MISCARRIAGE TREATMENT AND FUTURE PREGNANCY OUTCOME

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MISCARRIAGE

Definition: the spontaneous loss of a pregnancy before 24 weeks of gestation

Affects up to 15% of known pregnancies

The majority of miscarriages occur in the first trimester (before 13 weeks of gestation).

During this presentation, miscarriage will refer to both 1st and 2nd trimester miscarriages together, unless otherwise specified

WHAT WILL BE COVERED IN THIS TALK

1) Preterm Birth Risk after Miscarriage
   a) Subtypes of Preterm Birth – Cause
   b) Subtypes of Preterm Birth – Gestational Age
2) Possible Mechanisms behind Miscarriage - Preterm Birth Association
   a) Evidence for the mechanisms
3) Factors influencing Miscarriage - Preterm Birth Association
4) Miscarriage and other Obstetric Outcomes
5) 2nd Trimester Miscarriage

MISCARRIAGE AND PRETERM BIRTH

Well-established link between miscarriage and subsequent risk of preterm birth (PTB)

PTB (delivery before 37 weeks) contributes to infant mortality and childhood morbidity, including chronic lung disease, sensory deficits, cerebral palsy, and cognitive impairments.

Rates of PTB are increasing in almost all countries with reliable data.

EVIDENCE OF MISCARRIAGE-PTB ASSOCIATION

Previous studies have consistently found an increased risk of PTB after one or more than one miscarriage.

A meta-analysis, which quantitatively combined the results of these previous studies, found that after taking into account potential confounders, relative to women with no previous miscarriages:

	All-cause PTB OR (95%CI)
1 miscarriage	1.43 (1.05-1.56)
2+ miscarriages	2.27 (1.98-2.81)

Swingle et al. 2009

MISCARRIAGE & PTB SUBTYPES

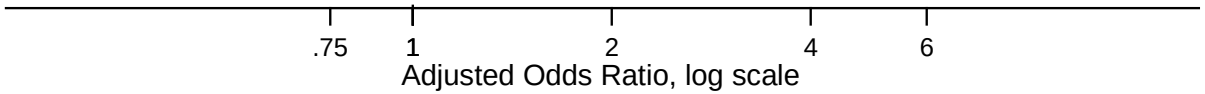
A range of PTB subtypes have been evaluated in relation to miscarriage:

1) Spontaneous

2) Induced
   a) induced due to pre-eclampsia
   b) induced due to preterm premature rupture of membranes (PPROM)
   c) induced due to other causes

MISCARRIAGE & PTB SUBTYPES

Cases/Participants	Number of Miscarriages	Odds Ratio (95% CI)	p-value
All-cause PTB			
38211/605763	1		
	2		
	3+		
Spontaneous			
24691/592243	1		
	2		
	3+		
Induced			
13520/581072	1		
	2		
	3+		
Induced with pre-eclampsia			
4088/571640	1		
	2		
	3+		
Induced with PPROM			
1137/567472	1		
	2		
	3+		
Induced with other causes			
9512/575847	1		
	2		
	3+		



Data: from all Scottish NHS hospitals, 1980-2008, 732 719 nulliparous women with a first live birth

Evidence for a dose-response relationship with all PTB outcomes

Oliver-Williams et al. 2015

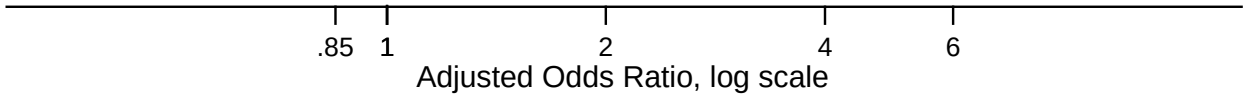
MISCARRIAGE & PTB SUBTYPES

PTB can occur at a range of different gestational ages: 24-36 weeks gestation:

1) Extremely PTB → 24-28 weeks
2) Very PTB → 29-32 weeks
3) Moderate PTB → 33-36 weeks

MISCARRIAGE & PTB SUBTYPES – GESTATIONAL AGE

Cases/Total	Gestational Age (weeks)	Odds Ratio (95% CI)	p-value
All-cause PTB			
2929/689681	24-28		
7156/693908	29-32		
35882/722634	33-36		
Spontaneous			
1883/688635	24-28		
3525/690277	29-32		
25054/711806	33-36		
Induced			
654/687406	24-28		
2250/689002	29-32		
7767/694519	33-36		
Induced with pre-eclampsia			
392/686755	24-28		
1377/686750	29-32		
3058/686773	33-36		
Induced with PPROM			
86/686449	24-28		
271/685644	29-32		
780/684495	33-36		
Induced with other causes			
565/686928	24-28		
1981/687354	29-32		
6966/690681	33-36		



Risk of all PTB outcomes associated with a history of 1+ miscarriages, varied over gestational age

- Except for induced PTB due to pre-eclampsia

Stronger associations were found for births at 24-28 weeks than at 33-36 weeks

- Except for induced PTB due to pre-eclampsia

Oliver-Williams et al. 2015

POSSIBLE MECHANISMS

Hypothalamic-pituitary-adrenal (HPA) axis

- The stress of having a previous miscarriage may activate the HPA axis
  - Particularly stress hormones: glucocorticoids, primarily, cortisol.
- Parturition in women involves a progressive cascade of events initiated by HPA activation
  - In term births this is largely driven by the fetal HPA axis.
  - In preterm births the maternal HPA axis may drive the process

Women with recurrent miscarriage have decreased levels of lipoxin A4, which controls glucocorticoid activities.

