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**Obstetric consequences of subfertility: A retrospective cohort study**

A L DoPierala<sup>a</sup>, S. Bhatta<sup>b</sup>, EA Raja<sup>d</sup>, S Bhattacharya<sup>b</sup> and S Bhattacharya<sup>c</sup>.

<sup>a</sup> School of Medicine and Dentistry, University of Aberdeen, Aberdeen, Scotland

<sup>b</sup> Obstetrics and gynaecology, Division of Applied Health Sciences , School of Medicine and Dentistry, Aberdeen Maternity Hospital, Aberdeen, Scotland

<sup>c</sup> Epidemiology Group, Division of Applied Health Sciences, School of Medicine and Dentistry University of Aberdeen, Aberdeen, Scotland

<sup>d</sup> Medical Statistics Team, Division of Applied Health Sciences, University of Aberdeen, Polwarth Building, Foresterhill, Aberdeen, Scotland

Corresponding author:

Dr Sohinee Bhattacharya

Lecturer Obstetric Epidemiology, University of Aberdeen

Dugald Baird Centre or Research on Women's Health

Aberdeen Maternity Hospital

Foresterhill

Aberdeen AB25 2ZI

Tel: +44 1224 438441

Fax: +44 1224 438486

e-mail: [sohinee.bhattacharya@abdn.ac.uk](mailto:sohinee.bhattacharya@abdn.ac.uk)

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## Abstract

**Objective:** To compare the risk of adverse pregnancy outcomes in women with and without subfertility and to investigate whether fertility treatment contributes to the adverse outcomes.

**Design:** Register based retrospective cohort study

**Setting:** Aberdeen, Scotland

**Population:** The exposed group included women with subfertility attending Aberdeen Fertility Clinic between 1989 and 2008 and delivering a singleton n= 3188 or twin n=350 at Aberdeen Maternity Hospital between 1992 and 2009. The unexposed cohort included the remainder of women, singleton=52443, twin=1125 delivering at Aberdeen Maternity Hospital between 1992 and 2009.

**Methods:** The Aberdeen Fertility Centre database and Aberdeen Maternity and Neonatal Databank were linked using Community Health Index numbers. Regression models were used to calculate risk ratios and 95% confidence intervals adjusting for potential confounders.

**Main outcome measures:** Maternal outcomes including preeclampsia, antepartum haemorrhage, preterm birth, induction of labour; delivery outcomes including operative vaginal delivery, caesarean section and offspring outcomes including low birthweight, stillbirth and neonatal death.

**Results:** Women with a history of subfertility and delivering a singleton were at a higher risk of pre-eclampsia (adjusted risk ratios and 95% confidence intervals) (1.18, 1.02-1.37), antepartum haemorrhage (1.32, 1.18- 1.47), induction of labour (1.21, 1.11-1.31) and very preterm delivery (<32 weeks) (1.96, 1.53- 2.49). Subfertile women delivering twins were at a higher risk of being delivered by emergency caesarean section (2.14, 1.26- 3.66). There were no significant differences in adverse outcomes for singleton pregnancies between the treated and untreated subfertile couples.

**Conclusion:** Subfertility per se, rather than fertility treatment was associated with increased risk of adverse outcomes in singleton pregnancies.

**Key words:** Subfertility, obstetric outcomes, pregnancy complications, cohort study.

## Introduction

Approximately one in six couples in the United Kingdom experience infertility, defined as a failure to conceive following 12 months of regular unprotected intercourse. Many of these couples subsequently go on to have children either spontaneously or with the assistance of fertility treatment<sup>1,2</sup>.

