Exploring the Association Between Altered Fetal Activity and Stillbirth

Alexander Heazell

Professor of Obstetrics

Tommy's Maternal and Fetal Health Research Centre

University of Manchester, UK

@MCR_SB_Research

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Objectives

- Review epidemiological evidence associating altered fetal activity and stillbirth
  - Reduced fetal activity
  - Single period of excessive fetal activity
- Present experimental findings demonstrating altered placental structure and function in altered fetal activity
- Consider interventional studies addressing maternal perception of altered fetal activity

Observational Studies to identify Associations (Risk Factors)

- Ideal – A prospective cohort study of whole population to study the outcome of interest
- Challenging for infrequent outcomes
- To identify 291 women with late stillbirth (≥28 weeks) would require 100,300 participants
- Alternative approach – Case-control design
- Attempt to minimise bias by conducting study in same populations

Awareness of FM associated with Stillbirth

Question	Response	Group				Unadjusted OR (95% CI)	Adjusted OR* (95% CI)	P-value
		Cases		Controls				
		Total	%	Total	%			
During this pregnancy did your healthcare provider tell you about or ask you to keep track of your baby's movement?	No	79	54.9	161	41.6	Reference	Reference	0.008
	Yes	65	45.1	226	58.4	0.59 (0.4, 0.86)	0.55 (0.36, 0.86)	
Did you keep track of your baby's movement during this pregnancy?	No	70	48.3	132	33.8	Reference	Reference	0.005
	Yes	75	51.7	259	66.2	0.55 (0.37, 0.8)	0.54 (0.35, 0.83)	
How would you describe this baby's usual movements?	Less than average movement	14	9.59	24	6.17	1.56 (0.77, 3.18)	2.21 (0.99, 4.98)	0.054
	Average movements	73	50	195	50.1	Reference	Reference	
	Above average movements	47	32.2	134	34.5	0.94 (0.61, 1.44)	0.90 (0.56, 1.44)	
	Constant movement	12	8.22	36	9.25	0.89 (0.44, 1.80)	0.98 (0.55, 2.11)	
Once you were aware of your baby's usual pattern of movement, was there any time your baby's movements were unusual?	No	27	19.3	200	52.5	Reference	Reference	<.0001
	Yes, a little bit less	35	25	96	25.2	2.7 (1.55, 4.72)	2.82 (1.52, 5.24)	
	Yes, significantly less	56	40	32	8.4	12.9 (7.17, 23.4)	14.13 (7.27, 27.45)	
	Yes, a little bit more	15	10.7	44	11.6	2.53 (1.24, 5.14)	2.61 (1.20, 5.66)	
	Yes, significantly more	7	5	9	2.36	5.76 (1.98, 16.7)	5.60 (1.69, 18.49)	
During the last two weeks of this pregnancy, did the STRENGTH of your baby's movements	Stay the same	66	46.5	180	49.2	Reference	Reference	<.0001
	Decrease	58	40.9	56	15.3	2.83 (1.78, 4.49)	2.53 (1.51, 4.23)	
	Increase	18	12.7	130	35.5	0.38 (0.21, 0.67)	0.42 (0.23, 0.78)	
During the last two weeks of this pregnancy, did the FREQUENCY of your baby's movements....	Stay the same	65	44.8	223	59.6	Reference	Reference	<.0001
	Decrease	73	50.3	76	20.3	3.29 (2.16, 5.03)	2.97 (1.86, 4.72)	
	Increase	7	4.83	75	20.1	0.32 (0.14, 0.73)	0.36 (0.15, 0.85)	

Heazell et al. *BMC Pregnancy and Childbirth* 2017

MiNESS Case Control Study

- 296 women with late stillbirth (>28 weeks) and 734 controls were recruited to Midland and North of England Stillbirth Study

