Screening For Peripartum Cardiomyopathies Using An AI-Enhanced Digital Stethoscope: A Randomized Clinical Trial

NCT05438576

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DISCLOSURES

• Dr. Adedinsowo is supported by the Mayo Building Interdisciplinary Research Careers in Women’s Health (BIRCWH) Program funded by the National Institutes of Health [grant number K12 HD065987].

• This trial was funded by Mayo Clinic (Centers for Digital Health and Community Health and Engagement Research) and in part by the Mayo Clinic BIRCWH Program

• Portable ECG, phonocardiogram recordings, and AI predictions using the digital stethoscope were extracted by the Eko Health team and sent to the coordinating center for analysis. Eko Health had no role in study design, data collection, data analysis, or data interpretation.
BACKGROUND

• Cardiovascular disease is a leading cause of death during pregnancy and postpartum

• In the U.S., cardiomyopathy is a key contributor
  • 2nd leading cause of death among Black women
  • Leading cause of death in the late postpartum period for all women

• Nigeria has the highest reported incidence of peripartum cardiomyopathy – 1 in 100 livebirths

• Diagnosis is challenging which leads to delayed recognition

• Symptoms due to physiologic adaptations of pregnancy often overlap with heart failure

BACKGROUND

- Global maternal mortality has remained either stagnant or worsened in many regions of the world
- Sub-Saharan Africa bears the highest burden of maternal deaths (70%)
  - South Sudan
  - Chad
  - Nigeria
    - highest absolute # of deaths @ 82,000 in 2020
- US maternal mortality rate is higher than other developed countries – trending up over the past 3 decades
U.S. MATERNAL MORTALITY
Events per 100,000 live births

Figure re-created using data from the National Center for Health Statistics. Hoyert, Donna L. Maternal Mortality Rates in the United States, 2021. Published: 03/16/2023. URL: https://stacks.cdc.gov/view/cdc/124678
METHODS

• We designed an open label, randomized, pragmatic clinical trial to evaluate the impact of AI guided screening on the diagnosis of pregnancy related left ventricular dysfunction (LVSD)

• Pregnant and postpartum women enrolled at six (6) sites were randomized in a 1:1 fashion to
  • Control arm
  • Intervention arm

• The primary endpoint was detection of LVSD, defined as left ventricular ejection fraction (LVEF) <50% by echocardiography.

• Trial Registration number: NCT05438576
METHODS

• ‘Attention’ Control arm: Standard 12-lead ECG* + Usual care

• Intervention: Standard 12-lead ECG* + Artificial intelligence enabled digital stethoscope recordings (ECG + phonocardiogram) at the point of care with AI results for LVSD available in real-time
  - Digital stethoscope recordings taken at:
    - V2 position
    - Angled
    - Handheld
  - Baseline echocardiograms obtained as part of the study protocol to assess the diagnostic performance of the AI-ECG

• The control arm received standard 12-lead ECGs* (including AI-predictions for age and sex) to control for the potential benefit that receiving an ECG might introduce to the study

*Attia et al. Age and Sex Estimation Using Artificial Intelligence From Standard 12-Lead ECGs. Circ Arrhythm Electrophysiol. 2019 Sep;12(9)
RESULTS

587 women were assigned to the intervention arm and 608 to the control arm.

