Rainbow Clinic: A Model for Antenatal Care in Pregnancies after Stillbirth

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Conflict of Interest

- The presenter is the Clinical Director of the Tommy’s Maternal and Fetal Health Research Centre, Manchester, UK and holds active grants to understand the cause of stillbirth and to evaluate the impact of specialist care in pregnancies after stillbirth from Tommy’s, Action Medical Research and the Holly Martin Stillbirth Research Fund.
- The presenter has no direct financial interests to declare.

Complications in Previous Pregnancy

- Stillbirth
- Neonatal Death
- Severe Congenital Abnormality
  - TOP for fetal abnormality
  - Stillbirth
  - Neonatal Death
- Severe Fetal Growth Restriction / Preeclampsia
Why are previous pregnancy complications important?
- Biomedical
- Risk of recurrence
- Psychological
- Anxiety / Stress during pregnancy
- Mother-infant bonding
- Mixed
- Impact of Stress

What are women’s experiences in subsequent pregnancies?

14 studies included (none from the UK)

Three main themes were identified;
- co-existence of emotions
- Ongoing grief and anxiety
- Isolation from friends and family

Helpful and unhelpful coping activities
- Delayed attachment
- Seeking control
- Seeking reassurance through interactions
- Interactions with care providers
- Interactions with their baby
- Interactions with technology

Line of Argument Synthesis
- Stillbirth or neonatal death profoundly alters the reality of subsequent pregnancies. To ‘survive’ the mire of anxiety and fears, parents frequently delay emotional engagement with their new pregnancy/baby. Misunderstanding of this self-protective behaviour and cultural misconceptions which underplay the lasting effects of perinatal loss deprive parents of support via traditional social networks. Well-intentioned health professionals attempt to meet needs by providing additional antenatal appointments and technological surveillance. However, normal antenatal findings provide only limited reassurance.
- Lack of understanding of the impact of perinatal death reduces the professional’s capacity to provide adequate emotional and psychological support during subsequent pregnancies. Targeted additional support was rated highly in delivering sensitive care.
Risk factors and Stillbirth

- The majority of stillbirths occur in women with no apparent risk factors (81%)
- Majority confer moderately increased risk
  - Advanced maternal age (>40) (1.6 - 3.6x)
  - Diabetes (2.7x), Hypertension (2.0x)
  - Cigarette smoking (1.3 - 1.6x), Alcohol >5u/wk (2.3x)
  - Reduced Fetal Movements (2 - 5x)
  - Small for Gestational Age (19.8x)
- Previous Stillbirth (5x)


Previous Stillbirth as a risk factor

- Systematic review of 13 cohort and 3 case-control studies
- 3,412,079 pregnancies,
- 99.3% had previous live birth and 24,541 (0.7%) a stillbirth
- 2.5% in women with a history of stillbirth
- 0.4% in women with a history of live birth
- Pooled odds ratio 4.83 (95% CI 3.77 – 6.18)

Lamont et al. BMJ 2015
Other complications in subsequent pregnancy
- Black et al. BJOG 2008
- Grampian region of Scotland
- Women with prior SB (n = 364) & live birth (n = 33,715)
- Women with previous SB
  - Increased risk of pre-eclampsia (OR 3.1, 95% CI 1.7-5.7)
  - Prematurity (OR 2.8, 95% CI 1.9-4.2)
  - Low birthweight (OR 2.8, 95% CI 1.9-4.5)
  - Placental abruption (OR 9.4, 95% CI 4.5-19.7)
  - Induction of labour (OR 3.2, 95% CI 2.4-4.2)
- Inneate vs. iatrogenic risks

Why do complications recur?
- Persistence/worsening of maternal medical conditions (hypertension, diabetes) or risk factors (smoking, obesity)
- Recurrent conditions
  - Inflammatory placental conditions
  - Maternal vascular complications
- Genetic conditions
  - Chromosomal disorders
  - Single gene disorders

Recurrent Placental Pathology is Key
Placental abnormalities persist in subsequent pregnancy

- SNAs and avascular villi both increased in stillbirth and remain elevated in subsequent pregnancy

