine and mefloquine, however, chloroquine use is limited by resistance in most parts of the world.[2] Furthermore, as a result of mefloquine resistance (documented in some parts of South-East Asia)[2] or contraindications to mefloquine (such as psychologic problems), some women may be left with no suitable prophylaxis options.

Atovaquone-proguanil (AP or Malarone®) remains effective for malaria prophylaxis and treatment, even in regions with high rates of resistance to other antimalarials.[3] However, AP is not recommended for use by pregnant women due to insufficient data on its safety in pregnancy.[4] Proguanil mono-therapy is considered safe in pregnancy.[4,5] There is more limited experience with the use of atovaquone in pregnancy, primarily for the treatment of both toxoplasmosis and babesiosis, where the benefit of treatment was deemed to outweigh the potential risks.[6]

Reproductive toxicity studies of AP conducted in rabbits demonstrated decreased foetal body lengths, increased early resorptions and post-implantation losses. These only occurred in the presence of maternal toxicity, at 1.3 times the estimated human exposure in treatment (the daily dose in treatment is 4 times the daily prophylactic dose).[4]

The limited available human data have not demonstrated an increased risk of adverse pregnancy and birth outcomes following exposures in pregnancy. A prospective study from an area of Thailand with high rates of resistant malaria compared oral quinine sulphate to oral artesunate plus AP among 81 women with uncomplicated malaria in their second or third trimesters of pregnancy. There were no differences in infant mean birth weight or congenital abnormality rates between the groups.[7] In another study in Thailand and Zambia, 26 women in their third trimester received AP for acute uncomplicated *Plasmodium falciparum* malaria; no serious adverse effects, including stillbirths, spontaneous abortions, or congenital anomalies, were observed.[8] Finally, a Danish registry-based study of a cohort of 570 877 live births, with 149 women exposed to AP during their first trimester, found no significant association between major congenital anomalies and AP exposure early in pregnancy.[9]

To provide additional information on the safety of AP during pregnancy, we analysed passively reported data on accidental exposures to AP during pregnancy and subsequent and birth outcomes.

## Methods

We obtained passively reported, redacted adverse event report (AER) data from GlaxoSmithKline LLC (GSK) between 13 May 1997 and 15 August 2017, regarding the outcomes of accidental exposures to AP during pregnancy. Consumers and healthcare providers worldwide voluntarily report adverse events to the manufacturers who report to MedWatch, the FDA's Safety Information and Adverse Event Reporting Program, using a standardized form, including patient demographics, pregnancy status, medication used, dose and adverse event details. Adverse events observed during clinical trials can also be submitted to this dataset.

### Data analysis

Patient demographics were analysed with regard to the mother's race, age, weight, and gravidity. Information on medication indication, duration, trimester of exposure and concurrent medications were examined. Infant demographics, gestational age, birth outcomes (live birth, miscarriage, stillbirth) and adverse outcomes were analysed using Epi Info 7 (CDC, Atlanta, GA) and SAS v9.3 (SAS Institute Inc., Cary, NC). Reported denominators indicate those with data available. Adverse outcomes were defined as any of the following: small for gestational age (SGA), low birth weight (LBW, <2500 gm), congenital anomalies, infant death, and a composite 'poor live birth outcome,' including preterm birth (PTB), LBW or SGA.

### Ethical review and confidentiality

The study was approved as non-human subject research by the office of the Associate Director for Science, Center for Global Health, at the US Centers for Disease Control and Prevention. De-identified data were obtained directly from GSK; there was no contact with subjects.

## Results

A total of 198 unique episodes of exposure to AP during pregnancy or breastfeeding with outcomes were reported out of 6732 reports submitted on AP.

### Maternal demographics

The median maternal age, reported for 155 women, was 32.0 years (range 14–53); 2.6% (4/155) were aged 14–19, 29% (45/155) were 20–29, 59.3% (92/155) were 30–39, 8.4% (13/155) were 40–49 and 0.7% (1/155) were 50–59. Average maternal weight, reported for 79 women, was 65.4 kg. Gravidity, reported for 23 women, ranged from 1 to 6; 47.8% (11/23) of the women were primigravid and 4.3% (1/23) were secundigravid. The mother's race was included in 62 reports; 3.2% (2/62) identified as Asian, 8.1% (5/62) as African American, 87% (54/62) as Caucasian and 1.6% (1/62) as other.