MiNESS Flow Diagram

MiNESS – Reduced FM

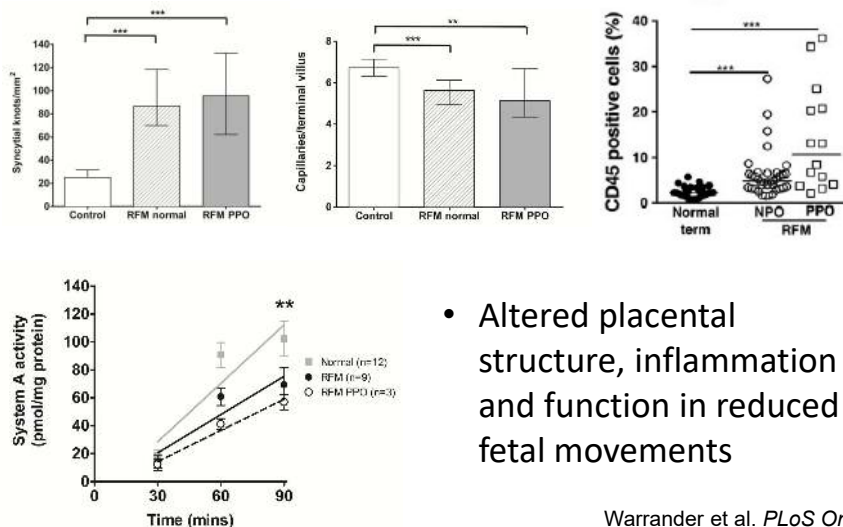|	Cases, n (%)	Controls, n (%)	Odds ratio (95% Confidence Interval)* χ^2, p values
Was there any time from 26 weeks of pregnancy that your baby's movements were less than usual?			
No	112 (38.7)	469 (64.2)	Reference: χ^2=66.69, p<0.0001
Once	88 (30.5)	156 (21.3)	2.36 (1.69 to 3.30)
Two times	39 (13.5)	65 (6.9)	2.51 (1.61 to 3.93)
Three or more times	50 (17.3)	41 (5.6)	5.11 (3.22 to 8.10)
In the last 2 weeks did the strength of your baby's movements			
Increase	53 (18.3)	455 (62.8)	0.15 (0.11 to 0.22)
Decrease	62 (21.4)	50 (6.9)	1.61 (1.05 to 2.46)
Stay the same	153 (52.8)	198 (27.3)	Reference: χ^2=169.96, p<0.0001
Unsure	22 (7.6)	22 (3.0)	1.29 (0.69 to 2.42)
In the last 2 weeks did the frequency of your baby's movements			
Increase	37 (12.7)	254 (34.8)	0.38 (0.26 to 0.56)
Decrease	86 (29.6)	63 (8.6)	3.54 (2.44 to 5.15)
Stay the same	153 (52.6)	397 (54.3)	Reference: χ^2=103.49, p<0.0001
Unsure	15 (5.2)	17 (2.3)	2.29 (1.12 to 4.70)

- Similar effects seen in case-control studies and large retrospective cohort
- Frequent FMs and hiccups were protective

Heazell et al. BMJ Open 2018

A Plausible Mechanism to link RFM, FGR and Stillbirth

Sequence of Fetal Response to Stress†

Sequence may vary according to the etiology and progression

Stress
Chronic respiratory and nutritive insufficiency

Primary adaptive response
Decreased fetal growth rate

Secondary adaptive response
Fetal energy conservation
Decreased fetal movement
Decreased fetal heart rate reactivity
Circulatory redistribution
Falling cerebral flow impedance
Rising umbilical and aortic impedance
Fetal growth preferred over placental growth
Increased efficiency of placental exchange
Polycythemia
Greater O_2 carrying capacity

Progressive decompensation
Hypoxia → respiratory acidosis → metabolic acidosis
High impedance in fetoplacental and systemic circulation results in absent end diastolic flow in umbilical arteries
Declining amniotic fluid volume → oligohydramnios
Loss of fetal movement
Loss of fetal heart rate reactivity and variability
Persistent late decelerations
Agonal pattern

Death

Note that the depicted sequence is an approximation and the actual course may vary depending upon the characteristics of the chronic deprivation and the individual fetal ability to cope.

† Reproduced with permission from Maulik, D. Doppler velocimetry for fetal surveillance: Adverse perinatal outcome and fetal hypoxia. In: Maulik, D (ed) Doppler ultrasound in obstetrics and gynecology, 1997; 349 New York, Springer Verlag. Copyright © 1997 Springer-Verlag.

RFM – A symptom of placental dysfunction

- Altered placental structure, inflammation and function in reduced fetal movements

Warrander et al. *PLoS One* 2012
Girard et al. *Am J Repro Immunol*, 2014

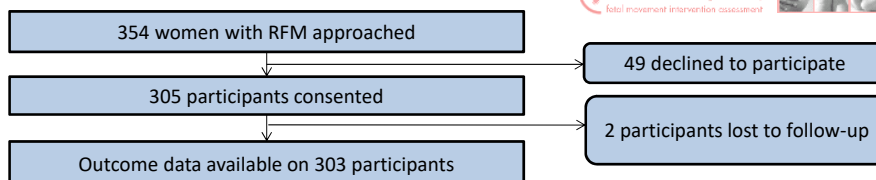# Retrospective analysis of stillbirths associated with RFM

- Exploration of database of perinatal deaths at SMH 2010 – 2017
- Neonatal deaths and terminations of pregnancy (TOP), fetal deaths <24 weeks were excluded.
- Included 283 antepartum and 18 intrapartum stillbirths
- 142 women (47.2%) had AFM or RFM, 159 had no evidence

