HHS Public Access

Author manuscript

Travel Med Infect Dis. Author manuscript; available in PMC 2024 April 08.

Published in final edited form as:

Travel Med Infect Dis. 2019 ; 32: 101519. doi:10.1016/j.tmaid.2019.101519.

Atovaquone-proguanil exposure in pregnancy and risk for adverse fetal and infant outcomes: A retrospective analysis

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Abstract

Background: Malaria in pregnancy can cause severe maternal and fetal complications. Chloroquine (CQ) and mefloquine (MQ) are recommended for chemoprophylaxis in pregnancy, but are not always suitable. Atovaquone-proguanil (AP) might be a viable option for malaria prevention in pregnancy, but more safety data are needed.

Methods: Data for pregnancies and live births among active duty military women, 2003–2014, from the Department of Defense Birth and Infant Health Research program were linked with pharmacy data to determine antimalarial exposure. Multivariable Cox and logistic regression models were used to assess the relationship of antimalarial exposure with fetal and infant outcomes, respectively.

Results: Among 198,164 pregnancies, 50 were exposed to AP, 156 to MQ, and 131 to CQ. Overall, 17.6% of unexposed pregnancies and 28.0%, 16.0%, and 6.1% of pregnancies exposed to AP, MQ, and CQ, respectively, ended in fetal loss (spontaneous abortion or stillbirth) (adjusted hazard ratios [aHR] = 1.46, 95% confidence interval [CI] 0.87–2.46; aHR = 1.06, 95% CI 0.72–1.57; and aHR = 0.47, 95% CI 0.24–0.94, respectively).

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CRediT authorship contribution statement

Julie R. Gutman: Conceptualization, Writing - original draft. **Clinton Hall:** Methodology, Formal analysis, Writing - original draft. **Zeina G. Khodr:** Methodology, Writing - review & editing. **Anna T. Bukowinski:** Methodology, Writing - review & editing. **Gia R. Gumbs:** Writing - review & editing. **Ava Marie S. Conlin:** Writing - review & editing. **Natalie Y. Wells:** Writing - review & editing. **Kathrine R. Tan:** Conceptualization, Writing - review & editing.

Declaration of competing interest

JRG, CH, ZGK, ATB, GRG, AMSC, NYW, KRT no conflict.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tmaid.2019.101519.

Conclusions: The small number of AP exposed pregnancies highlights the difficulty in assessing safety. While definitive conclusions are not possible, these data suggest further research of AP exposure in pregnancy and fetal loss is warranted.

Twitter line: More research on fetal loss following atovaquone-proguanil exposure in pregnancy is warranted.

Keywords

Atovaquone-proguanil; Pregnancy; Malaria; Teratogenicity; Active duty military women

1. Introduction

Malaria infection during pregnancy is associated with increased risk of complications for both mother and fetus [1]. The Centers for Disease Control and Prevention (CDC) advises pregnant women to avoid or delay travel to malaria-endemic regions; but if avoiding travel is not feasible, antimalarials must be used to prevent malaria [2]. Malaria chemoprophylaxis options for pregnant women are limited to chloroquine (CQ) and mefloquine (MQ) [2]. While there are decades of experience showing that these are safe options [3–7], widespread CQ resistance among *Plasmodium falciparum* parasites and some *P. vivax* parasites limits the use of CQ prophylaxis [2]. In some parts of South-East Asia, *P. falciparum* is also resistant to MQ, leaving pregnant women with no prophylaxis alternative [2]. Use of MQ is further limited by the possibility of neuropsychiatric adverse events, especially in those with a previous history of neuropsychiatric illnesses [8,9]. While not recommended by the World Health Organization (WHO) or CDC, some countries reserve doxycycline and atovaquone-proguanil (AP) as last-resort chemoprophylaxis options restricted to certain gestational periods.

AP is a combination drug effective for malaria prophylaxis and treatment, even in regions with high rates of resistance to other antimalarials [10]. Despite its efficacy, the US Food and Drug Administration does not recommend AP for use by pregnant women (at any gestational age) due to insufficient data on the safety of its use in pregnancy [11,12]. However, some information exists regarding the use of the individual components in pregnancy. Proguanil, which is metabolized into cycloguanil, blocks dihydrofolate reductase [13]. Although it has a long history of safe clinical use in pregnancy for the prevention and treatment of malaria [12,14,15], other antifolates have been linked to teratogenic effects following first trimester exposures [16]. Atovaquone, which blocks mitochondrial electron transfer, has been used in pregnancy in certain situations where the benefit was deemed to outweigh potential risks, such as for the treatment of toxoplasmosis, and in combination with azithromycin for the treatment of babesiosis [17,18]. *In utero* exposure to anti-mitochondrial agents can cause teratogenic effects, as described with antiretrovirals [19].