Subsequent Pregnancy Outcome

- What are the conditions we should be worried about?
  - Nijkamp et al. 2013
    - 163 stillbirths (after 16 weeks)
    - Classified using TULIP system
    - Recurrent fetal death in 6.7% of cases
    - Cause determined in 7/11 cases
    - Placental bed pathology, placental pathology
    - PPROM
    - Unknown cause

Maternal vascular underperfusion and subsequent pregnancy outcome

- 320 subsequent pregnancies in 3 Italian hospitals
  - 47 early pregnancy loss
  - 273 babies
    - 67 (24.5%) had adverse pregnancy outcome (perinatal death, FGR, preterm birth <34w, HIE, respiratory distress)
    - SB related to placental vascular disorders had higher risk of adverse neonatal outcome (39.6%) compared with unexplained SB or other causes (OR 2.1, 95%CI: 1.2–3.8)
    - Obesity independently predicts adverse perinatal outcome (OR 2.1, 95%CI: 1.1–4.3)
Cochrane Systematic Review

**Background**
- Investigations to Determine Cause
- Discussed at Practice Review Forum
- Perinatal Mortality Meeting
- Stillbirth Case Review
- Meeting with Parents
- Care in Next Pregnancy

**Methods**
A Cochrane systematic review assessing the effects of different interventions in reducing complications and improving outcomes following perinatal mortality. Meta-analysis

**Primary outcomes**
- Delivery rate of at-risk fetuses

**Conclusions & progress to date**
- The Cochrane systematic review assessed the effects of different interventions in reducing complications and improving outcomes following perinatal mortality.
- Meta-analysis
- Delivery rate of at-risk fetuses

Care Pathway after Perinatal Death

- Investigations to Determine Cause
- Discussed at Practice Review Forum
- Perinatal Mortality Meeting
- Stillbirth Case Review
- Meeting with Parents
- Care in Next Pregnancy

Management of future pregnancies begins in index pregnancy

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<tr>
<th>Reason</th>
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<td>Reduce other babies dying in future</td>
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<tr>
<td>Research</td>
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Table 2. Parent’s reasons for having a postmortem examination

- Find a reason
- Closure
- “Can I have any more children, doctor?”
Investigation of Stillbirth, Neonatal Death or Congenital Abnormality

- **Post-mortem**
  - New information changing diagnosis 9-11% of stillbirths
  - Additional information 22-76% of stillbirths
  - New information in 5% of NNDs, additional info 52%
  - Added information about recurrence in 27% of TOPFAs

- **Placental histopathology**
  - Reduction in the probability of an "unexplained" stillbirth (OR 0.17; 95% CI 0.04–0.70)

- **Chromosomal analysis**
  - Microarray finds genetic abnormalities in 8.8% of stillbirths

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Economic Evaluation

- Costs in next pregnancy range from £2,147 - £3,751
- Highest costs was previous stillbirth of unknown cause
- Care in next pregnancy from unknown cause £500 greater than known non-recurrent cause

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RCOG – Recommendations (1)

- Parents should be advised about the cause of stillbirth, chance of recurrence and any specific means of preventing further loss [GPP].
- Women should be offered general pre-pregnancy advice, including support for smoking cessation [C].
- Women should be advised to avoid weight gain if they are already overweight (body mass index over 25) and to consider weight loss [B].
- An offer should be made to discuss the potential benefit of delaying conception until severe psychological issues have been resolved [C].
RCOG Recommendations (2)

- Carers should be aware that while mothers tend to experience greater anxiety when conception occurs soon after a fetal loss, partners are more likely to suffer anxiety if conception is delayed [A].
- Parents can be advised that the absolute chance of adverse events with a pregnancy interval less than 6 months remains low and is unlikely to be significantly increased compared with conceiving later [B].
- The meeting should be documented for the parents in a letter that includes an agreed outline plan for future pregnancy [GPP].