Multivariable Logistic regression
- Stillbirths preceded by RFM:
  - Placental insufficiency more frequently as ReCoDe (aOR 2.8, 95% CI 1.6-5.0)
  - Less frequently had proteinuria (aOR 0.2, 95% 0.1-0.5)
  - Less frequently had previous pregnancy loss <24w (aOR 0.2, 95% CI 0.1-0.6)

ter Kuile et al. Submitted 2019

Can Clinical or Placental Factors Predict Fetal Compromise in RFM?

femina

354 women with RFM approached

49 declined to participate

305 participants consented

2 participants lost to follow-up

Outcome data available on 303 participants

- Normal 236 (77.4%)
- Poor Outcome 67 (22.0%)
  - 7 preterm SGA
  - 51 term SGA
  - 7 normally grown preterm infants
  - 4 grade 1 CS
    - 2 normally grown term infants to NICU
- Unknown 2 (0.7%)

Feature	OR
Number of FM/45 min	0.958
Diastolic BP	1.048
Estimated weight centile	0.952
Maximum pool depth	0.970
log[hCG]	0.364
log[hPL]	0.033

Dutton et al. *PLoS One* 2012

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hPL, PlGF and RFM

femina 2

- Second study of women with RFM (n=300) - adding PlGF (but not hPL) to standard assessment improved the prediction of adverse outcome.
- Area under the ROC curve improved from 0.75 (0.64-0.86) to 0.88 (0.80-0.95) with placental assessment.

- The sensitivity for adverse outcome improved from 9% (95% CI 4-19%) to 38% (95% CI 21-57%) with placental assessment.

6/20/2019
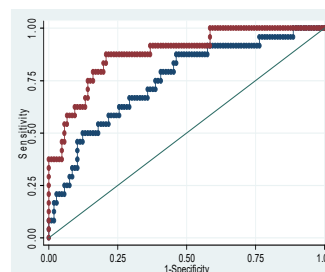
Summary - RFM

- Further epidemiological evidence associating RFM with stillbirth
- Regular activity is protective
- RFM is associated with histological placental abnormalities in live births and stillbirths
- Biochemical assessment of placental function may improve identification of adverse placental function in women with RFM

Intervention - A Power(ful) Problem

- To detect a 10% fall in stillbirth from 4 per 1,000 to 3.6 per 1,000 would require 371,404 participants in each arm of a trial
- To detect a 10% increase in induction of labour from 30% to 33% would require 3,763 participants
- A trial to demonstrate a 10% reduction in stillbirth could detect a 1% increase in IOL

AFFIRM Study –
Stepped Wedge Cluster Trial

AFFIRM Flowchart

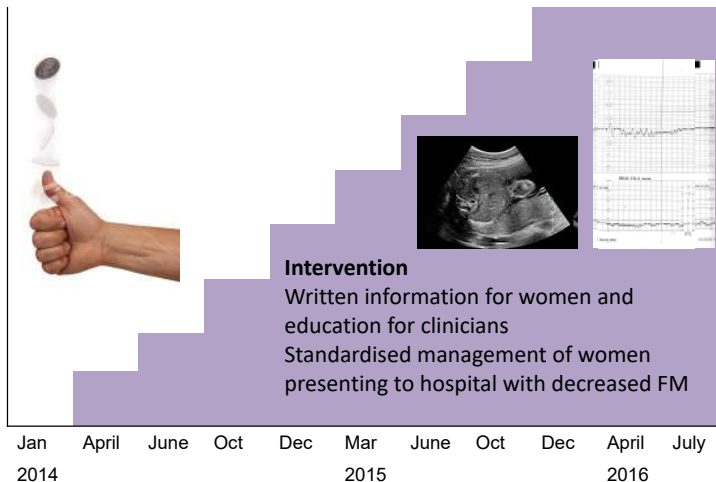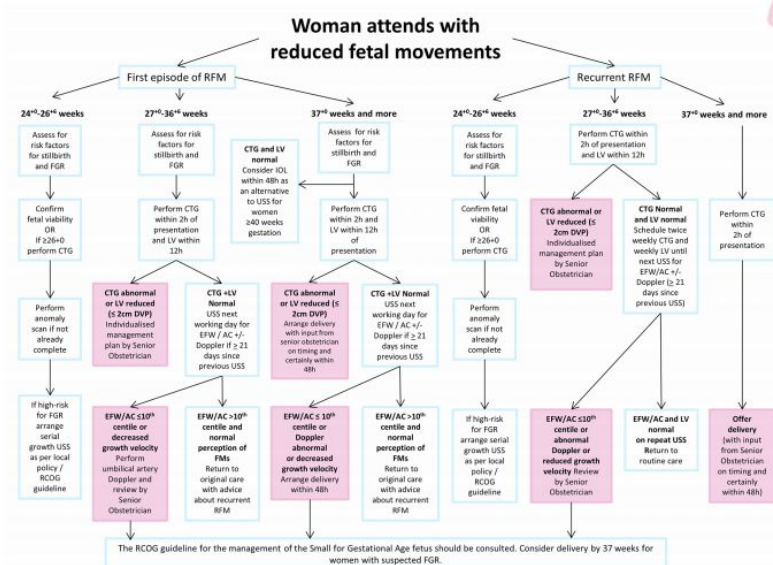# AFFIRM Comparison

