Fecundability among Danish pregnancy planners:

Studies on birth weight, gestational age and history of miscarriage

PhD dissertation

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Preface

The work presented in this thesis was carried out during my employment at the Department of Clinical Epidemiology at Aarhus University Hospital, Denmark.

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Thesis papers

Paper I

Wildenschild C, Riis AH, Ehrenstein V, Heitmann BL, Hatch EE, Wise LA, Rothman KJ, Sørensen HT, Mikkelsen EM. Weight at birth and subsequent fecundability: a prospective cohort study. PLoS One. 2014;9(4):e95257.

Paper II

Wildenschild C, Riis AH, Ehrenstein V, Hatch EE, Wise LA, Rothman KJ, Sørensen HT, Mikkelsen EM. A prospective cohort study of a woman´s own gestational age and her fecundability. Hum Reprod. 2015;30(4):947-956.

Paper III

Wildenschild C, Riis AH, Ehrenstein V, Hatch EE, Wise LA, Rothman KJ, Sørensen HT, Mikkelsen EM. Fecundability among women with a history of miscarriage. *In draft.*

List of abbreviations

TTP	Time to pregnancy
PCOS	Polycystic ovary syndrome
BMI	Body mass index
DOHaD	Developmental Origins of Health and Disease
FSH	Follicle stimulating hormone
LH	Luteinizing hormone
SGA	Small for gestational age
AGA	Appropriate for gestational age
LGA	Large for gestational age
AMH	Anti-Müllerian hormone
LMP	Last menstrual period
CPR	Civil Personal Register
CRS	Civil Registration System
DMBR	Danish Medical Birth Registry
DNPR	Danish National Patient Registry
ICD-8	International Classification of Diseases, 8^{th} revision
ICD-10	International Classification of Diseases, 10^{th} revision
FR	Fecundability ratio
CI	Confidence interval

Table of contents

1 Introduction

Most couples want to have children,[1-3] however, not all can conceive spontaneously or as quickly as anticipated. A detectable pregnancy is the last step in a sequence of events involving gamete production and transport, fertilization, zygote transport, and implantation of the blastocyst.[4] Dysfunction in any of the anatomical and physiological features required for these processes may lead to delayed conception or infertility. Delayed conception is defined as a pregnancy attempt time of 7-12 months.[5] According to the World Health Organization, clinical infertility is "a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse."[6] Among 20-44 year old women in developed countries attempting to conceive, point prevalence of infertility is 4%-17%, and its lifetime prevalence is 7%-26%.[7] The definitions of infertility and delayed conception reflect the ability of the majority of women to conceive within 6 months of pregnancy attempts.[8-10] Fecundability, which is the probability of conception during a given menstrual cycle assuming regular unprotected intercourse, is the inverse of time to pregnancy (TTP) measured in cycles.[11] Thus, fecundability is a measure of the capacity to conceive, with lower fecundability corresponding to a longer pregnancy attempt time.[11]

A number of diseases – e.g., cardiovascular disease, insulin resistance and diabetes, obesity, and metabolic syndrome[12] – may originate from adverse events during the prenatal period, often expressed by low weight and short gestational age at birth as surrogate markers of prenatal development.[13] Little evidence exists about whether a woman´s weight or gestational age at birth is associated with her fertility, i.e., her ability to conceive and deliver a baby.[11 14-16] Furthermore, a history of miscarriage (loss of a clinical pregnancy before 22 weeks of gestation)[17, 18] may affect subsequent fertility, but evidence is sparse[9, 19, 20]

This dissertation comprises three epidemiological studies that examined the role of a woman´s own birth weight, gestational age at birth, and history of miscarriage on her fecundability. The studies were based on data from a nationwide, prospective cohort study of Danish pregnancy planners, "Snart-Gravid,"[21, 22] combined with data from Danish national health registries.

2 Background

In the following, physiological processes and lifestyle risk factors for impaired fertility are described, and the putative mechanisms for an association between birth weight, gestational age at birth and history of miscarriage and reproductive health are discussed.

2.1 Infertility

Infertility is a complex condition, with various underlying pathologies. Causes of female infertility primarily include ovulatory dysfunction or tubal and peritoneal abnormalities, with a minority of cases attributable to cervical or uterine abnormalities.[23-25] Ovulatory dysfunction, which commonly results from polycystic ovary syndrome (PCOS), affects 25% of infertile women.[24, 25] Common tuboperitoneal causes of infertility, affecting around 20% of women, include tubal damage or obstruction, usually secondary to pelvic inflammatory disease (caused by, e.g., sexually transmitted disease), and pelvic adhesions (caused by, e.g., endometriosis or surgery).[24, 25] Prevalence of spermatozoa-mucus interaction defects or uterine pathology (e.g., uterine myomas or endometrial polyps) is around 5% among women with infertility.[23-25] For approximately 25% of couples, infertility is unexplained, i.e., no definite cause can be established after complete investigation.[24, 25]

Age is associated with changes in fertility[26-28] with fecundability peaking around age 30 years and declining thereafter.[29] Several modifiable lifestyle factors may also impact fertility, including extremes in body mass index (BMI),[30-32] smoking,[32-35] consumption of alcohol[36-38] and caffeine,[32, 39] and excessive exercise.[40, 41]

2.2 Birth characteristics and reproductive health

Prenatal exposures may play an essential role in the development of adult reproductive dysfunction, with environmental factors that influence fetal growth and development potentially also exerting long-term detrimental effects. The foundations of the biologic ability to reproduce are established when a woman herself is *in utero*, with the formation, growth, and maturation of reproductive organs and hormonal control systems.[42]

The “Developmental Origins of Health and Disease” (DOHaD) hypothesis posits that susceptibility of the embryo or fetus to intrauterine environmental stimuli during fetal development may cause structural or physiological damage that is not always ascertainable at birth.[43] According to the DOHaD hypothesis, the fetus makes adaptations *in utero* based on the predicted postnatal environment. These so-called “predictive adaptive” responses are made to hormonal or metabolic maternal cues that allow the fetus to anticipate its future *ex utero* environment and adjust its development accordingly with the aim of optimally meeting this environment. If there is a mismatch between the predicted and the actual postnatal environment, eventually disease may occur.[43-46] Severe stimuli such as poor placental function or maternal illness may induce an adaptive response with the aim of securing fetal survival and may be accompanied by a reduction in fetal growth or by preterm birth.[43-46]

At delivery, the newborn girl is weaned off the maternal and placental hormones, leading to surges in infant gonadotropin levels (follicle-stimulating hormone [FSH] and luteinizing hormone [LH]), estradiol, and increased follicular maturation.[47] Some studies showed stronger surges of FSH at 4 and 12 months postnatally in girls born small for gestational age (SGA) than in girls with an appropriate weight for gestational age (AGA),[48, 49] whereas others found no evidence of raised levels of FSH in SGA infants compared with AGA infants at a postnatal age of 2-3 months.[50, 51] Still, levels of anti-Müllerian hormone (AMH)[51] and estradiol[50, 51] were higher in SGA girls, suggesting an association of altered ovarian function with small size at birth.

Furthermore, some[52-54] but not all[55-58] studies suggest that menarche occurs earlier in girls born SGA or with a low birth weight. In one study, the youngest age at menarche was seen in girls with a birth weight below the median and BMI at age 8 years above the median, suggesting that the association between birth weight and age at menarche is mediated by accelerated postnatal growth.[52] Low birth weight followed by accelerated growth in infancy is associated with central adiposity and obesity, predisposing for obesity in adulthood[59-61] which is in turn associated with delayed fecundability.[30, 31] In addition, low birth weight and catch-up growth may be associated with subsequent insulin resistance and hyperinsulinemia,[60, 62, 63] which is in a pathway to PCOS.[64]

A series of studies of Spanish girls with precocious pubarche (appearance of pubic hair before age 8 years[47]) found them to have elevated levels of serum insulin and lipids, decreased levels of sex

hormone-binding globulin, and central adiposity, a profile reminiscent of the metabolic syndrome, which may precede ovarian hyperandrogenism or PCOS.[65-67] In line with this, such girls were more likely to be anovulatory than girls without this profile.[68] This sequence of events is more prevalent among those with low birth weight, especially in the presence of catch-up growth in weight. Thus, potential links between small size at birth, postnatal hormonal profile, reproductive development, and fertility have been observed, however, not all studies have corroborated the evidence for an association between birth weight and features of PCOS.[55, 69-71]

Some studies of adolescent girls born SGA at term reported reduced uterine and ovarian size,[72] increased levels of FSH, and decreased levels of estradiol, indicative of ovarian hyporesponsiveness to FSH,[73] and ovulation disturbances[74] compared with girls born AGA at term. Assessment of girls at age 14 years[72] with follow-up at age 18 years showed persistently reduced uterine and ovarian sizes, and elevated levels of FSH and LH among girls born SGA relative to girls born AGA.[49] Other studies reported no evidence of a persistent difference in the size of internal genitalia,[56, 75] numbers of ovarian follicles,[56] or adrenal and ovarian hormonal patterns[56] after the first 3 years of puberty in adolescent girls born SGA or AGA. This result was corroborated by other studies that found similar ovarian hormonal patterns in young women born SGA and AGA.[57, 58] Although AMH levels were raised among women born SGA and with catch-up growth in one study, and a high AMH level is associated with PCOS, androgen levels were similar to those in women born AGA.[58]

Conflicting results have also been reported in studies of women seeking infertility treatment. One study reported that women with female type infertility (female cause or combined cause, not further specified) were twice as likely to have been SGA at birth as women with unexplained infertility, or to have had low birth weight (<2,500 grams) than women with unexplained infertility or whose partner was infertile.[76] There was no evidence for an association between being born large for gestational age (LGA) and female type infertility.[76] In contrast, others found no convincing evidence for an association between low birth weight and ovulatory dysfunction[77] or diminished ovarian reserve (defined as receiving an embryo conceived by donated oocytes or having low response to ovarian hyperstimulation).[78] Furthermore, there was no evidence for an association between low birth weight and PCOS in this population.[78]

Studies investigating the association between preterm birth and postnatal endocrinology have reported an exaggerated activation of the hypothalamic-pituitary-ovarian axis among preterm infant girls, with a prolonged and stronger surge of FSH and LH, a subsequent delayed rise in AMH, and higher levels of estradiol and inhibin B during the first 3 postnatal months, relative to girls born at term.[50, 79, 80] The long-term relevance of such altered activation for ovarian development is unclear, however, sparse evidence suggests little association between preterm birth and age at puberty or menarche[53] or parameters of altered ovarian function such as aberrant AMH, LH, or FSH levels after adolescence.[58] A population-based study assessing self-reported symptoms of PCOS in relation to size and gestational age at birth reported similar proportions of women born preterm among those with and without symptoms.[71] In infertile populations, women with ovulatory dysfunction may be more likely to have been born preterm than infertile women with normal ovulation,[77] however, others found no evidence for an association between preterm birth and female type infertility.[76]

The existing evidence, albeit inconsistent, raises the possibility that the prenatal environment, with weight and gestational age at birth as markers of infant health, may have long-lasting consequences for reproduction. It is plausible that adaptive changes have a detrimental influence on reproductive maturation and ovarian and endocrine function through altered structure and function of reproductive organs and modification of the hypothalamic-pituitary-gonadal axis.[81] Thus, it is important to determine whether aberrant weight or gestational age at birth is associated with impaired fecundability, as a major outcome of reproduction.

2.3 Miscarriage and fertility

'Miscarriage' and 'spontaneous abortion' are terms used interchangeably for the spontaneous termination of pregnancy.[82] Since 'abortion' may also refer to an induced pregnancy termination, many prefer the term miscarriage[82] and this term will be used throughout this thesis.

A miscarriage or its treatment may impair subsequent fertility by several mechanisms. Despite its low incidence in developed countries,[82, 83] pelvic inflammatory disease after miscarriage may permanently damage the fallopian tubes through blockage or closure or adhesion formation, thus compromising or preventing fertilization.[84, 85] Surgical management of miscarriage may lead to

infection, cervical trauma or uterine perforation and intrauterine adhesions, which may interfere with implantation.[82, 86, 87] A recent meta-analysis reported a prevalence of intrauterine adhesions among women with previous miscarriage of 19.1% (95% CI: 12.8%-27.5%), with women having multiple miscarriages having twice the risk of adhesions compared with women with a single miscarriage (odds ratio [OR] 1.99 [95% CI: 1.32-3.00]), an association attributed primarily to recurrent curettage procedures.[88]

Women with a history of miscarriage have an increased risk of complications in a subsequent pregnancy, including repeated miscarriage,[89-92] threatened miscarriage,[93] preeclampsia,[93, 94] complications during delivery,[93] preterm delivery,[92-98] and perinatal death.[93, 96] Associations with subsequent preterm delivery are stronger for women with recurrent miscarriage than for women with a single miscarriage.[95, 97-99] Women with recurrent miscarriage are also more likely to experience obstetric complications (e.g., cervical incompetence, placenta previa, or breech presentation), and caesarean delivery than all women giving birth.[99-101] Elevated risks of adverse pregnancy outcomes among women with a history of miscarriage, with some evidence of a dose-response pattern, suggest that miscarriage has long-lasting, diverse effects on subsequent reproduction, possibly including fecundability.

2.4 Maternal reproductive history

Reproductive history tends to recur within families, as shown for preterm birth,[102-105] low birthweight,[105] miscarriage,[106-109] and family size.[110, 111] On the basis of familial clustering of reproductive outcomes, we hypothesized the existence of familial recurrence of decreased fecundability. With this hypothesis, reproductive outcomes of a woman´s mother – such as history of difficulty conceiving – may be considered proxy markers of the mother´s fecundability, which in turn may affect fecundability in her daughter.

Furthermore, unfavorable reproductive events – e.g., difficulty conceiving – are associated with subsequent low birth weight or preterm delivery of the offspring.[93-95, 103, 112-114] Therefore, maternal reproductive history may confound the association between her daughter´s weight or gestational age at birth and fecundability, or between the daughter´s miscarriage and

fecundability. The sequence of events of interest that was considered in this thesis is depicted in Figure 1.

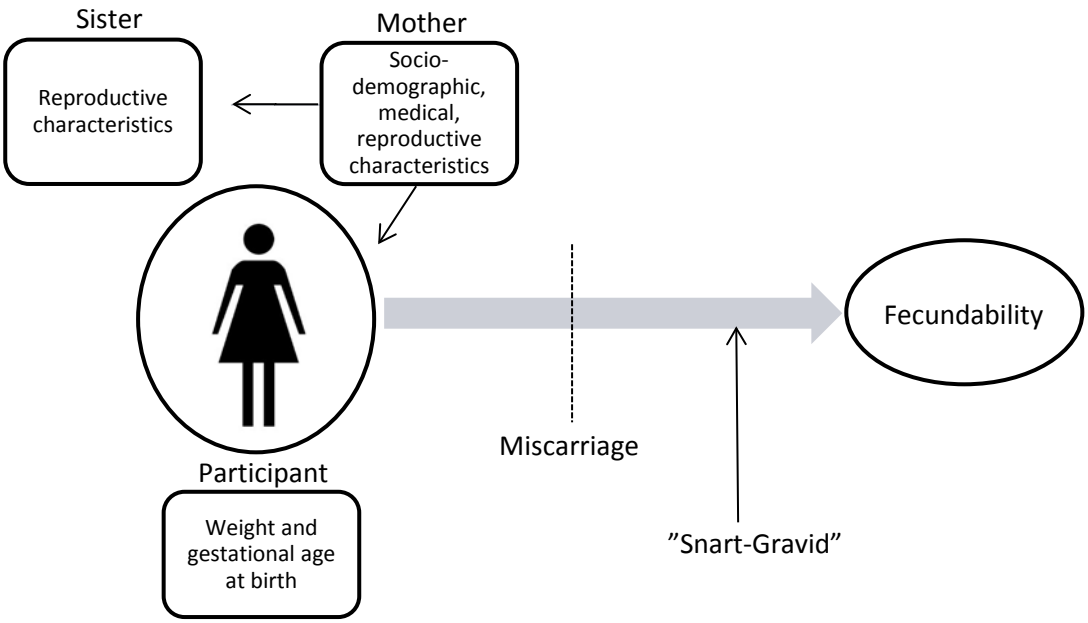

Figure 1. Overview of the sequence of events examined in this thesis, from a woman´s birth until assessment of her fecundability in the “Snart-Gravid” study, and potential confounding by maternal reproductive history.