Xu et al. 2013

POSSIBLE MECHANISMS

Surgical management of miscarriage

- Dilation and curettage (D&C)
  - D&C: widening/opening of the cervix (*dilation*) and the contents of the uterus are removed by scraping and scooping (*curettage*).
- Prostaglandins use
  - Synthetic prostaglandins are used to soften and dilate the cervix
  - D&C without prostaglandins there is a risk of causing damage to the cervix.
    - D&C without prostaglandins was used in previous decades.

IMPLICATIONS OF SURGICAL MANAGEMENT

If D&C without prostaglandins causes cervical damage then –

1) A change in management of miscarriage over time would lead to a weaker association between miscarriage and PTB over time.

As D&C is also used for surgical abortion –

2) A similar pattern of PTB risk with therapeutic abortion would be expected

EVIDENCE FOR SURGICAL MANAGEMENT MECHANISM

Data: Prospective cohort study, 2004-2011, 5,575 healthy nulliparous women from NZ, Australia, the UK and Ireland

- Risk is given relative to women with no previous pregnancy loss (miscarriage or abortion)

	Spontaneous PTB OR (95% CI)	Absolute risk
1 previous miscarriage, managed by D&C	1.64 (1.08-2.50)	6%
1 previous abortion, managed by D&C	1.83 (1.35-2.48)	7%

McCarthy et al. 2013

EVIDENCE FOR SURGICAL MANAGEMENT MECHANISM

Changes in the management of miscarriage over time may lead to a change in the magnitude of the association between miscarriage and PTB

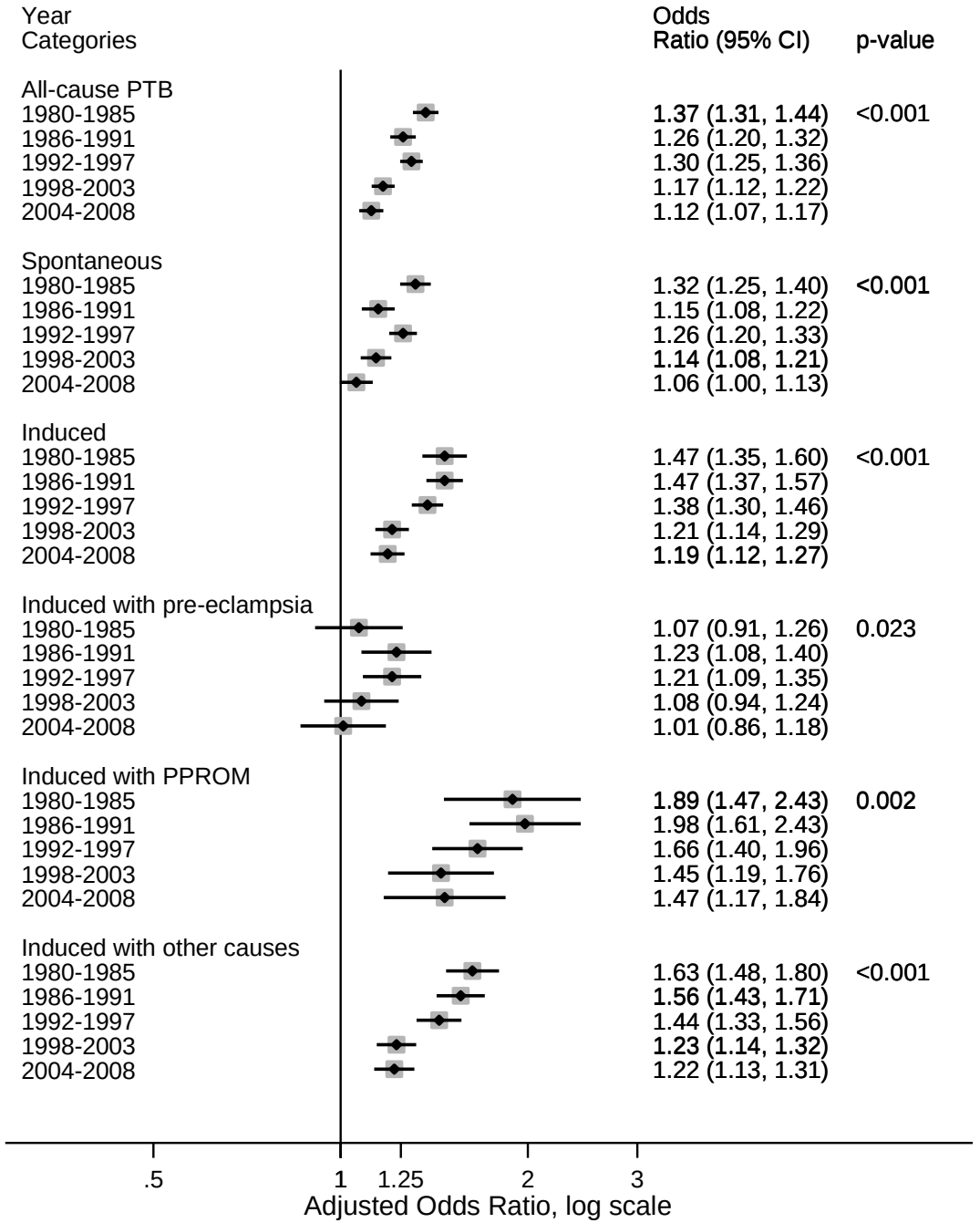
Evidence for change over time:

Data: All Scottish NHS hospitals, 1980-2008

Results stratified by category of year of delivery

Weakening of the association between a 1-unit increase in miscarriage and all PTB outcomes

- except inducted with pre-eclampsia



Oliver-Williams et al. 2015

IMPLICATIONS OF SURGICAL MANAGEMENT

If D&C without prostaglandins causes cervical damage then –

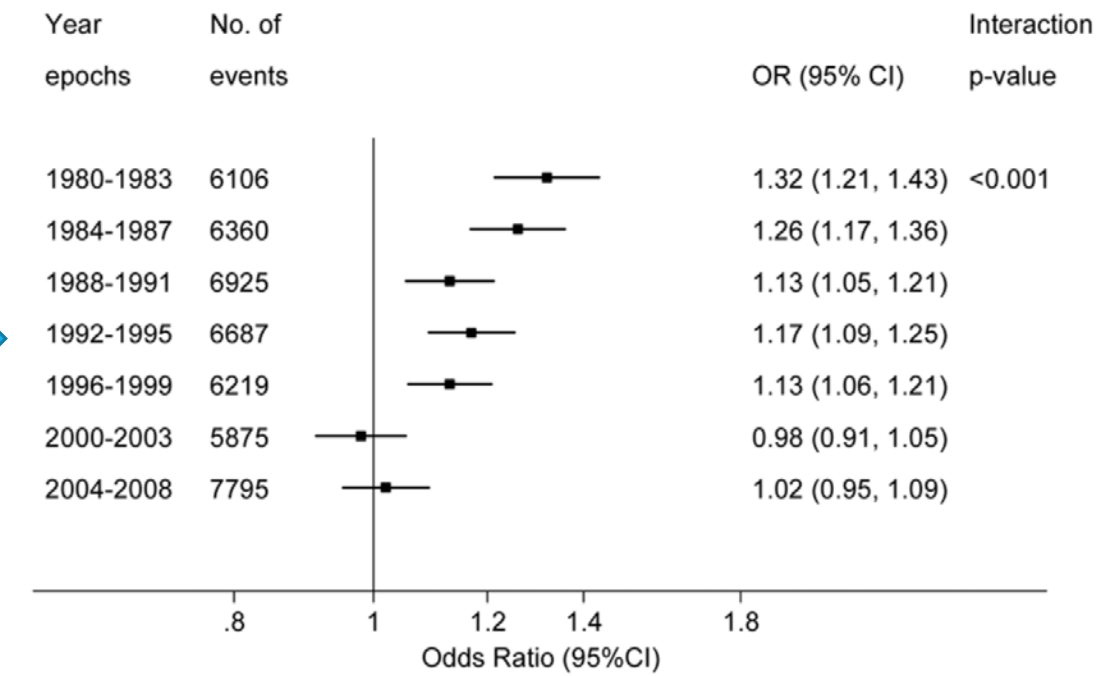
1) A change in management of miscarriage over time would lead to a weaker association between miscarriage and PTB over time.
   a) DEMONSTRATED CHANGE IN ASSOCIATION WITH TIME

As D&C is also used for surgical abortion –

2) A similar pattern of risk of PTB with therapeutic abortion would be expected

EVIDENCE FOR SURGICAL MANAGEMENT MECHANISM

Evidence of change in association between therapeutic abortion & all-cause PTB over time



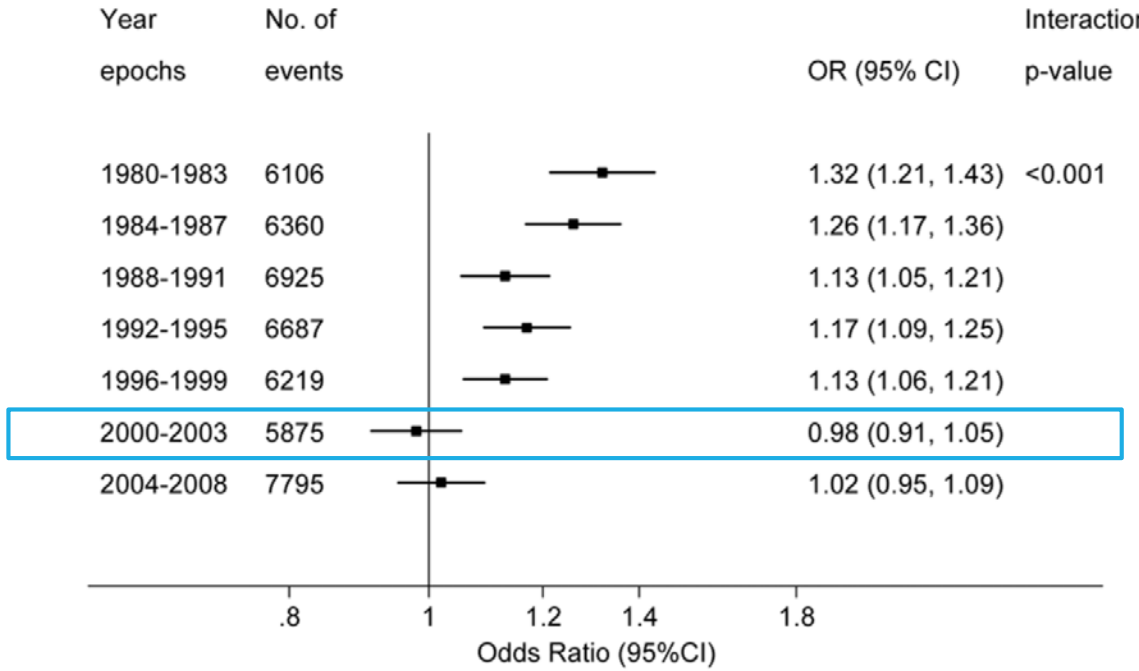
What about change in management?