Animal studies suggest that AP 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 [20].

The limited data available from human studies of AP in pregnancy have not demonstrated an increased risk of adverse birth outcomes. A prospective study carried out in an area of Thailand with high rates of resistant malaria enrolled 81 pregnant women with uncomplicated malaria in their second or third trimesters of pregnancy. Women received either quinine sulfate orally, or artesunate and AP orally. There were no differences in the mean birth weight or congenital abnormality rates in the infants between the groups [21]. Another study in Thailand and Zambia treated 26 women in their third trimester with AP for acute uncomplicated *P. falciparum* malaria; no serious adverse effects, including no stillbirths, were reported [22]. Finally, a Danish registry-based study of a cohort of 570,877 live births investigated inadvertent AP exposure in early pregnancy. Among 149 women exposed to AP, no significant association for exposure to AP between 3 and 8 weeks after conception and any major birth defects was found [23].

More evidence is needed to assess if AP is a safe option for malaria prevention in pregnant travelers [24]. While it would be ideal to conduct randomized trials where women were assigned to either AP or an alternate antimalarial, given the current status of knowledge of safety of these drugs in pregnancy, this is not feasible at present. Therefore, we must rely on large observational studies. In order to provide a better assessment of the safety of AP in pregnancy, we conducted an analysis of inadvertent exposures to AP during pregnancy and subsequent pregnancy and birth outcomes using data from the Department of Defense (DoD) Birth and Infant Health Research (BIHR) program.

2. Material and methods

2.1. Study population

The DoD BIHR program is an ongoing population-based surveillance and research effort established in 1998 [25]. BIHR program data are derived from the Military Health System Data Repository (MDR) and the Defense Manpower Data Center (DMDC), and include information on infants and pregnancies among military families (i.e., TRICARE beneficiaries). The MDR houses administrative medical encounter data for inpatient and outpatient encounters at both military and civilian treatment facilities. Medical encounters are coded with *International Classification of Disease, Ninth/Tenth Revision, Clinical Modification* (ICD-9/10-CM) diagnostic and procedure codes, and Current Procedural Terminology (CPT) codes, which are used to define the infant and pregnancy populations and outcomes of interest. For infants, medical data are collected through their first year of life. Same-sex multiple infants are excluded from BIHR due to difficulty distinguishing their medical records. Detailed methods for developing BIHR program data are described elsewhere [25].

The present study assesses both pregnancy and infant study populations. The pregnancy population was limited to military women who remained on active duty status throughout the duration of their pregnancy, and whose dates of last menstrual period (LMP) and end of pregnancy fell between January 1st, 2003 and December 31st, 2014. Pregnancies from

2015 onwards were not included because the algorithm used to define pregnancies has not been established for ICD-10-CM codes, which were introduced in late 2015. Pregnancies were excluded from analyses if they ended in an elective abortion, were considered ectopic or molar pregnancies, or had an unknown outcome. Multiple gestations were also excluded. Pregnancies were further excluded if the mother had implausible antimalarial prescription quantities (less than a week of prophylaxis for AP or less than a month of prophylaxis for CQ or MQ; this is the minimum length of time prophylaxis would be recommended) or a malaria diagnosis during pregnancy. The infant study population was comprised of any live born singleton infants resulting from the pregnancy population that were identified in BIHR program data.

Military policy is that pregnant women are not deployable; if pregnancy is diagnosed in a deployed woman, she is returned from deployment. However, 'non-deployable' women could be permanently stationed in an area requiring malaria chemoprophylaxis. The military follows CDC recommendations for malaria chemoprophylaxis, and would not knowingly prescribe AP to a pregnant woman, suggesting that all exposures occurring in this study were inadvertent.

2.2. Antimalarial exposure

Antimalarial exposure data were ascertained from the Pharmacy Data Transaction Service (PDTS) within the MDR. National drug codes and generic code numbers, in combination with medication brand and generic names, were used to identify prescriptions for AP, MQ, and CQ. Pregnancies were considered exposed if the antimalarial drug dispensing date fell between estimated dates of LMP and end of pregnancy. Estimated gestational age (EGA) of exposure was also considered and a separate variable was created to indicate antimalarial dispensed in the first trimester (≤13 weeks gestation). Only women with prescriptions for antimalarial prophylaxis were included; to ensure this, women were excluded if they had received pediatric doses or a prescription for less than seven tablets of AP or less than five tablets of MQ or CQ. Pregnancies/infants exposed to more than one antimalarial during pregnancy were included in the analyses for each of the antimalarials to which they were exposed.