2.5 Literature search and review

The literature search aimed at identifying evidence regarding the following:

- The association between weight at birth and fecundability (study I)
- The association between gestational age at birth and fecundability (study II)
- The association between history of miscarriage and fecundability (study III)

The electronic database PubMed was searched for studies in human populations published until April 2015, and the searches were limited to English, Danish, Norwegian or Swedish language literature. The following Medical Subject Headings (MeSH) terms were used for the exposures that we were interested in: "Birth Weight," "Infant, Low Birth Weight" (Study I); "Gestational Age," "Premature Birth," "Infant, Premature," "Infant, Postmature" (Study II); "Abortion, Spontaneous," "Abortion, Missed," "Embryo Loss," "Abortion, Habitual," and "Fetal Death" (Study III). The terms were alternately combined with "Fecundability" (free-text term), "Time to pregnancy" (free-text term), "Fertility" [MeSH], "Infertility" [MeSH], and "Pregnancy Rate" [MeSH].

2.5.1 Existing literature on weight and gestational age at birth and fecundability

A number of studies considered both weight and gestational age at birth; for this reason, articles assessing weight and/or gestational age at birth are presented in the following.

The terms for birth weight combined with the free-text term "Fecundability" revealed one relevant paper[14] and with the free-text term "Time to pregnancy" revealed one additional paper.[15] Combining with the MeSH terms "Fertility," "Infertility," or "Pregnancy Rate" did not identify any papers of interest. Broadening the criteria for determining relevant papers to not only concern fecundability, one additional paper was found by combining with "Pregnancy Rate."[115]

No relevant papers were found when we searched for studies on the association between gestational age at birth and fecundability. When we broadened the criteria of relevance to include papers that considered fertility as an outcome, one paper was identified using the terms for gestational age in combination with "Fertility."[116] An additional four papers were identified from a review about reproduction in preterm born infants.[117 16, 118-120] Of these, one reported no

estimates of association[118] and one gave an inadequate description of the exposure status of the participants[119] and were therefore excluded. The tables of contents of journals within the field of interest were checked monthly, revealing one more relevant paper.[114] One additional paper was identified by checking the reference lists of the retrieved literature.[121]

Only two of the retrieved papers assessed TTP according to weight and/or gestational age at birth.[14, 15] The other papers assessed fertility in the demographic sense, measured by registered births in national birth registries,[114-116, 120, 121] or by self-reported pregnancies and births.[16] We considered these studies to be valuable contributions to a topic that had seemingly attracted little attention and included them in our review. Thus, 8 studies on the association between weight or gestational age at birth and fertility were considered (Table 1).[14-16, 114-116, 120, 121]

A cohort study by Meas *et al.*, in France, reported little association between being born SGA and fecundability, relative to women born AGA.[14] In contrast, in the "Danish National Birth Cohort," Nøhr *et al.* found that relative to women born at term with a normal weight, women born at term with a weight ≤2,500 or >4,500 grams, and women born preterm with weight ≤1,500 grams or >3,500 grams, i.e., the low and high birth weight categories, were more likely to be subfecund (defined as TTP >12 months); adjusted ORs for women born at term with weight ≤2,500 and >4,500 grams were 1.2 (95% CI: 1.0-1.5) and 1.5 (95% CI: 1.0-2.0), and adjusted ORs for women born preterm with weight ≤1,500 and >3,500 grams were 1.8 (95% CI: 1.1-3.1) and 1.3 (95% CI: 0.7-2.4).[15] Associations with delayed conception (TTP 6-12 months) were less clear but suggested a similar pattern among women born at term.[15] A cohort study by Hack *et al.*, in the US, also reported a reduced probability of pregnancy or live birth among women with birth weight <1,500 grams.[16]

In a cohort study based on the national birth registry in Sweden, deKeyser *et al.* found little association between a birth weight <2,500 grams and subsequent fertility, however, the probability of reproduction was 20% lower among women with birth weight <1,500 grams, and 33% lower among women with birth weight <1,000 grams, compared with women with a normal birth weight.[114] Similarly, Ekholm *et al.* reported a 26% reduced probability of reproduction among women with birth weight <1,500 grams.[115] These results were strongest among the oldest women in the cohort. Of note, the population studied by Ekholm *et al.* was included in the study by

deKeyser *et al.*, with the latter extending the inclusion period. Neither study found convincing evidence for an association between being born SGA and fertility.[114, 115] In a similar cohort study based on the Uppsala Birth Cohort in Sweden, Goodman *et al.* found that lower birthweight was associated with a smaller lifetime number of children.[121]

Only a modest association between being born preterm at <37 gestational weeks and fertility has been reported,[114, 115] however, deKeyser *et al.* and Ekholm *et al.* found a 11%-19% reduced probability of reproduction among women born <32 weeks[114, 115] and a 31% reduced probability among women born <27 weeks of gestation, relative to women born at term.[114] Similarly to the results for birth weight, the association for gestational age was strongest among the oldest women.[114, 115] A pattern of decreasing fertility with lower gestational age at birth was corroborated by Swamy *et al.*, in Norway, and Goodman *et al.*,[116, 121] whereas Moster *et al.* reported a decline in fertility of 10% for all subcategories of preterm birth below 34 gestational weeks.[120] Importantly, the population studied by Swamy *et al*. was included in the study by Moster *et al.*

2.5.2 Limitations of the existing literature

The study by Meas *et al.*[14] was limited by a small number of participants, leading to an imprecise estimate of association. The study by Nøhr *et al.*[15] assessed the probability of TTP of 6-12 and >12 months according to weight for term and preterm births, rather than per-cycle TTP. Preterm birth was defined as birth occurring <37 gestational weeks, thus, a detailed examination of the effect of severity of preterm birth was not possible, and it could not be determined whether the increased probability of subfecundity among women born preterm with weight ≤1,500 grams was attributable to very preterm or moderately preterm birth. Both studies used retrospective data on TTP, which may be valid over short time spans[122] such as in the study by Nøhr *et al.*, which collected the data during pregnancy, but there was no description of the period of recall in the study by Meas *et al.* The assessment of TTP in that study considered the first pregnancy attempt, which could have occurred at an unspecified time before the study interview, potentially leading to less accurate data on TTP.[123] The historical cohort studies[114-116, 120, 121] contributed data on fertility measured as registered births, but did not reveal much about potential differences in the ability to conceive according to a woman´s birth characteristics. Thus, the existing evidence

revealed a lack of data on prospectively measured fecundability in relation to a woman´s weight and gestational age at birth.

Table 1. Studies of the association between weight and gestational age at birth and fertility

Author, year, country	Design	Population and data collection	Follow-up period	Measure of exposure	Measure of outcome	Main results
Meas *et al.*,[14] 2010, France	Cohort study	316 women born SGA and 374 women born AGA in 1971-1985, identified in a birth registry in Hagenau, France 403 women who had attempted to conceive reported their TTP by questionnaire	Identified and recruited to the study in 1994-2001 Follow-up in 2005-2008	SGA: weight below the 10th percentile for sex and gestational age according to local growth standard curves AGA: weight between 25th and 75th percentiles	Self-reported retrospective data on TTP for the first pregnancy attempt, in months	aHR for pregnancy relative to women who were AGA: 0.91 (95% CI:0.68-1.21)
Nøhr *et al.*,[15] 2009, Denmark	Cohort study	21,786 women enrolled in the nationwide "Danish National Birth Cohort" while pregnant Women were interviewed by phone at 16 and 30 weeks of gestation, and when the child was 6 and 18 months old and 7 years old Data on TTP reported at the first interview, and data on maternal weight and preterm birth reported at the 7-year follow-up	Women recruited in 1996-2002 Follow-up in 2005-2007	Term: ≤2,500; 2,501-3,000; 3,001-4,000; 4,001-4,500; >4,500 grams Preterm (<37 gestational weeks): ≤1,500; 1,501-2,000; 2,001-3,000; 3,001-3,500; >3,500 grams	Self-reported retrospective data on TTP: not planned, <6, 6-12, >12 months Non-planners were not included in the regression analysis	aOR for TTP >12 months relative to women born at term with weight 3,001-4,000 grams: Term, ≤2,500 grams: 1.2 (95% CI:1.0-1.5) Term, >4,500 grams: 1.5 (95% CI:1.0-2.0) Preterm, ≤1,500 grams: 1.8 (95% CI:1.1-3.1) Preterm, >3,500 grams: 1.3 (95% CI:0.7-2.4)
Hack *et al.*,[16] 2002, US	Cohort study	126 women with weight <1,500 grams, identified through hospital of birth, and 125 women born at term with normal birth weight, identified by a population-sampling procedure at 8 years of age in Cleveland, USA Data on previous	Born in 1977-1979 and followed up at 20 years of age	Very low birth weight, <1,500 grams	Self-reported occurrence of pregnancy and ≥1 live birth	aOR for pregnancy relative to women with normal birth weight: 0.5 (95% CI:0.3-0.9) aOR for live birth relative to women with normal birth weight: 0.4 (95% CI:0.2-0.9)

Author, year, country	Design	Population and data collection	Follow-up period	Measure of exposure	Measure of outcome	Main results
		pregnancies and births obtained by interview				
deKeyser *et al.*,[114] 2012, Sweden[a]	Historical cohort study	494,692 women identified in the Swedish Medical Birth Registry	Identified by birth in 1973-1983 and followed up by 2006	Birth weight: <1,000; 1,000-1,499; 1,500-2,499; <2,500 grams SGA: weight <2 s.d. below the mean weight for the gestational length LGA: weight >2 s.d. above the mean weight for the gestational length according to the Swedish standard Gestational age: <27 weeks; <32 weeks; 32-36 weeks; <37 weeks; >42 weeks	Giving birth to the first child as registered in the Swedish Medical Birth Registry	aHR for reproducing relative to women with normal birth weight: <u><1,000 grams:</u> 0.67 (95% CI:0.50-0.92) <u>1,000-1,499 grams:</u> 0.80 (95% CI:0.72-0.89) <u>1,500-2,499 grams:</u> 0.96 (95% CI:0.94-0.99) <u><2,500 grams:</u> 0.95 (95% CI:0.93-0.97) aHR relative to AGA: <u>SGA:</u> 1.01 (95% CI: 0.99-1.03) <u>LGA:</u> 1.01 (95% CI: 0.98-1.05) aHR relative to women born at term: <u><27 weeks:</u> 0.69 (95% CI:0.45-1.05) <u><32 weeks:</u> 0.81 (95% CI:0.75-0.88) <u>32-36 weeks:</u> 0.95 (95% CI:0.93-0.98) <u><37 weeks:</u> 0.94 (95% CI:0.92-0.96) <u>>42 weeks:</u> 1.01 (95% CI:0.99-1.04)
Goodman *et al.*,[121] 2009, Sweden	Historical cohort study	6,490 women in the Uppsala Birth Cohort	Identified by birth in 1915-1929 and followed up by 2002	Standardized birth weight for gestational age in quintiles Gestational age: ≤31 weeks; 32-36 weeks; ≥37 weeks	Total number of biological children as registered in the Swedish Multigenerational Registry	Coefficients from linear regression for number of children by birth weight (According to the paper´s Supplementary Appendix, Table 3): Quintile 1 (smallest): 0 Quintile 2: 0.07 Quintile 3: 0.20 Quintile 4: 0.12 Quintile 5: 0.17

Author, year, country	Design	Population and data collection	Follow-up period	Measure of exposure	Measure of outcome	Main results
						Regression coefficients for number of children by gestational age: ≥37 weeks: 0 32-36 weeks: -0.25 ≤31 weeks: -0.91
Ekholm *et al*.,[115] 2005, Sweden[a]	Historical cohort study	148,281 women identified in the Swedish Medical Birth Registry	Identified by birth in 1973-1975 and followed until 2001	Birth weight: <1,500 grams SGA: weight <2 s.d. below the mean weight for the gestational length according to the Swedish standard Gestational age: <32 weeks; <37 weeks	Giving birth to the first child as registered in the Swedish Medical Birth Registry	aHR for reproducing relative to women with normal birth weight: <u><1,500 grams:</u> 0.74 (95% CI:0.60-0.91) aHR relative to AGA: <u>SGA:</u> 1.09 (95% CI:1.04-1.14) <u>SGA defined as <3 s.d. below the mean weight:</u> 1.04 (95% CI: 0.94-1.16) aHR relative to women born at term: <u><32 weeks:</u> 0.89 (95% CI:0.74-1.07) <u><37 weeks:</u> 0.98 (95% CI:0.93-1.03)
Moster *et al.,*[120] 2008, Norway[b]	Historical cohort study	424,409 women born ≥23 weeks of gestation (calculated from the percentage of males in the cohort of 867,692 individuals), identified in the Medical Birth Registry of Norway	Identified by birth in 1967-1983 and followed through 2003	Gestational age: 23-27 weeks; 28-30 weeks; 31-33 weeks; 34-36 weeks; ≥37 weeks	Reproduction as registered in the Medical Birth Registry of Norway	aRR for reproducing relative to women born at term (According to the paper´s Supplementary Appendix, Table 4): <u>23-27 weeks:</u> 0.9 (95% CI:0.6-1.2) <u>28-30 weeks:</u> 0.9 (95% CI:0.8-1.0) <u>31-33 weeks:</u> 0.9 (95% CI:0.9-1.0) <u>34-36 weeks:</u> 1.0 (95% CI:0.9-1.0)
Swamy *et al*.,[116] 2008, Norway[b]	Historical cohort study	282,803 women born ≥22 weeks of gestation, identified in the Medical Birth Registry of Norway	Identified by birth in 1967-1976 and followed	Gestational age: 22-27 weeks; 28-32 weeks; 33-36 weeks; 37-42 weeks; ≥43 weeks	Reproduction, defined as any stillbirth or live birth recorded in the Medical Birth Registry of Norway	aRR for reproducing relative to women born at term: <u>22-27 weeks:</u> 0.78 (95% CI:0.65-0.93)

Author, year, country	Design	Population and data collection	Follow-up period	Measure of exposure	Measure of outcome	Main results
			through 2004			<u>28-32 weeks:</u> 0.89 (95% CI:0.86-0.93) <u>33-36 weeks:</u> 0.98 (95% CI:0.96-0.99) <u>≥43 weeks:</u> 1.00 (95% CI:0.99-1.01)

Abbreviations: SGA, small for gestational age; AGA, appropriate for gestational age; TTP, time to pregnancy; aHR, adjusted hazard ratio; CI, confidence interval; aOR, adjusted odds ratio; LGA, large for gestational age; aRR, adjusted risk ratio.

[a] Cohort in the study by deKeyser *et al.* includes the cohort in the study by Ekholm *et al.*

[b] Cohort in the study by Moster *et al*. includes the cohort in the study by Swamy *et al*.

