Antenatal MMS in Bangladesh: The JiVitA-3 Trial

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The 450 km² JiVitA Project Area

18 Unions
4 x area of Wash DC
Population: ~600,000
Density: 1130 /km²
60 Field Offices
750 Project Staff
Registered under JHUB
With NGO Affairs Bureau
MOA with MOHFW
Registered with DGDA

Labrique AB et al BMC Trials 2011
Original Investigation

Effect of Maternal Multiple Micronutrient vs Iron-Folic Acid Supplementation on Infant Mortality and Adverse Birth Outcomes in Rural Bangladesh

The JiVitA-3 Randomized Trial

Keith P. West Jr, DrPH; Abu Ahmed Shamim, MSc; Sucheta Mehra, MS; Alain B. Labrique, PhD; Hasmot Ali, MBBS, MPH; Sajjuddin Shaikh, PhD, MPH; Rolf D. W. Klemm, DrPH; Lee S-F. Wu, MHS; Maithilee Mitra, MS; Rezwanul Haque, MA; Abu A. M. Hanif, MBBS; Allan B. Massie, PhD; Rebecca Day Merrill, PhD; Kerry J. Schulze, PhD; Parul Christian, DrPH, MSc

JAMA 2014;312(24):2649-2658.

Funded by the Bill and Melinda Gates Foundation
GH614 Global Control of Micronutrient Deficiency
Maternal Multiple Micronutrient vs Iron-Folic Acid Supplementation Trial (JiVitA-3)

West KP et al JAMA 2014
1. Extended gestation age by 0.30 weeks (~2 days)
2. This led to significant increases in infant size at birth: in weight (54 g) and length (0.2 cm); arm, chest and head circumferences (0.1-0.25 cm); and Ponderal Index (0.2)

West KP Jr, Shamim AA, Mehra S et al JAMA 2014
The extended gestation led to a...
15% reduction in preterm birth

Extended gestation increased birth size and led to a...
12% reduction in LBW

But no significant effect on SGA (ie, no acceleration in fetal growth)

**Table 3. Risks of Preterm and Low-Weight Births Among Singletons by Maternal Supplement Allocation**

<table>
<thead>
<tr>
<th></th>
<th>Iron-Folic Acid Group</th>
<th>Multiple Micronutrient Group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preterm (gestational age &lt;37 wk)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. with gestational age known</td>
<td>13,333</td>
<td>13,475</td>
</tr>
<tr>
<td>No. born preterm</td>
<td>2,912</td>
<td>2,510</td>
</tr>
<tr>
<td>Rate per 100 live births</td>
<td>21.8</td>
<td>18.6</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>1 [Reference]</td>
<td>0.85 (0.80-0.91)</td>
</tr>
<tr>
<td>P value*</td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Low birth weight (&lt;2500 g)</strong>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. with birth weight known</td>
<td>10,530</td>
<td>10,642</td>
</tr>
<tr>
<td>No. with birth weight &lt;2500 g</td>
<td>4,809</td>
<td>4,725</td>
</tr>
<tr>
<td>Rate per 100 live births</td>
<td>45.7</td>
<td>40.2</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>1 [Reference]</td>
<td>0.88 (0.85-0.91)</td>
</tr>
<tr>
<td>P value*</td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Small for gestational age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. with gestational age and size</td>
<td>10,099</td>
<td>10,161</td>
</tr>
<tr>
<td>No. born small for gestational age</td>
<td>6,479</td>
<td>6,405</td>
</tr>
<tr>
<td>Rate per 100 live births</td>
<td>64.2</td>
<td>63.0</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>1 [Reference]</td>
<td>0.98 (0.96-1.01)</td>
</tr>
<tr>
<td>P value*</td>
<td></td>
<td>.13</td>
</tr>
</tbody>
</table>

*West KP Jr, Shamim AA, Mehra S et al JAMA 2014*
Had no overall effect on infant mortality to 6 mo of age (5% reduction, p=0.36)

or on neonatal mortality (2% reduction, p=0.78),

...or on post-neonatal mortality to 6 mo: a 19% reduction was not SS (RR=0.81, p=0.11)

reduced risk of still birth by 11% (RR=0.89, p=0.02)
Effects of MM vs IFA on Infant Mortality

15% lower mortality in girls, not boys

Males
MM: n=7414
IFA:   n=7204

Females
MM: n=6935
IFA:   n=6959

Blue: MM
Black: IFA
RDA amounts of vit A, D, E, B1, B2, B3, B6, folic acid, B12, C, Fe, Zn, Cu, Se, I vs Fe and folic acid alone (MM vs IFA)

- 44,567 pregnancies; 28,516 live births
- Increased GA by 0.3 weeks and thus: birth weight by 54 g, therefore -
  - Reduced preterm by 15%
  - Reduced LBW by 12%
  - Reduced still birth by 11%
  - Reduced infant mortality – in girls but not boys
  - Led to a healthier pregnancy & infant

JAMA 2014;312(24):2649-2658.

Funded by the Bill and Melinda Gates Foundation

DSM through Sight & Life produced 16 m supplements & provided technical assistance
Micronutrient Deficiencies in 3\textsuperscript{rd} Trimester by Supplement Group, JiVitA-3, Bangladesh

- No effects on iron or folate status
- Reductions in, but not elimination of, multiple micronutrient deficiencies

Schulze et al. J Nutr 2019
Micronutrients are Essential Throughout Pregnancy & Gestation

Maternal Multiple Micronutrient Supplementation Stabilizes Mitochondrial DNA Copy Number in Pregnant Women in Lombok, Indonesia

Lidwina Priliani,1,2 Elizabeth L Prado,3,4 Restuadi Restuadi,1,5 Diana E Waturangi,2 Anuraj H Shankar,3,6 and Safarina G Malik1

TABLE 3 The Δ mtDNA-CN proportions of 108 pregnant women enrolled in the Supplementation with Multiple Micronutrients Intervention Trial study by supplementation group

<table>
<thead>
<tr>
<th>MtDNA-CN change</th>
<th>MMN (n = 54)</th>
<th>IFA (n = 54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 10% decrease</td>
<td>14 (25.9)</td>
<td>13 (24.1)</td>
</tr>
<tr>
<td>No change</td>
<td>12 (22.2)</td>
<td>3 (5.6)</td>
</tr>
<tr>
<td>&gt; 10% increase</td>
<td>27 (51.9)</td>
<td>38 (70.4)</td>
</tr>
<tr>
<td>p2</td>
<td></td>
<td>0.021</td>
</tr>
</tbody>
</table>

Antenatal Micronutrients and the Mitochondrial Genome: A Glimpse of Future Nutritional Investigation

Sun Eun Lee,1 Michael F Fenech,2 and Keith P West, Jr1

MMS may improve health of materno-placental mitochondria and, thus, bioenergetics of pregnancy
Policy Implications: Antenatal Multiple Micronutrient vs IFA Supplementation

- Antenatal MMN supplementation –
  - Extends gestation by 2-3 days, thus reducing risks of preterm birth, low birth weight and still birth by ~10-15%
  - May also reduce mortality by 10-15%
  - May have long term effects on offspring: on cognition, metabolic syndrome and growth
- Multiple micronutrient supplementation should be combined with adequate prenatal and essential obstetric and neonatal care
Acknowledgements

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