2.3. Fetal and infant outcomes

The fetal outcome of interest was fetal loss, which includes spontaneous abortions, stillbirths, and other losses not identified as ectopic or molar pregnancies. The most common type of loss, spontaneous abortion, was analyzed separately. Among losses, spontaneous abortion was defined using ICD-9-CM codes for a missed or spontaneous abortion (632 and 634.xx) and/or CPT codes indicating treatment of incomplete, missed, or septic abortion (59,812, 59,820, 59,821, 59,830) on an encounter record on or before 22 weeks EGA; if codes for other types of fetal loss appeared on the same record, the loss was not considered a spontaneous abortion.

Infant outcomes of interest included growth problems *in utero*, preterm birth (birth completed before 37 weeks gestation), low birthweight (LBW; birth weight under 2500 g), small for gestational age (SGA), and major birth defects. Growth problems *in utero*

were defined by ICD-9-CM codes for slow fetal growth and fetal malnutrition (764.xx) on maternal or infant records. Methods for defining preterm birth and LBW have been previously described [25]. SGA was determined by ICD-9-CM codes indicating light-for-dates (764.0x and 764.1x) on the infant record within the first 28 days of life, or ICD-9-CM codes indicating poor fetal growth (656.5x) on the maternal delivery record [26]. Major birth defects were selected for inclusion in analyses based on definitions from the Vaccine Safety Datalink and the National Birth Defects Prevention Network [27,28], in combination with input from a physician (A.S.C.) and a certified medical coder (see Supplementary Table 1 for ICD-9/10-CM codes and details); categories of birth defects required relevant diagnoses in the first year of life, either on one inpatient record or two outpatient records on different days.

Due to an anticipated small number of exposed cases, preterm birth, LBW, and SGA indicator variables were combined in analyses as “any adverse live birth outcome.” A subsequent variable including birth defects, “any adverse live birth outcome or birth defect,” was also assessed.

2.4. Demographics and covariates

Maternal demographic and occupational characteristics were obtained from the DMDC. Covariates of interest included age at conception (17–19, 20–24, 25–29, 30–34, 35 + years), self-reported race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other/unknown), service branch (Army, Navy, Air Force, Marine Corps, Coast Guard), rank (enlisted vs. officer), education (no high school diploma, high school diploma, education beyond high school, unknown), and marital status (married vs. unmarried or unknown). Rank was assessed as a proxy for education, as data on educational attainment is historically unreliable.

Receipt of any vaccinations that are generally contraindicated in pregnancy (yes vs. no) was assessed as a proxy for lack of pregnancy recognition, and was treated as time-varying depending on the statistical model used. Vaccines of interest were identified by vaccine administered code sets (CVX codes) and include vaccinations against measles, mumps, and rubella (CVX codes 003–007, 038, 094); tuberculosis (019); varicella (021); influenza (intranasal administration only, 111, 125, 149, 151); rabies (018, 040, 090, 175, 176); yellow fever (037, 183, 184); and typhoid (025).

2.5. Statistical analyses

Descriptive statistics were calculated for select maternal and infant characteristics, stratified by antimalarial exposure in pregnancy. For multivariable models, selection of confounders was based on prior literature and associations observed in previous BIHR studies [29,30].

For maternal outcomes, time-dependent multivariable Cox proportional hazards models accounting for left truncation at start of pregnancy care were used to estimate hazard ratios (HRs) and 95% confidence intervals (CI) for associations with antimalarial exposure in pregnancy and fetal loss or spontaneous abortion [31]. Crude models controlled for maternal age at conception (continuous), while adjusted models additionally controlled for service branch, rank, marital status, and exposure to vaccinations not routinely recommended

in pregnancy, which was treated as time-varying. For analyses of spontaneous abortion, observations were censored at date of pregnancy loss or 22 weeks EGA. For adverse infant outcomes, unconditional multivariable logistic regression models estimated odds ratios (ORs) and 95% CIs for associations with antimalarial exposure in pregnancy. Crude and adjusted models controlled for the same factors mentioned above, though receipt of vaccinations not routinely recommended in pregnancy was treated as a simple binary covariate. For analyses of both fetal and infant outcomes, separate models assessed 1) any pregnancy antimalarial exposure and 2) first trimester antimalarial exposure only.

All statistical analyses were performed using SAS, version 9.4 (Cary, NC).