2.5.3 Existing literature on history of miscarriage and fecundability

Initially, the MeSH terms for miscarriage (see p. 9) were combined with the free-text term "Fecundability," generating no relevant papers. Combining the terms with the free-text term "Time to pregnancy" identified four papers.[20, 124-126] An additional five relevant papers were identified when we used the MeSH terms "Fertility"[127, 128] or "Infertility."[129-131] Two additional papers were identified from a recent systematic review about reproduction following miscarriage,[88 132, 133] one paper was identified from the tables of contents of a journal within the field of interest,[19] and two papers were identified by checking the reference lists of the retrieved articles.[9, 134]

Seven of the studies did not include a comparison group, but gave descriptive values of probabilities of conception of 68% to 83% within 6 months of pregnancy attempts,[130, 134] 74% to 89% within 12 months of attempts,[124, 127, 129, 133] and 45% within 12 months of attempts in a cohort of previously infertile women.[125] Four studies compared the probabilities of conception after miscarriage among women receiving surgical treatment versus women receiving medical or conservative treatment, and reported probabilities of conception within 12 months of attempts of 60% to 80%, with similar probabilities in the groups compared in the respective four studies.[126, 128, 131, 132] Because of the lack of a comparison group of women without miscarriage in these studies, they were excluded from further review. Thus, three studies were considered (Table 2).[9, 19, 20]

In a prospective cohort study of pregnancy planners in the US, Sapra *et al.* examined TTP in successive pregnancy attempts among women with pregnancy loss.[19] Relative to fecundability before pregnancy loss, fecundability after pregnancy loss was lower in the first and the second post-loss pregnancy attempts (adjusted fecundability odds ratio [FOR] 0.42 [95% CI: 0.28-0.65] and 0.56 [95% CI: 0.11-2.79]).[19] In a cross-sectional study of pregnant women in the UK, Hassan *et al*. compared self-reported TTP before and after a miscarriage in the previous pregnancy with TTP before and after a previous live birth.[20] Women with a miscarriage in their previous pregnancy were more likely to have a TTP above the median for their current pregnancy than before their miscarriage (adjusted risk ratio [RR] 2.1 [95% CI: 1.4-3.0]), and more likely to have a TTP above the median than women whose previous pregnancy resulted in a live birth (adjusted OR 2.1 [95% CI: 1.6-2.6]). In line with this finding, the probability of conception within 12 months of attempts was lower after a miscarriage than after a live birth (76% and 83%, respectively, $p<0.001$).[20] Contrary to

these results, a prospective cohort study of pregnancy planners in China, by Wang *et al.*, reported that early pregnancy loss in a preceding cycle was associated with increased odds of clinical pregnancy in a subsequent cycle (adjusted OR 2.0 [95% CI: 1.3-3.0]).[9]

2.5.4 Limitations of the existing literature

In the study by Sapra *et al.*,[19] the median post-LMP gestational age of pregnancy losses was 35 days (5%: 26 days; 95%: 81 days), thus, the results primarily concerned women with early losses and may not apply to the fecundability among women with miscarriages overall. Women provided data on TTP for up to 3 pregnancy attempts during 12 months of follow-up, suggesting that women with low fecundability were underrepresented; the TTP for the first attempt was at or below 6 cycles among the study participants. Furthermore, the study included only 70 women, of whom 61 contributed a second and 9 contributed a third attempt, leading to imprecise results. Hassan *et al.*[20] used self-reported, retrospective data on TTP, raising the possibility that recall was differential by previous pregnancy outcome. In addition, all study participants were pregnant, thus excluding women who had not conceived after miscarriage. In the study by Wang *et al.*,[9] the assessment of pregnancies only considered those occurring after an early pregnancy loss, and not miscarriages overall. Given the paucity of evidence and the inconsistent findings, further investigation of the association between history of miscarriage and fecundability is warranted.

Table 2. Studies of the association between history of miscarriage and fecundability

Author, year, country	Design	Population and data collection	Follow-up period	Measure of exposure	Measure of outcome	Main results
Sapra *et al.,*[19] 2014, US	Prospective cohort study	70 pregnancy planners, recruited in Michigan and Texas, US Women who conceived during the study and had a subsequent pregnancy loss could re-enter and continue their pregnancy attempts Women tested for pregnancy from the day of expected menses and recorded results of tests in a daily journal	12 months	Pregnancy loss: negative urine pregnancy test subsequent to one positive pregnancy test *or* clinically confirmed pregnancy loss	Time from start of unprotected intercourse until pregnancy confirmed by a single positive hCG-test	aFOR in the second attempt relative to the first attempt:* 0.42 (95% CI:0.28-0.65) aFOR in the third attempt relative to the first attempt:* 0.56 (95% CI:0.11-2.79) *: First attempt=before the pregnancy loss.
Hassan *et al.*,[20] 2005, UK	Cross-sectional study	2059 pregnant women with ≥1 previous pregnancy attending antenatal clinics in the UK Women completed a questionnaire on previous pregnancy outcomes and TTPs for their pregnancies		Miscarriage or live birth in the most recent pregnancy	Self-reported retrospective TTP for current and previous pregnancies, defined as time from exposure to unprotected intercourse until conception The pregnancy directly before the current one was defined as the index pregnancy	aRR for TTP >median after miscarriage relative to before miscarriage: 2.1 (95% CI:1.4-3.0) aOR for TTP >median after miscarriage relative to after live birth: 2.1 (95% CI:1.6-2.6)
Wang *et al.*,[9] 2003, China	Prospective cohort study	518 nulliparous pregnancy planners in China Women collected daily morning urine specimens for hCG testing until pregnancy or for 12 months, whichever came first	12 months	Early pregnancy loss: loss of a clinically unrecognized pregnancy before 6 weeks after onset of LMP	Time from start of unprotected intercourse until clinical pregnancy, defined as hCG-confirmed pregnancy that lasted ≥6 weeks after LMP	aOR for clinical pregnancy in a subsequent cycle relative to early pregnancy loss in a preceding cycle: 2.0 (95% CI:1.3-3.0)

Abbreviations: hCG, human chorionic gonadotropin; aFOR, adjusted fecundability odds ratio; CI, confidence interval; TTP, time to pregnancy; aRR, adjusted risk ratio; aOR, adjusted odds ratio; LMP, last menstrual period.

3 Aims of the thesis

From the literature review of the existing evidence on associations between weight and gestational age at birth and fertility, it emerged that no study has assessed fecundability using prospectively collected data on TTP. Furthermore, the evidence on the potential relation between history of miscarriage and subsequent fecundability was sparse, and results were inconsistent. On this basis, we conducted our studies with the following hypotheses and aims:

Study I aimed to examine the association between a woman´s weight at birth and her fecundability while adjusting for potential confounding by maternal reproductive history. We hypothesized that women with a low weight at birth would have lower fecundability than women with a birth weight within the normal range.

Study II aimed to examine the association between a woman´s gestational age at birth and her fecundability while adjusting for potential confounding by maternal reproductive history. We hypothesized that women who were born preterm would have lower fecundability than women born at term.

Study III aimed to examine the association between a woman´s history of miscarriage and her fecundability. We hypothesized that women with a history of miscarriage would have lower fecundability than women with no such history.

4 Subjects and methods

4.1 Data sources

The studies were conducted within the population of participants of "Snart-Gravid," an Internet-based prospective cohort study of time to pregnancy.[21, 22, 135] Data on participants´ birth characteristics, previous pregnancy outcomes and characteristics of the participants´ mothers were obtained from "Snart-Gravid," the Danish Medical Birth Registry and the Danish National Patient Registry (Tables 3 and 4).

In Denmark, the national health care system provides universal access to tax-funded health care.[136] Discharge diagnoses are recorded in the registries by law, ensuring nationwide and almost complete coverage,[137-139] and individual-level linkage of hospital contacts is possible by use of the Civil Personal Register (CPR) number.[140, 141] The "Snart-Gravid" study and the registries used are described below.

4.1.1 The "Snart-Gravid" study

The "Snart-Gravid" study was initiated in June 2007 and concluded follow-up in August 2012.[21] The study aimed at prospectively assessing the impact of several lifestyle and behavioral factors on TTP among women attempting to conceive. Recruitment to the study was initiated with an advertisement on a Danish health-related website (www.netdoktor.dk), and followed up by a coordinated media strategy. Enrollment and primary data collection were conducted by self-administered questionnaires accessible on the study website, and contact with participants was managed through the website and via e-mail.[21]

Women eligible to participate were Danish residents, 18-40 years old at study entry, attempting to conceive, in a relationship with a male partner, not using fertility treatment, and willing to provide their CPR number.[21] Potential participants in the study completed a consent form and a screening eligibility questionnaire, followed by a baseline questionnaire with items on socio-demographics, lifestyle and behaviors, medical and reproductive history – including previous pregnancy outcomes – and number of months that they had already attempted to conceive.[21] During the first 6 months of recruitment, participants were randomly selected to receive either a short- or a long-form version of the baseline questionnaire in order to evaluate the effect of questionnaire length.

Because there were no material differences in enrollment or completeness of data from the two versions of the questionnaire, all participants received the long-form version after this period.[135] Participants were contacted bi-monthly for up to 12 months after enrollment and asked to complete a follow-up questionnaire, which included items on changes in relevant characteristics and whether pregnancy had occurred. Follow-up ended on the date of conception or after 12 months post-enrollment, whichever came first.[21] Data obtained from the "Snart-Gravid" study are presented in Table 3.

Table 3. Data sources and type of data obtained

Source	Year of initiation	Unit of observation	Type of data obtained
The "Snart-Gravid" study	2007	Person	Participant: CPR number, TTP, age at study entry, height and weight, educational level, lifestyle factors (e.g., consumption of alcohol and caffeine, smoking, and exercise), medical conditions, age at menarche, menstrual cycle regularity, gravidity, parity, history of pregnancy attempts ≥12 months, history of consultation with a physician due to difficulty conceiving, intercourse frequency, previous pregnancy outcomes with dates Participants´ mothers: educational level (also for fathers), smoking during pregnancy, history of difficulty conceiving, history of miscarriage (studies I and II)
The Danish Civil Registration System (CRS)	1968	Person	CPR number, date of birth, identity of mother and siblings, emigration
The Danish Medical Birth Registry (DMBR)	1968*	Birth/person	CPR number, date of birth, birth weight, gestational age at birth, single/multiple gestation, birth order, live births and stillbirths for participant, mothers´ life-time parity, mothers´ age at time of delivery, mothers´ marital status at time of delivery, mothers´ self-reported miscarriages (study III), mothers´ preterm deliveries of siblings, dates of all events
The Danish National Patient Registry (DNPR)	1977	Hospital contact	CPR number, miscarriages, induced abortions and ectopic pregnancies for the participant, mothers´ diagnosis of pre-eclampsia, hypertension and diabetes during pregnancy, mothers´ and sisters´ miscarriages (study III), dates of all events

*Data available since 1973.

Table 4. Diagnosis codes for medical conditions and pregnancy outcomes in the Danish National Patient Registry*

Medical condition or pregnancy outcome	ICD-8	ICD-10
Hypertension	400-404, 637.00	
Pre-eclampsia	637.03, 637.04, 637.09, 637.19, 637.99	
Diabetes	249, 250, 634.74	
Miscarriage	634.61, 643, 645.1	DO021, DO03, DN969
Induced abortion	640, 641, 642	DO04, DO05, DO06
Ectopic pregnancy	631 excl. 631.90	DO00

*Live births and stillbirths were identified in the DMBR by CPR numbers, and not by diagnosis codes.

4.1.2 The Danish Civil Registration System

The Danish Civil Registration System (CRS) was established in 1968. The registry contains information on gender, date and place of birth, place of residence, and vital status on all Danish residents, who are assigned a CPR number at the time of birth or immigration.[140, 141] The CPR number is a unique 10-digit identification number, consisting of the date of birth and a four-digit gender-specific code. It enables accurate identification of an individual´s contacts with the Danish health care system, as recorded in national registries, and facilitates identification of the individual´s family relations because parents and their offspring can be linked through this number.[140, 141] For women born since 1935, the registry contains complete information on all of their children, enabling identification of siblings through the maternal CPR number.[142] The percentage of persons who can be linked to their mother in the registry was 99% in 1960 and 100% by 1970, with similar numbers for linkage to fathers.[140, 142]

4.1.3 The Danish Medical Birth Registry

The Danish Medical Birth Registry (DMBR) was established in 1968 and contains computerized records of more than 99% of hospital or at-home live- and stillbirths in Denmark since 1973.[137, 143] At the time of birth, the attending midwife makes a medical notification of the newborn to the DMBR and a civil notification to the CRS, as required by law.[137] Data were reported on paper forms in 1973 to 1996; since 1997, data on hospital-based live births have been reported electronically to the Danish National Patient Registry, while paper forms are still used to report stillbirths and at-home births.[137, 144] The aggregated data are linked with the CRS before being accessible in the DMBR.[137]

From the DMBR, we obtained data on weight and gestational age at birth, previous live- and stillbirths, and several covariates (Table 3). Data on weight at birth were recorded in categories of 250 grams until 1979, in categories of 10 grams from 1979 to 1990, and in full grams from 1991,[137, 145] however, records of birth weight showed digit preference with rounding to the nearest 50 or 100 grams throughout this period.[146] Data on gestational age at birth were recorded as 'born at term' or in number of weeks pre-term (1, 2, 3, 4, 5-6, 7-8, 9-11, or ≥12 weeks before term) until 1978 and in full weeks from 1978 to 1996.[145, 147] Thus, until 1978, the birth notification stated only whether the infant was born at term or preterm; in 1978 to 1982, the first day of the LMP was reported to the registry, and from 1983, both the LMP and the due date were reported in the birth notification. The DMBR did not record whether the due date was determined from LMP or prenatal ultrasound measurement.[148]

A report from 1990 showed that nationwide, around 20% of pregnant women in Denmark did not receive an ultrasound examination,[149] indicating that a non-negligible proportion of values of gestational age were based on date of the LMP in the early years of the DMBR. Data on gestational age were validated for 1,662 Danish births occurring in the period 1982 to 1987.[143] The level of agreement between data on gestational age in the DMBR and the medical records was estimated to be 43% when defining agreement as identical gestational week, 87% when redefining agreement as a difference within one week, and 96% when defined as two weeks´ difference.[143] Generally, the DMBR record overestimated gestational age by one week compared with the medical record.[143] To ensure that we used uniformly collected data on gestational age at birth, in studies I and II, we restricted the population to women born since 1978.

4.1.4 The Danish National Patient Registry

The Danish National Patient Registry (DNPR) was established in 1977, and contains records of all admissions to somatic hospitals from then on.[138, 139] Since 1995, outpatient contacts, emergency room visits and psychiatric hospital contacts have also been registered.[138, 139] Inpatient and outpatient contacts to private hospitals and clinics have been registered since 2003.[139] Records include the date of admission and discharge, treatments and procedures performed, and the discharge diagnosis, including one primary diagnosis and one or more optional secondary diagnoses.[138]

From the DNPR, we obtained data on previous miscarriages, induced abortions, and ectopic pregnancies, in addition to data on covariates (Tables 3 and 4). Diagnoses were coded according to the International Classification of Diseases, 8th edition (ICD-8) from 1977 to 1993, and according to the 10th edition (ICD-10) since 1994.[138, 139] The validity of miscarriage diagnoses in the DNPR is considered to be high, with an estimated positive predictive value (PPV) of 97.4% (95% CI: 92.7%-99.5%) in the period 1980-2008. The PPV did not vary appreciably according to period (1980-1994 or 1995-2008), or which revision of the ICD was in use.[18]

4.2 Study designs and study populations

All three studies in this thesis were prospective cohort studies conducted among "Snart-Gravid" participants. Women were enrolled from June 2007 until August 2011, and follow-up concluded in August 2012. During this time, a total of 6,033 women responded to the baseline questionnaire after confirming their eligibility for the study. From among the baseline respondents, we made a number of exclusions, which are illustrated in Figure 2 (studies I and II), and Figure 3 (study III).
Of note, in study II, we excluded participants according to the same criteria as in study I, however, we did not exclude women with missing information on multiple gestation by self-report if data from the DMBR indicated that they were singletons. Therefore, the study population consisted of 2,773 women in study I and 2,814 women in study II.
In study III, the final study population consisted of 977 women after exclusions.