RCOG Green Top Guideline 55

RCOG Recommendations (3)

- Recommended screening for detection of small-for-gestational age infants in next pregnancy
  - Women who have a major risk factor (Odds Ratio [OR] > 2.0) should be referred for serial ultrasound measurement of fetal size and assessment of wellbeing with umbilical artery Doppler from 26–28 weeks of pregnancy
  - In high risk populations uterine artery Doppler at 20–24 weeks of pregnancy has a moderate predictive value for a severely SGA neonate.

RCOG Green Top Guideline 31

Practice in the UK

- Responses from 127 (73%) maternity units
- 547 women who had experienced care in a pregnancy after a stillbirth
Practice in the UK

<table>
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<th>Policy/guideline/patient pathway</th>
<th>Yes</th>
<th>No</th>
<th>Don't know</th>
<th>N (%)</th>
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<tr>
<td>Unit has a written policy/guideline/patient pathway</td>
<td>95 (99%)</td>
<td>5 (0.5%)</td>
<td>2 (0.2%)</td>
<td>102 (100%)</td>
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Women’s Experience in the UK

- 80.4% of women returned to the unit where their baby died.
- Saw range of professionals at first appointment 42% saw a consultant obstetrician. Only 52% felt ‘well prepared’ for their pregnancy after 1st visit.
- Regarding frequency of visits 74% considered frequency appropriate, but 22% wanted to be seen more often.
- Most women had additional surveillance including: ultrasound scans (75%), additional appointments (69%) and 60% offered an early pregnancy ‘viability’ ultrasound.
- 59% of women had >2 additional contacts between routine appointments. Usually triage or day unit.

Rainbow Clinic

- Multidisciplinary Specialist Clinic (1 Obs, 1 MW)
  - Psychological Support
  - Continuity of Care
  - Directed investigations
  - Research
- Placental profile – 17 & 23 weeks
- Shared care with relevant services
  - Diabetes / Hypertension Clinic
Care in Subsequent Pregnancy after Stillbirth

Interventions in Subsequent Pregnancy

- Stop cigarette smoking [B]
  - Räsänen S et al. 2013 – Smoking cessation in first trimester reduced risk of stillbirth to same as non-smokers
  - Couttingius et al. 2006 – smoking in next pregnancy reduced in women had experienced a stillbirth (OR 0.76) compared to non-fatal outcomes
- Aspirin [A]
  - Roberge et al. 2013 – 75-150mg Aspirin <16/40 has greater effect in reducing perinatal death (RR = 0.41 vs. 0.93)
- Low molecular weight heparin [B-]
  - Kupferminic et al. 2011 – LMWH in women with inherited thrombophilia 0% recurrence vs. 7% untreated
  - Kupferminic et al. 2011b – LMWH in women with placental findings without thrombophilia 6% treated vs 22% in untreated

Interventions not routinely used in the UK, but may be used in USA

- Reddy et al. 2010
  - Fetal movement counting from 28 weeks
  - CTG (Non-stress tests) from 32 weeks (or 2 weeks before stillbirth occurred)
  - Stress-test
Panel of ultrasound investigation

- Fetal biometry PLUS
- Combination of placental size, morphology, umbilical and uterine artery Doppler measurements

Abnormal placental shape and structure precedes poor outcome

- Toal et al. AmJOG 2007;196:363.e1 - e7
- 212 women with high-risk pregnancies
- Additional scan at 19-23 weeks to assess placental morphology with uterine artery Doppler

RESULTS: The odds of the development of adverse outcomes were significantly less in women with all normal test results (preeclampsia/HEDLIP (odds ratio, 0.2; 95% CI, 0.1 - 0.4)), preterm delivery (odds ratio, 0.1; 95% CI, 0.06-0.3), small for gestational age delivery (odds ratio, 0.2; 95% CI, 0.09-0.3), early-onset IUGR (0), and LUF (odds ratio, 0.05; 0.01 - 0.2). Combining these women with two (n = 21) or three (n = 15) abnormal test results together predicted 14 of 19 severe IUGR and 15 of 22 LUF cases.