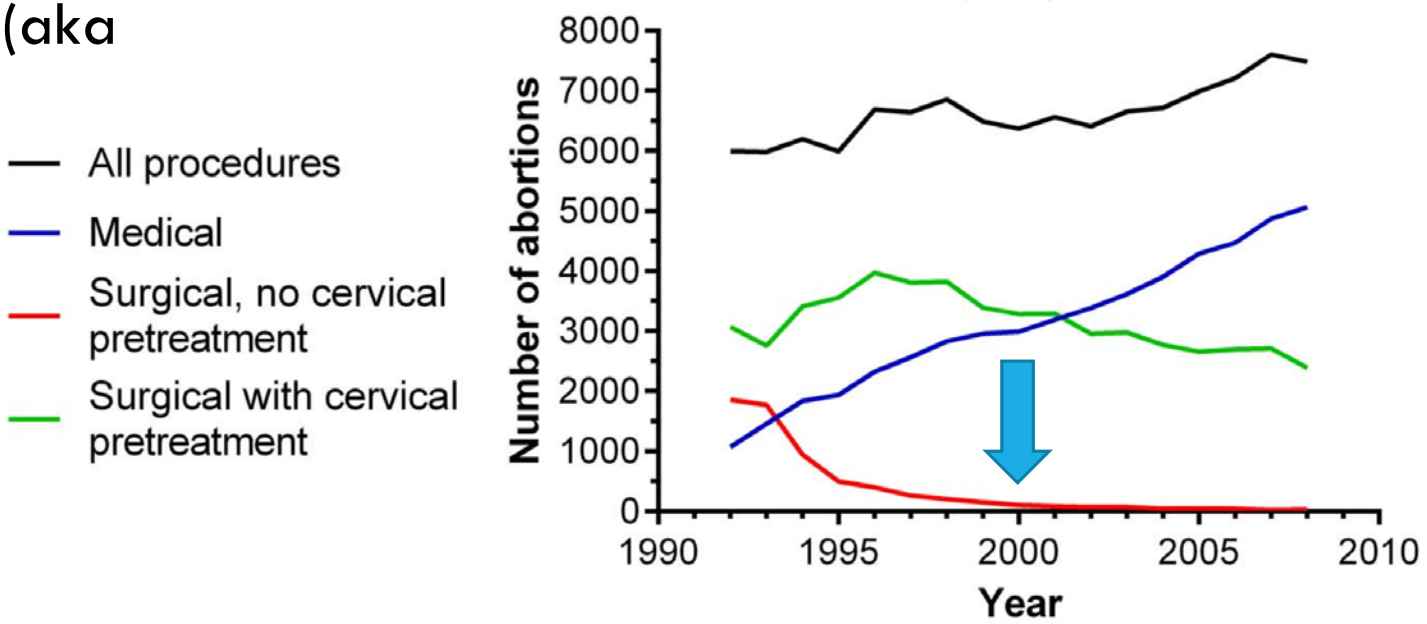
No data collected on method of miscarriage management in Scotland, but there is data for therapeutic abortion, which also uses D&C with/without prostaglandins

Oliver-Williams et al. 2013.

EVIDENCE FOR SURGICAL MANAGEMENT MECHANISM

- The loss of abortion-PTB association occurs at 2000-3
- At the same time, surgical abortions without cervical pre-treatment (aka prostaglandins) stopped





Oliver-Williams et al. 2013.