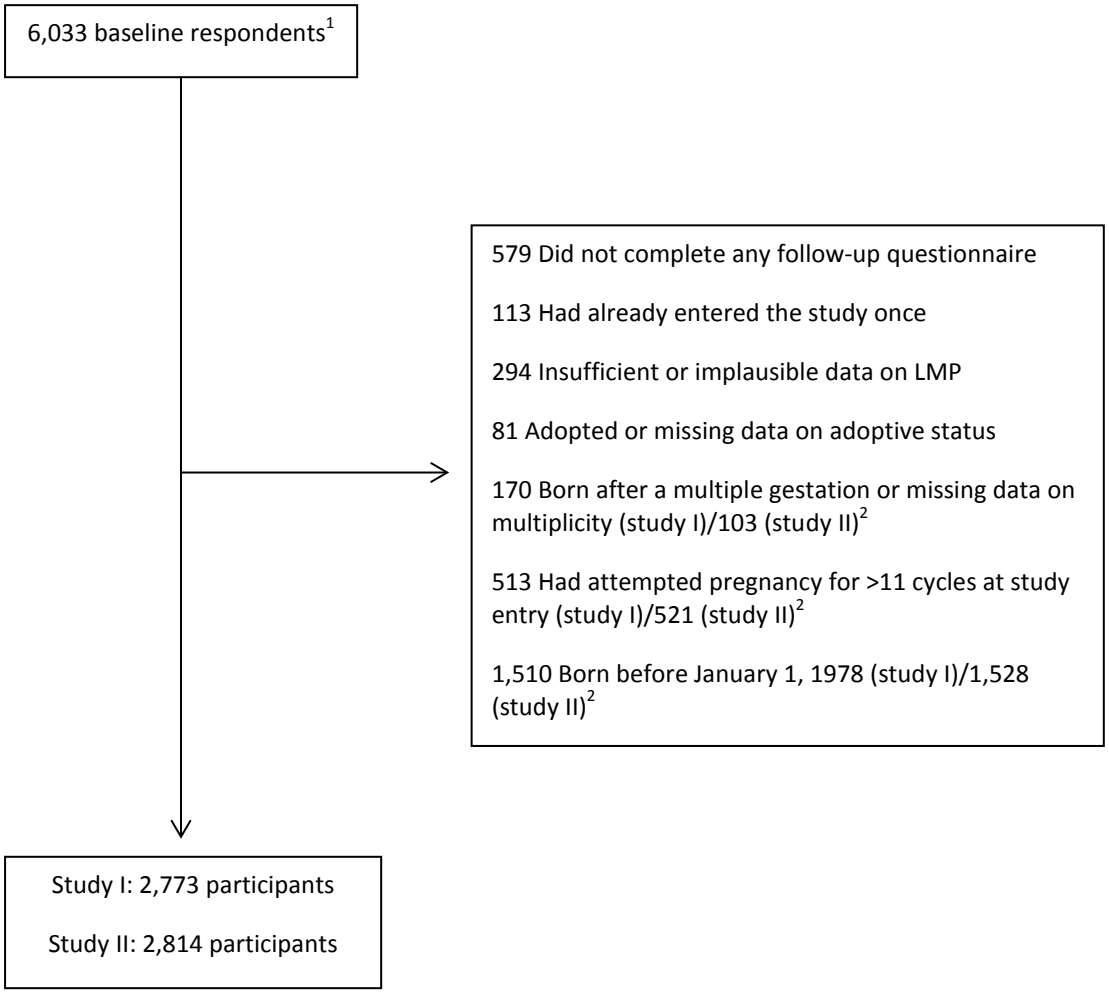

Figure 2. Flow chart for studies I and II

[1] In the published paper for study II, we subtracted 521 women with pregnancy attempt time >11 cycles at entry from the number of baseline respondents, resulting in 5,512 baseline respondents.

[2] In study I, we excluded women with missing data on multiple gestation by self-report. In study II, we did not exclude women with missing data on multiplicity if they were singletons according to the DMBR, resulting in 41 more participants in study II than in study I. Furthermore, exclusions were performed in a different sequence in the published paper for study I and in this figure, giving different numbers of women excluded by each criterion when comparing numbers in this figure with those presented in the paper for study I. This figure presents numbers of women excluded in the same sequence in studies I and II.

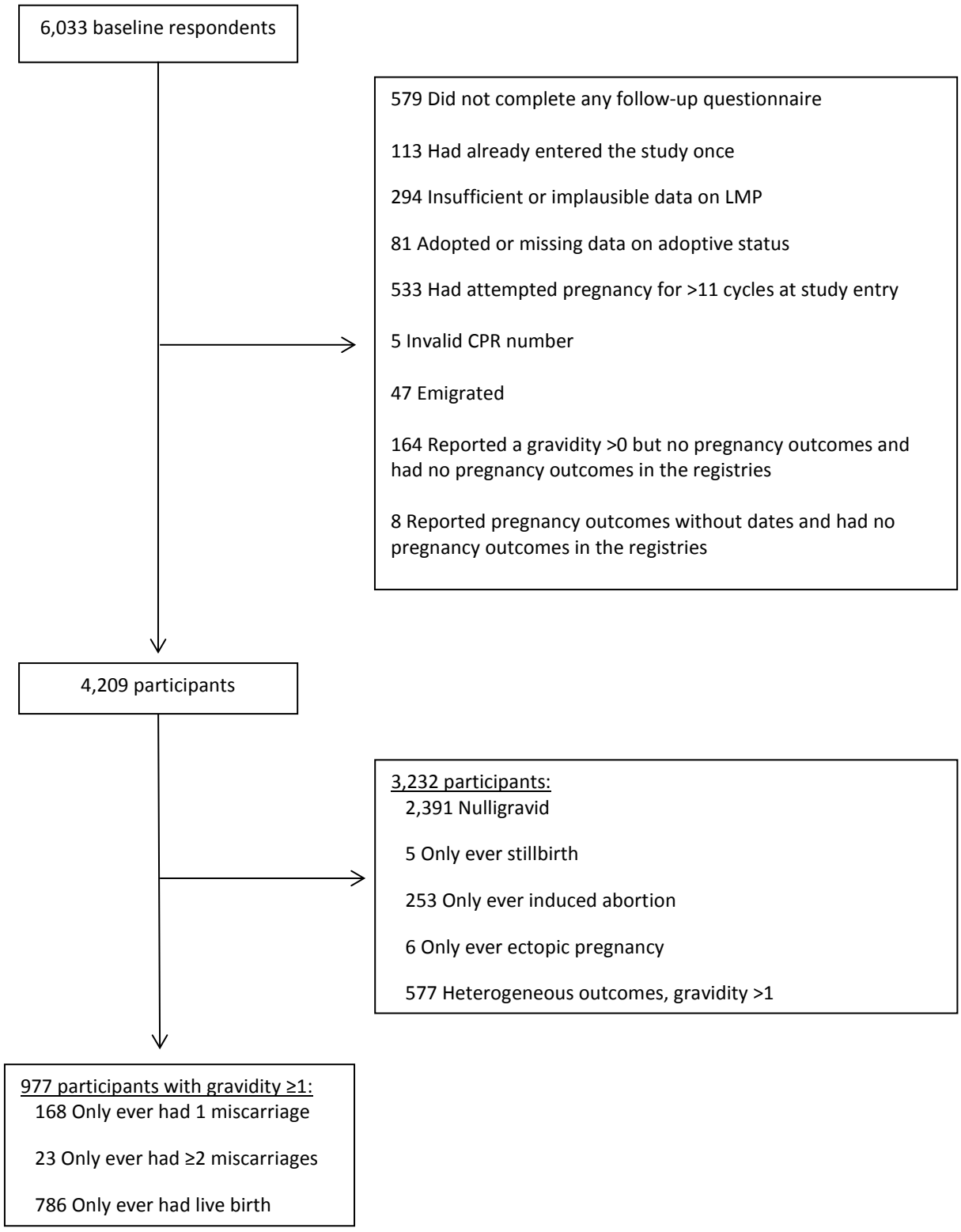

Figure 3. Flow chart for study III

4.3 Assessment of the study exposures

4.3.1 Birth weight

In study I, we categorized data on weight at birth as <2,500; 2,500-2,999; 3,000-3,999 (reference); and ≥4,000 grams. Within categories of each completed gestational week at birth, we also computed a z-score for each participant using the following formula:[150]

$$z\text{-}score = \frac{(observed\ birth\ weight - mean\ birth\ weight)}{standard\ deviation}$$

The gestational-week specific means and standard deviations of birth weight were obtained from the birth weight distribution of all Danish girls born in 1978 to 1992 – the period of the participants´ births – as recorded in the DMBR. The z-scores were grouped into the categories ≤-2; -2-≤-1; -1-≤0; 0-≤1 (reference); 1-≤2; and >2. Calculating z-scores for birth weight is an alternative approach to assessing birth size and allows for comparison of infants of differing relative weights that is unbiased by different distributions of gestational age at birth.[151]

4.3.2 Gestational age at birth

In study II, we categorized the data on gestational age at birth as preterm, <37 weeks (with subcategories <34 and 34-36 weeks); term, 37-41 weeks (reference); and post-term, ≥42 weeks.[152] We also examined gestational age in one-week categories (<32, each completed week 32-42, and ≥43 weeks, with 40 weeks as the reference).

We considered potentially implausible values of weight for gestational age at birth by assessing whether there were any values of weight for gestational age that were more than 3 standard deviations above or below the mean birth weight for gestational age in the population of Danish girls born during 1978 to 1992.[120] There were no implausible values identified by this method.

4.3.3 History of miscarriage

Miscarriage was defined as the loss of an embryo or fetus before 22 gestational weeks.[18] Women who had experienced only live birth served as the reference group because these women had

demonstrated their fertility and had no history of fetal loss (stillbirth, ectopic pregnancy, or miscarriage).

On the baseline questionnaire, participants reported previous pregnancies and the outcome of each pregnancy (live birth, stillbirth, miscarriage, induced abortion, ectopic pregnancy, or other) with dates. To reconstruct women´s reproductive histories, we combined the self-reported data with registry data. Cases of discordance between the two sources of data were solved as follows: If a woman did not report any pregnancy outcomes on the baseline questionnaire but had a record of ≥1 miscarriages in the DNPR and no record of other types of pregnancy outcomes, she was considered to have had miscarriage(s) as her only pregnancy outcome. Women reporting miscarriage as their only type of pregnancy outcome at baseline and with no record of a pregnancy outcome in the registries were considered to have had a history of miscarriage only. In cases of discrepancy between self-report and registry, the woman was considered to have had heterogeneous outcomes, unless her gravidity was one, in which case the registry record was considered to represent the true outcome. Using this approach, we ensured inclusion of miscarriages regardless of whether they resulted in a hospital contact. Women with live birth as their only pregnancy outcome were identified by the same strategy.

4.4 Assessment of outcome: fecundability

The outcome in the three studies was fecundability, which is measured by TTP.[153] TTP is defined as the number of non-contracepting cycles that it takes a couple to achieve a clinically recognized pregnancy, counting from the onset of regular sexual activity.[11, 153]

At baseline, participants reported the number of months that they had already attempted to become pregnant, the LMP date, and their usual cycle length. In each follow-up questionnaire, they reported their LMP and whether they were currently pregnant or had had a pregnancy termination (miscarriage, induced abortion, or ectopic pregnancy) since the previous follow-up. We estimated TTP by the following formula:[30]

$$TTP = \frac{days\ of\ pregnancy\ attempts\ at\ baseline}{days\ in\ usual\ cycle} + \frac{(date\ of\ most\ recent\ LMP - date\ of\ study\ entry)}{days\ in\ usual\ cycle} + 1$$

An extra cycle was added because the average woman was likely to be at mid-cycle when she entered the study. Clinically recognized pregnancy was defined as a pregnancy that was confirmed by a home pregnancy test or by physician´s examination.

4.5 Assessment of covariates

To characterize the study populations and to adjust for confounding, we included data on participants´ socio-demographic, lifestyle and reproductive characteristics, as well as data on the participants´ mothers´ socio-demographic, medical and reproductive characteristics, obtained from the "Snart-Gravid" study and from the registries.

Potential confounders were chosen *a priori*, based on literature and the availability of relevant data. The variables included as potential confounders were risk factors for impaired fertility,[29-32, 35, 114, 154, 155] with an association with the respective exposures.[89, 90, 114, 156-160] In studies I and II, we considered as confounders maternal hypertension, pre-eclampsia, and diabetes because these conditions are associated with infant weight and gestational age at birth[161-164] and may impact daughters´ fecundability.[165] In addition, in studies I and II, we hypothesized that maternal history of difficulty conceiving, miscarriage, preterm birth, and lifetime parity were potential confounders (cf. p. 7). Data on mothers´ history of miscarriage were obtained from participants´ reports in studies I and II, and from the DNPR and DMBR in study III. For study III, we also obtained data on participants´ sisters´ history of miscarriage from the DNPR as a proxy measure of familial proclivity to miscarriage.

4.6 Ethics and permissions

The "Snart-Gravid" study was approved by the Danish Data Protection Agency, which also granted the permission to extract data from the DNPR and the DMBR (record no. 2013-41-1922). The "Snart-Gravid" study was also approved by the Institutional Review Board at Boston University. All participants gave their written consent before completion of questionnaires.

4.7 Statistical analyses

4.7.1 Descriptive statistics

In each study, we constructed contingency tables of distributions of baseline characteristics by exposure category of the women. We used frequencies and proportions to summarize categorical variables and means and medians as appropriate to summarize continuous variables.

4.7.2 Proportional probabilities regression

We fitted proportional probabilities regression models to estimate crude and adjusted fecundability ratios (FR) with 95% confidence intervals (CI).[166] The FR represents the average cycle-specific probability of conception among the exposed divided by that among the unexposed, with values below 1 indicating lower relative fecundability (equivalent to longer TTP), and values above 1 indicating higher relative fecundability (equivalent to shorter TTP).[166] The proportional probabilities model resembles the Cox proportional hazards model, however, it uses discrete time-to-event data as the counting unit of time.[167] This approach is appropriate in the analysis of TTP because each menstrual cycle represents a single ovulatory opportunity, thus, the number of cycles at risk for pregnancy is a discrete measure.[166, 168]

Women entered the risk set at the time of study entry and contributed menstrual cycles at risk until confirmed pregnancy or right-censoring. Right-censoring occurred if the woman started fertility treatment, discontinued her pregnancy attempts, withdrew from the study, failed to respond to questionnaires during follow-up (i.e., had partial follow-up), or had attempted to conceive for 12 menstrual cycles. Cycles of pregnancy attempt that occurred before study entry were left-truncated, i.e., if a woman had attempted to conceive for 2 cycles at study entry, she entered the risk set starting at cycle 3.[166] By this approach, the assignment to risk set for women who had attempted to conceive for one or more cycles before study entry was determined by their number of cycles at risk of pregnancy, and not by the number of cycles since they entered the study.[167] In study III, the number of cycles of pregnancy attempts at study entry considered only the cycles following the most recent miscarriage or live birth. We checked the assumption of proportional probabilities by examining the FRs stratified by TTP <6 cycles and ≥6 cycles and found the assumption to be fulfilled in all three studies.

In study I, we computed FRs by category of birth weight (with weight 3,000-3,999 grams as the reference) adjusted for gestational age and year of birth (model 1); second, we included mother´s age, marital status, smoking, hypertension, and pre-eclampsia during pregnancy and parents´ educational level (model 2); third, we included mother´s history of difficulty conceiving and history of miscarriage, mother´s lifetime parity, and participant´s birth order (model 3). Accelerated weight gain in infancy, often exhibited by infants with a low birth weight, is associated with overweight or obesity,[61] which in turn is associated with lower fecundability.[30, 31] On this basis, in a subanalysis we assessed the potentially mediating effect of pre-pregnancy BMI on the association between birth weight and fecundability by stratification and adjustment.

In study II, we calculated FRs by aggregated categories of gestational age (using 37-41 weeks as the reference), adjusted for year of birth, mother´s age, marital status, smoking, hypertension, pre-eclampsia, and diabetes during pregnancy and parents´ educational level (model 1); second, we included mother´s history of difficulty conceiving, history of miscarriage, history of preterm birth, and mother´s lifetime parity (model 2).

In study III, we computed FRs for women with a history of only miscarriage (1 or ≥2) relative to women with a history of only live birth, adjusted for age and year of first miscarriage or live birth, higher education, BMI, history of pregnancy attempts ≥12 months, and history of consultation with a physician due to difficulty conceiving. To examine the effect of miscarriage recency on fecundability, we calculated FRs for women who had their miscarriage <1 or ≥1 year before initiating their current pregnancy attempts, restricted to women with a gravidity of one to exclude potential confounding by parity. We also assessed whether the miscarriage-fecundability association varied by mother´s or sister´s history of miscarriage to evaluate confounding by familial proclivity to miscarriage.

4.7.3 The Kaplan-Meier method

We used the Kaplan-Meier method, allowing for left-truncation and right-censoring, to estimate cumulative probabilities of conception within 3, 6 and 12 cycles of pregnancy attempts in studies I and II and to compute the curve of the probability of conception within 12 cycles of pregnancy attempts in study III.

4.7.4 Restricted cubic splines regression

In study II, we assessed the potential non-linear relation between gestational age and fecundability using restricted cubic splines to depict the trend in fecundability ratio by level of gestational age at birth.[169]

4.7.5 Sensitivity analyses

We conducted a number of sensitivity analyses to assess the robustness of the results to changes in methods, models, or assumptions.[170]

In study I, we restricted to term births in addition to using adjustment to control for confounding by gestational age. Furthermore, we examined fecundability according to gestational-week-specific z-scores for birth weight.