Component	Control (based on RCOG guideline)	Intervention
Information	RCOG developed leaflet – picked up by Tommy's/MAMA Academy and Kick's Count. Women should be advised to be aware of their baby's individual pattern of movements. If they are concerned about a reduction in or cessation of fetal movements after 28 weeks of gestation, they should contact their maternity unit. No formal FM counting.	AFFIRM Study leaflet given before 24 weeks' gestation. More information about when fetal movements should start. Babies developing a pattern of movements. Why are babies' movements important? Women advised to contact maternity unit if they are concerned., no gestation specified on the leaflet.
Management	Take a history	Take a history
FH	Auscultate FH to exclude fetal death (Only action if <28w)	Auscultate FH to exclude fetal death (Only action if <26w)
CTG	CTG to exclude fetal compromise if the pregnancy is over 28+0 weeks of gestation.	CTG to exclude fetal compromise if the pregnancy is over 26+0 weeks of gestation (to be performed within 2h of presentation).
USS	Ultrasound scan assessment should be undertaken as part of the preliminary investigations of a woman presenting with RFM after 28+0 weeks of gestation if the perception of RFM persists despite a normal CTG or if there are any additional risk factors for FGR/stillbirth. No role for biophysical profile When a woman recurrently perceives RFM, ultrasound scan assessment should be undertaken as part of the investigations. Follow SGA guideline if baby small on USS.	Ultrasound scan for liquor volume within 12h Ultrasound scan for fetal biometry next working day + LV if not done and umbilical artery Doppler. If recurrent RFM, twice weekly CTG and weekly LV and umbilical artery Doppler.
Delivery	No recommendation to deliver infants for RFM alone	Consider IOL for women >40w on first presentation with RFM Consider IOL for women with recurrent RFM >37w with RFM

AFFIRM results

- Study had information from large number of births
  - Intervention (n=227,860), Control (n=157,692), Washout (n=23,623) Total (n=409,175)
- Intention to treat analysis of SBs ≥24 weeks
  - 4.06 vs 4.4 per 1,000 livebirths aOR 0·90 (0·75–1·07)
  - In unit with 5,000 births 5 fewer (11 fewer to 3 more)
- On treatment analysis
  - 3.09 vs 4.31 per 1,000 livebirths aOR 0.88 (0.76-1.02)

Norman et al. *Lancet* 2018

AFFIRM Results – Secondary Outcomes

	Intervention (n=227 860)	Control (n=157 692)	Adjusted OR (95% CI)	p value	Absolute effect (95% CI) per 10 000 pregnancies or per 10 000 babies*
Preterm pregnancy	17 376 (7·7%)	11 228 (7·3%)	1·05 (1·00–1·10)	0·050	34 more (0–68 more)
Caesarean section	64 572 (28·3%)	40 231 (25·5%)	1·09 (1·06–1·12)	<0·0001	162 more (105–218 more)
Induction at ≥39 weeks' gestation	57 815 (39·8%)	33 317 (33·6%)	1·08 (1·04–1·11)	<0·0001	165 more (88–245 more)
Induction of labour	83 499 (40·7%)	49 952 (35·8%)	1·05 (1·02,1·08)	0·0015	108 more (41–177 more)
Elective delivery	111 837 (54·6%)	67 227 (48·2%)	1·04 (1·01–1·07)	0·0123	91 more (20–160 more)
Elective delivery at ≥39 weeks' gestation	76 247 (52·4%)	44 838 (45·2%)	1·05 (1·02–1·09)	0·0022	128 more (47–212 more)
Spontaneous vaginal delivery	130 658 (57·4%)	94 337 (59·8%)	0·90 (0·88–0·92)	<0·0001	256 fewer (319–194 fewer)
Admitted to neonatal unit	19 237 (10·1%)	13 029 (10·1%)	1·02 (0·97–1·07)	0·504	14 more (28 fewer to 59 more)*
Admitted to neonatal unit for >48 h	12 676 (6·7%)	8041 (6·2%)	1·12 (1·06–1·18)	<0·0001	68 more (32 to 105 more)*
Admitted to neonatal unit at ≥37 weeks' gestation	10 384 (6·0%)	7497 (6·5%)	0·95 (0·89–1·01)	0·091	32 fewer (66 fewer to 5 more)*
Small for gestational age (≤10th centile) delivered ≥40 weeks' gestation	3461 (1·5%)	3081 (2·0%)	0·86 (0·78–0·95)	0·0009	27 fewer (42–10 fewer)*
Preterm baby	19 815 (8·6%)	12738 (8·1%)	1·05 (1·00–1·10)	0·061	34 more (1 fewer to 72 more)*