FURTHER VARIATION IN PTB RISK AFTER MISCARRIAGE

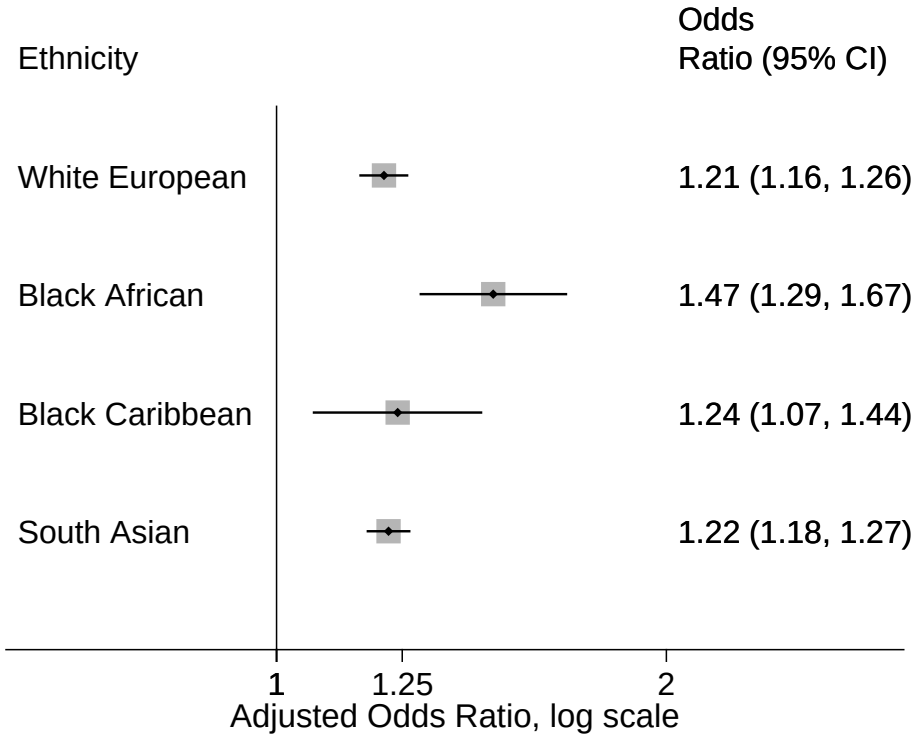
Other factors also influence the association between PTB risk after miscarriage:

1) Ethnicity
2) Inter-pregnancy Interval

FURTHER VARIATION IN PTB RISK AFTER MISCARRIAGE: ETHNICITY

Data: collected in London hospitals, 1988-2000, 196,040 nulliparous women

- A history of 1+ miscarriages was associated with preterm birth in all racial groups, but was strongest in black African women



Oliver-Williams et al. 2015

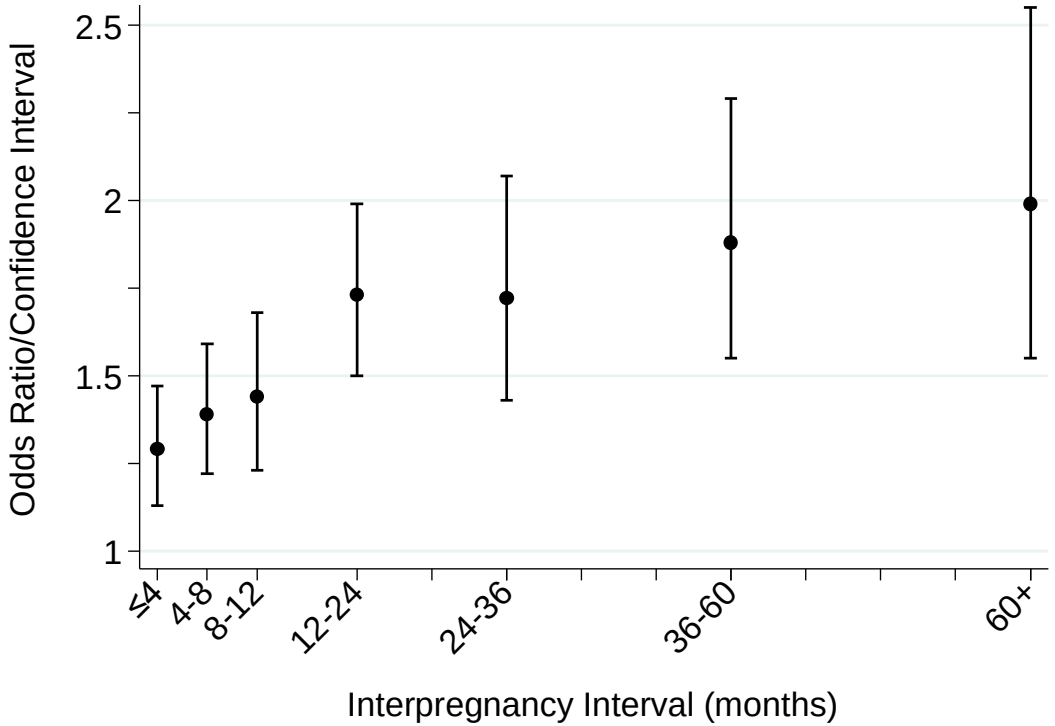
ETHNICITY: FURTHER VARIATION IN PTB RISK AFTER MISCARRIAGE

- Management of miscarriage is unlikely to vary by race
- However, there are racial disparities in cervical insufficiency.
  - Black women are at two-fold greater risk of cervical insufficiency than white women, which could compound any cervical damage arising from surgical management of miscarriage.

Oliver-Williams et al. 2015

INTER-PREGNANCY INTERVAL: FURTHER VARIATION IN PTB RISK AFTER MISCARRIAGE

Data: Danish population registries, 45,449 women having a livebirth preceded by a miscarriage and 9,752 women with two consecutive livebirths



Inter-pregnancy interval (months)	PTB OR (95%CI)	Very PTB (<34 weeks) OR (95%CI)
≤4	1.29 (1.13-1.47)	1.60 (1.30-2.02)
4-8	1.39 (1.22-1.59)	1.62 (1.27-2.06)
8-12	1.44 (1.23-1.68)	1.59 (1.20-2.11)
12-24	1.73 (1.50-1.99)	2.66 (1.76-2.91)
24-36	1.72 (1.43-2.07)	2.44 (1.78-3.34)
36-60	1.88 (1.55-2.29)	2.17 (1.53-3.09)
60+	1.99 (1.55-2.55)	2.22 (1.42-3.47)

Adjusted for: mother's age, social status at enrolment, change of social status between the two pregnancies

Basso et al. 1998

POSSIBLE MECHANISMS BEHIND INTER-PREGNANCY INTERVAL VARIATION

- Earlier pregnancy losses led to a shorter inter-pregnancy interval – earlier pregnancy losses are less likely to require surgical management.
- A pregnancy may enhance the functional capacity of the reproductive system, which can wane over time, and with longer intervals the risks to a mother and baby may resemble those in a primigravida.
- Factors associated with underlying subfertility, which can increase the time to the next pregnancy, could result in adverse perinatal outcomes.