3. Results

Of 243,168 pregnancies to active duty women identified between January 1st, 2003 and December 31st, 2014, 198,164 pregnancies were included in the analyses (Fig. 1). Of these, 197,835 were unexposed, 50 were exposed to AP, 156 to MQ, and 131 to CQ. Four pregnancies were exposed to both AP and MQ, one to AP and CQ, and three to MQ and CQ. None were exposed to all three. Women exposed to AP were older than unexposed women (median 30.5, range 19–43 vs median 24, range 17–54, respectively, p-value < 0.001); 18.0% of women exposed to AP were over 35 years compared to only 7.0% among unexposed women (p-value = 0.002) (Table 1; S1). Women exposed to AP were more likely to be exposed in the first trimester—94% of exposures were in the first trimester, whereas 85% and 74% of MQ and CQ exposures occurred in the first trimester, respectively (p-value AP vs MQ = 0.10; p-value AP vs CQ = 0.002) (Table S2; Fig. 2).

Overall, 17.6% of unexposed pregnancies and 28%, 16%, and 6% of pregnancies exposed to AP, MQ, and CQ, respectively, ended in fetal loss (adjusted HR = 1.46, 95% CI 0.87–2.46; 1.06, 95% CI 0.72, 1.57, and 0.47, 95% CI 0.24, 0.94, respectively). Numbers were similar when only considering first trimester exposure and when only assessing spontaneous abortion (Table 2).

There were data on 161,173 singleton live births; 160,892 were unexposed and 36 were exposed to AP, 130 to MQ, and 121 to CQ. Two infants were exposed *in utero* to both AP and MQ, one to AP and CQ, and three to MQ and CQ. Among unexposed infants, 2.9% were classified as having a major birth defect, while among those exposed to antimalarials, major birth defects were seen in 2.8% of those exposed to AP, 0.8% to MQ, and 2.5% to CQ (Table 3).

Among unexposed infants, 8.0% were preterm and 8.8% had a LBW; among those exposed to AP, 11.1% were preterm and 11.1% had a LBW. This was higher than with MQ or CQ (Table 3). Similarly, the proportion of infants born with any adverse live birth outcome was higher with AP exposure (19.4%) than with no exposure (11.4%), MQ exposure (6.9%), or CQ exposure (9.1%) (adjusted OR = 2.02, 95% CI 0.88, 4.60 for AP vs no exposure; adjusted OR = 0.59, 95% CI 0.30, 1.16 for MQ vs no exposure; adjusted OR = 0.74, 95% CI 0.40, 1.37 for CQ vs no exposure) (Table 4). There was not a significant difference when

assessing exposure at any time or first trimester exposure only, nor when birth defects were included in the composite outcome.

4. Discussion

We present data on AP exposures in a cohort of 198,164 pregnancies identified over an 11-year period. Among the 50 women in the cohort exposed to AP, we found a non-statistically significant increase in the risk of fetal loss and a composite adverse live birth outcome indicator (LBW, SGA, and preterm birth); these increased risks were not observed with either MQ or CQ. This highlights that until further data are available to better understand the risks, AP should not be used for prophylaxis or treatment in pregnant women, unless no other suitable alternatives are available. These data also highlight the difficulty in obtaining sufficient numbers to assess the safety of medication, particularly antimalarial medication, in pregnancy, as has been noted previously [24].

The relatively lower risk of adverse birth outcomes associated with MQ and CQ highlights the safety of these drugs in pregnancy as supported by the literature [6,7]. Decades of use of CQ in pregnancy has demonstrated its safety across wide dose ranges, from high doses for lupus to lower doses for malaria chemoprophylaxis [3,5,32]. Additionally, the fact that CQ exposure in pregnancy was associated with significantly lower rates of fetal loss as compared to unexposed pregnancies is speculated to be due to its anti-inflammatory properties [32].

This study lacked sufficient statistical power to detect associations between AP exposure and adverse fetal or infant outcomes. The very small number of exposed women makes a true estimation of the risk very difficult. While the numbers we found certainly raise some concern about the possibility of AP being associated with adverse events, the small sample sizes and wide confidence intervals limit the interpretation of our findings. With this limited sample size, a change of one exposed infant from affected to unaffected has major implication for the estimated risk. Further, the women in the AP exposure cohort were substantially older than women in the unexposed cohort, which could affect the risk of adverse birth outcomes. Although we adjust for maternal age in analyses, age-related factors that were unknown in our population, but may affect offspring risk for certain outcomes (e.g., parity), might result in residual confounding. It is also possible that other travel related exposures could have influenced birth outcomes, however, we have attempted to account for this by comparing women receiving AP to those receiving other antimalarials, particularly MQ, who are assumed to have similar risks related to travel.