Data are n (%). ORs are adjusted for maternal age, number of babies in the pregnancy and study time period and cluster. Data are missing for preterm pregnancy (4307 [1·1%]), caesarean section (95 [0·02%]), induction at ≥39 weeks (140 930 [36·6%]), induction of labour (41 183 [10·7%]); elective delivery (41 239 [10·7%], elective delivery at ≥39 weeks' gestation 140 945 [36·6%]), spontaneous vaginal delivery (95 [0·02%]), admitted to neonatal unit (72 405 [18·5%]), admitted to neonatal unit for >48h (72 405 [18·5%]), admitted to neonatal unit at ≥ 37 weeks' gestation (103 029 [26·3%]), small for gestational age (≤10th centile) delivered ≥40 weeks' gestation (6963 [1·8%]), and preterm baby 4372 [1·1%]). OR=odds ratio. *Absolute effect sizes are per 10 000 babies for outcomes of neonatal unit admission, born small for gestational age, or preterm baby.

Table 3: Pregnancy and baby secondary outcomes

Norman et al. *Lancet* 2018

ReMIT-2

NOTTINGHAM CLINICAL TRIALS UNIT

Multicentre randomised controlled pilot trial

Standard care informed by results of an additional placental factor blood test vs standard care in women with reduced fetal movement (RFM) ≥ 36^{+0} weeks gestation

STUDY PROTOCOL — Open Access

Reduced fetal movement intervention Trial-2 (ReMIT-2): protocol for a pilot randomised controlled trial of standard care informed by the result of a placental growth factor (PlGF) blood test versus standard care alone in women presenting with reduced fetal movement at or after 36^{+0} weeks gestation

Lindsay Armstrong Buisseret[1], Eleanor Mitchell[1], Trish Hepburn[1], Lelia Duley[1], Jim G. Thornton[1], Tracy E. Roberts[2], Claire Storey[3], Rebecca Smyth[4] and Alexander E. P. Heazell[5,6]

- Recruitment period - 9 months; trial recruited from 8 sites
- Trial recruitment target was 175 - 225 participants

Participant Flow — ReM?T-2

Recruitment exceeded the minimum required each month to reach the lower target of 175 participants!
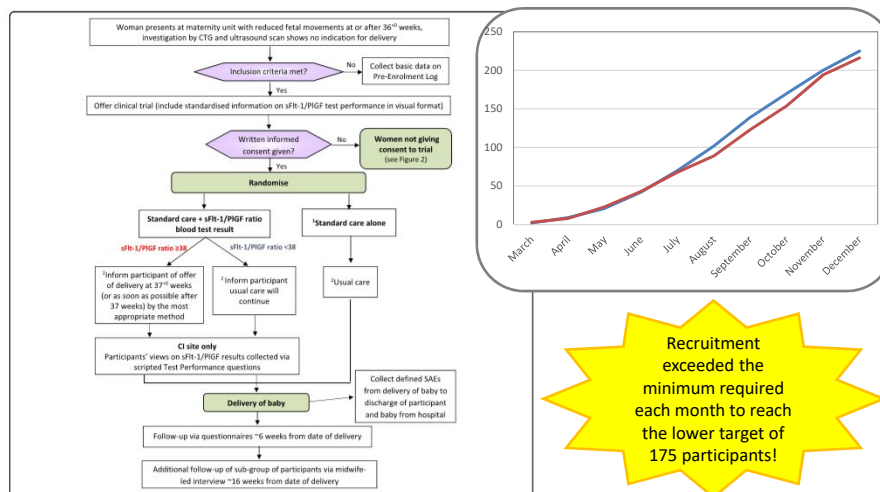
Armstrong-Buisseret et al. *Trials.* 2018 Oct 1;19(1):531

Postnatal Views on Trial — ReM?T-2

	All participants (n=131)
Would agree to participate in ReMIT-2 all over again	
Definitely	100 (76%)
Possibly	27 (21%)
Probably not	2 (2%)
Definitely not	0 (-)
Missing	2 (2%)
Participant felt the results of the tests altered the care they received	
Definitely	26 (20%)
Possibly	22 (17%)
Probably not	37 (28%)
Definitely not	43 (33%)
Missing	3 (2%)
Participant felt reassured by the results of the tests they had	
Definitely	93 (71%)
A little bit	24 (18%)
Not much	9 (7%)
Not at all	3 (2%)
Missing	2 (2%)

Summary –
RCTs of Placental Biomarker(s) in RFM

- Individual RCT of women with RFM ≥36w is feasible with high rates of compliance with the intervention
- Further work needed to determine the most sensitive biomarker
- Definitive clinical trial would need to be large as relevant outcome(s) are uncommon
  - Composite adverse outcome rate 6%
  - Reduction from 6% to 4.5% (3,470 in each arm)

Conclusions – RFM Intervention Studies

- Large studies possible with cluster designs
- Adherence to intervention varied in AFFIRM
- Likely some effect in stillbirth reduction
  - Not a solution in isolation
- RFM is not a reason for IOL in isolation <39w
- Need to combine RFM with investigations
  - Biochemical tests of placental function may offer opportunity to focus intervention on women with placental dysfunction

Increased Fetal Movements

INVEST

- Could *increased* fetal movements (IFMs) be a modifiable risk factor for stillbirth?