Subfertile women conceiving spontaneously appear to be at a higher risk of obstetric and perinatal complications<sup>3-5</sup> which persists after adjusting for factors such as age and parity<sup>3</sup>. A recent systematic review and meta-analysis<sup>5</sup> of 14 studies has reported a higher risk of preterm birth in subfertile women, pooled crude odds ratio 1.38 (95% CI 1.25-1.54). The pooled analysis was done on a total of 1 269 758 births of which 68 885 were preterm. 8.2% of births in the infertile group were preterm compared to 5.4% in the fertile group<sup>5</sup>. The common link between subfertility and adverse outcomes has not been established. Previous studies investigating adverse pregnancy outcomes in subfertile women have presented data on singleton pregnancies<sup>3,4,5</sup>. There are fewer studies on twin pregnancy outcomes in subfertile women presumably due to small sample sizes and the more complex analysis such as multilevel modelling or generalised estimating equations with robust standard errors required due to non-independence of the outcomes studied.

Pregnancies following fertility treatment have a higher incidence of adverse maternal and perinatal outcomes<sup>6-10</sup> and underlying subfertility is thought to be the major risk factor<sup>11</sup>. There is therefore a need to disentangle the contributions of subfertility per se and fertility treatment towards the development of adverse pregnancy outcomes<sup>5</sup>.

Our study aims to investigate maternal, delivery and offspring outcomes in singleton and twin pregnancies in women with a history of subfertility compared to a population with normal fertility. We also aim to evaluate whether fertility treatment including ovulation induction, intrauterine insemination and in vitro- fertilisation, increased the risk of adverse

pregnancy outcomes by comparing pregnancy outcomes in treatment dependent and treatment independent conceptions in subfertile women.

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**Methods:**

**Ethics Statement:** The chairs of the steering committees for Aberdeen Maternity and Neonatal Databank and Aberdeen Fertility Centre Database approved the use of the data for this study. Formal ethical approval was not considered necessary by the North of Scotland Research Ethics Service.

**Study Population:** This study was conducted by linking routinely collected information from two databases, Aberdeen Maternity and Neonatal Databank (AMND) and the Aberdeen Fertility Centre Database (AFCD). The AMND was set up in 1950 and holds routinely collected information on all pregnancies occurring at Aberdeen Maternity Hospital and is the only maternity hospital serving the area in the North East of Scotland<sup>12</sup>. Data in AMND is recorded in a standardised manner using the International Classification of Diseases (ICD) 9 codes. The second database, AFCD was established in 1989 and contains routinely collected clinical data on all couples attending Aberdeen Fertility Clinic, which is the only fertility centre in the region<sup>3</sup>. The data bases are subjected to stringent quality checks. Details of the data quality assurance mechanism for the AMND can be accessed online at [www.abdn.ac.uk/amnd](http://www.abdn.ac.uk/amnd).

All deliveries taking place in Aberdeen Maternity Hospital between 1st January 1992 and 31st December 2009 were considered for inclusion. There were 55,631 singleton and 1,475 twin deliveries during this period of which 3,188 and 350 had a history of subfertility respectively. Maternal characteristics including age, Body Mass Index at the time of booking for antenatal care, parity, socio-economic status and smoking status, the mode of delivery as well as any maternal and offspring complications relevant to our outcomes were extracted from the AMND. The Community Health Index number (a unique numeric identifier, allocated

to each patient on first registration with the health care system in Scotland) was used to link these patients to the AFCD. This enabled the identification of women who attended the fertility clinic in Aberdeen. The details of the type, duration and treatment of infertility were extracted from the AFCD. The duration of follow up of subfertile women was from presentation at Aberdeen Fertility clinic until delivery.

Study Design: A retrospective cohort study design was applied where women with subfertility formed the exposed cohort while the remainder of women who delivered during the same time period in the maternity hospital formed the unexposed cohort.

Women were defined as subfertile and referred to the fertility clinic if they had a delay in achieving conception for more than 12 months despite regular unprotected sexual intercourse or had a known condition causing subfertility such as amenorrhoea, polycystic ovaries or tubal damage.

Outcomes studied with definitions:

Maternal outcomes studied included pre-eclampsia (diastolic blood pressure  $> 90$  mm Hg on two occasions at least four hours apart or a single reading of  $>110$  mm Hg from 20 weeks gestation onwards in a previously normotensive woman associated with proteinuria of  $0.3\text{g}/24$  hours), antepartum haemorrhage (any bleeding from the vagina after 24 weeks gestation and until the onset of labour), placental abruption (premature separation of placenta prior to labour), placenta praevia (presence of placenta in the lower uterine segment), preterm birth (birth before 37 completed weeks gestation) and very preterm-birth (birth before 32 weeks of gestation).