MISCARRIAGE AND OTHER OBSTETRIC OUTCOMES

Miscarriage has been found to be associated with a range of other outcomes

1) Neonatal Death
2) Stillbirth
3) Delivery of a small for gestational age / low birth weight infant
4) Miscarriage Recurrence
5) Other outcomes

MISCARRIAGE AND OTHER OBSTETRIC OUTCOMES

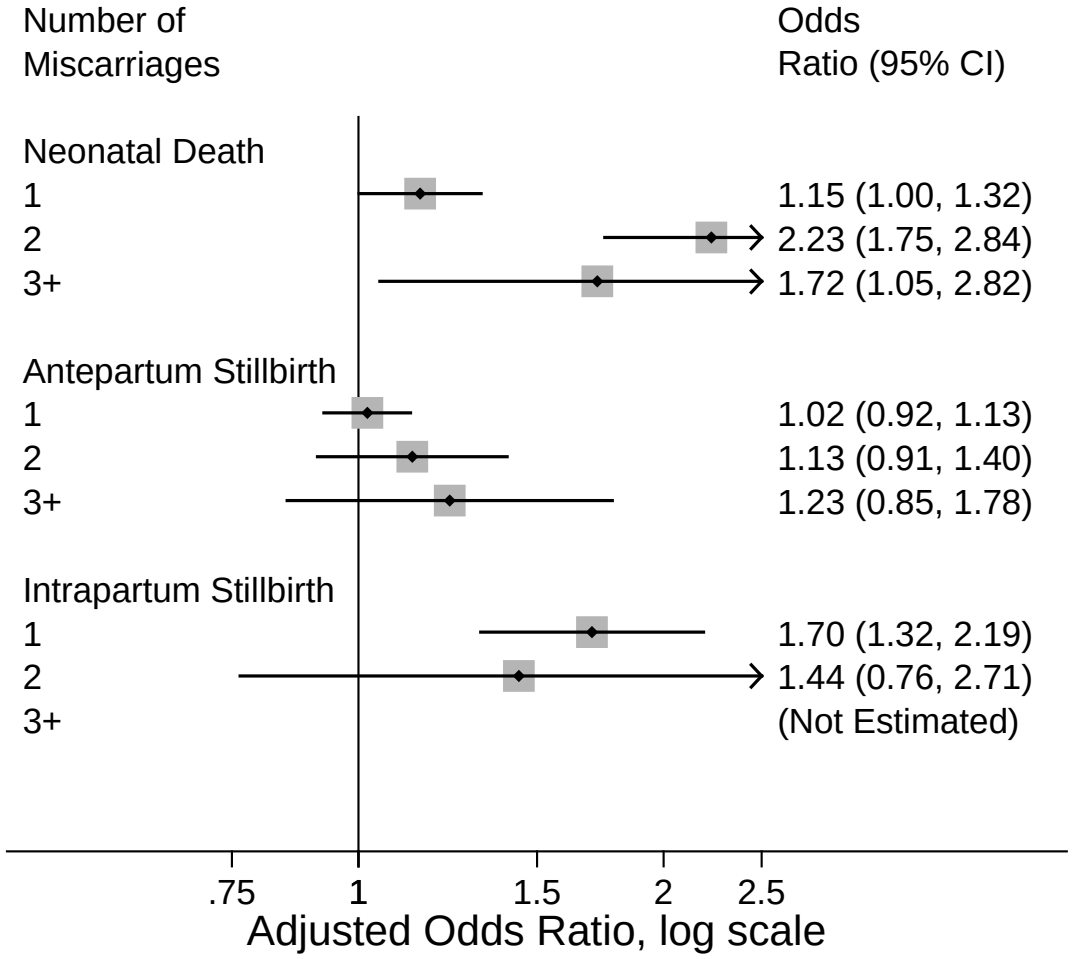
Neonatal Death

- Risk of neonatal death for women with a miscarriage, compared with primiparous women: OR=2.3 (99%CI: 1.1-4.8)
- Increased risk
- Risk attenuates with adjustment for prematurity

Stillbirth

- Risk of delivering a stillborn infant in women with a miscarriage, compared with primiparous women:

  OR=3.6 (99%CI: 2.0-6.5)
- APSB
  - Increased risk? & dose-response relationship
- IPSB
  - Increased risk

