National Women's Health Study (NWHS)

A population-based survey of miscarriage and infertility

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The Miscarriage Association

COMMUNITY FUND

The Miscarriage Association

Miscarriage

- Relatively under-researched condition, partly because of difficulty in studying events in early pregnancy

- Studies usually clinically based, leading to incomplete ascertainment of early miscarriage (selection bias) and can also be limited in ability to consider past reproductive outcomes

- Difficulty in advising women how best to maximise their chances of a successful pregnancy due to a lack of data

- Recognition that guilt is an important factor, so even negative results could be of value

Need to ask the women themselves

The Miscarriage Association

Known Risk Factors

- Mother's age
- Previous fetal death
- Infertility
  … however, interaction between age, parity, infertility, previous pregnancy loss are complex and not entirely understood
- Infections (STDs, malaria), chronic illness
- Nausea associated with reduced risk

Unconfirmed/inconsistent risk factors include:

- Maternal smoking
- Alcohol consumption
- Caffeine intake
- Stress and emotional well-being
- Exercise
- Diet
- Occupational exposures

Many behavioural and social risk factors have been reported, but most remain controversial or unconfirmed; few studies have examined these in the context of nausea or other potential confounders

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Specific Objectives with respect to miscarriage

- To obtain population-based estimates of miscarriage prevalence in the UK

- Investigate the association between biological, lifestyle and behavioural factors on risk of miscarriage

Methods - BMC Public Health 2004; 4:35

Results – BJOG 2007; 114:170-186

NWHS

- Unusual

→ Study subjects <u>not</u> identified via medical records of any kind

… but from the UK electoral register
… so "population-based"

→ Not outcome restricted
… woman's whole reproductive experience

NWHS

- 60,000 women randomly selected from computerised electoral registers (England, Scotland, Wales, N Ireland)
- Only women likely to be between the ages of 18-55 included (based on name)

Postal survey - Two-stage design

1: One-page questionnaire
   - screening questions
   - brief details of full reproductive history

2: Detailed questionnaire to all women ever pregnant / attempting pregnancy
   - detailed reproductive history
   - questions about themselves and behavioural and lifestyle factors in pregnancy (plus the father)

- Information leaflet enclosed with questionnaire
- Freephone helpline
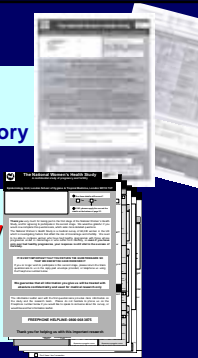
Response

Stage 1 (screening):
Response from 26,120 women
(30,661 pregnancies)

46%

Stage 2 (targeted):
Response from 7,508 women
(18,391 pregnancies)

73%

Stage 1 response of 46% (26,120 women)

Good for "cold" postal survey

BUT … ?biased response?

Need unbiased data for population estimates

→ **Compared with published national data (ONS)**
(stillbirth rates, multiple delivery rates, age at first birth)

NWHS data in line with key reproductive indicators
(particularly last 20 yrs)

Confident data representative

Results

- Huge amount of data
- Some of the more interesting findings will be highlighted
  - Population based estimates
  - Risk factors

LIFETIME RISK OF MISCARRIAGE
among women aged >=40 years at survey

20% women had had one or more miscarriage
in their reproductive lifetime *(majority had one only)*

1.4% women had had >=3 **miscarriages**

No. miscarriages per woman aged >=40 yrs *(n = 6,640)*
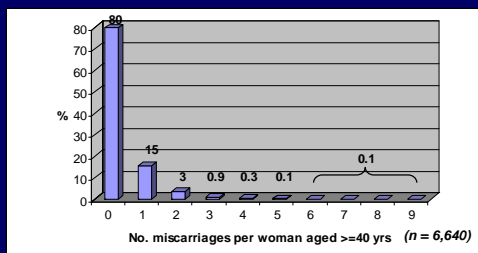
LIVEBIRTH AFTER MISCARRIAGE
among women aged >=40 years at survey

Among women
who had suffered at least one miscarriage
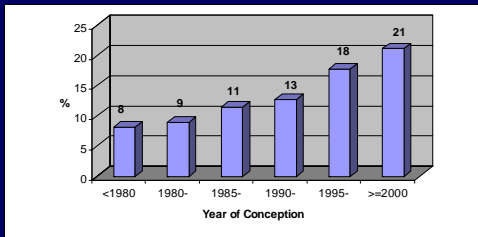and had one or more subsequent pregnancy