The primary analysis was conducted using the modified intention to treat principle. To be included in the analysis, the participant needs to be randomized and complete at least the baseline assessments and testing.
## RESULTS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
<th>Intervention Arm (N=587)</th>
<th>Control Arm (N=608)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (IQR), years</td>
<td>1,195</td>
<td>31 (27-35)</td>
<td>31 (26-35)</td>
</tr>
<tr>
<td>Race (Black) - no. (%)</td>
<td>1,195</td>
<td>587 (100.0%)</td>
<td>608 (100.0%)</td>
</tr>
<tr>
<td>Status at Study Entry - no. (%)</td>
<td>1,195</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Pregnant</td>
<td>1,195</td>
<td>423 (72.1%)</td>
<td>451 (74.2%)</td>
</tr>
<tr>
<td>- Postpartum</td>
<td>1,195</td>
<td>164 (27.9%)</td>
<td>157 (25.8%)</td>
</tr>
<tr>
<td>Weight (IQR), kg</td>
<td>1,195</td>
<td>70 (60-80)</td>
<td>70 (60-83)</td>
</tr>
<tr>
<td>Height (IQR), cm</td>
<td>1,195</td>
<td>161 (157-165)</td>
<td>161 (157-165)</td>
</tr>
<tr>
<td>SBP (IQR), mmHg</td>
<td>1,193</td>
<td>110 (100-120)</td>
<td>110 (100-120)</td>
</tr>
<tr>
<td>DBP (IQR), mmHg</td>
<td>1,193</td>
<td>70 (60-80)</td>
<td>70 (60-80)</td>
</tr>
<tr>
<td>Resting heart rate (IQR), bpm</td>
<td>1,195</td>
<td>87 (80-95)</td>
<td>88 (80-95)</td>
</tr>
<tr>
<td>Hemoglobin (IQR), g/dL</td>
<td>1,016</td>
<td>11 (10-12)</td>
<td>11 (10-12)</td>
</tr>
<tr>
<td>Hematocrit (IQR), %</td>
<td>1,056</td>
<td>33 (30-35)</td>
<td>33 (30-35)</td>
</tr>
<tr>
<td>Urinalysis + for protein - no. (%)</td>
<td>1,147</td>
<td>61 (10.9%)</td>
<td>62 (10.6%)</td>
</tr>
<tr>
<td>Chronic hypertension</td>
<td>1,195</td>
<td>27 (4.6%)</td>
<td>23 (3.8%)</td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td>1,195</td>
<td>24 (4.1%)</td>
<td>28 (4.6%)</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>1,194</td>
<td>19 (3.2%)</td>
<td>18 (3.0%)</td>
</tr>
<tr>
<td>Eclampsia</td>
<td>1,195</td>
<td>6 (1.0%)</td>
<td>4 (0.7%)</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>1,195</td>
<td>5 (0.9%)</td>
<td>12 (2.0%)</td>
</tr>
</tbody>
</table>
RESULTS (Primary)

A total of 1,195 participants enrolled across six teaching hospital in Nigeria were included in the final analysis.

The primary endpoint was detected in

- 24 (4.1%) patients in the intervention arm and
- 11 (1.8%) patients in the control arm.

AI-guided screening (digital stethoscope maximum prediction across all locations recorded) doubled cardiomyopathy detection.

Odds ratio 2.3 (95% CI: 1.1, 4.8; p=0.019)
In the intervention arm, the digital stethoscope had AUC values of

- 0.95 for detection of LVEF <50% and
- 0.98 for detection of LVEF <40%

RESULTS (Secondary)

<table>
<thead>
<tr>
<th>A: LVEF &lt;50%</th>
<th>B: LVEF &lt;40%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>Sensitivity</td>
</tr>
<tr>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>0.50</td>
<td>0.75</td>
</tr>
<tr>
<td>0.75</td>
<td>1.00</td>
</tr>
</tbody>
</table>

AUC: 0.952 (0.917, 0.987)
Accuracy: 80.4% (77.0%, 83.5%) (472/587)
Sensitivity: 92.3% (74.9%, 99.1%) (24/26)
Specificity: 79.9% (76.3%, 83.1%) (448/561)
PPV: 17.5% (11.6%, 24.9%) (24/137)
NPV: 99.6% (98.4%, 99.9%) (448/450)

AUC: 0.981 (0.967, 0.994)
Accuracy: 80.1% (76.6%, 83.2%) (470/587)
Sensitivity: 100.0% (83.2%, 100.0%) (20/20)
Specificity: 79.4% (75.8%, 82.6%) (450/567)
PPV: 14.6% (9.2%, 21.6%) (20/137)
NPV: 100.0% (99.2%, 100.0%) (450/450)
RESULTS (Secondary)

Analysis performed to test for differential effects by strata.

We anticipated sparse data with stratification due to a low number of events overall.