Delivery outcomes studied were operative vaginal delivery, and elective & emergency caesarean sections.

Offspring adverse outcomes analysed were low birth weight (weight at birth of less than 2,500 grams), stillbirth (the delivery of a dead baby after 24 completed weeks of gestation)

and neonatal death (death of the neonate from the first day of life until the end of the first week following delivery).

Statistical analysis: Separate datasets were analysed for singleton and twin pregnancies.

Statistical analysis of maternal demographics was performed using the independent t-test for normally distributed continuous variables, Mann-Whitney U test for non-parametric variables and Chi squared test for categorical variables.

Analysis of the outcomes of singleton pregnancies was performed using univariate and multivariate regression models. General linear model with a binomial distribution and log link function (log binomial model) was used for outcome factors which were binary and multinomial logistic regression models for outcomes that were nominal. Multivariate models were adjusted for year of delivery as well as maternal characteristics found to differ significantly ( $P \leq 0.05$ ) at the baseline comparison. These factors were maternal age, booking BMI, socioeconomic status, smoking status and parity.

Clinical risk factors deemed to be influential in the outcome under investigation were also adjusted for in the multivariate models. For the outcome of placental abruption, pre-eclampsia was adjusted for due to the higher incidence of placental abruption in women with pre-eclampsia. This has been illustrated using a Directed Acyclic Graph in the supplementary figure S1. Gestational age and pre-eclampsia were adjusted for in the analysis of type of labour as gestational age can influence the decision about the type of labour and pre-eclampsia could warrant induction of labour. For the outcome of type of delivery, induction of labour was included in the model as induced labours are known to have a higher incidence of interventional deliveries. For the stillbirth analysis, gestational age was adjusted as prematurity is known to be associated with stillbirths. The multivariate model with emergency C-section as an outcome converged after removing maternal parity from the model.

Risk Ratio (RR) and its 95% confidence interval (CI) were reported as strength of association. The analyses were carried out using SPSS version 22 (Chicago, Illinois) and Stata MP version 13 (STATA Corp, Texas USA).

Offspring outcomes in twin pregnancies were analysed using generalised estimating equations to take into account the similarities between twins sharing the same mother. Multivariate analysis was adjusted for year of delivery and maternal age, gravidity, smoking, socio-economic status and the type of twin pregnancy based on chorionicity and zygosity. The outcome, type of labour was also adjusted for gestational age and pre-eclampsia for the reason previously stated. Preterm delivery was adjusted for induction of labour. Statistical significance for these analyses was set at  $p \leq 0.05$ .

Power calculation: As preterm birth has been reported most consistently in the literature to be associated with subfertility, the power calculation was based on this outcome. A preliminary interrogation of the AFCD indicated that there were approximately 3000 subfertile women eligible for inclusion in the study. Using a two sided test and 1:4 ratio of exposed to unexposed cohorts, this gave us 99% power at 5% significance level to demonstrate an odds ratio of 1.38<sup>5</sup> in the risk of spontaneous preterm birth, assuming a background prevalence of 6.3% in the unexposed population<sup>13</sup>. For twin deliveries we had 89% power at 5% significance level to detect a difference of 10% in preterm deliveries, assuming a prevalence of 50% preterm births<sup>13</sup> in the unexposed cohort (Odds ratio of 1.50).

Missing data: There were no missing data in the exposure and outcome variables. As there was less than 3% missing data in the covariates, complete case analysis was done.

