Strategies for screening and stillbirth prevention

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Incidence SIDS & stillbirth in Scotland

Deaths per 1,000 births

Year

Smith GCS, NEJM, 2004
Research on new methods

• Many studies have evaluated tests to prevent stillbirth in low risk women
  – Routine scanning for fetal growth
  – Doppler ultrasound

• Not been shown to reduce number of deaths


Addressing sources of failure

• Risk assessment may not work
• Intervention may not work
  – If no effective intervention, no basis for screening
Developing tools for risk assessment

- Timing of stillbirth (preterm - term)
- Incorporating multiple factors (age, obesity, smoking, results of blood tests, scans)
- Comprehensible format
- Studying a rare event
Timing of stillbirth

• Stillbirth can occur from 22 weeks to 40 weeks and beyond

• Are risk factors for preterm stillbirths the same as those for stillbirth at term?

• How can one decide?
  – Time to event analysis
Time to event analysis

• Series of statistical methods designed to study survival after cancer diagnosis
• Life table analysis, Kaplan-Meier analysis and Cox proportional hazards model
• Example:
AFP and stillbirth. 1

Data from 84,769 first pregnancies in West of Scotland. Smith GCS et al, J Soc Gyn Invest 2006;13:483A
Top 5% msAFP

Data from 84,769 first pregnancies in West of Scotland. Smith GCS et al, J Soc Gyn Invest 2006;13:483A
Significance of gestation

- AFP in the top 5% associated with an overall 3-fold risk of stillbirth
- Could have led to trial of routine elective delivery at 37 weeks among women with raised AFP
- Would have yielded negative result
Developing tools for risk assessment

• Timing of stillbirth (preterm - term)
• Incorporating multiple factors
• Comprehensible format
• Studying a rare event
Multivariable analysis

• Many factors associated with stillbirth risk
• Some may increase risk, some may reduce it
• Requires sophisticated multivariable statistical methods
  – Cox proportional hazards regression
  – Logistic regression
Problem with statistical models

- Difficult to apply in practice
- Example of model for SIDS based on pregnancy outcome

The logistic-regression equation was as follows: $\text{log odds} = -3.583 + \text{age}(-0.440) + \text{parity}(0.372) + \text{birth weight}(-0.379) + \text{male}(0.454) + \text{married}(-0.551) + \text{smoker}(1.116)$, where male, married, and smoker are indicator variables $= 1$ if true or $0$ if other and all continuous variables are expressed as the same units listed in Table 2.

Smith & White, Pediatrics. 2006;117:60-6
Bayes’ theorem

- Posterior odds = prior odds x likelihood ratio
- Prior odds is odds for population
- Each individual has a series of characteristics which modify the background odds and yield an individual odds, which can be converted into a predicted risk

'An Essay Towards Solving a Problem in the Doctrine of Chances' (1763)
Rev Thomas Bayes
Logistic regression models in a Bayesian format

• In collaboration with Ian White, senior scientist at MRC Biostatistics Unit, Cambridge

• Developed novel method for converting logistic regression models as tables of likelihood ratios
The full logistic regression model for calculating ALLRs is

\[ \log(\text{odds}|x_1, x_2, \ldots, x_n) = \alpha + \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_n x_n \]  

(1)

where \( x_1, x_2, \ldots, x_n \) are the predictor variables, \( \beta_1, \beta_2, \ldots, \beta_n \) are their regression coefficients, and \( \alpha \) is the constant. Let the fitted values of \( \alpha, \beta_1, \beta_2, \ldots, \beta_n \) be \( \hat{\alpha}, \hat{\beta}_1, \hat{\beta}_2, \ldots, \hat{\beta}_n \).

The log likelihood ratio for \( x_1 \), for example, may be defined as the log odds of the outcome conditional on \( x_1, x_2, \ldots, x_n \) minus the log odds of the outcome conditional on \( x_2, \ldots, x_n \). The latter odds cannot in general be derived from equation 1 because the effects of the omitted \( x_1 \) are partly picked up by \( x_2, \ldots, x_n \); the true likelihood ratio for \( x_1 \) therefore depends on the values of \( x_2, \ldots, x_n \). We have created ALLRs that do not depend on the values of \( x_2, \ldots, x_n \).

To create the ALLRs, we force the coefficients in the second model to be the same as those estimated in the first model, but allowing a different intercept:

\[ \log(\text{odds}|x_2, \ldots, x_n) = \alpha_1^* + \hat{\beta}_2 x_2 + \ldots + \hat{\beta}_n x_n \]  

(2)

In this model, only the parameter \( \alpha_1^* \) is to be estimated; the other parameters take their fitted values from equation 1. We can then calculate the ALLR for \( x_1 \) as

\[ \text{ALLR}_1 = \hat{\alpha} + \hat{\beta}_1 x_1 - \hat{\alpha}_1^* . \]  

(3)

This procedure is repeated for each variable \( x_2, \ldots, x_n \) to calculate \( \text{ALLR}_2, \ldots, \text{ALLR}_n \).