This study was limited by the use of administrative medical claims data to define outcomes of interest and to estimate LMP and EGA (and therefore the exposure window used for assessment), which will result in misclassification. For live births, a previous validation of BIHR program data showed that ICD-9-CM codes provide an accurate assessment of EGA (and therefore LMP/exposure window, preterm birth) and birthweight in this military population, thus limiting the extent of misclassification attributable to ICD coding errors [33]. However, not all outcomes of interest have been validated (e.g., fetal loss), nor have estimates of LMP/EGA been validated for pregnancies that do not end in a live delivery.

As taking AP in pregnancy is not recommended, it is likely that it was only dispensed to women who were not aware of their pregnancy status, as evidenced by the fact that nearly all the exposures to AP occurred very early in pregnancy, while exposure to MQ and, even more so, CQ were more uniform across pregnancy. Data from the PDTS were used to ascertain both exposure and timing of exposure; it is possible that the drug dispensing date was not when the woman actually started taking the drug, and it is possible that upon learning she was pregnant, she stopped, or had not taken it at all. This may have led to misclassification of both the exposure and the timing of exposure. However, sources of differential misclassification were not identified for either exposure or outcome variables, and thus we assume that any misclassification is nondifferential and biases results toward the null. Finally, to attempt to adjust for any confounding resulting from the fact that nearly all exposures to AP likely occurred in women unaware of their pregnancy status we controlled for a number of variables (e.g., marital status, age, receipt of vaccinations generally contraindicated in pregnancy).

Given the potential concerns, it is hard at this point to recommend a randomized controlled trial where pregnant women are intentionally exposed to AP. However, other more feasible study designs could include observational studies involving the development of pregnancy registries where AP (or any other drug) exposure and outcomes were captured systematically prospectively during pregnancy or at the time of delivery, including a re-examination of BIHR program data once ICD-10 algorithms have been established. Even with this study population of active duty military women who frequently travel internationally to malaria affected areas for their occupation, only 50 cases of AP exposure were found, highlighting the need for larger populations. There may be other pre-existing datasets which include this information, such as in countries where the data from multiple registries could be linked to assess birth outcomes following AP exposure, as we have done here, and has been done in previous publications [23]. To address the potential for misclassification that can occur with medical claims and pharmacy dispensing data, linked survey data asking further about timing of medication exposure may be helpful and strengthen future studies. While post-marketing surveillance provides an important means of identifying specific risks, it is less useful than a pregnancy registry as denominator data are not available, complicating the assessment of risk [34]. It is imperative to examine larger numbers of exposed pregnancies in order to provide a better understanding of the potential risks and benefits of using AP in pregnancy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We would like to acknowledge Katherine J. Snell, BS, from the Department of Defense Birth and Infant Health Research program, for her contributions to this study.

Role of the funding source

Report No. 19–66 was supported by the U.S. Navy Bureau of Medicine and Surgery under work unit no. 60504. The funding source had no involvement in the study design; collection, analysis, or interpretation of data; the writing of the report; or the decision to submit the article for publication.

Report No. 19–66 was supported by the U.S. Navy Bureau of Medicine and Surgery under work unit no. 60504. The study protocol was approved by the Naval Health Research Center Institutional Review Board in compliance with all applicable Federal regulations governing the protection of human subjects. Research data were derived from an approved Naval Health Research Center, Institutional Review Board protocol number NHRC.1999.0003. Use of trade names is for identification only and does not imply endorsement by the Centers for Disease Control and Prevention, the Public Health Service, or the U.S. Department of Health and Human Services. The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, Centers for Disease Control and Prevention, nor the U.S. Government.

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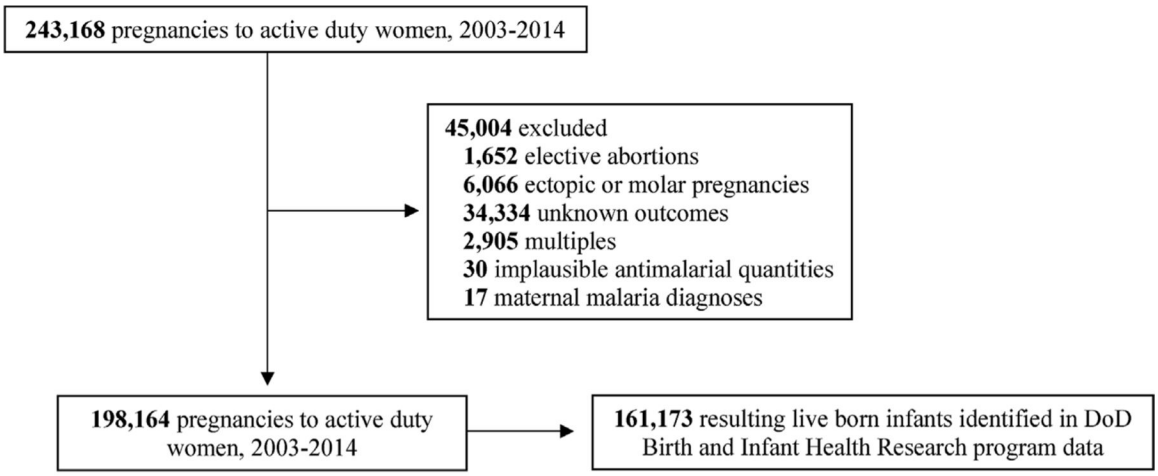