91%
had had at least one livebirth

PREGNANCY-BASED MISCARRIAGE RATES
All Stage 2 pregnancies

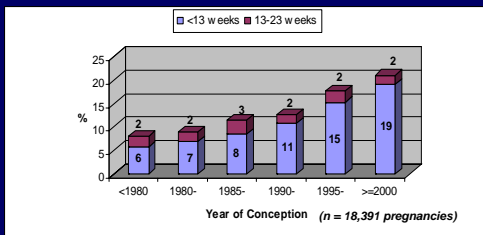**Strong increasing trend over time**

… most probably due to increased detection

(n = 18,391 pregnancies)

PREGNANCY-BASED MISCARRIAGE RATES
All Stage 2 pregnancies

Marked increase in early miscarriage over time

(n = 18,391 pregnancies)

Risk factors for first trimester miscarriage
(Case-control study)

603 cases
who had had a
first trimester
miscarriage
1980->

6,116 controls
who had had a
pregnancy progressing
beyond 13 wks
1980->

Most recent pregnancy (plus all miscarriages since 1995)

Results virtually identical if restrict to
*pregnancies conceived >=1995*

"Established" risk factors

Pregnancy Order and Previous Miscarriage

Risk almost doubles if you have had a miscarriage
BUT
Risk reduces by almost half after a successful pregnancy

Preg	No previous miscarriages	1 previous miscarriage	2 previous miscarriages	3 previous miscarriages
1	1.0 (Ref)	-	-	-
2	0.5 (0.4 – 0.7)	1.9 (1.2 – 2.9)	-	-
3	0.7 (0.5 – 1.0)	0.9 (0.6 – 1.3)	3.3 (1.5 – 7.4)	-
4	0.7 (0.4 – 1.0)	0.9 (0.6 – 1.4)	1.5 (0.8 – 2.8)	3.0 (0.8 – 12.2)

Adjusted for year of conception and maternal age

Maternal age at conception
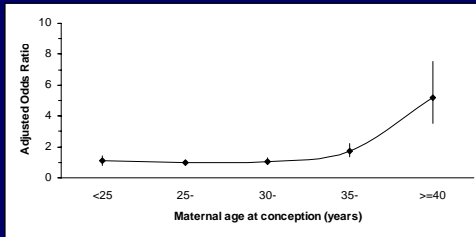
Age (yrs)	Adjusted Relative Risk (95% CI)
<25	1.1 (0.8 - 1.5)
25-29	1.0 (Reference)
30-34	1.1 (0.9 - 1.3)
35-39	1.8 (1.4 – 2.2)
>=40	5.2 (3.5 – 7.5)

Adjusted for year of conception, previous miscarriage and previous livebirth

Time taken to conceive

	Frequency (%) among controls	Adjusted* Relative Risk (95% CI)	Further adjusted for fertility treatment
Unplanned	29%	2.2 (1.0 - 1.8) ?????	2.2 (1.8 – 2.8)
<3	42%	1.0 (Ref)	1.0 (Ref)
3 - 6	15%	1.3 (1.0 – 2.1)	1.3 (1.0 – 1.8)
7 – 11	7%	1.5 (1.8 – 3.2)	1.4 (1.0 – 2.1)
>=12 mths	8%	2.4 (1.8 – 3.2)	2.0 (1.4 – 2.8)

*Adjusted for year of conception, maternal age, previous miscarriage, previous livebirth

Fertility diagnosis

	Frequency (%) among controls	Adjusted* Relative Risk (95% CI)	Further adjusted for fertility treatment
Ovulation problems	3%	1.3 (0.9 - 1.9)	1.0 (0.7 – 1.6)
Tubal problems	1%	2.7 (1.5 – 4.9)	2.3 (1.2 – 4.2)
Endometriosis	1%	1.2 (0.6 – 2.4)	1.0 (0.5 – 1.9)
Other female diagnosis	2%	1.7 (1.2 – 2.6)	1.5 (1.0 – 2.2)
Poor sperm quality	2%	1.4 (0.9 – 2.1)	1.2 (0.8 – 1.9)
Other male diagnosis	1%	2.0 (1.0 – 3.9)	1.7 (0.9 – 3.5)
"Unexplained"	2%	1.0 (0.6 – 1.6)	0.8 (0.5 – 1.4)