## **Results**

### **Singletons**



Baseline Characteristics for women with subfertility (exposed cohort) and women without subfertility (unexposed cohort)

Of the 55,631 women who delivered singletons during the study period, 3,188 had attended Aberdeen Fertility Clinic. Data were available on 52,443 women with singleton pregnancies that occurred in the general population during the same time period. A comparison of the maternal characteristics is shown in Table 1. Women with a history of subfertility were older (32.1 years versus 27.9 years;  $p < 0.01$ ), had higher BMI ( $p < 0.01$ ) and were less likely to be smokers ( $p < 0.01$ ) in comparison with the women with no history of subfertility.

Univariate analysis: exposed and unexposed cohort

On univariate analysis, risk ratios (RR) showed higher risk of pre-eclampsia (RR 1.43, 95% CI 1.24-1.64), antepartum haemorrhage (RR 1.26, 95% CI 1.13-1.41), placental abruption (RR 1.50, 95% CI 1.19- 1.89) and placenta praevia (RR 2.30, 95% CI 1.54-3.44) among those with subfertility. In the same group, there was also a higher risk of induction of labour (RR 1.30, 95% CI 1.20-1.40), elective caesarean section (RR 1.76, 95% CI 1.55-1.99), emergency C-section (RR 1.42, 95% CI 1.33-1.51), forceps delivery (RR 1.14, 95% CI 1.03-1.25), vacuum extraction (RR 1.15, 95% CI 1.04-1.27) and very preterm delivery (RR 1.90, 95% CI 1.51-2.39) when compared to the women without subfertility. ( Table 2)

Multivariate analysis: exposed and unexposed cohort

On multivariate analysis, adjusting for maternal confounding factors such as maternal age, parity, BMI, smoking and socio-economic status, adjusted risk ratios (ARR) for pre-eclampsia (ARR 1.18; 95% CI 1.02 - 1.37), antepartum haemorrhage (ARR 1.32 ; 95% CI 1.18 - 1.47) and very preterm birth (ARR 1.96, 95% CI 1.53-2.49) remained high. Induction of labour (ARR 1.21; 95% CI 1.11-1.31) and elective (ARR 1.19; 95% CI 1.04 - 1.36) and emergency (ARR 1.19; 95% CI 1.12 - 1.28) were adjusted for gestational age and remained significantly higher in the subfertile group. There was almost a doubling of the risk of very

preterm birth (ARR 1.96 (95% CI 1.53, 2.49) in couples with a history of subfertility after adjustment for maternal factors and induction of labour. (Table 2)

#### Baseline characteristics for treatment dependent and treatment independent conceptions

Table 1 also presents the comparison of maternal characteristics between the group of subfertile women who conceived spontaneously and those who conceived after treatment. Subfertile women who conceived spontaneously were more likely to be multiparous suffering from secondary infertility and current or ex-smokers (ever smoked).

#### Univariate and Multivariate Analysis: treatment dependent and treatment independent conceptions

To detect the effect of fertility treatment on outcomes, analysis was done to compare outcomes of subfertile women who required treatment to conceive (n= 1403) to those who conceived spontaneously (n= 1497). Unadjusted and adjusted risk ratios were not significantly different between the treated and untreated subfertile couples. (Table 3).

#### Subgroup analysis of treatment dependent conceptions comparing types of treatment provided

We performed descriptive statistics comparing the no treatment subfertile group with those who had ovulation induction only, or ART with and without ovulation induction (data not presented) but found no statistically significant differences in the outcomes. Unfortunately due to low numbers in each fertility treatment group we did not have the power to investigate the effect of various fertility treatments on obstetric outcomes as part of the current study design. These data are presented in supplementary table S1.

## **Twins**

### Univariate and Multivariate analysis: exposed and unexposed cohort

Between 1992 and 2009 there were 1,475 twin pregnancies resulting in the delivery of 2,950 babies. Of these, 350 occurred in women who attended Aberdeen Fertility Clinic and 1,125 occurred in women with no known fertility problems. On univariate analysis, pregnancies in subfertile women were found to be at an increased risk of placenta praevia (RR 9.8, 95%CI 1.97- 48.77), delivery by elective caesarean section (RR 1.59, 95%CI 1.19-2.14) and emergency caesarean section (RR 2.01, 95%CI 1.5- 2.68). Following multivariate analysis women attending Aberdeen Fertility Clinic remained to be at an increased risk of delivery by emergency C-section (ARR 2.14, 95%CI 1.26-3.66). (Table 4)

### Treatment dependent versus Treatment independent conceptions

In the twin pregnancy group, 312 pregnancies occurred following fertility treatment and 29 had spontaneous conception. Data were missing on treatment status for 9 pregnancies which accounted for 2.6% of the total sample in this group. Due to the small size of the subgroup, no further analyses were carried out.