### Medication

Only 3.5% (7/198) of exposures were for treatment; the others occurred among women taking malaria prophylaxis. Three quarters (145) of the reports included the duration of AP, with an average of 18 days (range 2–87 days).

Of the 163 with information on timing of exposure available, the majority (158, 96.9%) occurred in the first trimester. Two women (1%) had exposure in second trimester; one woman reported exposure in both first and second trimesters. Four women (2%) were exposed during breastfeeding. No reported exposures occurred in the third trimester.

Concurrent antimalarial medication was reported uncommonly: artesunate (3.4%, 6/198), chloroquine (0.5%, 1/198), pyrimethamine (0.5%, 1/198) and halofantrine (0.5%, 1/198). Twenty-eight women were taking a total of 47 other medications, excluding folate, multivitamins and acetaminophen.

### Pregnancy and infant outcomes

Birth outcomes were available for 191 pregnancies, excluding those exposed while breastfeeding; 69.1% (132/191) were live births,19.4% (37/191) were miscarriages and 11.5% (22/191) were elective terminations. Of the elective terminations, eight were due to foetal abnormalities (Table 1), two were as a result of the exposure to AP despite no evidence of foetal abnormalities, seven were due to social reasons, and five had no reason indicated in the report.

Of the 78 (59.1%) live births with gestational age available, 10 (12.8%) were premature. Average weight, length and head circumference at birth were 3.3 kg (range 1.9–5.5 kg; n = 86 infants), 50.5 cm (range 39.0–56.0 cm; $n$ = 35 infants), and 34.8 cm (range 31.5–49.0 cm; $n$ = 22 infants), respectively.

LBW was reported in 7.0% of infants (6/86), SGA in 3.5% (3/85) and the composite ‘poor live birth outcome’ in 13.7% (14/102). Nearly one quarter (22.8%, or 31/136) of pregnancies resulted in an infant with a birth defect. These included four genetic anomalies and four that were likely genetic, leaving 23 that might have been related to AP exposure (Table 1). There did not appear to be a pattern to the congenital anomalies to suggest a specific effect related to AP exposure, nor were there any concomitant medications known to cause congenital anomalies.

Three infant deaths were reported. In two, no cause for death was identified; the third case was an infant with anencephaly.

## Discussion

Due to the systematic exclusion of pregnant women from clinical trials, there is a greater need for reliance on post-marketing surveillance data to assess the safety of medications in pregnancy. AER data on AP exposure in pregnancy demonstrated a rate of miscarriage similar to the cumulative probability of miscarriage reported among the US and Kenyan populations(19.7% and 18.9%, respectively).[10,11] While the rate of congenital anomalies

reported here is higher than that reported in the general populations (7% overall and 3% in the USA),[12,13] this must be interpreted cautiously, as the denominator does not reflect all AP exposures in pregnant women, only those reported to GSK. Although AP exposure during pregnancy is a reportable adverse event, there is likely a bias towards reporting cases resulting in poor outcomes. Reporting bias is evident by the fact that three published studies of *in utero* AP exposure selectively provided data to GSK. Pasternak *et al*. reported to GSK only regarding one infant with congenital anomalies, however, in their publication they report two infants with congenital anomalies out of a total of 149 (147 unaffected).[9] Reuvers et al. reported to GSK regarding five out of seven infants with congenital anomalies, and reported none of the 158 unaffected infants.[14] A third study by McGready *et al*. reported results for only five of the 27 infants in the study, all of whom were unaffected.[15] Including the three unreported cases of infants with congenital anomalies, as well as the 330 unreported, unaffected infants from the three studies, reduces the proportion of pregnancies ending in miscarriage or spontaneous abortion to 15.1% and the proportion with congenital anomalies to7.2%, far closer to the expected numbers. However, the data can still be useful for generating hypotheses and flagging safety concerns. For this analysis, the ability to detect potential patterns in congenital anomalies was limited by the lack of details for four infants with congenital anomalies. But for those that did have details, the lack of a pattern of similar malformations among infants provided some reassurance.