Fig. 1.
Pregnancy and infant population exclusion criteria.

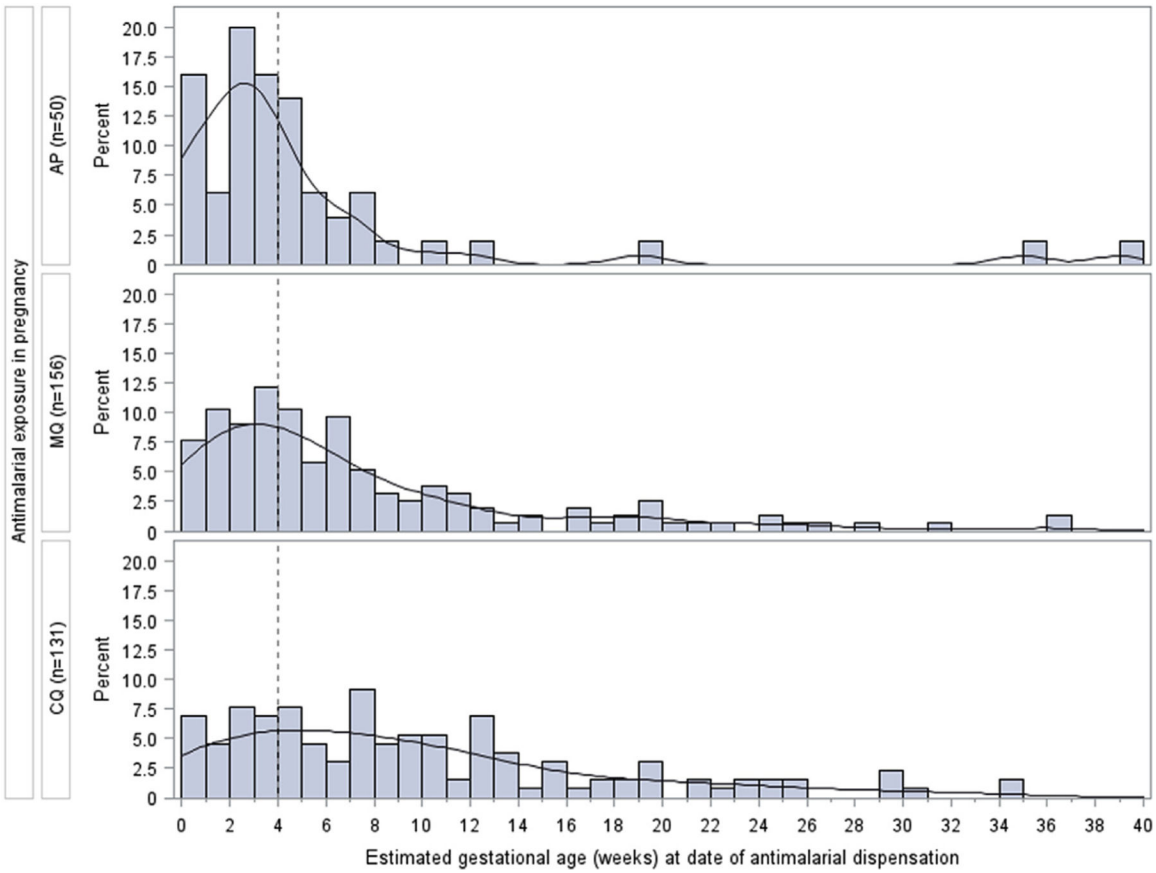

Fig. 2.

Comparative histogram of estimated gestational age (weeks) at exposure to atovaquone-proguanil (AP), mefloquine (MQ), or chloroquine (CQ) in pregnancy, measured at date of antimalarial dispensing. The dotted reference line indicates estimated earliest date of pregnancy detection.