Women may appear more than once in table; RRs relative to not having problem

*Adjusted for year of conception, maternal age, previous miscarriage, previous livebirth

The Father

Paternal Age
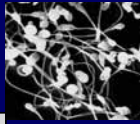
	Frequency (%) among controls	Adjusted Relative Risk (95% CI)
<25	7%	1.2 (0.8 - 1.7)
25 -	27%	1.0 (Ref)
30 -	38%	1.1 (0.8 – 1.3)
35 -	20%	1.2 (0.9 – 1.6)
40 -	6%	1.0 (0.7 – 1.5)
>=45	3%	1.6 (1.1 – 2.5)

Adjusted* for year of conception, maternal age, previous miscarriage, previous livebirth

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Change of father

	Frequency (%) among controls	Adjusted Relative Risk (95% CI)
First pregnancy	21%	1.3 (0.9 - 1.8)
Same father as previous pregnancy	73%	1.0 (Ref)
Different father from previous pregnancy	7%	1.7 (1.2 – 2.3)

Adjusted* for year of conception, maternal age, previous miscarriage, previous livebirth

Diet and behaviour

Pre-pregnancy BMI (weight/height^2)

	Frequency (%) among controls	Adjusted Relative Risk (95% CI)
<18.5 (underweight)	4%	1.7 (1.2 – 2.5)
18.5 – 24.9 (normal)	70%	1.0 (Ref)
25.0 – 29.9 (overweight)	20%	1.0 (0.8 – 1.2)
>=30 (obese)	7%	0.9 (0.7 – 1.3)

Adjusted for year of conception, maternal age, previous miscarriage, previous livebirth

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Nausea

Age (yrs)	Adjusted Relative Risk (95% CI)
No nausea	1.0 (Ref)
Nausea	0.3 (0.2 – 0.3)
Mild/moderate nausea	0.3 (0.3 – 0.4)
Severe nausea	0.1 (0.04 – 0.1)

*Adjusted for year of conception, maternal age, previous miscarriage, previous livebirth

Vitamin supplementation

	Frequency (%) among controls	Adjusted[*] Relative Risk (95% CI)	Further adjusted for nausea
No vitamins	38%	1.0 (Ref)	1.0 (Ref)
Any vitamins	62%	0.5 (0.4 – 0.6)	0.5 (0.4 – 0.7)
Folic acid	44%	0.5 (0.4 – 0.6)	0.5 (0.4 – 0.7)
Iron	18%	0.3 (0.2 – 0.4)	0.3 (0.2 – 0.5)
Zinc	1%	0.5 (0.2 – 1.2)	0.5 (0.2 – 1.3)
Vitamin C	2%	0.6 (0.3 – 1.0)	0.6 (0.3 – 1.1)
Pregnancy preparations	6%	0.5 (0.4 – 0.7)	0.6 (0.5 – 0.9)
Other multivitamin tablets	5%	0.6 (0.4 – 0.9)	0.7 (0.4 – 1.0)
Other vitamins	2%	0.5 (0.3 – 1.0)	0.6 (0.3 – 1.0)

Women may appear more than once in table; all RRs relative to no vitamins

[*]Adjusted for year of conception, maternal age, previous miscarriage, previous livebirth

Daily consumption of fresh fruit and vegetables

Fresh fruit & vegetables	Frequency (%) among controls	Adjusted[*] Relative Risk (95% CI)	Further adjusted for nausea
Less than once a day	7%	1.0 (Ref)	1.0 (Ref)
Every day/most days	93%	0.5 (0.4 – 0.7)	0.5 (0.4 – 0.7)

[*]Adjusted for year of conception, maternal age, previous miscarriage, previous livebirth

Other foods consumed every day

93% ate **dairy products** daily: 0.7 (0.5 – 1.0)

16% consumed **sugar substitutes** daily: 1.1 (0.9 - 1.4)

3% ate **soya products** daily: 1.1 (0.7 - 1.7)

55% ate **chocolate** daily: 0.8 (0.7 - 1.0)

Adjusted for year of conception, maternal age, previous miscarriage, previous livebirth, nausea