It is unsurprising that most reported exposures happened in the first trimester, since AP is not currently recommended for pregnant women in most countries,[16] and accidental exposure is most likely to occur periconceptionally. This has been similarly reported in a study of accidental exposures to antimalarials among female physicians and scientists; 1.2% reported exposure to AP in pregnancy, all within the first trimester.[17] Early pregnancy, when the foetus is developing, is the period of highest risk. Thus, additional safety data are critical.

Despite limited safety data, there are some countries in Europe where malarone is not contraindicated in pregnancy; in France, either AP or quinine are recommended for treatment of uncomplicated malaria in first trimester; and in Austria, AP is listed as an option for prophylaxis when chloroquine or mefloquine are contraindicated.[18,19] Post-marketing surveillance, or other studies, in these countries could help to add to the currently available data on the safety of malarone in pregnancy.

Of the AP-exposed pregnancies reported in this database, there were no outstanding signals of poor pregnancy outcomes, but a questionably higher rate of congenital anomalies with no apparent pattern. The findings of this analysis are difficult to interpret because of the limitations of AER data. These data are insufficient to make a recommendation about the use of AP during pregnancy. Given that inadvertent exposure to antimalarials in pregnancy is not uncommon, and the need for an alternative option for malaria prevention in pregnancy, better data are needed on the outcomes of infants exposed to AP.

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**Table 1.**

List of congenital anomalies among infants with in utero exposure to atovaquone-proguanil

| Organ classification | Description of congenital anomaly |
|---|---|
| Cardiac | Tetralogy of Fallot |
| Cardiac | Foetal heart malformation via echo [elective termination] |
| Cardiac | Ventricular septal defect |
| GI | Gastroschisis |
| GI | Atresia of duodenum and ileus |
| Hearing | Congenital hearing loss |
| Hip | Congenital hip dysplasia |
| Hip | 'Clicking hip' (suspected dislocation- *possible Congenital hip dysplasia)*, birth mark on left leg |
| Lymph | 6 cm cystic hygroma on the left ear |
| Minor/muscoloskeletal | Polydactyly (sixth finger on left hand and remnant finger on right hand) |
| Neuro | Anencephaly |
| Neuro | Anencephaly [elective termination] |
| Neuro | Meningocele [elective termination] |
| Neuro | Neural Tube Defect |
| Renal | Congenital hydronephrosis |
| Renal | Bilateral pyelon canalicular dilation of the kidneys |
| Unspecified | 'Unspecified birth defect' |
| Unspecified | 'Confirmation of malformation of the foetus: via CVS [elective termination] |
| Unspecified | 'Unspecified birth defect' |
| Unspecified/infectious (possible congenital infection) | Flattened and deviated nasal deformity, ulcerated skin on nose, lesions on scalp |
| Unspecified | 'Abnormal foetal development' via US [elective termination] |
| Unspecified | Neck tumefaction (swelling) |
| Genetic | Trisomy 21 via amniocentesis [elective termination] |
| Genetic | Congenital hypothyroidism caused by Pendred Syndrome |
| Genetic | Trisomy 21 |
| Genetic | Treacher-Collins Syndrome, hypoplasia (right ear and right thumb), facial asymmetry, deafness |
| Unspecified/genetic (possible chrom 13 | Corpus callosum agenesis, ventricular dilation, oesophageal atresia, interruption of aortic arch |

| Organ classification | Description of congenital anomaly |
|---|---|
| deletion), Neuro/cardiac/GI | [elective termination] |
| Unspecified | Dorsonuchal oedema, bone of the nose not detectable and length of femur below 5th percentile via sonogram; normal chromosomes [elective termination] |
| Unspecified/genetic, GU/cardiac/neuro | Infant scrotal hypospadias, mitral insufficiency and central coordination disturbances |
| Cardiac/GI/genetic (possible VACTERL) | Tetralogy of Fallot, anal atresia |
| Unspecified/genetic | Hypoglycemia, seizure, leucodystrophy (possible Pelizeaus Merbachers disease) |