In study II, we calculated FRs by one-week categories of gestational age (with 40 weeks´ gestation as reference). Measures of gestational age that are determined from the LMP may be overestimated, compared with measures obtained from ultrasound examination.[171, 172] Thus, assuming that gestational length was primarily determined from the LMP during the birth years of our cohort, we assessed potential misclassification of gestational age in the DMBR by subtracting one week from each observed value and repeating the analysis for one-week categories of gestational age.

In all studies, we made a restriction to women who had attempted to conceive only for up to 3 or 6 cycles at study entry to evaluate associations among the participants that we assumed to have the highest fecundability. In study III, we repeated the main analysis with a restriction to women with a gravidity of one to remove confounding by parity.

4.7.6 Missing values

Less than 5% of values were missing for most variables obtained from the DMBR, however, there were 5% and 17% missing values of birth weight and gestational age, respectively. Missing observations of gestational age were primarily attributable to a change in the reporting of this variable to the DMBR in 1978,[137, 146] contributing to 13% to 31% missing values of gestational age

in the years 1978 to 1981 (decreasing over the years)[145] whereas proportions of missing values of this variable ranged between 0.3% and 1.6% from 1982 to 1992.[173]

For most variables reported in the "Snart-Gravid" study, proportions of missing values were below 2%, with the exception of mother´s smoking during pregnancy (8% missing), mother´s history of difficulty conceiving (17% missing), and mother´s history of miscarriage (20% missing). Furthermore, there were missing values of the variables on consultation with a physician due to difficulty conceiving (26% missing), and mother´s and father´s educational level (30% and 35% missing, respectively). Missing values for the latter three variables were largely attributable to the fact that they were not included in the short version of the baseline questionnaire that half of the participants were randomized to complete during the first 6 months of the study.

On the assumption that observations were missing at random, we used multiple imputation by chained equations to impute missing values for exposures and covariates, except in study III, where only the covariates had missing values and were imputed. We considered all variables used in the analyses, including measures of outcome, in the multiple imputation procedure and generated five data sets.[174] To assess the robustness of the results, in study II, we also created 40 imputed data sets, corresponding to the highest proportion of missing values.[175] Repeating the main analysis on the basis of 40 imputed data sets yielded results that were close to those based on 5 imputed data sets. For this reason, 5 imputed data sets were considered to be sufficient for the analyses. In addition, we evaluated the findings based on imputed data by supplementing with complete case analyses in each study[174] (analyses that included participants with observed values of the variables of interest only and excluded those with missing values), obtaining results that were similar to those based on the imputed data sets.

Statistical analyses were conducted using Stata version 12.0 (StataCorp., College Station, TX, USA), and SAS version 9.2 (SAS Institute Inc., Cary, NC, USA) in all three studies.

5 Results

5.1 Study participants

Of 2,814 women, there were 1,787 (64%) who became pregnant within 12 cycles of attempts, 216 women (8%) who initiated fertility treatment, 116 women (4%) who discontinued their pregnancy attempts or resigned from the study, and 245 women (9%) who stopped responding to follow-up questionnaires and provided no reason for not continuing their participation in the study, i.e., had partial follow-up. A total of 450 women (16%) did not become pregnant during follow-up and were censored after 12 cycles of pregnancy attempts, in accordance with the definition of infertility.

5.2 Partial follow-up

Women with partial follow-up contributed cycles at risk for as many cycles as they were observed in the study and were censored on the date of completion of their last follow-up questionnaire. Overall, the mean birth weight was slightly lower among women with partial follow-up than among women who completed the study, but the distribution of gestational age at birth was similar. Comparing the proportions of women with low birth weight (<2,500 grams) or born preterm (<34 gestational weeks) who had partial follow-up with exposed women with complete follow-up according to baseline characteristics, we found slight differences primarily by maternal factors. However, these findings were based on only 17 (study I) and 5 (study II) women with low birth weight or born preterm who had partial follow-up. In study III, women with a history of miscarriage and with partial follow-up were more likely to be obese (BMI ≥30 kg/m^2) and to previously have attempted to become pregnant ≥12 months than women with miscarriage who had complete follow-up, however, this result was based on data for 9 women.

5.3 Study I: Weight at birth and fecundability

Among the 2,773 women included in the study, the mean birth weight was 3,315 grams (95% CI: 3,295-3,334 grams), and 3,326 grams (95% CI: 3,307-3,345 grams) in the 2,432 (87.7%) women who were born at term. One hundred and two (3.7%) participants had been born preterm, and 239 (8.6%) had been born post-term.

Women with a birth weight <2,500 grams were more likely than women with a birth weight within the normal range to have a history of ≥12 months attempting a pregnancy, to be obese (BMI ≥30 kg/m^2), to have longer duration of pregnancy attempts at study entry, and to have a frequency of intercourse ≥4 times per week. They were also more likely to be first-borns, to have a parent with only lower secondary education, and a divorced or widowed mother who smoked during pregnancy, was diagnosed with hypertension or pre-eclampsia during pregnancy, had a history of difficulty conceiving or miscarriage, and a lifetime parity of at least four children (Table 5).

Table 5. Characteristics of 2,773 women and their mothers according to categories of birth weight

	Birth weight, grams			
Characteristic	<2,500	2,500-2,999	3,000-3,999	≥4,000
No. of women, (%)	119 (4.3)	488 (17.6)	1,866 (67.3)	300 (10.8)
Age at study entry, mean, years	26.1	26.4	26.5	26.5
Born at term, %	54.6	89.8	90.5	80.3
Age at menarche, mean, years	12.6	12.7	12.9	12.9
Irregular menstrual cycles, %	26.1	25.0	28.7	27.7
Gravidity ≥1, %	32.8	37.3	33.1	33.0
Parity ≥1, %	21.0	21.7	20.0	20.3
History of pregnancy attempts ≥12 months, %	16.8	11.9	7.8	6.3
BMI, kg/m², %				
<18.5	5.9	5.9	4.0	3.0
18.5-24.9	53.8	60.5	64.6	62.0
25.0-29.9	21.9	18.0	20.3	22.7
≥30	18.5	15.6	11.1	12.3
No. of cycles of attempted pregnancy at study entry, %				
0-1	41.2	48.6	47.7	46.7
2-3	23.5	22.8	21.9	27.0
4-6	21.0	16.4	17.3	17.7
7-11	14.3	12.3	13.1	8.7
Intercourse frequency ≥4 times/week, %	26.1	22.8	21.1	23.0
Mother´s age at time of delivery, median	25	25	26	26
Mother´s marital status at time of delivery, %				
Married	61.3	62.1	65.1	71.7
Unmarried	31.1	34.4	31.2	24.7
Divorced/widowed	7.6	3.5	3.7	3.7
Mother´s education, 9^{th}-10^{th} grade, %	69.8	60.9	57.2	59.0
Father´s education, 9^{th}-10^{th} grade, %	74.0	64.6	67.3	71.7
Mother smoked during pregnancy, %	57.1	51.8	31.4	22.0
Mother had hypertension, %*	3.4	0.4	0.8	1.0
Mother had pre-eclampsia, %*	7.6	3.3	1.6	2.7
Mother´s history of difficulty conceiving, %	19.3	18.9	13.3	15.0
Mother´s history of miscarriage, %	42.0	28.9	24.5	18.3
Mother´s lifetime parity, %				
1	10.9	12.1	9.4	6.3
2-3	68.9	74.6	76.9	76.0
≥4	20.2	13.3	13.7	17.7
Birth order of participant, %				
First-born	54.6	56.4	45.2	32.0
Second-born	27.7	29.7	37.1	47.0
>Second-born	17.7	13.9	17.7	21.0

Abbreviation: BMI, body mass index.

*Mother diagnosed with hypertension or pre-eclampsia during pregnancy with the participant.

The cumulative probability of conception within 3, 6, and 12 cycles was 47% (95% CI: 44%-50%), 67% (95% CI: 65%-70%), and 83% (95% CI: 82%-85%), respectively. After adjustment for gestational age and year of birth, the FRs for birth weight categories <2,500, 2,500-2,999 and ≥4,000 grams, compared with 3,000-3,999 grams, were 1.01 (95% CI: 0.75-1.36), 1.00 (95% CI:

0.88-1.13), and 1.07 (95% CI: 0.94-1.23) (Table 6). Results remained unchanged after further adjustments for maternal socio-demographic and medical characteristics and markers of fecundability. The FRs were not affected by restricting the analysis to women born at term. Repeating the analyses using categories of weight at birth defined by z-scores yielded similar results to those based on weight in grams (see paper I for results).

Results were consistent when we restricted to women with up to 6 cycles of pregnancy attempts at study entry, and were unchanged by controlling for participants´ BMI (results not shown).

Table 6. Fecundability by categories of birth weight

					Unadjusted model		Adjusted model 1		Adjusted model 2		Adjusted model 3	
	Birth weight, grams	No. of women	No. of cycles	No. of pregnancies	FR	95% CI	FR	95% CI	FR	95% CI	FR	95% CI
All women, N=2,773	<2,500	119	504	66	0.89	0.71-1.12	1.01	0.75-1.36	0.99	0.73-1.34	0.98	0.72-1.32
	2,500-2,999	488	1,979	314	0.97	0.86-1.09	1.00	0.88-1.13	0.99	0.87-1.12	0.99	0.87-1.13
	3,000-3,999	1,866	7,461	1,176	1	Reference	1	Reference	1	Reference	1	Reference
	≥4,000	300	1,131	201	1.10	0.96-1.26	1.07	0.94-1.23	1.08	0.94-1.24	1.07	0.93-1.24
Born at term, N=2,432	<2,500	65	230	36	0.98	0.69-1.38	1.01	0.70-1.46	1.01	0.69-1.46	1.00	0.69-1.45
	2,500-2,999	452	1,786	277	0.96	0.84-1.09	0.97	0.85-1.11	0.96	0.84-1.10	0.97	0.84-1.12
	3,000-3,999	1,814	6,782	1,069	1	Reference	1	Reference	1	Reference	1	Reference
	≥4,000	279	947	166	1.11	0.95-1.29	1.10	0.94-1.28	1.09	0.93-1.27	1.08	0.93-1.26

Abbreviations: FR, fecundability ratio; CI, confidence interval.

Model 1: Adjusted for participant´s gestational age and year of birth.

Model 2: Model 1 + mother´s age, mother´s marital status, mother´s and father´s educational level, mother´s smoking, mother´s hypertension, and mother´s pre-eclampsia during pregnancy with the participant.

Model 3: Model 2 + mother´s history of difficulty conceiving, mother´s history of miscarriage, mother´s lifetime parity, and participant´s birth order.

5.4 Study II: Gestational age at birth and fecundability

Of 2,814 study participants, 19 (0.7%) had been born <34 weeks, 89 (3.2%) at 34-36 weeks, 2,463 (87.5%) at 37-41 weeks, and 243 (8.6%) at ≥42 weeks of gestation (Table 7). Women who had been born <34 weeks of gestation were slightly younger at study entry than women born at term. They were less likely to have irregular cycles or to have previously been pregnant or given birth. They were more likely to have a history of pregnancy attempts ≥12 months, to have attempted pregnancy for more than three cycles at study entry, to have a father with only lower secondary education, and to have a mother who was 20-24 years old at delivery, married, who smoked during pregnancy, was diagnosed with pre-eclampsia, had a history of difficulty conceiving, miscarriage, or preterm birth, and a parity of at least four children.

Kaplan-Meier estimates for the cumulative probability of conception were 12% (95% CI: 0%-31%), 28% (95% CI: 0%-50%), and 48% (95% CI: 11%-69%) within 3, 6, and 12 cycles, respectively, for women born <34 weeks of gestation, and 47% (95% CI: 43%-49%), 67% (95% CI: 65%-70%), and 84% (95% CI: 82%-85%) within 3, 6, and 12 cycles, respectively, for women born at 37-41 weeks of gestation.

Table 7. Characteristics of 2,814 participants and their mothers according to categories of gestational age at birth

	Gestational age, weeks			
Characteristic	<34	34-36	37-41	≥42
No. of women (%)	19 (0.7)	89 (3.2)	2,463 (87.5)	243 (8.6)
Age at study entry, mean (s.e.), years	25.1 (0.6)	26.6 (0.3)	26.5 (0.1)	26.3 (0.2)
Weight at birth, mean (s.e.), grams	1,572 (102.5)	2,476 (51.8)	3,326 (9.6)	3,638 (29.4)
Age at menarche, mean (s.e.), years	12.8 (0.4)	12.5 (0.1)	12.9 (0.0)	12.8 (0.1)
Irregular menstrual cycles, %	21.1	14.6	28.2	27.6
Gravidity ≥1, %	15.8	37.1	33.4	39.1
Parity ≥1, %	10.5	24.7	20.0	24.7
History of pregnancy attempts ≥12 months, %	31.6	11.2	8.9	5.4
No. of cycles of attempted pregnancy at study entry, %				
0-1	42.1	46.1	47.2	49.0
2-3	21.1	20.2	23.3	18.5
4-11	36.8	33.7	29.5	32.5
Mother´s age at time of delivery, %				
<20	0.0	5.6	4.1	3.3
20-24	47.4	37.1	32.5	38.7
25-29	26.3	25.8	38.9	38.3
≥30	26.3	31.5	24.5	19.8
Mother´s marital status at time of delivery, %				
Married	73.7	57.3	65.3	63.4
Unmarried	21.1	40.5	30.9	33.3
Divorced/widowed	5.3	2.3	3.8	3.3
Mother´s education, 9^{th}-10^{th} grade, %	57.9	60.7	57.9	60.9
Father´s education, 9^{th}-10^{th} grade, %	79.0	70.8	67.3	69.1
Mother smoked during pregnancy, %	52.6	49.4	34.7	26.8
Mother had hypertension, %*	0.0	1.1	0.9	0.8
Mother had pre-eclampsia, %*	10.5	10.1	2.0	1.2
Mother had diabetes, %*	0.0	4.5	0.5	0.0
Mother´s history of difficulty conceiving, %	26.3	14.6	14.6	15.2
Mother´s history of miscarriage, %	42.1	37.1	24.5	25.1
Mother´s history of preterm birth, older sibs, %	26.3	16.9	3.7	2.1
Mother´s history of preterm birth, all sibs, %	42.1	22.5	6.1	3.7
Mother´s lifetime parity, %				
1	5.3	14.6	10.6	8.6
2-3	68.4	73.0	76.9	78.2
≥4	26.3	12.4	12.5	13.2

Abbreviation: s.e., standard error.
*Mother diagnosed with hypertension, pre-eclampsia or diabetes during pregnancy with the participant.

Crude FRs were 0.37 (95% CI: 0.17-0.81) for women born <34 weeks, 1.05 (95% CI: 0.82-1.34) for women born at 34-36 weeks, and 1.11 (95% CI: 0.94-1.30) for women born at ≥42 weeks of gestation, relative to women born at 37-41 weeks´ gestation (Table 8). Results were similar after adjustment for year of birth and mothers´ socio-demographic and medical characteristics and markers of maternal fecundability.

Table 8. Fecundability by four categories of gestational age at birth

				Unadjusted model		Adjusted model 1		Adjusted model 2	
Gestational age, weeks	No. of women	No. of cycles	No. of pregnancies	FR	95% CI	FR	95% CI	FR	95% CI
<34	19	109	6	0.37	0.17-0.81	0.39	0.18-0.84	0.38	0.17-0.82
34-36	89	371	60	1.05	0.82-1.34	1.04	0.80-1.34	1.03	0.80-1.34
37-41	2,463	9,845	1,571	1	Reference	1	Reference	1	Reference
≥42	243	877	150	1.11	0.94-1.30	1.13	0.96-1.33	1.13	0.96-1.33

Abbreviations: FR, fecundability ratio; CI, confidence interval.
Model 1: Adjusted for participant´s year of birth, mother´s age, mother´s marital status, mother´s and father´s educational level, mother´s smoking, mother´s hypertension, mother´s pre-eclampsia, and mother´s diabetes during pregnancy with the participant.
Model 2: Model 1 + mother´s history of difficulty conceiving, mother´s history of miscarriage, mother´s history of preterm birth, and mother´s lifetime parity.

Table 9 shows the association between gestational age and fecundability for each completed gestational week of birth. The resulting adjusted FRs from this analysis did not suggest a material association with fecundability for any category of gestational age, except for women born <34 weeks of gestation. Within this category, we found similar effect estimates for women born in the three subcategories, <32, 32, and 33 weeks of gestation.