A small correction factor must be added to the ALLRs in order to ensure that the sum of the overall log odds and all the ALLRs is exactly equal to the log odds computed from equation 1. The appropriate correction factor is \( c_d d \), where \( d = \hat{\alpha} - \hat{\alpha}_0 + \sum_i (\hat{\alpha}_i^* - \hat{\alpha}) \), \( \hat{\alpha}_0 \) is the overall log odds, and \( \sum_i c_i = 1 \). In this paper, \( d = -0.021 \) and all correction factors were smaller than 0.01 in magnitude. To ensure that values of each \( \text{ALLR}_i \) straddle 1, \( c_i \) is calculated as \( m_i/(m_1 + \ldots + m_n) \) where \( m_i \) is the sample minimum or maximum (depending on whether \( d \) is positive or negative) of \( \text{ALLR}_i \).

At the end of this procedure, the sum of the overall log odds and all the ALLRs exactly equals the log odds computed from equation 1. Our procedure is therefore nothing more than a restatement of the results of the logistic regression in an easily interpretable format.
Using the model in practice

Unmarried, LR = 1.23
20 years old, LR = 1.83
Parity 1, LR = 1.06,
Smoked during pregnancy, LR = 1.59
Male infant, LR = 1.23
Birth weight 2600g, 1.58

Summary likelihood ratio:
1.23 x 1.83 x 1.06 x 1.59 x 1.23 x 1.58 = 7.37

Risk of SIDS approximately 1 in 200
Developing tools for risk assessment

- Timing of stillbirth (preterm - term)
- Incorporating multiple factors (age, obesity, smoking, results of blood tests, scans)
- Comprehensible format
- **Studying a rare event**
Studying a rare event

- Stillbirth affects approximately 1 in 200 pregnancies in Western Europe
- Stillbirth at term 1 to 2 per 1000
- If factor associated with x2 increase in risk, need to study 35,000 – 70,000 to have 90% chance of detecting effect
- Difficult and expensive
Secondary analysis of data

- Utilise routinely collected or research data collected for other purposes to study stillbirth
- Scottish Stillbirth & Infant Death Enquiry
- Use record linkage to combine with
  - CUBS study (Down syndrome screening)
  - Clinical biochemical data from regional lab
  - Nationally collected pregnancy data
Secondary analysis of data

• Advantages
  – Cheap and very cost effective
  – Allows large scale studies

• Disadvantages
  – Routinely collected data prone to errors
  – Fields limited, may not include all relevant
  – Tends to lack details

• Gold standard: prospective cohort study
Intervention

• Screening is only justified if there is an effective intervention
• Meta-analysis of trials of umbilical artery Doppler
• Five trials, only one had a management protocol for an abnormal result (more scans!)
Reasons for lack of progress?

• We have no well characterised screening tool
• We have no intervention that is clearly effective
Strategy for preventing stillbirth

- Delivery is the simplest and most effective intervention
- Has potential to cause harm
- Leads to a focus on designing trials where the intervention is delivery at early term gestations (e.g. start of 37 weeks)
- One third of all stillbirths occur at term
- Evaluate in a randomised controlled trial
Design of trial

- Screen all women
- Identify women in the top 5% of predicted risk
- Randomly allocate half to delivery at 37 weeks
- Conceal result in other half
- Assessment perinatal mortality and long term outcome in the two groups
Designing an interventional study

• Are we good enough at risk assessment to proceed to a study with this intervention?
• Depends on
  – How good we would have to be?
  – How good are we right now?
## Power calculation

<table>
<thead>
<tr>
<th>Likelihood ratio top 5% of predicted risk</th>
<th>Estimated PNM in control group*</th>
<th>Number of screen positive women required</th>
<th>Total population to be screened</th>
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<tr>
<td>3</td>
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<tr>
<td>20</td>
<td>35.8</td>
<td>600</td>
<td>12000</td>
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</tbody>
</table>

Assumptions:
Background risk of stillbirth is 1.8 per 1000 (Smith, AJOG, 2001)
Intrapartum stillbirth and neonatal death in both groups = 1 per 1,000.
80% power to detect difference at P<0.05 (two sided)
How good are our current tests?

• Model using AFP, hCG, maternal age, height, body mass index, socio-economic deprivation score, and smoking:
  – Top 5% predicted risk carries a likelihood ratio of 3.1
  – Not good enough

Data from 84,769 first pregnancies in West of Scotland. Smith GCS et al, J Soc Gyn Invest 2006;13:483A

- Large scale prospective cohort study
- Combine maternal characteristics, biochemical tests and ultrasound measurements
- Use time to event analysis to assess variation in relation to gestational age
- Characterise screening performance of combined model
Plan: Part 2.

- Screen low risk population and estimate stillbirth risk
- Identify women with increased risk of stillbirth at or beyond 37 weeks
- Randomly allocate to routine care or elective delivery
Problems

• Large scale observational study will be expensive
• Focus on stillbirth at term – maximum reduction will be about one third
• Difficult to feel comfortable about not intervening among women at increased risk of stillbirth
• However, without RCT data, population-based screening will not be funded
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