Table 1

Population characteristics by atovaquone-proguanil exposure in pregnancy, 2003–2014.[a]

Characteristics	Pregnancies				Infants (singleton)			
	Unexposed		Exposed		Unexposed		Exposed	
Total	197,835		50		160,892		36	
Maternal age at conception								
Median (range)	24.0 (17–54)		30.5 (19–43)		24.0 (17–54)		30.0 (19–39)	
17–19 years	15,974	(8.1)	1	(2.0)	12,929	(8.0)	1	(2.8)
20–24 years	85,303	(43.1)	10	(20.0)	70,058	(43.5)	9	(25.0)
25–29 years	54,311	(27.5)	11	(22.0)	44,960	(27.9)	7	(19.4)
30–34 years	28,374	(14.3)	19	(38.0)	23,123	(14.4)	15	(41.7)
35 + years	13,873	(7.0)	9	(18.0)	9822	(6.1)	4	(11.1)
Maternal race/ethnicity								
Non-Hispanic white	94,718	(47.9)	22	(44.0)	77,537	(48.2)	17	(47.2)
Non-Hispanic black	54,052	(27.3)	7	(14.0)	43,280	(26.9)	3	(8.3)
Hispanic	27,159	(13.7)	11	(22.0)	22,026	(13.7)	10	(27.8)
Other or unknown	21,906	(11.1)	10	(20.0)	18,049	(11.2)	6	(16.7)
Maternal service branch								
Army	68,413	(34.6)	17	(34.0)	53,871	(33.5)	12	(33.3)
Navy	51,276	(26.0)	14	(28.0)	42,351	(26.3)	11	(30.6)
Air Force	58,699	(29.7)	18	(36.0)	48,523	(30.2)	13	(36.1)
Marine Corps	15,065	(7.6)	1	(2.0)	12,475	(7.8)	0	(0.0)
Coast Guard	4382	(2.2)	0	(0.0)	3672	(2.3)	0	(0.0)
Maternal rank								
Enlisted	170,940	(86.4)	26	(52.0)	138,803	(86.3)	20	(55.6)
Officer	26,895	(13.6)	24	(48.0)	22,089	(13.7)	16	(44.4)
Maternal education								
No high school diploma	11,229	(5.7)	0	(0.0)	8724	(5.4)	0	(0.0)
High school diploma	137,048	(69.3)	16	(32.0)	111,613	(69.4)	13	(36.1)
More than high school	46,026	(23.3)	32	(64.0)	37,737	(23.5)	22	(61.1)
Unknown	3532	(1.8)	2	(4.0)	2818	(1.8)	1	(2.8)

Characteristics	Pregnancies				Infants (singleton)			
	Unexposed		Exposed		Unexposed		Exposed	
Maternal marital status								
Married	140,861	(71.2)	41	(82.0)	117,820	(73.2)	30	(83.3)
Unmarried or unknown	56,974	(28.8)	9	(18.0)	43,072	(26.8)	6	(16.7)
Timing of antimalarial exposure								
First trimester	N/A		47	(94.0)	N/A		33	(91.7)
Second or third trimester	N/A		3	(6.0)	N/A		3	(8.3)
Receipt of vaccination(s) generally contraindicated in pregnancy								
No	180,945	(91.5)	40	(80.0)	146,383	(91.0)	27	(75.0)
Yes	16,890	(8.5)	10	(20.0)	14,509	(9.0)	9	(25.0)

[a]Data presented as N (percent %).

Table 2

Hazard ratios (HRs) and 95% confidence intervals (CIs) for associations with antimalarial exposure in pregnancy and fetal loss among active duty women in the United States military, 2003–2014.

Exposure and timing	Total N	All fetal losses[a]				Spontaneous abortion			
		n	(%)	HR[b]	HR (95% CI)[c]	n	(%)	HR[b]	HR (95% CI)[c]
None (reference)	197,835	34,889	(17.6)	1.00	–	30,030	(15.2)	1.00	–
Atovaquone-proguanil									
Any exposure	50	14	(28.0)	1.40	1.46 (0.87, 2.46)	13	(26.0)	1.50	1.55 (0.90, 2.67)
First trimester exposure	47	14	(29.8)	1.53	1.59 (0.94, 2.67)	13	(27.7)	1.61	1.67 (0.97, 2.88)
Mefloquine									
Any exposure	156	25	(16.0)	1.06	1.06 (0.72, 1.57)	20	(12.8)	0.98	0.96 (0.62, 1.49)
First trimester exposure	132	22	(18.2)	1.21	1.20 (0.80, 1.78)	20	(15.2)	1.15	1.12 (0.72, 1.74)
Chloroquine									
Any exposure	131	8	(6.1)	0.52	0.47 (0.24, 0.94)	6	(4.6)	0.45	0.41 (0.18, 0.91)
First trimester exposure	97	8	(8.3)	0.63	0.57 (0.29, 1.14)	6	(6.2)	0.56	0.50 (0.23, 1.11)

[a] Includes spontaneous abortions, stillbirths, and other losses not identified as ectopic or molar pregnancies or elective abortions.

