Malaria prevention in Pregnancy: Facing the challenges of limited drug options

By

TK Mutabingwa
PE Duffy
Fried Michal
Malaria in pregnancy: some statistics on burden

- 50 M women pregnant per year in areas of malaria transmission
- MIP responsible for 6 deaths per 1000 live births across Africa
- Effective prevention reduces infant mortality by up to 18%
- MIP important preventable cause of maternal and perinatal morbidity & mortality
Malaria in Pregnancy: Public Health Importance

- Pregnant women have higher densities and prevalence of parasitemia
- Stable transmission:
  - Women in 1st & 2nd pregnancies most affected
  - Parasitemia prevalence highest 20-36 weeks
  - Clinical malaria higher in 2nd and 3rd trimesters
HIV and Malaria in Pregnant Women

- HIV-positive women have higher prevalence and densities of peripheral and placental parasitemia
- Effect seen in HIV-positive women of all gravidities
MOMS Project Findings in Muheza - Hidden Burden

- Placental malaria
  - increases risks of malaria hospitalization throughout early childhood
  - increases infant mortality
  - increases risk of maternal hypertension
- Reported usage of SP as IPTp
  - decreases placental malaria rates only after first pregnancy
  - marginal benefits on birth weight
Cost-effective tools to fight malaria during pregnancy

- **Treatment**
  - *Case management*

- **Prevention**
  - *Intermittent preventive treatment (IPTp)*
  - *Insecticide-treated nets (ITNs)*
Intermittent Preventive Therapy

Benefit:

Mothers → less malaria
     less anaemia

Infants → fewer LBWs
     lower IMR

Conception  10  Quickening  20  30  Birth

Rx  Rx
Two major issues for use of antimalarials in IPT during pregnancy:

Is the drug toxic to the woman or the foetus during 2nd or 3rd trimesters, or to the infant during lactation?

Is the drug use strategy and its implementation likely to have a benefit--to reduce the burden of malaria during pregnancy?

What are the risks?
Limited Drug Options: Why?

- Few new drugs under development
- Drug resistance
- Limited knowledge on safety
- Systematic exclusion of pregnant women from clinical drug trials
Countries with at least one study indicating chloroquine total failure rate ≥ 20%

Countries with at least one study indicating chloroquine total failure rate ≥ 10%

No recent data available
Countries with at least one study indicating mefloquine total failure rate ≥ 20%
Countries with at least one study indicating mefloquine total failure rate ≥ 10%
Mefloquine total failure rate < 10%
No failure reported
No recent data available
Understanding safety, efficacy and effectiveness

- Clinical drug trials in pregnancy
- Drug kinetics
- Pharmacovigilance
- Post-marketing surveillance
IPTp Studies in Morogoro, Tanzania

- Comparison of three IPTp regimens for efficacy and safety in pregnant women and their offspring. *Led by TK Mutabingwa*.
- Effect of IPTp regimens on malaria-related immunity and outcomes during early childhood. *Led by PE Duffy*. 
The IPTp studies in Morogoro, Tanzania

- Study regimens
  - SP
  - SP + Azithromycin
  - Mefloquine
  - ? Chloroquine + Azithromycin
Study Center
Morogoro Regional Hospital

MOMS Laboratory in Morogoro
Active, prospective surveillance

Pregnant woman exposed - ACT or not

Hospital

Antenatal Clinic

Health Centre

Dispensary

Follow up during pregnancy & after delivery

Assessment

- Fetal viability
- % spontaneous abortions
- % intrauterine deaths/stillbirths
- % anomalies in live borns, stillborns, in-utero deaths (ACT vs antimalarials) by exposure interval, dose
- Determination of maternal mortality (ACT vs antimalarials)
- Determination of neonatal mortality

• Deterioration proportion of LBW (ACT vs. other antimalarials)
• Assess developmental delays ACT vs. other antimalarials
• Not able to address issue of fetal resorption in 1st trimester
Contributing to Prospective surveillance - Registry

- Active prospective surveillance
- Multi-center registry
  - Enrollment of all exposed women
  - Bangladesh, Zanzibar, Senegal, other countries introducing ACT where prospective monitoring in pregnancy is possible, likely to be complete
- Links to general Pharmacovigilance
- Links to “Making Pregnancy Safer”
Program opportunity

In most countries of Africa >70% of pregnant women attend antenatal clinics
Knowledge gaps

- What is the risk-benefit of IPTp in malaria
  - For antimalarials given as mono-therapy (e.g. SP) or in combination

- Is there an added benefit from ACTs in IPT?

- There are research studies planned for IPT
  Where? What drugs, comparators, endpoints

- Can planned endpoints be pooled to strengthen power, understanding of benefit

- Can planned studies include detailed safety monitoring of outcomes
COUNTRIES IMPLEMENTING ACT POLICIES IN THE WHO AFRICAN REGION

ACT Policy = 10

EMRO Region
Recently completed Clinical Drug Trials in Pregnancy

- Treating symptomatic malaria, Muheza, Tanzania (TK Mutabingwa et al)
  - Regimens: SP, SP+AQ, AQ+AS, LapDap

- Treating malaria infection, Nkoranza, Ghana (Harry Tagbor et al)
  - Regimens: CQ, SP, AQ, SP+AQ
  - Broad objective (for both studies): Efficacy, safety & tolerability.
Parasitological failure rate, pregnant women cf children <5, Muheza

Parasitological failure %

- SP
- AQ+SP
- AQ+AS
- Lapdap
- AL

- Pregnant women
- Children 2002-4
Summary and Conclusions

- Malaria in pregnancy remains a major disease of public health importance despite identified control tools.
- Drug resistance limits effectiveness of SP-IPTp, necessitating urgent search for alternative drug regimens.
- Response to drug treatments in pregnancy differs from those in children.
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