Safety and efficacy of artemisinins vs quinine for the case-management of malaria in pregnancy: two meta-analyses

Prof Feiko ter Kuile, Liverpool School of Tropical Medicine

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Investigators

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Outline

• Case management of non-severe malaria in pregnancy (i.e. oral treatment)
  – Use of ACTs

• Two meta-analyses summarizing 25 years of studies
  – 2\textsuperscript{nd} and 3\textsuperscript{rd} trimester: Efficacy of ACTs vs quinine (meta-analysis)
  – 1\textsuperscript{st} trimester: Safety of artemisinins vs quinine (meta-analysis)
WHO Treatment Guidelines
Malaria in Pregnancy April 2015

2nd & 3rd trimester
• ACTs (3 days) since 2003
• Quinine + clindamycin (7d)
  • (if ACTs not available)

1st trimester
• Quinine + clindamycin (7d)
• Artemisinins not recommended unless
  • in severe disease
  • no other drugs available
  • Rescue therapy; e.g. Quinine failures
EFFICACY 2ND AND 3RD TRIMESTER: ACTs vs QUININE

Parasite clearance non-severe malaria in pregnancy
Meta-analysis comparing efficacy, safety and tolerance of ACTs vs quinine for the case-management of malaria in 2nd and 3rd trimester

Artemisinin-Based Combination Therapy Versus Quinine or Other Combinations for Treatment of Uncomplicated Plasmodium falciparum Malaria in the Second and Third Trimester of Pregnancy: A Systematic Review and Meta-Analysis

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Background and objectives
meta-analysis 2\textsuperscript{nd} and 3\textsuperscript{rd} trimester

• ACTs: most efficacious antimalarials available
• WHO recommends ACTs for Rx of non-severe malaria in the 2\textsuperscript{nd}/3\textsuperscript{rd} trimester
• Quinine continues to be used
  – poor compliance
    • high daily dosing schedule
    • poor tolerability
  – poor compliance $\rightarrow$ incomplete treatment $\rightarrow$ treatment failures
• Review of trials to assess efficacy, safety and tolerability of ACTs vs. quinine
  and other (non-ACT) drugs in the 2\textsuperscript{nd} and 3\textsuperscript{rd} trimester
• To help policy makers to make informed decisions
Study Design and Methods
meta-analysis 2\textsuperscript{nd} and 3\textsuperscript{rd} trimester

• All trials in pregnant women
  – Comparing ACTs vs. non-ACTs (e.g. quinine)
  – 2\textsuperscript{nd} and 3\textsuperscript{rd} trimester
  – Data on efficacy and safety

• Source: Malaria in Pregnancy Library: http://library.mip-consortium.org/

• Meta-analysis: Random effects models
Results meta-analysis 2\textsuperscript{nd} and 3\textsuperscript{rd} trimester
6 trials, 3 from Africa, 3 from Thailand

• **Efficacy**: PCR-adjusted failure rate by days 28 to 63
  – failure rate with quinine 20.5\% in Thailand, and 2.4\% in Africa
  – failure rate with ACTs 80\% lower compared to quinine (all doses supervised)
  – pooled risk ratio [PRR] random effects, PRR=0.20; 95\% CI, 0.08–0.49; 4 trials

• **Safety**: No differences in fetal deaths and congenital abnormalities

• **Tolerance**: ACTs associated with less
  – tinnitus (noise/ringing in ears) by 81\% (95\% CI 79-97), 4 studies
  – dizziness by 36\% (95\% CI 7-56); 3 studies
  – vomiting by 67\% (95\% CI 27-85); 3 studies
Summary efficacy and safety 2\textsuperscript{nd} and 3\textsuperscript{rd} trimester

• ACTs, compared to quinine, are
  – more effective
  – better tolerated
  – easier to administer

• Strongly supports WHO’s policy to treat 2\textsuperscript{nd} and 3\textsuperscript{rd} trimester malaria in pregnancy with ACTs

• Their use should be encouraged among health workers
SAFETY 1ST TRIMESTER: ARTEMISININS VS QUININE (META-ANALYSIS)

Miscarriage, stillbirth, birth defects
Safety of artemisinins in the first trimester

background

• Animal models: Concerns about in-vitro embryo-toxicity and teratogenicity of artemisinins in animal models at low doses
  – In humans, equivalent to 6-12 weeks gestation
• Class effect: observed with all artemisinins