Results virtually identical if restrict to pregnancies conceived >=1995

The Caffeine story

Estimated caffeine consumption per day (mg/day)
(from coffee, tea and cola)

Caffeine (mg per day)	Frequency (%) among controls	Adjusted Relative Risk (95% CI)	Further adjusted for nausea
None	11%	1.0 (Ref)	1.0 (Ref)
<151	20%	1.2 (0.8 – 1.7)	1.0 (0.7 – 1.5)
151 – 300	25%	1.2 (0.9 – 1.8)	0.9 (0.6 – 1.3)
301 – 500	21%	1.5 (1.1 – 2.2)	1.0 (0.7 – 1.5)
> 500	23%	1.7 (1.2 – 2.4)	1.1 (0.8 – 1.7)

Trend: P=0.0003   Trend: P=0.67

*Adjusted for year of conception, maternal age, previous miscarriage, previous livebirth

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Alcohol and Smoking

Alcohol consumption in the first 12 weeks

(a) Frequency

Frequency of alcohol consumption	Frequency (%) controls	Adjusted* Relative Risk (95% CI)	Further adjusted for nausea
Did not drink	40%	1.0 (Ref)	1.0 (Ref)
Stopped when found pregnant	17%	1.1 (0.8 – 1.4)	1.0 (0.8 – 1.3)
Less than once a week	24%	1.1 (0.9 – 1.4)	1.0 (0.8 – 1.3)
At least once a week	18%	1.5 (1.2 – 1.9)	1.3 (1.0 – 1.6)
Every day	0.3%	3.8 (1.3 – 11.3)	3.2 (1.0 – 10.6)

*Adjusted for year of conception, maternal age, previous miscarriage, previous livebirth

Alcohol consumption in the first 12 weeks

(b) Amount

Average amount consumed per week (standard UK units)	Frequency (%) controls	Adjusted* Relative Risk (95% CI)	Further adjusted for nausea
None	50%	1.0 (Ref)	1.0 (Ref)
<7 units	13%	1.0 (0.8 – 1.3)	0.9 (0.7 – 1.2)
1 – 7 units	27%	1.3 (1.1 – 1.6)	1.2 (1.0 – 1.5)
>7 – 14 units	6%	1.2 (0.9 – 1.8)	1.2 (0.8 – 1.7)
> 14 units	3%	1.6 (1.1 – 2.5)	1.4 (0.9 – 2.3)

*Adjusted for year of conception, maternal age, previous miscarriage, previous livebirth

Smoking in the first 12 weeks

	Frequency (%) among controls	Adjusted* Relative Risk (95% CI)	Further adjusted for nausea
Did not smoke	76%	1.0 (Ref)	1.0 (Ref)
Smoked	24%	1.0 (0.9 – 1.3)	1.0 (0.8 – 1.2)
Stopped when found out pregnant	6%	0.8 (0.6 – 1.2)	0.8 (0.5 – 1.3)
<5 per day	6%	1.0 (0.7 – 1.4)	0.9 (0.6 – 1.2)
5-10 per day	6%	0.9 (0.6 – 1.4)	0.8 (0.5 – 1.2)
11-20 per day	5%	1.7 (1.2 – 2.4)	1.4 (1.0 – 2.1)
21-30 per day	1%	1.3 (0.6 – 3.0)	1.3 (0.6 – 2.9)

*Adjusted for year of conception, maternal age, previous miscarriage, previous livebirth

Work in pregnancy

Work during pregnancy

	Frequency (%) among controls	Adjusted* Relative Risk (95% CI)
Not in paid employment	35%	1.0 (Ref)
Full-time	34%	1.1 (0.9 – 1.4)
Part-time	27%	1.0 (0.8 – 1.3)
Unemployed / student	4%	1.3 (0.9 – 2.1)

Was your job generally demanding and/or stressful?

	Frequency (%) controls	Adjusted* Relative Risk (95% CI)	Further adjusted for nausea
No	90%	1.0 (Ref)	1.0 (Ref)
Yes	10%	1.2 (1.0 – 1.6)	1.3 (1.0 – 1.7)

*Adjusted for year of conception, maternal age, previous miscarriage, previous livebirth

Does stress (in general) during pregnancy affect risk ?