## **Discussion**

### Main Findings

We found that singleton pregnancies in subfertile women were more likely to be complicated by pre-eclampsia and antepartum haemorrhage with an almost doubling of the risk of delivering very prematurely (<32 weeks). These women were also more likely to undergo induction of labour, vaginal operative delivery and caesarean section.

In subfertile women, fertility treatment (including assisted conception) did not appear to increase further the risk of any maternal and offspring complications.

Twin pregnancies in subfertile women appeared to be at increased risk of emergency caesarean section.

### Strengths and Limitations

One of the strengths of this study is the comparison of outcomes in treatment dependent and treatment independent singleton pregnancies in subfertile couples, the results of which suggest the association of subfertility with adverse outcome irrespective of treatment. This study is also one of the first of its kind to report on outcomes of twin pregnancies in subfertile women. Also, access to linked data from two large databases (AMND and AFCD) over an extended period of time in a geographically defined area gave us the opportunity to study a larger cohort of women than in previous similar studies.

This study has a number of limitations. The women studied were based in Aberdeen, Scotland which is an affluent area where the population is ethnically homogenous with the majority of residents being Caucasian<sup>14</sup>. Therefore, generalizability of our results to other areas- especially those with socioeconomic deprivation and different ethnic composition, is limited. Additionally, subfertile couples who did not seek help or who received fertility treatment elsewhere may not have been identified in this study. The proportion of women in this is likely to be small as there are no other fertility centres in the region and therefore unlikely to introduce significant bias. We were also unable to find the impact of individual fertility treatments on the outcomes as the numbers for this subgroup analysis were small, although we found no effect of fertility treatment as a whole. There was also insufficient numbers to explore the outcomes in the treatment dependent and treatment independent pregnancies in the twin group. Finally, it was not possible to adjust for residual confounding.

### Interpretation (Findings in the light of other evidence)

#### Subfertility and Maternal outcomes

Pre-eclampsia is an outcome identified as being more common in couples with subfertility<sup>3, 4</sup>. Our findings supported this and our results showed that subfertile couples with singleton pregnancies had increased risk of pre-eclampsia. This association was not found in the twin pregnancy group. Some research has been done exploring a possible correlation<sup>16</sup>. One study has proposed some factors delaying clinically recognized conception may also be in a causal pathway for preeclampsia<sup>17</sup>.

Our findings were similar to those of previous studies which have reported an increased incidence of antepartum haemorrhage (APH) in subfertile couples. The underlying reason for this is difficult to explain. Some authors have suggested that this is due to abnormal implantation associated with assisted reproductive technology<sup>17</sup>. We did not find an increased association in those who received fertility treatment. Perhaps this finding can be explained by an increased level of anxiety in mothers conceiving following a period of subfertility, leading them to seek medical attention for minor bleeds during pregnancy.

Preterm birth has emerged as the most frequently observed adverse outcome in subfertile couples across various studies<sup>3-5, 18</sup>. Our results are in agreement with findings from a previous Australian cohort study<sup>4</sup> which showed a doubling in the risk of preterm birth in subfertile women. A recent systematic review and meta-analysis<sup>5</sup> found a moderate increase in the risk of preterm birth in women who conceive without treatment after a long delay, pooled crude odds ratio (OR 1.38, 95% CI 1.25, 1.54). The meta-analysis included 14 studies with a total population of 1 269 758 births out of which 68 885 were preterm. 8.2% of births in the infertile group were preterm compared to 5.4% in the fertile group<sup>5</sup>

### Subfertility and type of delivery

Increased rates of interventional deliveries have been noted in subfertile couples, both in the singleton and twin pregnancy groups<sup>19, 20</sup>. The proposed reason for this observation is that it could be linked to the increased anxiety about these pregnancies in mothers and perhaps physicians<sup>20</sup> who may have a lower threshold for intervening in pregnancy.

