“Do No Harm” – Myth or Mandate?: Recent Experiences with Preterm Interventions

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Overview

- The principle: “Do no harm”
- Signals, severity and setting
- Learning from current interventions for management of preterm labor and care of the preterm newborn
- Highlight a couple of preterm birth related conundrums
Primum non nocere

- Latin phrase that means “first, do no harm”.
- From the Greek: ἐπὶ δηλήσει δὲ καὶ ἁδική ἐὑρξεῖν, meaning “to abstain from doing harm”, found in The Hippocratic Oath (5th Century BCE)

12th-century Byzantine manuscript of the Hippocratic Oath.
1.2 million intrapartum stillbirths

>1 million neonatal deaths

~113,000 maternal deaths

75% neonatal deaths

48 hrs around birth

Intrapartum stillbirths
Number of deaths in women
Number of deaths in neonates

When are deaths occurring?

Labor and the day of birth is the time of greatest risk of death and disability

Source: Lancet Every Newborn series, paper 2, 2014
Severity of PTB - Preterm Births by Gestational Age and Region for 2010

- 5% of PTB are born less than 28 weeks.
- 10% of PTB are born from 28 to less than 32 weeks.
- 85% of PTB are born from 32 to 37 weeks.

Source: Blencowe et al. National, regional and worldwide estimates of preterm birth rates in the year 2012
Setting: Where 15 million preterm babies receive care

Can we reach scale care interventions that require high functioning care facilities?
“This isn’t a matter of holding hands and singing *Kumbyai.*”

Barack Obama   March 24th, 2015
Potential for lives saved (and lost) through steroid injections for women in preterm labor

Respiratory complications due to lung immaturity (RDS) are the commonest cause of death in very preterm babies.

Single course of antenatal corticosteroids (ACS) to women in preterm labour:

• 31% Mortality reduction (RR 0.69, 95% CI 0.58 to 0.81) for babies in NICU settings where ventilation (+/-surfactant) is standard of care (Cochrane review)
• 53% reduction in mortality in 4 studies in middle income countries (RR 0.47, 95% CI 0.35 to 0.64) again with advance preterm care
• These settings differ significantly than care settings in low income countries
• 2014 ACT trail in LMICs showed no change in mortality for low birth weight 95%tile, and increased mortality in treatment arm of 3.5/1000 compared to control group (usual care)

However, this approach is reported to have the potential to save about 400,000 babies each year if reached 95% of women in preterm labor (LiST analysis)
Potential for lives saved through KMC

KMC is a care approach for preterm and LBW babies:
- Continuous skin-to-skin contact
- Establish immediate and exclusive breastfeeding
- Early discharge from facility with early follow-up
- Neonatal mortality reduction of 40% RR 0.60 (95% CI 0.39-0.93) with NICU care for all babies
- Mortality reduction 51% for babies < 2000 gm, in NICU facilities, clinically stable and started within one week compared to incubator care
- Little evidence for estimate of the measure of effect in LICs
- This intervention may require significant adaption

Promoted to have the potential to save about 450,000 babies each year if reached 95% of preterm babies (LiST analysis)

Chap 5 and 5, Born too Soon
Impact data from Lawn et al. Int J Epid: 2010,
Conde Aguedelo Cochrane review 2011
Chlorhexidine application to cord

- **WHO RECOMMENDATION 6: Cord care (newborns – excluding PTB and LBW)**
  - Daily chlorhexidine (7.1% chlorhexidine digluconate aqueous solution or gel, delivering 4% chlorhexidine) application to the umbilical cord stump during the first week of life is recommended for term newborns who are born at home in settings with high neonatal mortality (30 or more neonatal deaths per 1000 live births)

- Evidence shows effective in reducing newborn mortality, and mortality reduction greatest in preterm babies and when applied in 24 hours following birth

- **Is caution needed if PTB?**
  - Question of neurotoxicity in use with preemies under 32 weeks
  - Case reports of chemical burns with preemies under 32 weeks in both aqueous and alcohol based CHX products
  - Additional risk with methemaglobanemia from exposure to PCA CHX through cleansing on incubators

- Should single-dose within 24 hours of birth be recommended for PTB?

*WHO recommendation on postnatal care of the mother and newborn 2013*
<table>
<thead>
<tr>
<th>Preterm intervention</th>
<th>Primary benefit</th>
<th>Risk for preterms</th>
<th>Challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antenatal Corticosteroids</td>
<td>Improves lung maturity</td>
<td>Newborn mortality, maternal infection magnified by inappropriate use</td>
<td>Limit use to appropriate settings, GA determination, Realign expectations</td>
</tr>
<tr>
<td>Continuous skin to skin contact</td>
<td>Warmth, hygiene, nutrition, neuro–endocrine</td>
<td>Maternal isolation (siblings, maternal separation, HH economy), Low effectiveness</td>
<td>Pre/post stabilization in high mortality context, Acceptance/compliance, Develop appropriate LIC models</td>
</tr>
<tr>
<td>Oxygen</td>
<td>Reduces hypoxemia</td>
<td>ROP</td>
<td>Appropriate monitoring, Appropriate titration, Availability</td>
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<tr>
<td>CPAP</td>
<td>Improves RDS survival</td>
<td>Improved respiratory care at potential cost to warmth and nutrition</td>
<td>Shift focus from machine to baby with training in comprehensive care</td>
</tr>
<tr>
<td>Resuscitation Device</td>
<td>Positive pressure ventilation</td>
<td>Under–ventilation, Tidal volume</td>
<td>Appropriate mask size must be available for LBW, Stimulation and ENC</td>
</tr>
<tr>
<td>Chlorhexidine</td>
<td>Reduces cord infection</td>
<td>Chemical burn to skin, Unknown neurotoxicity, Rare methemaglobinemia</td>
<td>Single application for PTB, Additional exposures (cleaning agents, other applied substances)</td>
</tr>
<tr>
<td>Essential newborn care</td>
<td>Warmth, hygiene, nutrition, neuro–endocrine</td>
<td>Over–shadowed</td>
<td>Lacks sophistication, better evidence of effect taken as a whole</td>
</tr>
<tr>
<td>Incubator Care</td>
<td>Warmth</td>
<td>Improved warmth at potential cost to feeding and contact</td>
<td>Maintenance, thermal control, skin to skin contact, machine focus over care</td>
</tr>
<tr>
<td>Early PNC antibiotics</td>
<td>Reduces sepsis risk</td>
<td>Gut micro–flora, Bacterial resistance</td>
<td>Over–exposure to ab tx, correct identification of risk, ID other causes</td>
</tr>
</tbody>
</table>