• WHO: artemisinins contraindicated in the first trimester because of limited experience in the first trimester in humans
  – Implications for women of child bearing age, not just pregnant women
  – Has been shown to be difficult to implement in resource poor settings
  – ACTs 1st line Rx in general population (DHA-piperaquine/ other ACTs)
  – Lots of potential of inadvertent exposure to ACTs
Safety of artemisinins in the first trimester

Objective and Methods

• Objective: To compare the risk of adverse pregnancy outcomes between artemisinin and quinine exposures in 1st trimester in Africa

• Individual patient level data (IPD) meta-analysis

• Inclusion criteria for studies
  – Confirmed artemisinin exposures in 1st trimester
  – Internal comparison group (e.g. quinine)
  – Prospective follow-up:
    • Pregnant women enrolled before outcome was known

• Record linkage ANC data (outcome) with adult OPD data (exposure)
Safety of the artemisinins in the first trimester
Meta-analysis: 30,618 pregnancies
Artemisinin N=709; Quinine N=948

First-trimester artemisinin derivatives and quinine treatments and the risk of adverse pregnancy outcomes in Africa and Asia: A meta-analysis of observational studies

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Safety of the artemisinins in the first trimester
Meta-analysis: Artemisinin N=709; Quinine N=948
Miscarriage and stillbirth

<table>
<thead>
<tr>
<th>Study</th>
<th>Artemisinin #Miscarriage/ #Total</th>
<th>Quinine #Miscarriage/ #Total</th>
<th>Adjusted Hazard Ratio (95%CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artemisinin vs Quinine, 1st Trimester</td>
<td>14/ 488</td>
<td>4/ 103</td>
<td>0.52 (0.14, 1.87)</td>
<td>0.316</td>
</tr>
<tr>
<td>IPD Africa</td>
<td>23/ 183</td>
<td>92/ 842</td>
<td>0.78 (0.45, 1.34)</td>
<td>0.365</td>
</tr>
<tr>
<td>SMRU Thailand</td>
<td></td>
<td></td>
<td>0.73 (0.44, 1.21)</td>
<td>0.228</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.348)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis

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<table>
<thead>
<tr>
<th>Study</th>
<th>Artemisinin #Stillbirth/ #Total</th>
<th>Quinine #Stillbirth/ #Total</th>
<th>Adjusted Hazard Ratio (95%CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artemisinin vs Quinine, 1st Trimester</td>
<td>10/ 534</td>
<td>5/ 105</td>
<td>0.29 (0.08, 1.02)</td>
<td>0.053</td>
</tr>
<tr>
<td>IPD Africa</td>
<td>0/ 120</td>
<td>6/ 510</td>
<td>- (-, -)</td>
<td>-</td>
</tr>
<tr>
<td>SMRU Thailand</td>
<td></td>
<td></td>
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Safety of the artemisinins in the first trimester
Meta-analysis: Artemisinin N=709; Quinine N=948
Pregnancy loss: Miscarriage or stillbirth

Combining miscarriage and stillbirth as ‘pregnancy loss’

• HR = 0.58 (95% CI 0.36, 1.02), \( p = 0.099 \)
  – i.e. The hazard of losing a pregnancy is about 42% lower in women treated with artemisinins compared to women treated with 7 days of quinine
  – But difference not significant
Safety of the artemisinins in the first trimester Meta-analysis: Artemisinin N=709; Quinine N=948

Major birth defects

• All within the expected range (1-2%)

• No difference between artemisinins and quinine
  – Artemisinins: 1.5% (95% CI 0.6%-3.5%)
  – Quinine: 1.2% (95% CI 0.6%-2.4%)

• Also no difference in the distribution across organ system classes between treatment groups, but numbers were small
Safety of the artemisinins in the first trimester
Summary Meta-analysis

- In Africa, ACT exposures very common in early pregnancy

- Compared to quinine, the artemisinins are not associated with an increased risk of spontaneous abortions, or stillbirths, or birth defects
  - No difference in miscarriage or stillbirth rates
  - No difference in birth defects
Safety of the artemisinins in the first trimester

Conclusions

• Malaria in 1\textsuperscript{st} trimester is known to be associated with pregnancy loss (miscarriage or stillbirth)