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

ELSEVIER

Excessive fetal movements are a sign of fetal compromise which merits further examination

Alexander E.P. Heazell[a,b,*], Tomasina Stacey[c], Louise M. O'Brien[d], Edwin A. Mitchell[e], Jane Warland[f]

Table 1
Summary of recent studies investigating the association of reduced fetal movements and excessive fetal movements with stillbirth.

Study Identifier	Study type	Question	Women who experienced stillbirth		Women with live births		Unadjusted Odds Ratio	
			Reduced Fetal Movements (%)	Excessive Fetal Movements (%)	Reduced Fetal Movements (%)	Excessive Fetal Movements (%)	Reduced Fetal Movement	Excessive Fetal Movement
Rayburn et al. 1980	Cohort	Participants kept diaries during pregnancy	–	–	–	47 (5%)	–	–
Stacey et al. 2011	Case-Control	Participants were asked to describe their baby's movements, in particular whether any change in frequency or strength had occurred AND whether they had perceived vigorous movement	45 (29.0%)	32 (20.9%)	36 (11.6%)	16 (5.3%)	2.36 (1.26–3.77)	4.51 (2.20–9.10)
Warland et al. 2015	Cohort	Once you were aware of your baby's usual pattern of movements was there any time that your baby's movements were unusual?	522 (30.9%)	149 (8.9%)	–	–	–	–
Linde et al. 2015	Cohort	How do you remember the fetal movement during the 48 h that preceded the diagnosis of intrauterine death?	106 (65%)	22 (10%)	–	–	–	–
Heazell et al. 2017	Case-Control	Once you were aware of your baby's usual pattern of movements was there any time that your baby's movements were unusual?	56 (40%)	42 (30.4%)	32 (8.4%)	24 (6.7%)	12.9 (7.17–23.4)	4.24 (2.36–7.62)

STARS Study

The STARS Study

Study of Trends and Associated Risks for Stillbirth

Warland *et al*. BMC Pregnancy and Childbirth (2015) 15:172
DOI 10.1186/s12884-015-0602-4

BMC
Pregnancy & Childbirth

RESEARCH ARTICLE   **Open Access**   CrossMark   **Cohort Study**

An international internet survey of the experiences of 1,714 mothers with a late stillbirth: the STARS cohort study

Jane Warland[1*], Louise M. O'Brien[2], Alexander E. P. Heazell[3], Edwin A. Mitchell[4] and the STARS consortium

RESEARCH ARTICLE   **Open Access**   CrossMark   **Case Control Study**

Stillbirth is associated with perceived alterations in fetal activity – findings from an international case control study

Alexander E. P. Heazell[1,2*], Jane Warland[3], Tomasina Stacey[4], Christin Coomarasamy[5], Jayne Budd[1], Edwin A. Mitchell[5] and Louise M. O'Brien[6]

Findings from STARS

- Cohort (n=1,714)
  - 8.5% reported a period of intense fetal activity
  - Women were less concerned about this compared to reduced FMs (6.4% vs. 13.8%)
- Case-Control (n=153 stillbirths, n=480 controls)
  - Women who had a stillbirth more likely to report a sudden single episode of excessive fetal activity (aOR 4.30, 95% CI 2.25–8.24) in preceding 2 weeks.
  - Perception of changes in fetal activity described differently to healthy controls e.g. vigorous activity was described as "frantic", "wild" or "crazy" compared to "powerful" or "strong".

Findings from Case Control Studies

Study Identifier	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)*
MiNESS; Heazell et al. 2017	1.47 (0.94-2.31)	2.10 (1.06-4.17)
STARS; Heazell et al. 2017	4.24 (2.36-7.62)	4.30 (2.25-8.24)
TASS; Stacey et al. 2011	4.51 (2.23-9.10)	6.81 (3.01-15.41)

- Similar effect sizes seen in three different populations
- Retrospective study – subject to recall / selection bias

INVEST Study

- Prospective observational cohort study women reporting IFMs in two UK tertiary maternity hospitals.
- Hypothesis - women with IFM will have a higher incidence of adverse pregnancy outcome compared to women reporting normal fetal movements
- The placentas and umbilical cords from women who report IFMs will demonstrate morphological, structural, and/or functional abnormalities compared to women reporting normal movements.