Source: James A. Litch
“This ain't no party, this ain't no disco. This ain't no fooling around. No time for dancing, or lovey dovey. I ain't got time for that now.”

- David Byrne
Comparison of gestation age determination methods

<table>
<thead>
<tr>
<th>Method</th>
<th>Accuracy</th>
<th>Details</th>
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<tbody>
<tr>
<td>Early ultrasound scan</td>
<td>+/- 5 days if first trimester</td>
<td>Estimation of fetal crown-rump length +/- biparietal diameter / femur length between gestational age 6 – 18 weeks</td>
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<td></td>
<td>+/- 7 days after first trimester</td>
<td>Ultrasound not always available in low-income settings and rarely done in first trimester</td>
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<td>May be less accurate if fetal malformation, severe growth restriction or maternal obesity</td>
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<tr>
<td>Fundal Height</td>
<td>+/- 3 weeks</td>
<td>Distance from symphysis pubis to fundus measured with a tape measure</td>
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<td>Feasible and low cost</td>
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<td></td>
<td>In some studies similar accuracy to LMP</td>
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<td></td>
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<td>Potential use with other variables to estimate GA when no other information available</td>
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<tr>
<td>Last menstrual period</td>
<td>+/- 14 days</td>
<td>Women's recall of the date of the first day of her last menstrual period</td>
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<td>Most widely used</td>
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<td>Lower accuracy in settings with low literacy. Affected by variation in ovulation and also by breastfeeding. Digit preference</td>
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<tr>
<td>Birthweight as a surrogate of gestational age</td>
<td>More sensitive/specif. at lower gestational age e.g. &lt;1500 g most babies are preterm</td>
<td>Birthweight measured for around half of the world's births</td>
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<tr>
<td></td>
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<td>Requires scales and skill. Digit preference</td>
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<tr>
<td>Newborn examination</td>
<td>+/- 13 days for Dubowitz, higher range for all others</td>
<td>Validated scores using external +/-or neurological examination of the newborn e.g. Parkin, Finnstrom, Ballard and Dubowitz scores</td>
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<td>Mainly specialist use so far. More accurate with neurological criteria which require considerable skill. Potential wider use for simpler scoring systems</td>
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<td>Accuracy dependant on complexity of score and skill of examiner. Training and ongoing quality control required to maintain accuracy</td>
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<tr>
<td>Best obstetric estimate</td>
<td>Around +/- 10 days (between ultrasound and newborn examination)</td>
<td>Uses an algorithm to estimate gestational age based on best information available</td>
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<td>Commonly used in high-income settings</td>
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<td></td>
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<td>Various algorithms in use, not standardized</td>
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</table>

Source: Parker et al (Master’s Thesis)
Point estimate of effect

• ACS as an example of the limitations of the Point Estimate of Effect (PEE)
  – Compared with placebo, corticosteroid therapy was associated with significantly fewer fetal and neonatal deaths (RR 0.77, 95% CI 0.67 to 0.89, 13 studies, 3627 infants) in high resource settings.
  – However, actually no change in fetal deaths in sub-analysis
  – Documented opposite effect (increased neonatal deaths) when applied in different settings (ACT Trial)
• Estimates of effect are specific to the conditions in which they were studied.
• We get in to deep water when we combine estimates of effect for different interventions, taken from different studies/situations to estimate a pooled effect, and then apply them to a new context.
Accelerating preterm birth survival

What have we learned?

Preterm birth is a syndrome with shared pathways and risk factors, resulting in many potential intervention points.

Taken together, interventions to reduce preterm birth can impact a number of related outcomes including mortality.

Interventions directed to improve preemie survival in LICs are challenging and have risks of harm.

Gestational age estimation remains a major barrier to safe effective care in low resource settings.

Context matters – has a remarkable impact on the measure of effect.

Effectiveness and safety trials can inform difficult decisions, but are lacking in low resource settings.

Learn by doing. Evaluate as we go forward. Programs with strong evaluation components can inform further investment.
Is this the best goalkeeper save ever?

Many still believe this Gordon Banks save from Pele for England against Brazil at the 1970 World Cup in Mexico is the best goalkeeper save of all time.

In 2013, the UK Royal Mail assembled its Home Nations dream team of postage stamps to celebrate the 150th anniversary of the Football Association.

It takes a whole field of players, not just one player with an impressive performance, to win the World Cup.
It is not about any one intervention, as impressive as it might appear.
Questions/Discussion