Table 9. Fecundability according to gestational age at birth, by completed week

				Unadjusted model		Adjusted model 1		Adjusted model 2	
Gestational age, weeks	No. of women	No. of cycles	No. of pregnancies	FR	95% CI	FR	95% CI	FR	95% CI
<32	*11*	*70*	*4*	*0.38*	*0.15-0.98*	*0.40*	*0.15-1.03*	*0.40*	*0.15-1.04*
32	*4*	*24*	*1*	*0.31*	*0.05-2.09*	*0.32*	*0.05-2.21*	*0.30*	*0.04-2.08*
33	*4*	*15*	*1*	*0.42*	*0.06-2.79*	*0.43*	*0.06-2.82*	*0.39*	*0.06-2.54*
<34	19	109	6	0.37	0.17-0.81	0.39	0.18-0.85	0.38	0.17-0.83
34	15	61	11	1.14	0.65-2.02	1.15	0.63-2.11	1.12	0.61-2.06
35	24	94	19	1.19	0.78-1.82	1.18	0.77-1.82	1.17	0.75-1.80
36	50	216	30	0.94	0.62-1.42	0.93	0.61-1.42	0.94	0.62-1.42
37	134	566	80	0.96	0.77-1.20	0.97	0.77-1.22	0.97	0.76-1.22
38	267	1,083	159	0.91	0.74-1.11	0.91	0.74-1.12	0.90	0.74-1.11
39	472	1,836	308	1.04	0.91-1.17	1.05	0.93-1.20	1.05	0.92-1.19
40	1,105	4,481	711	1	Reference	1	Reference	1	Reference
41	485	1,879	313	1.01	0.89-1.15	1.02	0.90-1.16	1.02	0.90-1.16
42	209	765	128	1.11	0.92-1.32	1.14	0.95-1.36	1.14	0.95-1.37
≥43	34	112	22	1.09	0.71-1.66	1.12	0.74-1.70	1.11	0.73-1.69

Abbreviations: FR, fecundability ratio; CI, confidence interval.
Model 1: Adjusted for participant´s year of birth, mother´s age, mother´s marital status, mother´s and father´s educational level, mother´s smoking, mother´s hypertension, mother´s pre-eclampsia, and mother´s diabetes during pregnancy with the participant.
Model 2: Model 1 + mother´s history of difficulty conceiving, mother´s history of miscarriage, mother´s history of preterm birth and mother´s lifetime parity.

Figure 4 shows a smoothed graph for the relation between fecundability and gestational age at birth, throughout the range from 28 to 44 completed weeks, using restricted cubic splines. The smoothed curve indicates increasing fecundability with increasing gestational age at birth from 28 weeks until about 35 weeks and is then nearly level with only small fluctuations from the reference value through the highest gestational ages.

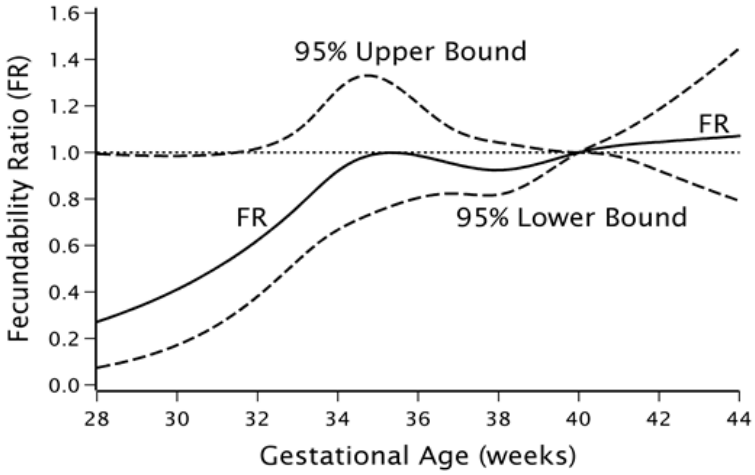

Figure 4. Association between gestational age at birth and fecundability, fitted by restricted cubic splines
The dashed lines indicate the 95% confidence interval (CI). The reference level for the fecundability ratio (FR) was 40 weeks of gestation. The curves were adjusted for participant´s year of birth; mother´s age, marital status, smoking status, hypertension, pre-eclampsia, diabetes, history of difficulty conceiving, miscarriage, preterm birth and lifetime parity; and mother´s and father´s educational level. Five knot points were located at 33, 34, 38, 40, and 42 weeks of gestation.

To assess the influence of misclassification of gestational age on our results, we subtracted one week from each observed value of gestational age, assuming that it was overestimated in the DMBR. The adjusted FR for women born <34 weeks according to this categorization was 0.64 (95% CI: 0.40-1.04) and thus still reduced compared with women born at 40 weeks of gestation (see paper II for results). The FRs were unaffected by restriction to women with up to 3 cycles of pregnancy attempts at study entry (see paper II for results).

5.5 Study III: History of miscarriage and fecundability

Of 977 women in the study population, 786 women had a history of live birth only, 168 women had a history of 1 miscarriage, and 23 women a history of ≥2 miscarriages (Table 10). Women with a history of miscarriage tended to be younger, more likely to have had their first pregnancy event after 2007, have no higher education, have intercourse ≥4 times/week, and more likely to have attempted to become pregnant for at least 4 cycles at study entry than women with live births. Among women with ≥2 miscarriages, there was a lower prevalence of irregular menstrual cycles, an elevated prevalence of BMI ≥30 kg/m^2, history of pregnancy attempts ≥12 months and having consulted a physician due to difficulty conceiving, as well as familial history of miscarriage.

Table 10. Characteristics of 977 participants who experienced only miscarriage or only live birth

Characteristic	Only ever 1 miscarriage	Only ever ≥2 miscarriages	Only ever live birth
No. of women	168	23	786
Age at study entry, mean (s.e.), years	27.9 (0.3)	27.5 (0.9)	30.6 (0.1)
Age at first pregnancy event, mean (s.e.), years*	26.3 (0.3)	25.0 (1.0)	27.1 (0.1)
Calendar year of first pregnancy event, %*			
<2003	10.1	17.4	20.0
2003-2007	53.0	60.9	75.5
>2007	36.9	21.7	4.6
Higher education, %			
None	14.3	17.4	8.5
<3 years	33.9	30.4	30.7
3-4 years	31.6	30.4	38.4
>4 years	20.2	21.7	22.4
BMI, kg/m^2, %			
<18.5	1.8	4.4	3.4
18.5-24.9	67.9	39.1	58.5
25.0-29.9	17.9	26.1	23.2
≥30.0	12.5	30.4	14.9
Irregular menstrual cycles, %	24.4	13.0	22.4
Intercourse frequency ≥4 times/week, %	17.3	26.1	11.8
No. of cycles of attempted pregnancy at study entry, %			
0-1	34.5	30.4	55.6
2-3	28.0	17.4	20.6
4-6	26.2	21.7	12.7
7-11	11.3	30.4	11.1
History of pregnancy attempts ≥12 months, %	13.7	30.4	19.0
History of consultation with a physician due to difficulty conceiving, %	15.5	30.4	21.0
Miscarriage in mother or sister, %	26.8	30.4	22.0

Abbreviations: s.e., standard error; BMI, body mass index.
*First pregnancy event=first miscarriage or first live birth.

Crude Kaplan-Meier estimates for the cumulative probability of conception within 6 and 12 cycles of pregnancy attempts were 69% (95% CI: 62%-75%) and 85% (95% CI: 80%-88%) for women with a history of 1 miscarriage, 46% (95% CI: 21%-63%) and 69% (95% CI: 49%-82%) for women with a history of ≥2 miscarriages, and 76% (95% CI: 74%-79%) and 89% (95% CI: 87%-90%) for women with previous live birth. Figure 5 shows that the differences in the adjusted cumulative probabilities of conception associated with miscarriage were largest during the first 6 cycles of pregnancy attempts, gradually tapering off by 12 cycles.

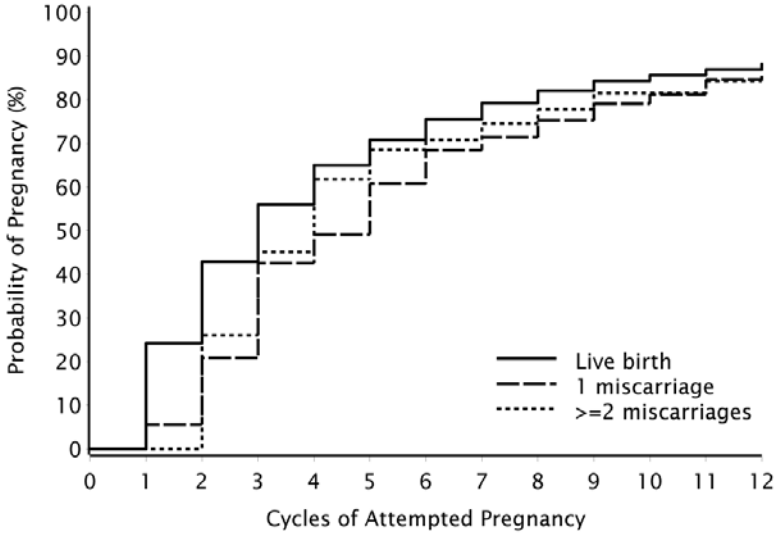

Figure 5. Adjusted cumulative probabilities of conception after miscarriage or live birth*
*Adjusted for age at first miscarriage or live birth, calendar year of first miscarriage or live birth, higher education, body mass index, history of pregnancy attempts ≥12 months, and history of consultation with a physician due to difficulty conceiving.
Adjusted cumulative probability of conception with 95% confidence intervals (CI), 6 cycles:
1 miscarriage: 68% (62%-74%); ≥2 miscarriages: 71% (52%-82%); live birth: 75% (74%-77%)
Adjusted cumulative probability of conception with 95% CI, 12 cycles:
1 miscarriage: 85% (81%-89%); ≥2 miscarriages: 85% (73%-92%); live birth: 88% (87%-89%)

After adjustment for confounding, the FRs were 0.87 (95% CI: 0.71-1.07) for women with a history of 1 miscarriage, and 0.65 (95% CI: 0.36-1.17) for women with a history of ≥2 miscarriages (Table 11). When we restricted to women with gravidity of 1 at entry into the study, the result was similar for 1 miscarriage (FR 0.85 [95% CI: 0.69-1.05]). The FRs were not appreciably different after restriction to women with ≤3 cycles of pregnancy attempts at study entry (see paper III for results).

Table 11. Fecundability among women who have only had miscarriage, gravidity ≥1

				Unadjusted model		Adjusted model*	
Pregnancy outcome	No. of women	No. of cycles	No. of pregnancies	FR	95% CI	FR	95% CI
Only miscarriage							
Total	191	727	121	0.87	0.73-1.04	0.85	0.70-1.03
1	168	632	111	0.91	0.76-1.09	0.87	0.71-1.07
≥2	23	95	10	0.60	0.33-1.07	0.65	0.36-1.17
Only live birth	786	2,796	565	1	Reference	1	Reference

Abbreviations: FR, fecundability ratio; CI, confidence interval.
*Adjusted for age at first miscarriage or live birth, calendar year of first miscarriage or live birth, higher education, body mass index, history of pregnancy attempts ≥12 months, and history of consultation with a physician due to difficulty conceiving.

Among women with gravidity of 1, the adjusted FR for women who had their miscarriage <1 year before initiating their current pregnancy attempts was 0.86 (95% CI: 0.68-1.08), and 0.82 (95% CI: 0.52-1.29) for women with miscarriage ≥1 year before current attempts. The FRs from the analysis with stratification by mothers´ or sisters´ history of miscarriage did not differ appreciably from the crude FRs (results not shown).

6 Discussion

6.1 Main findings

Study I: Weight at birth and fecundability

We found little evidence to support an association between weight at birth and fecundability. This finding was robust for different definitions of low birth weight and for the controlled confounders, including proxy markers of maternal fecundability.

Study II: Gestational age at birth and fecundability

Among women born before 34 completed weeks of gestation, fecundability was 62% lower than among women born at term, whereas fecundability did not appear to be different among women born at 34-36 or ≥42 weeks of gestation. Proxy markers of maternal fecundability did not confound the associations.

Study III: History of miscarriage and fecundability

We found a 13% decrease in fecundability among women with a history of one miscarriage, and a 35% decrease among women with history of at least 2 miscarriages, relative to women with a history of only live birth. The cumulative probability of conception was lower among women with miscarriage, but this difference gradually diminished and had disappeared by 12 cycles of pregnancy attempts.

6.2 Comparison with the existing literature

6.2.1 Weight and gestational age at birth and fecundability

The lack of an association between weight at birth and fecundability found in our study is in agreement with the findings by Meas *et al.* of little association between being born SGA and fecundability among 403 women who had attempted to conceive.[14] In contrast, when examining the outcome of TTP >12 months retrospectively among women who had conceived, Nøhr *et al.* found that the extremes of birth weight were associated with reduced fecundity.[15] By comparison, the outcome in our study was defined as the average cycle-specific probability of conception in a cohort of pregnancy planners, including also women who did not conceive. The methodological differences in the two studies may be responsible for the different results in our study compared with those of Nøhr *et al.*

A comparison of our findings with studies that assessed fertility measured as registered births in national registries is complicated by the fact that those studies do not necessarily convey information on potential differences in fecundability, since they may not only reflect a biological mechanism.[114, 115, 121] Still, the results appear to corroborate ours in that small size at birth – at least for SGA and weight <2,500 grams – may have little influence on fertility.

We did not differentiate birth weights of <1,500 grams from those <2,500 grams because of sparse data, which may have masked an association for very low birth weight. Several studies have reported that a birth weight <1,500 grams is associated with a reduced probability of pregnancy or giving birth.[16, 114, 115] Because a birth weight <1,500 grams is a marker of preterm birth,[13] Nøhr *et al.* speculated that their finding of a prolonged TTP in women born preterm with a weight ≤1,500 grams was likely related to very preterm birth,[15] however, that study did not have available data to explore the effect of gestational age in detail. In study II, we addressed this issue by assessing fecundability in categories of preterm, term and post-term birth, and in one-week categories of gestational age. We found a decreased fecundability among women born <34 gestational weeks, with strong point estimates in the subcategories <32, 32, and 33 weeks of gestation, although the confidence intervals included a range of parameter values. The restricted cubic splines curve showed that fecundability increased with increasing gestational age at birth from 28 weeks until about 35 weeks, with only small fluctuations from the reference of 40 weeks through higher gestational ages.

In corroboration of these results, the studies that assessed fertility as registered births found a detrimental effect on fertility primarily in women born before 32 weeks´ gestation,[114-116, 121] with some studies showing a pattern of decreasing fertility with even lower gestational age.[114, 116] Again, those results may not only reflect a decrease in fecundability and should be cautiously compared with our findings.

Despite this limitation, when taken together, our finding of impaired fecundability among women born before 34 gestational weeks appears to support results from previous studies. We, like others, had no data to evaluate in more detail the underlying pathways for the association. Preterm birth can be considered a marker for an adverse intrauterine milieu, and as such, the observed association may be related to intrauterine exposures interfering with later fertility, as proposed by the DOHaD hypothesis. Furthermore, immaturity of reproductive organs and the hypothalamic-pituitary-ovarian axis at preterm birth may impact future fertility. Thus, it is unclear to what degree the association might be related to preterm birth in itself or to unmeasured or unknown conditions that predispose to preterm birth and later fecundity impairment.

6.2.2 History of miscarriage and fecundability

We expanded the existing evidence by combining self-reported data on miscarriages with data recorded in registries to reconstruct women´s reproductive histories. Furthermore, we used prospectively measured TTP to assess the association between history of miscarriage and fecundability. In contrast to our findings, Wang *et al.* observed that early pregnancy loss in a preceding cycle was associated with increased odds of achieving a clinical pregnancy in a subsequent cycle.[9] That study considered pregnancy losses occurring before 6 weeks post-LMP. In addition, the study population consisted of nulliparous women who were younger than women in our cohort (mean age 25 years vs. 30 years) and excluded those with a history of pregnancy attempts ≥12 months, indicating that they were reproductively healthier than women in our study. Two previous studies reported longer TTP among women with a history of miscarriage.[19, 20] Sapra *et al.* observed decreased fecundability in successive pregnancy attempts within 12 months of a pregnancy loss.[19] Women in that study tested for pregnancy from the day of expected menses, facilitating the detection of early as well as later pregnancy losses, as shown by a median post-LMP gestational age of pregnancy loss of 35 days (5%: 26 days, 95%: 81 days). Hence, similar

to the study by Wang *et al.*, these were primarily early losses. Because most pregnancies among Danish women are planned,[176, 177] it is plausible that women in our study would have been vigilant to pregnancies occurring before enrolling in the "Snart-Gravid" study and thus might have reported a previous early pregnancy loss when asked about their history of miscarriage. However, we had no data on gestational length at the time of miscarriage and could not evaluate whether the effect on fecundability differed between early and later pregnancy losses.