INVEST Participants

Characteristic	Number	Data
Age (years)	63	30 (21-43)
BMI (kg/m^2)	62	26.4 (17-50)
Gravidity	63	3 (1-13)
Parity	63	1 (0-11)
Pregnancies ending before 24 weeks' gestation	63	1 (0-9)
Ethnicity (n,(%))	63	
White British		44 (69.8)
Mixed		5 (7.9)
Pakistani		5 (7.9)
Eastern European		2 (3.2)
Chinese		2 (3.2)
South East Asian		1 (1.6)
Western European		1 (1.6)
Middle Eastern		1 (1.6)
East African		1 (3.2)
Cigarette Smoking (n,(%))	63	2 (3.2)
Alcohol Use (n,(%))	63	3 (4.8)
Administration of IM Steroids (n,(%))	63	1 (1.6)
Past Medical and/or Surgical History(n,(%))	63	29 (46)
Prescribed Medications (n,(%))		24 (38)

INVEST – Presentation

Characteristics of Presentation	Number	Result
Gestation at Presentation	63	243 days (194-287)
Blood Pressure on Admission with IFMs	60	
Systolic (mmHg)		116 (84-137)
Diastolic (mmHg)		68 (56-90)
Cardiotocography findings		
Baseline (bpm)	59	139 (121-156)
Variability (bpm)	55	12 (4-20)
Accelerations present (n(%))	55	55 (100)
Decelerations present (n(%))	55	3 (5.5)
Number of Fetal Movements per 30 minutes	49	49 (1.7-227.25)
Amniotic Fluid Index at Presentation: (n(%))	49	
Normal		47 (75.8)
Oligohydramnios		2 (3.2)
Maximum Pool Depth at Presentation: (n(%))	53	
Normal		50 (79.37)
Polyhydramnios		2 (3.17)
Oligohydramnios		1 (1.59)
Normal Placental Scan Appearance? (n(%))	52	
Yes		45 (71.4)
No		7 (11.1)

INVEST – Outcomes (1)

Outcome	Number	Result
Presentation with RFMs before the end of pregnancy? (n(%))	63	
Yes		22 (34.9)
Obstetric problems before the end of pregnancy? (n(%))		
Yes	63	15 (23.8)
Fetal sex: (n(%))		
Male		26 (41.3)
Female		37 (58.7)
Gestation at delivery (days)	63	274 (249-292)
Preterm births (<37 weeks) (n(%))	63	5 (7.9)
Induction of labour (n(%))	63	32 (50.8)
Mode of Delivery:	63	
NVD		35 (55.6)
INS		11 (17.5)
ELCS		10 (15.9)
EMCS		7 (11.1)
Birthweight (grams)	62	3414.1 (2492-3930)
Birth weight centile	63	53.8 (1.9-99.7)
Birth weight centile thresholds (n(%))	63	
<3rd centile		2 (3.2)
<10th centile		4 (6.4)
>90th centile (CHECK N HERE)		5 (8.1)

INVEST Outcomes (2)

Birth Outcomes		
Apgar 1 minute	62	9 (6-10)
Apgar 5 minute	62	10 (9-10)
Arterial pH	34	7.19 (7.02-7.34)
Arterial BE	33	7.6 (⁻0.7 - ⁻14.1)
Venous pH	33	7.3 (7.16-7.44)
Venous BE	35	5.2 (⁻1.1 - ⁻11.7)
Admission to NICU	63	4 (6.4)
Total composite adverse outcomes	63	7 (11.1)

- No perinatal deaths recruited during this study period
  - One reported IFM at her postnatal visit but did not present to maternity unit with symptom
- No significant increase in proportion of babies with adverse pregnancy outcome compared to general population

Factors associated with adverse outcome in women presenting with IFM

| Factor	Univariate analysis Odds Ratio (95% CI)	P value
Maternal Age	1.15 (0.98, 1.35)	0.07
BMI	1.02 (0.88, 1.18)	0.79
Gravidity	1.30 (1.02, 1.65)	0.03
Parity	1.02 (0.64, 1.63)	0.93
Pregnancy loss <24w	2.26 (1.19, 4.30)	0.01
White ethnic group	0.30 (0, 2.17)	0.26
Cigarette smoker	3.33 (0, 44.9)*	1.00
Alcohol use	2.07 (0, 21.1)*	1.00
Past Medical History	0.87 (0.18, 4.23)	0.86
Prescribed medication	1.25 (0.25, 6.14)	0.78
Systolic Blood Pressure	1.02 (0.95, 1.10)	0.49
Diastolic Blood Pressure	1.04 (0.95, 1.14)	0.35
Number of FMs in 30 minutes (Quartile)	0.80 (0.34, 1.86)	0.60
Decelerations on CTG	1.69 (0, 17.25)*	1.00
Estimated Fetal Weight Centile	0.99 (0.96, 1.83)	0.67
Estimated Fetal Weight 10th centile	2.07 (0, 21.11)	1.00
Abnormal Amniotic Fluid Index	10.75 (0.56, 206.44)	0.12
Abnormal Maximal Pool Depth	1.49 (0.27, 8.05)	0.65
Abnormal Placental Calcification	1.07 (0, 9.26)*	1.00
Uterine Artery Notch	4.20 (0.32, 55.06)	0.27
Subsequent presentation with RFM	1.46 (0.30, 7.20)	0.47
Subsequent obstetric complications	0.55 (0.06, 5.00)	0.60
Fetal Sex (male)	1.87 (0.33, 10.50)	0.48