Placental Ultrasound and Histology

A

B

C

D
Next Pregnancy Outcome

- Before Rainbow Clinic
  - 78/294 (29%) of women had one subsequent completed pregnancy after perinatal death
  - 8/294 (3%) had two subsequent completed pregnancies
  - Interval between date of perinatal death and date of subsequent birth was 13 months (Range 7-20 months)
  - 2 stillbirths both <3rd centile & preterm (2% stillbirth rate)
    - Initial – Lethal Congenital Anomaly; 2nd – FGR and umbilical cord accident
  - 12% <10th centile – 5 born pre-term, 6 born at term
  - Pre-term delivery: 20/294 (21%)

Next Pregnancy Outcome

- After Rainbow Clinic (n=84)
  - 1 SB (n=70), 2 SB (n=2), NND/Late Misc/TOP (n=9)
  - Average 5 appointments (Range 1-10)
  - 51 (61%) had Aspirin, 10 (12%) had LMWH.
  - No recurrent SB or NNDs
  - Average gestation 37w5d (28-40 weeks)
    - 8 preterm (10%)
  - 39 IOL, 14 Elective CS
  - 6 NICU admission

Classification and Outcome

- Initial SB classified as **fetal growth restriction**
  - 12% subsequently had a birthweight ≤10th centile
- Initial SB classified as **placental insufficiency**
  - 13% subsequently had a birthweight ≤10th centile
- Initial SB classified as **thrombophilia / APLS**
  - None had a birthweight <10th centile
  - All received LMWH and Aspirin
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<th>Period</th>
<th>Total births (n)</th>
<th>Live births (n)</th>
<th>Births &lt;37w (%)</th>
<th>IOL (%)</th>
<th>El CS (%)</th>
<th>Em CS (%)</th>
<th>SVD (%)</th>
<th>Instrumental Delivery (%)</th>
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Outcomes compared to published data

- Outcomes comparable with published data.
- Need to examine CS vs. IOL rates

Published data obtained from Black et al. BJOG 2008
Social Return on Investment

- £1.78 return for every £1 invested

**Figure 1: Breakdown of Rainbow Clinic social value by area**

Conclusion

- Women and their families need different care in pregnancies and complications
- Prior stillbirth is a risk factor for a second stillbirth
- Planning for subsequent pregnancy has its origins in investigations following stillbirth, NND or TOP.
- Further studies are needed
  + Interpret information from PM + placental exam
  + What are the best tests in a subsequent pregnancy?
  + Inform clinical practice / change management
  + Interventions

Some (Simple) Changes

- Investigate initial event(s)
- Identify patients (stickers)
- Continuity of care
- Address parents’ anxieties
- Targeted, individualised care
Patient example – Unexpected T21

- PM found VSD missed antenatally
- Chromosomal analysis - Trisomy 21
- Perinatal Mortality Meeting - A1 – Trisomy 21
- Parents checked for unbalanced translocation - negative
- Plan made for next pregnancy
- Early amniocentesis
- Scan for reassurance in Rainbow Clinic

Patient example – APLS

- PM Declined. Birthweight < 3rd centile 2.4kg @ 39 weeks gestation
- Placental Histology - multiple infarcts of different ages occupying 20% placenta. Massive perivillous fibrin deposition
- Lupus anticoagulant demonstrated
- Perinatal Mortality Meeting - A7, C4, F5 – FGR, Placental Insufficiency, APLS
- Lupus anticoagulant rechecked at PN visit – remained positive
- Early viability scan
- Aspirin and Low molecular weight heparin
- Placental profile + Growth scans every 2 weeks
- Delivery live preterm SGA male
Patient example – “Unexplained”

- 39 week stillbirth weighing 3100g (20th centile)
- Placental histology – increased syncytial knots, <10% infarction
- All other investigations negative
- Perinatal Mortality Meeting – II – No relevant condition identified
- First trimester serum screening (low PAPP-A)
- Placental profile – positive (bilaterally notched uterine arteries)
- Initial EFW – 80th centile. Scanned every 3 weeks in Rainbow Clinic
- Reduction in EFW at each scan
- IOL at 37 weeks – Live female birthweight 20th centile

Thank you for your attention

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