Hassan *et al.* also reported an increased TTP after a miscarriage, based on retrospective data obtained from women with miscarriage or live birth in their previous pregnancy.[20] If women with miscarriage were more likely than women with a live birth to overestimate their subsequent TTP, or more likely to overestimate TTP after their miscarriage relative to before their miscarriage, recall bias would contribute to the observed associations. Despite the differences across studies in measures of miscarriage and TTP, our findings appear to support the evidence of a delay in conception among women who had a miscarriage in their most recent pregnancy. Still, we also found that among women with a miscarriage, the probability of pregnancy by 12 cycles of attempts was similar to that of women with previous live birth, suggesting that although women with miscarriage may experience a lower average probability of conception, this may be attributable to early cycles of subsequent pregnancy attempts.

It is plausible that impaired fertility after a miscarriage is related to fallopian tube damage from infection or to intrauterine adhesions that can result from e.g., infection or dilatation and curettage procedures, compromising fertilization or implantation of the blastocyst.[23, 82, 84-87] Women with multiple miscarriages may be more likely to have intrauterine adhesions than women with a single miscarriage,[88] which might contribute to explain why women with ≥2 miscarriages in our study had lower fecundability than women with 1 miscarriage. Our ability to examine plausible biological mechanisms was, however, limited by the fact that we did not have data on gynecologic complications associated with miscarriage.

6.3 Methodological considerations

In the following, potential threats to the internal validity of our findings are discussed, as well as issues with the precision of the estimates of association and generalizability of the study results.

6.3.1 Selection bias

Our studies were restricted to pregnancy planners who self-referred to the "Snart-Gravid" study. This may raise concern about selection bias because the most fecund women in the population of women at risk for pregnancy may not have been included; women who become pregnant unintentionally or who become pregnant very quickly after discontinuing contraception will be underrepresented in our study sample.[178] Still, planned pregnancy may not be an indicator of low fecundability, especially in Denmark, where up to 80% of women plan their pregnancies.[176, 177] Selection bias would occur if factors related to both the three exposures and TTP affected the probability of study participation among eligible women, leading to an observed association between, e.g., gestational age at birth and fecundability among participants that differed from that among non-participants.[179] It seems unlikely that volunteering would be related to co-occurring suboptimal birth characteristics and impaired fecundability. Furthermore, weight and gestational age at birth are not established determinants for impaired fecundability, and studying these birth characteristics was not a stated objective of the "Snart-Gravid" study.

To assess whether our findings were biased from the inclusion of women with prolonged pregnancy attempts, we did a sensitivity analysis with restriction to women who had attempted to conceive for up to 3 (study II) or up to 6 cycles (study I) at study entry, i.e., women who were considered to have the highest fecundability. Results from these analyses were closely similar to the overall FRs in both studies, suggesting that the inclusion of women with longer pregnancy attempt times at study entry did not introduce substantial bias. Thus, the presence of selection bias as a major contributor to our finding of a lower fecundability among women born <34 gestational weeks seems unlikely. Likewise, in study III, we made a restriction to women with up to 3 cycles of pregnancy attempts at study entry. The FRs from this analysis were not appreciably different from the overall FRs, suggesting that fecundability was similar in this subset of women and that selection bias was not of major concern.

The recruitment of study participants via the Internet may raise concern about selection bias if there were reason to believe that the associations we observed would be different among Internet users and non-users. A recent study based on the "Snart-Gravid" cohort examined several associations between maternal characteristics and pregnancy outcomes, as recorded in the DMBR, and reported that well-known exposure-outcome associations – e.g., maternal BMI and pre-

eclampsia – were similar among study participants and the general population of Danish women giving birth, suggesting that the inclusion criteria imposed in "Snart-Gravid" of pregnancy planning and Internet use did not introduce substantial selection bias.[180] Thus, that study adds support to the notion that our results were not likely to have been affected by this type of bias.

We assessed potential selection bias caused by partial follow-up by comparing baseline characteristics according to exposure status of women with partial and complete follow-up in each study. Generally, we found only slight differences, with the most notable being that women with previous miscarriage and partial follow-up were more likely to be obese and to previously have attempted to become pregnant for ≥12 months than women with miscarriage who had complete follow-up. The expected bias of our results would be an underestimation of the deleterious effect of miscarriage on fecundability, however, because there were only 9 women with previous miscarriage and partial follow-up, this mechanism is unlikely to have biased our results.

6.3.2 Information bias

Erroneous measurement of exposure or outcome variables may introduce information bias.[179] If misclassification of study exposures is independent of outcome status, then misclassification is non-differential, and generally biases the estimate of association towards a null effect. If, however, misclassification of the study variables is not independent, the resulting misclassification would be differential, and the association could be either underestimated or exaggerated.[179]

In our studies, women reported the number of months that they had already been attempting to conceive at study entry. Thus, the assessment of cycles at risk relied, in part, on report of months of current pregnancy attempts, which could lead to some misclassification. Further, data on LMP and recognition of pregnancy were collected bimonthly and not during each cycle, which could also introduce misclassification. Still, it may be reasonable to assume that recalled LMP would be highly accurate among pregnancy planners.

Data on birth weight in the DMBR showed digit preference with rounding to the nearest 50 or 100 grams, and were not recorded in a uniform manner during the birth years of our cohort,[137, 145, 146] leading to some degree of misclassification into incorrect categories of birth weight. Such

misclassification would be independent of later TTP, i.e., non-differential, and may have diluted an association if there was one.

The registration of data on gestational age also changed over time, however, we excluded participants born before 1978 to obtain uniformly collected data on gestational age. In addition, it was not recorded whether the due date was determined from LMP or ultrasound examination. Because ultrasound was not in extensive use to estimate gestational age during the 1980s, the birth years of the majority of our cohort, a non-negligible proportion of data on gestational age would have been based on LMP, leading to a systematic overestimation of gestational length compared with ultrasound examination.[171, 172] We assessed the effect of misclassification of gestational age by subtracting one week from each observed value, yielding a weaker estimate of association for women born <34 gestational weeks. Thus, measurement error of gestational age may have contributed to a decrease in observed FR, causing bias away from the null. Since determination and reporting of this variable to the registry was unlikely to differ according to later TTP, misclassification was non-differential.

In study III, we were able to combine registry and self-reported data on previous pregnancy outcomes, improving the completeness of miscarriage ascertainment when compared with each data source alone. The PPV of miscarriages in the DNPR is estimated to be 93%-100%,[18] reflecting a high specificity of this diagnosis in the registry.[181] A study comparing interview data on previous miscarriage with data from the DNPR estimated that 30% of miscarriages reported by women were not recorded in the registry, the majority of which were presumably early, non-hospitalized miscarriages.[182] On the other hand, recall of prior miscarriages may depend on duration of the pregnancy and time since the event, with losses occurring at an early gestation or several years ago less likely to be recalled.[183-185] Because we supplemented women´s self-reports with registry-based data, the number of unidentified miscarriages was probably limited.

Pregnancy recognition bias may have affected our results if early miscarriage was recognized as such by some women, and considered a normal menstrual period by others, leading to a false prolongation of TTP.[167] If women with previous miscarriage monitored themselves more intensely for pregnancy by testing earlier or more frequently than women with previous live birth, they would be more likely to recognize an early loss, whereas women with previous live birth would be

more likely to miss it. If differential recognition of pregnancy operated, the FRs that we observed might be biased towards the null. However, as all study participants were actively trying to become pregnant, it is likely that they would be alert to whether pregnancy had occurred, regardless of previous pregnancy outcome. Over 96% of participants in "Snart-Gravid" confirmed their pregnancy using a home pregnancy test,[186] suggesting that recognition of pregnancy may have been unrelated to the woman´s pregnancy history. Thus, differential misclassification of cycles at risk or determination of pregnancy is not a probable explanation for our results in study III.

6.3.3 Confounding

Confounding arises from the confusion or mixing of extraneous effects with the effect of interest.[179] A confounder is defined as a variable that is associated with the exposure, is a risk factor for the outcome or a marker for the risk factor, and not an intermediate step in the causal pathway between the exposure and the outcome.[179] Due to the observational nature of our studies, unmeasured and unknown confounding cannot be ruled out.

We controlled confounding by adjustment, stratification, and restriction. In studies I and II, we adjusted for participants´ mothers´ socio-demographic and medical characteristics, and fecundability markers. Adjustment for maternal characteristics was limited by the availability of data from registries and by the participants´ knowledge about such factors. Residual confounding can result from misclassification of the confounding variable because it reduces the degree to which the confounder can be controlled, implying that confounding is still present after adjustment.[179] For instance, data on the participants´ mothers´ medical conditions during pregnancy, i.e., hypertension, pre-eclampsia, or diabetes, were likely to have been incompletely ascertained. Participants´ mothers with these conditions who did not have a hospital encounter would not be registered in the DNPR. Likewise, data on the participants´ mothers´ history of difficulty conceiving and history of miscarriage were reported by the participants, who may not have known the correct answer to these questions. However, there was little change in our estimates when we adjusted for these characteristics, suggesting that even if we had been able to obtain complete data, confounding by such factors would not explain our results. Still, preterm birth has a multifactorial etiology, involving e.g., genetic factors,[102, 103, 187] that may also predispose

to impaired fecundability. Thus, unmeasured confounding due to genetic factors or maternal characteristics is not unlikely.

Behaviors such as smoking, alcohol and caffeine consumption, and excessive exercise may confound the association between miscarriage and fecundability.[32-34, 36, 40, 159, 188, 189] Although the available data considered current exposure to such lifestyle factors at the time of study entry, and not at the time of previous miscarriage or live birth, we examined potential confounding by these factors. As we found that adjustment did not affect the estimates, we did not include these variables in the analyses. We also assessed the prevalence of conditions such as thyroid disease, diabetes and uterine fibroids, which may be associated with an increased risk of miscarriage and impaired fecundity,[190-193] however, none of these conditions were sufficiently prevalent when measured to meaningfully produce confounding. In addition, women with infertility may be more likely to have a miscarriage,[89, 90, 160, 194] which was also reported by Hassan *et al.*[20] Ideally, we would have had access to data on fecundability prior to the miscarriage, however, we adjusted for measures of previous difficulty with achieving a pregnancy, which did not appreciably change our estimates. Still, as mentioned, we cannot rule out that unmeasured and unknown confounding affected our results.

6.3.4 Precision

We quantified the precision of the associations using 95% CIs, which is a measure of uncertainty due to random variability of the point estimate.[195, 196] The numbers of women in several subcategories were small in our studies, resulting in wide CIs which indicated that our findings were sensitive to random error.[195] Still, in study I, the FRs were close to the null value of 1, suggesting little association between weight at birth and fecundability. In study II, the FR showed a strong adverse effect of birth <34 gestational weeks. The FRs for the subcategories <32, 32, and 33 gestational weeks varied from 0.30 to 0.40, all of which were strong point estimates consistent with a deleterious effect of early gestational age on fecundability, however, the CIs for these categories included a broad range of values, from strong effects to little or no association. Because of the reduced precision of the estimates in these subcategories, which limited our ability to make a sound interpretation of the results, we chose to conduct the main analysis using the combined category <34 gestational weeks. Similarly, results in study III were imprecise, particularly for

women with ≥2 miscarriages for whom the result was compatible with a range of possibilities, from little or no effect to stronger adverse effects. Estimates accompanied by wide CIs should be interpreted cautiously.

6.3.5 Generalizability

Generalizability of study results refers to whether they can be considered to apply to persons outside of the source population (i.e., Danish pregnancy planners) and is presupposed on the internal validity of the study findings.[179] When studying biologic relations, what is important is not whether the study population is representative of characteristics in the source population, but whether it is representative of the effect that one wants to study.[197, 198] Thus, if the biologic relations between the exposures that we assessed and fecundability differed for the population that we studied and others, the generalizability of our results would be limited.[179]

As mentioned, a recent study of the "Snart-Gravid" cohort showed that internal comparisons in our population did not appear to be affected by a lack of representativeness.[180] For the associations that we observed between weight or gestational age at birth and fecundability, it is probable that they would be generalizable to women who were not included in the studies, as it seems unlikely that the biologic relation would differ for study participants and non-participants. Thus, if our findings are correct, they may well apply to other populations with high proportions of planned pregnancies. Similarly, our finding of a prolonged TTP in women with a history of miscarriage agrees with those of previous studies,[19, 20] suggesting that these findings are also likely to apply to similar populations with a high prevalence of pregnancy planning.

6.4 Conclusions

The main strengths of our studies include the prospective collection of data on TTP, collection of data on exposures independently of data on outcome, the combination of registry-based and self-reported data to assess history of miscarriage, and a low proportion of women with partial follow-up. The main limitation of our studies was the relatively small size of the study populations. Although the "Snart-Gravid" cohort is large, some necessary restrictions in our studies resulted in small subgroups in the extreme exposure categories. For this reason, some results were sensitive to random error, and should be interpreted with caution.

In sum, we found little evidence for an association between weight at birth and fecundability, and this result was robust after changes in the definition of birth weight. We observed a pronounced decrease in fecundability among women born before 34 weeks of gestation. This result may have been biased away from the null by non-differential misclassification of gestational age in the DMBR, as suggested by the sensitivity analysis. However, after we considered this possibility, fecundability still appeared to be reduced among these women. Adjustment for markers of maternal fecundability made little difference to our results, thus, our hypothesis that maternal reproductive history might confound the associations was not supported. Still, we could not rule out that unmeasured and unknown confounding contributed to the observed decrease in fecundability among women born preterm.

Furthermore, we observed a reduced fecundability among women with a history of miscarriage, most pronounced among women with at least 2 miscarriages, although this finding was imprecise. Our results also suggested that this reduction may be attributable to early cycles of subsequent pregnancy attempts.

7 Perspectives

Prolonged pregnancy attempts can lead to considerable emotional distress for couples who attempt to have a child, and clinical interventions to establish causes and treat infertility may come with appreciable psychological, physiological, and economic costs for those who seek help. Thus, fecundity impairments are a substantial burden for individuals and health care systems with a major public health impact. Improved understanding of the determinants of delayed conception and infertility is necessary to aid prevention, and to improve treatment and counseling for women and their partners.

The studies in this thesis add to the limited knowledge on the influence of suboptimal birth characteristics – as measured by weight and gestational age – on women´s fecundability. We did not find evidence for an association between low weight at birth and fecundability, however, our findings suggest that women born before 34 gestational weeks have decreased fecundability. The underlying biologic pathways for impaired fecundability among women born preterm are not clear. For instance, it is uncertain to what degree immaturity at preterm birth may in itself affect subsequent fecundability and to what degree common factors that predispose to preterm birth and decreased fecundability contribute to the association. Our studies were not designed to examine specific adverse prenatal lifestyle and environmental exposures or their timing during pregnancy, or genetic factors that might contribute to explain the associations that we observed. In addition, postnatal and childhood growth trajectories may be important for reproductive development, thus, future studies may consider the influence of gestational age at birth and determinants of child and adolescence growth and development, including endocrinology, on fecundability. In addition, studies using infant, childhood, adolescence and adult data to ascertain the sequence of events that may lead to well-known pathological processes underlying infertility are wanted.

Our data suggested that women with a history of miscarriage may have decreased fecundability. Based on this finding and in light of previous studies, such women might best be counselled to expect a short-term delay in conception after a miscarriage. Further insight into the biological mechanisms for impaired fecundability after miscarriage is warranted to provide targeted advice to affected couples, i.a., regarding fecundability after early and later pregnancy losses.