	Frequency (%) controls	Adjusted* Relative Risk (95% CI)	Further adjusted for nausea
Happy / relaxed / in control	61%	1.0 (Ref)	1.0 (Ref)
Stressed / anxious / depressed	19%	2.5 (2.0 – 3.0)	3.0 (2.5 – 3.8)
Periods of both	8%	1.1 (0.8 – 1.6)	1.2 (0.9 – 1.7)
Other	12%	1.4 (1.0 – 1.8)	1.7 (1.3 – 2.3)

*Adjusted for year of conception, maternal age, previous miscarriage, previous livebirth

No. of stressful/traumatic events in first 12 weeks (e.g. bereavement, divorce, serious illness)

	Frequency (%) controls	Adjusted* Relative Risk (95% CI)	Further adjusted for nausea
None	69%	1.0 (Ref)	1.0 (Ref)
1	25%	1.4 (1.1 – 1.7)	1.5 (1.2 – 1.8)
2	5%	1.6 (1.1 – 2.4)	1.7 (1.2 – 2.6)
>=3	1%	2.4 (1.1 – 5.3)	3.3 (1.4 – 7.7)

*Adjusted for year of conception, maternal age, previous miscarriage, previous livebirth

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Other significant risk factors
Adjusted* Relative Risk (95% CI)

- Not living with the father of the baby – 1.7 (1.3 – 2.4)
- Previous termination of pregnancy (ever) – 1.6 (1.2 – 2.2)
- Bleeding during sexual intercourse – 2.1 (1.5 – 3.1)
- Assisted conception – 1.8 (1.2 – 2.7)

*Adjusted for year of conception, maternal age, previous miscarriage, previous livebirth

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Summary of findings

(1) Factors associated with INCREASED risk of miscarriage

Socio-demographic factors
Maternal age >35 years
Not living with the father of the baby

Pre-pregnancy BMI
Being underweight

Obstetric factors
Previous miscarriage
Longer time to conception
Infertility problems, particularly tubal infertility
Assisted conception
Previous termination of pregnancy

Indicators of stress
Being stressed or anxious
Experiencing >=1 stressful/traumatic event
Having a stressful job

Alcohol
Regularly drinking alcohol
High alcohol consumption

Paternal factors
Changing partners
Paternal age >45 years

Other factors
Bleeding during sexual intercourse

(2) Factors associated with DECREASED risk of miscarriage

Obstetric factors
Previous livebirth
Nausea

Vitamins & diet
Taking vitamins (in particular folic acid & iron)
Eating fresh fruit & vegetables daily
Eating dairy products daily
Eating chocolate daily
(Possibly eating white meat and fish twice weekly or more)

Indicators of wellbeing
Feeling happy and relaxed
Planned pregnancy
Sexual intercourse (no bleeding)

(3) Factors found NOT TO BE ASSOCIATED with risk of first trimester miscarriage

Socio-demographic factors
Social class
Education

Obstetric factors
Pregnancy order (over and above effect of previous pregnancy outcome)
Short pregnancy interval
Pre-eclampsia in previous pregnancies

Work
Full-time work
Sitting or standing for 6 hours or more per day at work
Lifting heavy objects or people at work

Diet
Eating eggs, soya products, sugar substitutes *and red meat*
Caffeine consumption (after accounting for nausea)

Smoking and alcohol
Smoking
Moderate and occasional alcohol consumption (after accounting for nausea)

Exercise
Strenuous exercise

Paternal smoking and alcohol
Paternal pre-conceptual alcohol
Paternal pre-conceptual smoking (and during the first 12 weeks)

Note of Caution

Where we have found effects, we need to think carefully about "alternative" explanations
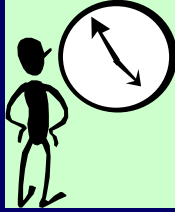
We have done a lot of statistical testing

Strengths

Population data which appears representative

Valuable data which is not available elsewhere

Thanks for listening

Any questions or thoughts on follow-up?

Full references

- Methods –

Maconochie N, Doyle P, Prior S.

The National Women's Health Study: Assembly and Description of a Population-based Reproductive Cohort.

BMC Public Health 2004; 4: 35

- Results –

Maconochie N, Doyle P, Prior S, Simmons R.

Risk Factors for First Trimester Miscarriage – Results from a UK-population-based Case-control Study.

BJOG 2007; 114: 170 - 186