• ACTs more effective than quinine, well tolerated and already widely used in 1\textsuperscript{st} trimester

• Quinine is not well tolerated and poor compliance to 7 day treatment $\rightarrow$ untreated malaria

• Safety data is limited but doesn’t indicate any safety signal with artemisinins in humans

• Targeted surveillance needed to be able to detect signal for congenital malformations

• Artemisinins should be added as treatment option in 1\textsuperscript{st} trimester pregnancy
Safety of the artemisinins in the first trimester

Limitations

• Limited statistical power to detect differences by individual regimens or brands
  – Conclusions are based on ‘class’ effect of artemisinins
  – 90% were artemether-lumefantrine

• Limited statistical power to detect differences in birth defects
  – Not designed to assess cardio-vascular effects

• But, …. represents 25 years of work, largest safety cohort followed prospectively to date for antimalarials
WHO Evidence Review Group (ERG) & Malaria Policy Advisory Committee (MPAC)

July 2015: WHO convened an Evidence Review Group for malaria in pregnancy

September 2015: Data further reviewed by MPAC:

“….. MPAC recommends the review of the WHO Guidelines for the treatment of malaria to consider the timely inclusion of ACT as a first-line therapeutic option for (first trimester) uncomplicated falciparum malaria.”
Summary ACTs vs quinine

- **Malaria** more severe in pregnancy: requires prompt, safe and effective treatment

- **Efficacy**: ACTs are
  - more effective
  - better tolerated
  - easier to administer (3 vs 7 days)

- **Safety**: Compared to quinine, artemisinins are not associated with an increased risk of spontaneous abortions, or stillbirths, or congenital malformations

- **Conclusion**: Risk-benefit balance in favour of ACTs; should replace quinine in all 3 trimesters of pregnancy

- **Policy**: WHO potential policy update may include use of ACTs in 1st trimester (Dec ‘17)
Investigators

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Safety of artemisinins in first trimester of prospectively followed pregnancies: an observational study

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Summary
Background Artemisinins, the most effective antimalarials available, are not recommended for falciparum malaria during the first trimester of pregnancy because of safety concerns. Therefore, quinine is used despite its poor effectiveness. Assessing artemisinin safety requires weighing the risks of malaria and its treatment. We aimed to assess the effect of first-trimester malaria and artemisinin treatment on miscarriage and major congenital malformations.

Interpretation First-trimester falciparum and vivax malaria both increase the risk of miscarriage. We noted no evidence of an increased risk of miscarriage or of major congenital malformations associated with first-line treatment with an artemisinin derivative compared with quinine. In view of the low efficacy of quinine and wide availability of highly effective artemisinin-based combination therapies, it is time to reconsider first-trimester antimalarial treatment recommendations.
RESEARCH ARTICLE

First-trimester artemisinin derivatives and quinine treatments and the risk of adverse pregnancy outcomes in Africa and Asia: A meta-analysis of observational studies

Stephanie Dellicour1,*, Esperança Sevène2,3,4, Rose McGready4,5, Halidou Tinto6, Dominic Moshag7, Christine Manyando8, Stephen Rulisa9, Meghna Desai10, Peter Ouma11, Martina Onoko11, Anifa Vala3, Maria Rupérez3,12, Eusébio Macete9, Clara Menéndez3,12, Seydou Nakanabo-Diallo6, Adam Kazienga6, Innocent Valéa6, Gregory Calip13, Orvalho Augusto3, Blaise Genton14,15, Eric M. Njunju16, Kerryn A. Moore17,18, Umberto d’Alessandro19,20,21, Francois Nosten15, Feiko ter Kuile1, Andy Stergachis22,23,*

Abstract

Background
Animal embryotoxicity data, and the scarcity of safety data in human pregnancies, have pre-
vented artemisinin derivatives from being recommended for malaria treatment in the first tri-

Conclusions
Compared to quinine, artemisinin treatment in the first trimester was not associated with an increased risk of miscarriage or stillbirth. While the data are limited, they indicate no differ-
ence in the prevalence of major congenital anomalies between treatment groups. The bene-
fits of 3-d artemisinin combination therapy regimens to treat malaria in early pregnancy are likely to outweigh the adverse outcomes of partially treated malaria, which can occur with oral quinine because of the known poor adherence to 7-d regimens.
Funding

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• European Developing Clinical Trials Partnership (EDTCP)