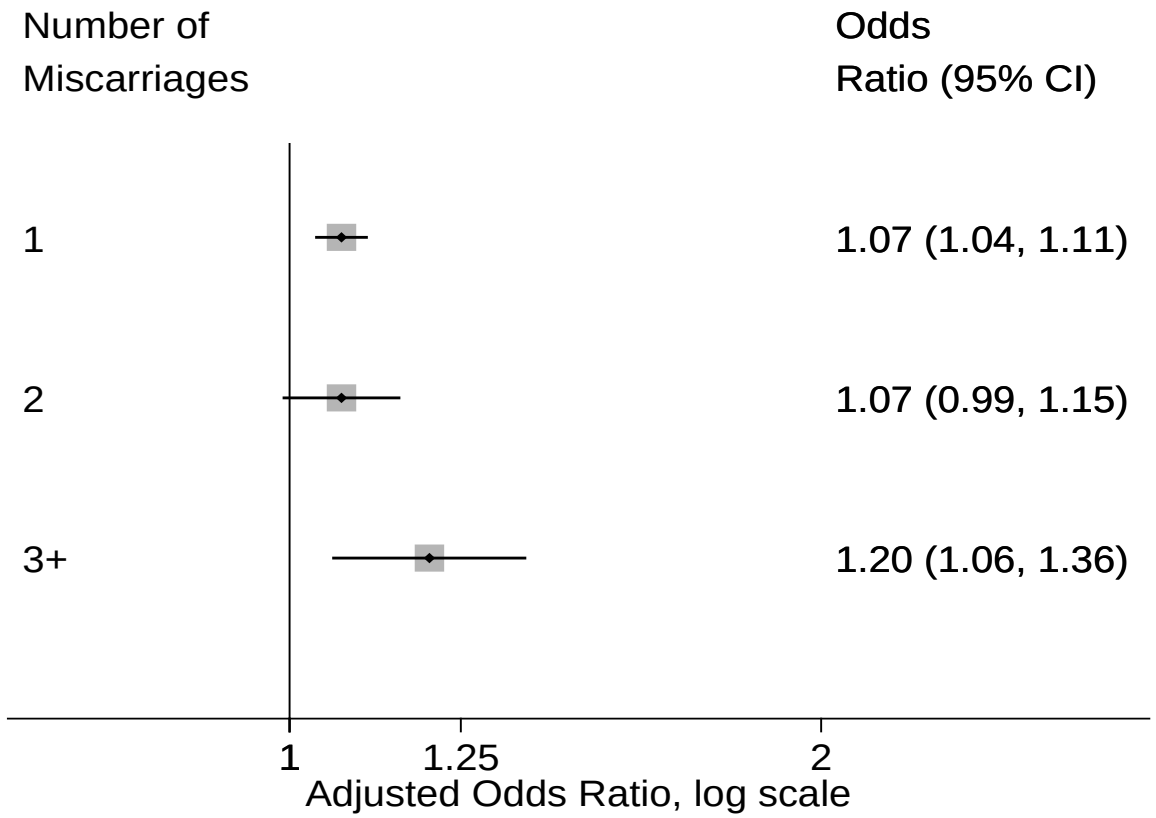


MISCARRIAGE AND SMALL FOR GESTATIONAL AGE / LOW BIRTH WEIGHT INFANT

Risk of delivery of an infant with birthweight <2500g in women with a miscarriage, compared with primiparous women: OR=1.6 (1.3-2.1)

Increased risk for delivery of a small for gestation age infant

Data: All Scottish NHS Hospitals, 1980-2008

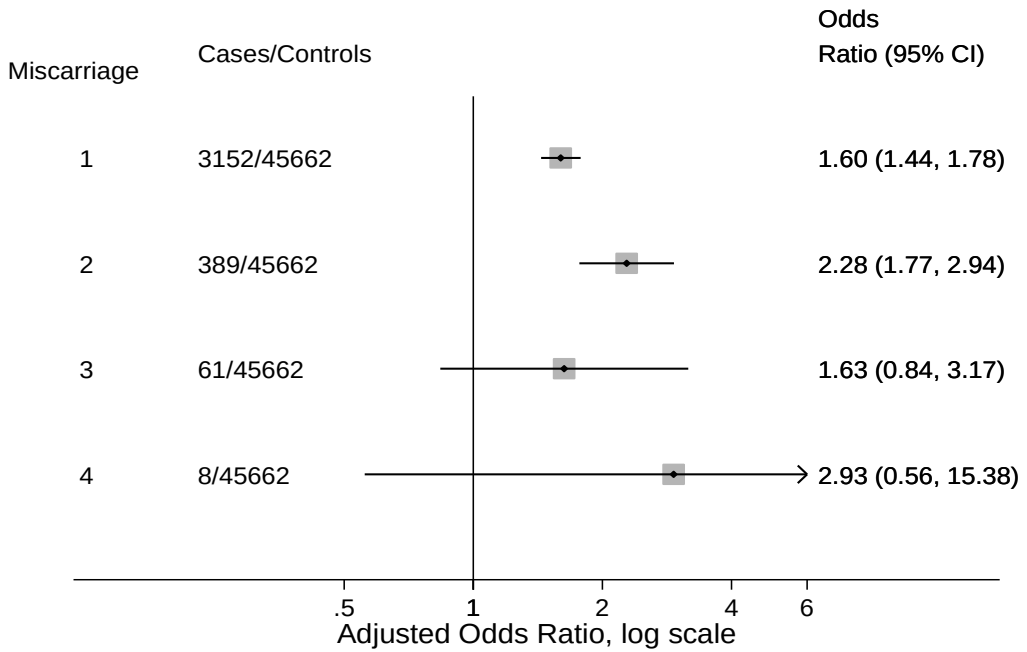


MISCARRIAGE AND OTHER OBSTETRIC OUTCOMES

Miscarriage recurrence

Data: Scottish Databank, 1950-2000, 151,011 pregnancies.

