A prospective, observational study on causes of stillbirths in African women from South Africa.

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Overview

» Background and rationale
» Aims and study setting
» Methods
» Results
» Conclusion
» Acknowledgements

Background and Rationale

» Approximately 2.6 million stillbirths in 2015, 90% of which occurred in low-middle income countries
» Causes of stillbirths are premised on use of vital registration and verbal autopsy data that has been reported to be of poor quality and inconsistence
» A systematic review on causes of stillbirths (2009-2016) concluded that 41-44% if stillbirths in LMIC are still unexplained, however verbal autopsy and retrospective hospital audit reviews concluded that 16% are due to infection
» Most stillbirth studies have been absent of biological investigation, making it difficult to specify causes of infection and diagnosis

Reinebrant et al., BJOG. 2018;125(2):212-24.
Aims and study setting

**AIMS**
- Prospective, hospital-based observational study
- To determine the cause of stillbirths among South African women, specifically focusing on investigating the role of invasive bacterial infections

**SETTING**
- Chris Hani Baragwanath Academic Hospital (CHBAH), Soweto, Johannesburg
- Public sector tertiary, teaching hospital, >3000 bed.
- ~32,000 deliveries per annum in Soweto, ~70% at CHBAH (~60/day)
- High risk deliveries and patients with concerning signs referred to CHBAH from community PHC
- Stillbirth rate: 22.5/1000 births

Methods

- Prospective, hospital-based study from October 2014 – November 2015 in Soweto, South Africa
- Women (≥18 years) with intra-uterine foetal death (IUFD), or who delivered a stillbirth were identified by study staff at CHBAH (labour ward, antenatal)
- Consent obtained from mother to investigate stillborn infant and placenta
- ≥22 weeks gestational age and/or ≥500 grams birth-weight
- Maternal medical record review,
- Placental macroscopic and histopathology investigation
- Stillbirth blood culture (cord/heart stab)

Methods II

- Data were entered into a study-specific database
- Parents were offered counselling and invited back to research unit to discuss results of investigations performed

Classification of cause of stillbirth

- Individual cases were reviewed by at least two obstetricians and was classified using a modified Stillbirth Collaborative Research Network (SCRN) classification system
- The SCRN classification records conditions as being “present” but not necessarily contributory to the stillbirth, or as a “possible” or “probable” cause of death with varying level of evidence
- Bacteria previously reported as possible causes of stillbirth evaluated for causality
- results were interpreted with circumspection

**Laboratory Methods**

**Placentas**
- Retrieved from delivery room, weighed and a wedge of placental parenchyma and membranes resected and placed in a sterile container
- Remaining placentas, membranes and cord were immersed in 10% buffered formalin and transported to Lancet Laboratories
- Weighed, measured and examined macroscopically
- A histopathologist processed for routine haematoxylin and eosin staining using standard protocols

**Stillborn Blood**
- Cord or skin surface was decontaminated with alcohol solution
- Cord/ stillborn heart blood (0.5-5ml) was inoculated into BacT/ALERT PF Plus bottle and evaluated using the BacT/Alert microbial system
- Positive cultures from all samples were gram stained and further identification using manual methods
- Syphilis screening of the stillbirth blood was performed at the NHLS
  - Treponema Pallidum Haemagglutination Assay (TPHA) and positive samples confirmed using Rapid Plasma Reagent
- An aliquot of serum was archived at -70°C Celsius

**Study flowchart:**

- Stillbirth rate: 22.3/1000 births
- Median age – 27 years old
- 18% of mothers were 35 years of age or older
- 16.9% of mothers are obese
- 6.5% of mothers have had previous stillbirth/s
- 74.1% of mothers delivered vaginally, while 25.9% delivered CS
- 27.9% of mothers are HIV infected, with 91.5% of them being on ARVs
- 31.6% of mothers experienced pregnancy induced hypertension
Clinical features of stillbirths:
- 18% of fetuses had intrauterine growth restriction
- 60.2% BW ≥ 1500g
- 22.9% 33–37 weeks
- 36.7% Term

Classification of stillbirths
- 2/3 macerated,
- 1/3 fresh stillbirth

Placental findings
- Cord abnormalities were more common among intrapartum (5.6%) than antepartum cases (0%; p=0.002)
- Presence of chorioamnionitis was histologically confirmed in 25.3% of placentas, 95.9% categorized as acute
- The extent of placental inflammatory cellular infiltrate was available for 78.7% (59/75) of placentas with chorioamnionitis:
  - Grade II in 42.4%
  - Grade III in 11.9%
- Upon placental dissection, infarcts were evident in 50.3% of placentas

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- Grade II in 42.4%
- Grade III in 11.9%
- Upon placental dissection, infarcts were evident in 50.3% of placentas.
**Blood bacterial culture**

- 37.3% (n=81) stillbirths had bacteria isolated from blood
- 54.3% (n=44) of these samples had pure growth of the probably pathogenic bacteria

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>% of SB blood with bacteria plus contaminant</th>
<th>% of SB with Pure growth of bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterococcus faecalis</td>
<td>13.8%</td>
<td>7.7%</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>10.4%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Group B streptococci (GBS)</td>
<td>5.7%</td>
<td>4.0%</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>3.4%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>4.0%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Enterobacter sp</td>
<td>2.0%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Enterococcus faecium</td>
<td>1.3%</td>
<td>1.0%</td>
</tr>
</tbody>
</table>

**Placenta bacterial culture**

- 61.9% of placentas had potentially pathogenic bacteria isolated
- 21.1% of these samples had pure growth of probably pathogenic bacteria

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</tbody>
</table>

**Causes of stillbirth**

1. Maternal medical conditions – 21.5% 18.8% hypertensive disorders 2% diabetes
2. Placental/foetal infections – 19.5% 15.8% foetus invasive bacterial infection
3. Pathological placental conditions – 9.1% 9.1% inflammation 8.7% circulatory abnormalities
4. Clinical obstetric complications – 18.1% 15.1% abruptio placenta
Conclusion

» Majority of the causes of the stillbirths were potentially preventable, treatable, or for which interventions could be developed
» The inclusion of placental investigation in the study, generally absent from previous published studies from LMIC, resulted in 19.1% of stillbirth causes being attributed to pathological placental conditions
» Limitations of our study included absence of complete diagnostic autopsy and karyotyping, which were useful in identifying a cause of stillbirth
» Observations highlight the need for further research investigating causes of stillbirths in diverse LMIC settings.
» A maternal vaccine against GBS may reduce GBS-related stillbirths.

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