Macroscopic Placental findings in IFM

Macroscopic feature	Control (n=5)	IFM (n=19)	p value
Trimmed placental weight(g)	442(327.5-550.6)	482(35.1-777)	0.68
Fetal/Placental Weight Ratio	6.8 (4.5-9.5)	7(1.4-9.6)	0.53
Minimum diameter(cm)	20 (16.2-22)	17(12.8-19.3)	0.02*
Maximum diameter(cm)	25.3(20.8-27.3)	20.5(17.0-29.8)	0.05
Mean diameter(cm)	22.7(18.3-23.3)	18.3(14.7-23.7)	0.01*
Placental roundness	1.3(1.2-1.4)	1.3(1.2-9.3)	0.41
Placental surface area(cm^2)	405.9(264.2-428.1)	265.2(171.9-430.6)	0.02*
% of maternal surface abnormal pale areas	0.3(0.2-0.4)	0.3(0-0.3)	0.26

- Placentas from women with IFM were smaller, but not lighter

Microscopic Placental findings in IFM
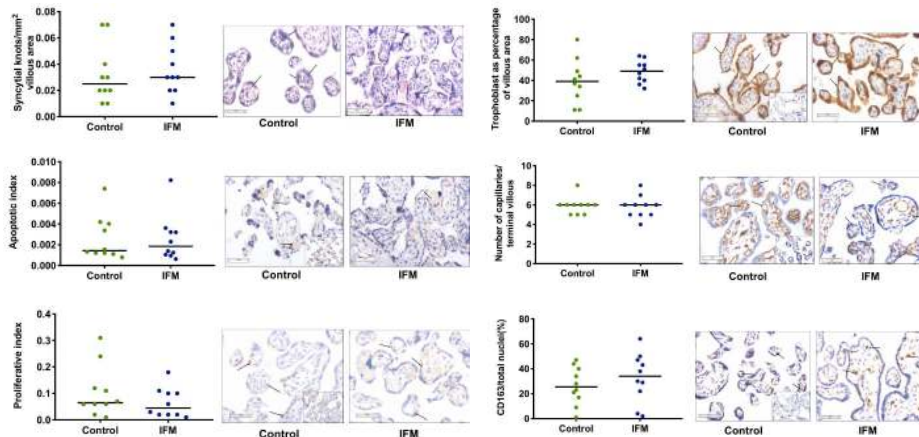
- No difference in placental cell turnover, vascularity or inflammation in IFM placentas

Biochemical markers of placental function in maternal serum in IFM
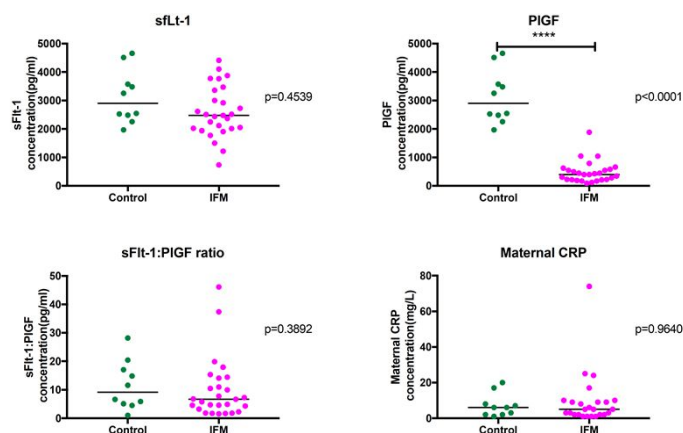
• Significant reduction in placental growth factor levels in IFM, no difference in maternal CRP

Summary - IFM

• IFM have been associated with stillbirth in several retrospective studies
• INVEST provides pilot data regarding adverse outcomes in women with IFMs in a prospective cohort study
• IFM was associated with some placental changes
  – Cord studies pending
• More prospective studies of IFM are needed
  – Focus on language women use
• Findings could be incorporated into clinical management guidelines e.g. #movementsmatter

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