The direction of the effect estimates were similar across strata

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Overall</th>
<th>Control Arm</th>
<th>Intervention Arm</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Region</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northern Nigeria</td>
<td>395</td>
<td>31/395</td>
<td>11/202</td>
<td>20/193</td>
<td>p=0.16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7.8% (5.4%, 11.0%)</td>
<td>5.4% (2.7%, 9.5%)</td>
<td>10.4% (6.4%, 15.6%)</td>
<td>2.0 (0.9, 4.3)</td>
</tr>
<tr>
<td>Southern Nigeria</td>
<td>800</td>
<td>4/800</td>
<td>0/406</td>
<td>4/394</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.5% (0.1%, 1.3%)</td>
<td>0.0% (0.0%, 0.9%)</td>
<td>1.0% (0.3%, 2.6%)</td>
<td>9.4 (0.5, 174.6)</td>
</tr>
<tr>
<td><strong>Age group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p=0.08</td>
</tr>
<tr>
<td>&lt;30 years</td>
<td>521</td>
<td>21/521</td>
<td>9/267</td>
<td>12/254</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.0% (2.5%, 6.1%)</td>
<td>3.4% (1.6%, 6.3%)</td>
<td>4.7% (2.5%, 8.1%)</td>
<td>1.4 (0.6, 3.4)</td>
</tr>
<tr>
<td>30+ years</td>
<td>674</td>
<td>14/674</td>
<td>2/341</td>
<td>12/333</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.1% (1.1%, 3.5%)</td>
<td>0.6% (0.1%, 2.1%)</td>
<td>3.6% (1.9%, 6.2%)</td>
<td>6.3 (1.4, 28.5)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p=0.22</td>
</tr>
<tr>
<td>Hausa</td>
<td>337</td>
<td>27/337</td>
<td>10/174</td>
<td>17/163</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>8.0% (5.3%, 11.4%)</td>
<td>5.7% (2.8%, 10.3%)</td>
<td>10.4% (6.2%, 16.2%)</td>
<td>1.9 (0.8, 4.3)</td>
</tr>
<tr>
<td>Other</td>
<td>858</td>
<td>8/858</td>
<td>1/434</td>
<td>7/424</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.9% (0.4%, 1.8%)</td>
<td>0.2% (0.0%, 1.3%)</td>
<td>1.7% (0.7%, 3.4%)</td>
<td>7.3 (0.9, 59.3)</td>
</tr>
<tr>
<td><strong>Status at Entry</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p=0.96</td>
</tr>
<tr>
<td>Pregnant</td>
<td>874</td>
<td>3/874</td>
<td>1/451</td>
<td>2/423</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.3% (0.1%, 1.0%)</td>
<td>0.2% (0.0%, 1.2%)</td>
<td>0.5% (0.1%, 1.7%)</td>
<td>2.1 (0.2, 23.7)</td>
</tr>
<tr>
<td>Postpartum</td>
<td>321</td>
<td>32/321</td>
<td>10/157</td>
<td>22/164</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>10.0% (6.9%, 13.8%)</td>
<td>6.4% (3.1%, 11.4%)</td>
<td>13.4% (8.6%, 19.6%)</td>
<td>2.3 (1.0, 5.0)</td>
</tr>
<tr>
<td><strong>HDP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p=0.07</td>
</tr>
<tr>
<td>No</td>
<td>1,052</td>
<td>29/1,052</td>
<td>11/536</td>
<td>18/516</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.8% (1.9%, 3.9%)</td>
<td>2.1% (1.0%, 3.6%)</td>
<td>3.5% (2.1%, 5.5%)</td>
<td>1.7 (0.8, 3.7)</td>
</tr>
<tr>
<td>Yes</td>
<td>143</td>
<td>6/143</td>
<td>0/72</td>
<td>6/71</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.2% (1.6%, 8.9%)</td>
<td>0.0% (0.0%, 5.0%)</td>
<td>8.5% (3.2%, 17.5%)</td>
<td>14.4 (0.8, 260.4)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>1,195</td>
<td>35/1,195</td>
<td>11/608</td>
<td>24/587</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.9% (2.0%, 4.0%)</td>
<td>1.8% (0.9%, 3.2%)</td>
<td>4.1% (2.6%, 6.0%)</td>
<td>2.3 (1.1, 4.8)</td>
</tr>
</tbody>
</table>
STRENGTHS

Strengths/Advantages:

• Pragmatic design, engaged staff, rapid accrual
• Large, prospective trial evaluating an AI intervention in an obstetric sample
• Use of a portable, battery-operated device
• Real-time AI results
• Validation of the AI-intervention in the intervention arm
• Enrollment of a predominantly Black, ethnically, and regionally diverse, obstetric population in Nigeria
LIMITATIONS

Limitations

• Pragmatic design – participants seen at teaching hospitals (cardiologist + echocardiography)
  • Cardiomyopathy prevalence at tertiary centers may not be reflective of the general obstetric patient population in Nigeria

• Selected cutpoint (LVEF <50%) did not match categorizations used at model derivation
  • Original model developed by Mayo Clinic was trained to detect LVEF ≤ 35% and then retrained using single leads to detect LVEF < 40% for use with the digital stethoscope
CONCLUSION

1. AI-guided screening resulted in double the number of cardiomyopathy cases diagnosed (OR: 2.3) suggesting that up to half are likely undetected with usual care.

2. AI-guided screening using a digital stethoscope is effective for detection of left ventricular systolic dysfunction among pregnant and postpartum women (AUC 0.95, Sens 92%, Spec 80%)

3. This intervention has the potential to improve cardio-obstetric care by reducing delays in the diagnosis of a life-threatening but treatable condition.
THANKS TO OUR STUDY TEAM

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