Our results were similar and found a higher risk of instrumental delivery in singletons and increased risk of emergency caesarean section in both the singleton and twin group.

### Subfertility and Offspring Outcomes

We found no evidence to suggest that, in either singleton or twin pregnancies, babies born following a history of subfertility were worse off than those without such history. This is not consistent with previous studies that have found an increased risk of low birth weight, fetal growth restriction and perinatal death among subfertile couples<sup>18, 21, 22</sup>. Preterm birth is thought to be the underlying factor associated with the increased risk of low birth weight<sup>18</sup> and perinatal death in this group<sup>22</sup>.

### Fertility treatment and adverse maternal and offspring outcomes

Fertility treatments, including assisted conception have been reported to be associated with adverse obstetric and perinatal outcomes<sup>6-8, 10, 23</sup>. The risk has been found to be higher irrespective of the type of treatment used<sup>10, 23</sup>. Singletons of women receiving ovulation induction for fertility treatment were found to be small for gestational age<sup>23</sup>. A systematic review and meta-analysis of obstetric outcomes of IVF/ICSI pregnancies found that singleton pregnancies had a higher risk of antepartum haemorrhage, hypertensive disorders of pregnancy, preterm rupture of membranes, caesarean section, gestational diabetes and induction of labour<sup>6</sup>. An earlier meta-analysis reported similar findings that IVF singletons have significantly increased risk of preterm birth and low birth weight<sup>7</sup>. A study on IVF twins have also found an increased risk of preterm birth when compared to spontaneous

conceptions matched for maternal age<sup>8</sup>. The reason for this association was explored by a systematic review and meta-analysis<sup>11</sup> which concluded that subfertility was the major underlying risk factor for this and that the effect of hormonal stimulation and/or IVF techniques such as embryo culture could be contributory. It is worth noting that many of the relevant studies have used a general population rather than a population of subfertile women with treatment independent pregnancies as the unexposed group.

We did not find any effect of fertility treatment in singleton pregnancies on any of the maternal and offspring adverse outcomes. However, we could not specify the risks associated with individual fertility treatments due to small numbers.

### Clinical Implications

While pregnant women with a history of subfertility and the clinicians involved in their care may be more anxious with a lower threshold for intervention, our data indicate that they do appear to be a high risk group. Health care professionals involved in the antenatal care of these women should be made aware of this and the fact that regular visits could reduce some of these adverse outcomes<sup>24</sup>.

### Conclusion

The results of this study support existing data showing an increased risk of adverse obstetric and perinatal outcomes in women with subfertility. The major driver for this appears to be subfertility per se, rather than fertility treatment. Further studies would be useful to investigate mechanisms underlying subfertility and adverse pregnancy outcomes. In the interim greater vigilance is required in the management of pregnancies in women with a history of infertility.

## **Authors' roles**

Anastasia DoPierala conducted the analysis of the data under supervision of SilB and SohB and wrote the initial manuscript.

Dr Sohinee Bhattacharya and Professor Siladitya Bhattacharya designed the study and supervised the project. They also oversaw the writing of the paper and edited the manuscript.

Dr Smriti Bhatta interpreted the findings and edited the final manuscript.

Dr Edwin Amalraj Raja checked the statistical analysis and contributed to the final manuscript.

All authors contributed to the final draft of the manuscript.

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**Disclosure of Interests:** The authors declare that they have no conflicts of interest.

**Ethics Statement:** The chairs of the steering committees for Aberdeen Maternity and Neonatal Databank and Aberdeen Fertility Centre Database (Caldecott guardians) approved and gave permission for the use of the data for this study. Formal ethical approval was not considered necessary by the North of Scotland Research Ethics Service.

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