The risk of the next pregnancy ending in miscarriage was modelled relative to women with no previous miscarriage.



Risk of a subsequent miscarriage was greater after 1 miscarriage, and this increased further after 2 miscarriages.

Adjusted for age, square of age, year of event & smoking

Bhattacharya et al. 2010

INTER-PREGNANCY INTERVAL AFTER MISCARRIAGE AND OTHER OBSTETRIC OUTCOMES

Data: from Scottish hospitals, 1981-2000, 30,937 women who had a miscarriage in their first recorded pregnancy and subsequently became pregnant

Inter-pregnancy interval (months)	Miscarriage OR (95%CI)	Ectopic pregnancy OR (95%CI)	Induction of labour OR (95%CI)
<6	0.66 (0.57-0.77)	0.48 (0.34-0.69)	1.08 (1.02-1.23)
6-12	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
12-18	0.98 (0.80-1.21)	0.99 (0.63-1.57)	0.96 (0.85-1.09)
18-24	0.99 (0.78-1.27)	0.65 (0.34-1.23)	1.05 (0.89-1.23)
>24	0.99 (0.84-1.18)	1.97 (1.42-2.72)	0.94 (0.82-1.08)

Adjusted for maternal age at first pregnancy, social deprivation category, year of first miscarriage & other obstetric outcomes

Basso et al. 1998

MISCARRIAGE AND OTHER OBSTETRIC OUTCOMES

Less or inconsistent evidence for:

- Pre-eclampsia
  - Decreased risk of pre-eclampsia, OR=0.23 (0.0006-1.43) relative to nulliparous women
  - Specifically late miscarriage (13-27 weeks), whereas early miscarriage did not.
  - Possible mechanism: Enhanced immnuological tolerance, as pre-eclampsia has been proposed to develop from an immunologic intolerance between maternal and foetal/paternal tissues
- Low Apgar score
  - 9.7% of women with 1 previous miscarriage, vs 5.3% in nulliparous & 4.4% in primparous women
- Congenital malformations
  - 12.0% of women with 1 previous miscarriage, vs 6.3% in nulliparous & 5.4% in primparous women
- Bleeding in early pregnancy
  - RR = 1.57, CI 95% = 1.41–1.75, compared to primiparous women.
- Caesarean delivery
  - RR = 1.25, CI 95% = 1.07–1.47; compared to primiparous women

Eras et al. 2000; Campbell et al. 1985; Schoenbaum et al. 1980; Kashanian et al. 2006

OUTCOMES FOLLOWING 2ND TRIMESTER MISCARRIAGE

Less research on 2nd trimester miscarriage

- 2nd trimester miscarriage recurrence
  - Greater risk compared to those with prior PTB, OR=15.2 (95%CI: 2.9-80.2), or a full-term delivery, OR=24.4 (95%CI: 2.8-210.3)
- Preterm Birth
  - An inter-pregnancy interval of 6 months or less had no significant effect on the risk of subsequent second-trimester loss (adjusted OR=0.83, 95%CI: 0.27-2.52) or PTB (AOR=1.32, 95%CI: 0.20-8.60).

Edlow et al. 2007

OUTCOMES FOLLOWING 2ND TRIMESTER MISCARRIAGE

Data: American women with a pregnancy loss at 13-24 weeks

5% had a subsequent Stillbirth

6% Neonatal death

- Higher rates than either women who delivered preterm in their index pregnancy, or those who delivered at term.

However, few studies have looked at risk in relation to miscarriage treatment

Goldenberg et al. 1993

KEEP IN MIND

A number of issues and limitations arise when assessing miscarriage:

1) Recall bias
2) Ascertainment problems
3) Sample sizes for some of these studies, (especially those limited to second trimester miscarriage) are small, resulting in wide confidence intervals
4) Data from hospital records may only include women who have come into hospital contact for their miscarriage – so results may not be generalizable to all women
5) Selection of the correct comparison is a challenging issue
   a) Nulliparous women?
   b) Primiparous women?
   c) Women with 1 previous therapeutic abortion?

SUMMARY

1) Miscarriage is associated with increased PTB risk
   a) Found for a range of different causes of PTB
   b) Stronger associations are found for PTBs at an earlier gestational age
2) D&C without prostaglandins may be a cause behind Miscarriage – PTB association
   a) Evidenced by a weakening of the association over time, mirroring the change in treatment practices
   b) Similar association between abortion & PTB which has also weakened over time
   c) Activation of the HPA-axis may be another possible mechanism
3) Ethnicity & inter-pregnancy interval influence obstetric outcomes after miscarriage
4) Prior miscarriage has also been found to be associated with other adverse outcomes including neonatal death and stillbirth
   a) These may be partly influenced by the risk of prematurity that has been found previously
   b) Unfortunately, few studies have looked at risk in relation to miscarriage treatment

ACKNOWLEDGEMENTS

FURTHER VARIATION IN PTB RISK AFTER MISCARRIAGE: INTER-PREGNANCY INTERVAL

Data:

An interpregnancy interval >12 months associated with an increased risk of PTB compared with women who conceived <6 months later: OR=2.8 (95%CI: 1.9–4.8), adjusted for smoking, pregnancy specific variables.

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