[b] Model adjusted for maternal age at conception.

[c] Model adjusted for maternal age at conception, service branch, rank, marital status, and exposure to vaccinations generally contraindicated in pregnancy.

Table 3

Infant characteristics by atovaquone-proguanil (AP), mefloquine (MQ), or chloroquine (CQ) exposure in pregnancy, 2003–2014.[a]

Infant characteristics	Antimalarial exposure							
	None		AP		MQ		CQ	
Total	160,892		36		130		121	
Infant sex								
Male	82,314	(51.2; 50.9–51.4)	19	(52.8; 37.0–68.0)	66	(50.8; 42.3–59.2)	54	(44.6; 36.1–53.5)
Female	78,578	(48.8; 48.6–49.1)	17	(47.2; 32.0–63.0)	64	(49.2; 40.8–57.7)	67	(55.4; 46.5–63.9)
Adverse infant outcomes								
Growth problems *in utero*	4783	(3.0; 2.9–3.1)	2	(5.6; 1.5–18.1)	1	(0.8; 0.1–4.2)	3	(2.5; 0.8–7.0)
Any major birth defect	4622	(2.9; 2.8–3.0)	1	(2.8; 0.5–14.2)	1	(0.8; 0.1–4.2)	3	(2.5; 0.8–7.0)
Low birth weight (< 2500 g)	14,176	(8.8; 8.7–9.0)	4	(11.1; 4.4–25.3)	5	(3.9; 1.7–8.7)	9	(7.4; 4.0–13.5)
Preterm birth (< 37 weeks)	12,795	(8.0; 7.8–8.1)	4	(11.1; 4.4–25.3)	6	(4.6; 2.1–9.7)	7	(5.8; 2.8–11.5)
Small for gestational age	6237	(3.9; 3.8–4.0)	4	(11.1; 4.4–25.3)	3	(2.3; 0.8–6.6)	5	(4.1; 1.8–9.3)
Any adverse live birth outcome[b]	18,340	(11.4; 11.2–11.6)	7	(19.4; 9.8–35.0)	9	(6.9; 3.7–12.6)	11	(9.1; 5.2–15.5)
Any adverse live birth outcome[b] or birth defect	21,746	(13.5; 13.3–13.7)	7	(19.4; 9.8–35.0)	10	(7.7; 4.2–13.6)	13	(10.7; 6.4–17.5)

[a] Data presented as N (percent %; 95% confidence intervals).

[b] Any adverse live birth outcome defined as preterm birth, low birthweight, or small for gestational age.

Table 4

Odds ratios (ORs) and 95% confidence intervals (CIs) for associations with antimalarial exposure in pregnancy and adverse live birth outcomes among infants of active duty women in the United States military, 2003–2014.

Exposure and timing	Total N	Any adverse live birth outcome[a]				Any adverse live birth outcome[a] or birth defect			
		n	(%)	OR[b]	OR (95% CI)[c]	n	(%)	OR[b]	OR (95% CI)[c]
None (reference)	160,892	18,340	(11.4)	1.00	–	21,746	(13.5)	1.00	–
Atovaquone-proguanil									
Any exposure	36	7	(19.4)	1.90	2.02 (0.88, 4.60)	7	(19.4)	1.55	1.62 (0.71, 3.71)
First trimester exposure	33	6	(18.2)	1.74	1.85 (0.76, 4.48)	6	(18.2)	1.42	1.49 (0.62, 3.62)
Mefloquine									
Any exposure	130	9	(6.9)	0.58	0.59 (0.30, 1.16)	10	(7.7)	0.53	0.55 (0.29, 1.04)
First trimester exposure	107	7	(6.5)	0.55	0.56 (0.26, 1.21)	8	(7.5)	0.52	0.54 (0.26, 1.10)
Chloroquine									
Any exposure	121	11	(9.1)	0.78	0.74 (0.40, 1.37)	13	(10.7)	0.77	0.74 (0.42, 1.32)
First trimester exposure	87	8	(9.2)	0.79	0.76 (0.37, 1.56)	10	(11.5)	0.83	0.81 (0.42, 1.56)

[a] Any adverse live birth outcome defined as preterm birth, low birthweight, or small for gestational age.

[b] Model adjusted for maternal age at conception.

[c] Model adjusted for maternal age at conception, service branch, rank, marital status, and exposure to vaccinations generally contraindicated in pregnancy.