8 English summary

Aberrant weight and gestational age at birth have been associated with a number of diseases that occur later in life, and may also be related to impaired fertility. Not much is known about whether weight and gestational age at birth are associated with a woman´s ability to conceive, measured by fecundability. Furthermore, there is a lack of knowledge about the association between history of miscarriage and subsequent fecundability. Reproductive history tends to recur within families, raising the possibility that fecundability may also have a heritable component.

The studies in this thesis were conducted as prospective cohort studies that aimed at examining the association between 1) weight at birth, 2) gestational age at birth, and 3) history of miscarriage and fecundability. All studies were based on women enrolled in a Danish Internet-based prospective cohort study of pregnancy planners, "Snart-Gravid." Data on time to pregnancy to measure fecundability came from the "Snart-Gravid" study, as well as data on women´s socio-demographic, lifestyle, and reproductive characteristics, including previous pregnancies and pregnancy outcomes. We obtained data on weight and gestational age at birth from the Danish Medical Birth Registry. Data on history of miscarriage were combined from self-report and from the Danish National Patient Registry. Furthermore, information on women´s mothers´ socio-demographic, medical, and reproductive characteristics was obtained from women´s reports and from the aforementioned registries. Reproductive characteristics of women´s mothers – e.g., history of difficulty conceiving – were considered as proxy markers of maternal fecundability and included as potential confounders.

In study I, we included 2,773 women. The adjusted FRs for women with birth weights of <2,500, 2,500-2,999 and ≥4,000 grams were 0.98 (95% CI: 0.72-1.32), 0.99 (95% CI: 0.87-1.13), and 1.07 (95% CI: 0.93-1.24), relative to women born with a weight of 3,000-3,999 grams (normal weight). Results were similar when we restricted to women born at term and when we assessed birth weight using z-scores. Adjustment for maternal characteristics, including proxy markers of fecundability, made little difference to our results.

In study II, we included 2,814 women. Adjusted FRs for women with gestational age at birth of <34, 34-36 and ≥42 weeks were 0.38 (95% CI: 0.17-0.82), 1.03 (95% CI: 0.80-1.34) and 1.13 (95%

CI: 0.96-1.33), relative to women born at 37-41 gestational weeks (term). Proxy markers of maternal fecundability did not confound the associations.

In study III, we included 977 women. Relative to women with a history of only live birth, the adjusted FR was 0.87 (95% CI: 0.71-1.07) for women with 1 miscarriage, and 0.65 (95% CI: 0.36-1.17) for women with ≥2 miscarriages. Compared with women with previous live birth, the difference in the cumulative probability of conception was largest during the first 6 cycles of pregnancy attempts, gradually tapering off by 12 cycles of attempts.

In conclusion, we found little evidence for an association between weight at birth and fecundability, however, we observed decreased fecundability among women born before 34 weeks of gestation. In addition, our findings suggested a decreased fecundability among women with a history of miscarriage, most prominent among women with ≥2 miscarriages.

9 Dansk resumé

Lav fødselsvægt og gestationsalder kan være relateret til en række sygdomme som udvikles senere i livet, og muligvis også til nedsat fertilitet. Der findes ikke megen viden om, hvorvidt en kvindes fødselsvægt og gestationsalder har betydning for hendes evne til at blive gravid, målt ved hendes fekundabilitet. Der er desuden mangelfuld viden om, hvorvidt spontan abort påvirker efterfølgende fekundabilitet. Flere fødsels- og graviditetsudfald gentages fra mor til datter, hvilket rejser muligheden for, at også fekundabilitet kan have en arvelig komponent.

Denne afhandling bygger på tre prospektive kohorte studier, som havde til formål at undersøge associationerne mellem 1) en kvindes fødselsvægt og hendes fekundabilitet, 2) en kvindes gestationsalder og hendes fekundabilitet, og 3) tidligere spontan abort og efterfølgende fekundabilitet. Alle studier var baseret på deltagere i et dansk internetbaseret prospektivt kohortestudie for kvinder, som forsøgte at blive gravide, kaldet "Snart-Gravid". I dette studie blev der indsamlet data om tid til graviditet, som mål for fekundabilitet, i tillæg til data om livsstils- og socio-demografiske faktorer samt reproduktive karakteristika, herunder tidligere graviditeter og graviditetsudfald. Vi indhentede data om fødselsvægt og gestationsalder fra Fødselsregisteret, og data om tidligere spontane aborter fra kvinders oplysninger i "Snart-Gravid" og fra Landspatientregisteret. Desuden indhentede vi data om socio-demografiske faktorer, medicinske tilstande og reproduktive karakteristika for kvindernes mødre fra "Snart-Gravid" og fra førnævnte registre. Reproduktive karakteristika for kvindernes mødre – f.eks. om hun havde haft svært ved at blive gravid – blev betragtet som proxy markører for mødrenes fekundabilitet og indgik i analyserne som potentielle confoundere.

I studie I inkluderede vi 2.773 kvinder. De justerede FR for kvinder med en fødselsvægt på <2500, 2500-2999 og ≥4,000 gram var 0.98 (95% CI: 0.72-1.32), 0.99 (95% CI: 0.87-1.13), og 1.07 (95% CI: 0.93-1.24) i forhold til kvinder med en fødselsvægt på 3000-3999 gram (normalvægt). Vi fandt lignende resultater ved restriktion til kvinder født term, og i kategorier for fødselsvægt defineret ved z-scorer. Justering for proxy markører for kvindernes mødres fekundabilitet ændrede ikke vores resultater.

I studie II inkluderede vi 2.814 kvinder. De justerede FR for kvinder med en gestationsalder på <34, 34-36 og ≥42 uger var 0.38 (95% CI: 0.17-0.82), 1.03 (95% CI: 0.80-1.34) og 1.13 (95% CI: 0.96-1.33)

i forhold til kvinder med en gestationsalder på 37-41 uger (term). Justering for proxy markører for kvindernes mødres fekundabilitet medførte ikke ændring af vores resultater.

I studie III inkluderede vi 977 kvinder. Sammenlignet med kvinder, som kun havde haft tidligere levendefødsel, var de justerede FR 0.87 (95% CI: 0.71-1.07) for kvinder med én tidligere spontan abort og 0.65 (95% CI: 0.36-1.17) for kvinder med mindst to tidligere spontane aborter. Forskellen i kumulativ sandsynlighed for graviditet blandt kvinder med tidligere spontan abort eller tidligere levendefødsel var størst i løbet af de første 6 cyklers graviditetsforsøg, men denne forskel blev gradvist mindre og var ikke til stede efter 12 cyklers graviditetsforsøg.

Samlet set fandt vi ikke en sammenhæng mellem en kvindes fødselsvægt og hendes fekundabilitet. Derimod viste vores resultater nedsat fekundabilitet blandt kvinder født med en gestationsalder under 34 fulde uger. Desuden fandt vi nedsat fekundabilitet blandt kvinder som har haft spontan abort, mest udtalt blandt kvinder med mindst 2 tidligere aborter.

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11 Appendices

Appendix I: Paper I

Appendix II: Paper II

Appendix III: Paper III

Paper I

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PLOS ONE

Weight at Birth and Subsequent Fecundability: A Prospective Cohort Study

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Abstract

Objective: To examine the association between a woman's birth weight and her subsequent fecundability.

Method: In this prospective cohort study, we included 2,773 Danish pregnancy planners enrolled in the internet-based cohort study "Snart-Gravid", conducted during 2007–2012. Participants were 18–40 years old at study entry, attempting to conceive, and were not receiving fertility treatment. Data on weight at birth were obtained from the Danish Medical Birth Registry and categorized as <2,500 grams, 2,500–2,999 grams, 3,000–3,999 grams, and ≥4,000 grams. In additional analyses, birth weight was categorized according to z-scores for each gestational week at birth. Time-to-pregnancy measured in cycles was used to compute fecundability ratios (FR) and 95% confidence intervals (CI), using a proportional probabilities regression model.

Results: Relative to women with a birth weight of 3,000–3,999 grams, FRs adjusted for gestational age, year of birth, and maternal socio-demographic and medical factors were 0.99 (95% CI: 0.73;1.34), 0.99 (95% CI: 0.87;1.12), and 1.08 (95% CI: 0.94;1.24) for birth weight <2,500 grams, 2,500–2,999 grams, and ≥4,000 grams, respectively. Estimates remained unchanged after further adjustment for markers of the participant's mother's fecundability. We obtained similar results when we restricted to women who were born at term, and to women who had attempted to conceive for a maximum of 6 cycles before study entry. Results remained similar when we estimated FRs according to z-scores of birth weight.

Conclusion: Our results indicate that birth weight appears not to be an important determinant of fecundability.

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Background

Several studies have shown that individuals with a low weight at birth are at increased risk of developing morbidities in adulthood, possibly due to physiologic, metabolic, and hormonal changes during fetal life associated with insufficient growth [1–4]. Being born small for gestational age (SGA) is associated with earlier onset of puberty and menarche [5–8], and with abnormalities in ovarian development and functioning among adolescent girls, such as reduced uterine and ovarian size, lower ovulation rate and anovulation, and ovarian hyporesponsiveness to follicle stimulating hormone [9–12]. It is uncertain whether potentially compromised ovarian development and function in early life persist into adulthood and have long-term effects on reproduction.

A reduced probability of giving birth has been reported among women born before 32 full weeks [13–15] and among women born with a very low birth weight (<1500 grams) [13,15,16]. The few studies that have examined the association between birth weight and later ability to conceive had conflicting findings [17,18]. In the Danish National Birth Cohort, Nohr et al. reported an odds ratio for a time-to-pregnancy (TTP) greater than 12 months (indicative of infertility) of 1.2 (95% CI: 1.0;1.5) among women born at term with a weight ≤2,500 grams, and 1.8 (95% CI: 1.1;3.1) among women born preterm with a weight ≤1,500 grams, compared with women born at term with a weight of 3,001–4,000 grams [18]. In contrast, Meas et al. reported no increase in TTP among French women born SGA [17]. Both studies were restricted to women who became pregnant and

therefore assessed TTP conditional on the achieved pregnancy, using retrospectively collected TTP data. To our knowledge, no study has examined fecundability (i.e., the cycle-specific probability of conception) according to weight at birth.

Whether the association between weight at birth and subsequent health is attributable to direct effects of insufficient fetal growth or to underlying shared mechanisms, i.e., intergenerational factors with a potential influence on fetal growth and adult health, has been the subject of debate [19,20]. Familial clustering has been reported for extremes of birth weight [21], preterm birth [22–26], spontaneous abortion [27–29], and family size [30–32]. Little is known, however, about intergenerational patterns in fecundability. Reproductive characteristics of a woman's mother, such as number of children, difficulty conceiving, or history of spontaneous abortion may be proxy markers of the mother's fecundability, and in turn may affect fecundability of the woman. Several studies have found that mother's parity [13,15,33], mother's history of spontaneous abortion [34,35], and mother's history of infertility [36–38] were associated with low birth weight in her offspring. These findings imply that maternal fecundability could confound the putative association between daughter's birth weight and her fecundability. This potential confounding was not controlled in previous studies.

We examined the association between weight at birth and subsequent fecundability of women participating in a prospective cohort study of TTP, while controlling for potential confounding by reproductive characteristics of the women's mothers.

Subjects and Methods

Study population

In this study, we used data from the "Snart-Gravid" ("Soon Pregnant") study, which is a Danish internet-based prospective cohort study of pregnancy planners, designed to examine the influence of lifestyle and behavioral factors on fecundability. The study design and data collection have been described in detail elsewhere [39]. Briefly, participants were recruited and followed via the internet during 2007–2012. Eligible women were aged 18–40 years, in a stable relationship with a male partner, attempting to conceive, and not receiving fertility treatment. After giving informed consent, participants provided their Civil Personal Registration (CPR) number, a unique personal identifier assigned to all Danish citizens at birth. The CPR number permits unambiguous identification and linkage of persons in Danish administrative and medical registries [40]. At enrollment, participants completed a baseline questionnaire with items on demographics, lifestyle and behaviors, and medical and reproductive history, including months of trying to conceive. Participants subsequently completed bimonthly follow-up questionnaires until they reported pregnancy, discontinuation of pregnancy attempts, beginning of fertility treatment, or had been followed for 12 months (end of study observation), whichever came first. Follow-up questionnaires elicited information on changes in relevant exposures and whether pregnancy had occurred.

By August 2012, 6,033 women had enrolled in the study by responding to the baseline questionnaire. We excluded 579 women who did not complete a follow-up questionnaire, 113 repeated entries, 294 women with implausible or missing information on date of last menstrual period, 538 women who had attempted to conceive for more than 11 cycles at enrollment, and 226 women who had been adopted, born after a non-singleton gestation, or had missing data on multiplicity of gestation. In order to obtain uniformly recorded data on gestational age at birth from the Danish Medical Birth Registry (DMBR), we also excluded 1,510 women who were born before January 1, 1978. The remaining 2,773 women were included in the analyses.

Measures of weight at birth

We obtained data on the participants' weight at birth from the DMBR. This registry records over 99% of births in Denmark, reported prospectively by midwives attending the birth [41]. Data on birth weight were registered in categories of 250 grams in 1978, in categories of 10 grams during 1979–1990, and in exact grams after 1990 [42]. We categorized birth weight as $<$2,500, 2,500–2,999, 3,000–3,999, and $\geq$4,000 grams, and used 3,000–3,999 grams as the reference category. In additional analyses, we estimated z-scores for birth weight by each completed gestational week as (participant's birth weight – mean of birth weights for the gestational week of birth)/(the standard deviation of the mean of birth weights for the gestational week of birth) [43]. Estimation of mean birth weight and standard deviation in each gestational week was based on the birth weight distribution of Danish girls in the period 1978–1992 (i.e., the period of the participants' births), as registered in the DMBR. The z-scores were then grouped into 6 categories of $\leq$-2, -2-$\leq$-1, -1-$\leq$0, 0-$\leq$1, 1-$\leq$2, and $>$2, with 0-$\leq$1 as the reference category.

Measures of time-to-pregnancy (TTP)

The event of interest was participants' report of any pregnancy regardless of outcome. More than 96% of participants used a home pregnancy test to confirm conception [44]. At each follow-up, participants reported the date of their last menstrual period (LMP), whether they were currently pregnant, and occurrence since the previous follow-up of spontaneous abortion, therapeutic abortion, or ectopic pregnancy. Total number of menstrual cycles at risk of pregnancy (i.e., TTP) was calculated as (days of attempt time at study entry/usual cycle length)+(((LMP date from most recent follow-up questionnaire – date of study entry)/usual cycle length)+1). Participants could contribute information until their 12th cycle of attempted pregnancy to the analysis. Observed cycles at risk of pregnancy were defined as cycles contributed after study enrollment and were left-truncated. Thus, if a woman had already attempted to conceive for 8 cycles when she entered the study, she could contribute up to 4 more cycles after enrollment into the study, with her observed cycles starting at cycle 9 (delayed entry). The follow-up of women who started fertility treatment during follow-up was censored at the cycle in which they started the treatment.

Covariates

We obtained data on participants' gestational age at birth from the DMBR. Data on gestational age were based on the date of the pregnant woman's last menstrual period, corrected by ultrasound examination if performed, and registered in full weeks. Gestational ages of the participants were 28–44 completed weeks. We defined preterm to be a gestational age $<$37 weeks; full term to be 37–41 weeks; and post-term to be $\geq$42 weeks. From the DMBR, we also obtained information on participants' mothers' lifetime parity and participants' birth order by using the CPR number to identify mothers and siblings. Siblings born before establishment of the DMBR in 1973 were identified by the mothers' self-reported parity, which was also registered in the DMBR and has high validity [45]. Data on mothers' lifetime parity were divided into categories 1 (study participant was an only child), 2–3 children, and $\geq$4 children (reference category). Participants' birth order was categorized as first-born, second-born, or greater than second-born (reference category). Data on participants' mothers' history of difficulty conceiving (yes/no) and history of spontaneous abortion

(yes/no) were reported in the baseline questionnaire, and we defined participants' mothers without such history as the reference category. Reference categories were defined on the assumption that they represented mothers with normal fecundability.

From the DMBR we obtained data on mother's age and marital status at the time the participant was born. From the Danish National Registry of Patients (DNRP), which includes data on all admissions to Danish non-psychiatric hospitals since 1977, we obtained data on hospital diagnoses of hypertension or pre-eclampsia during the mother's pregnancy with the participant. These diagnoses were coded according to ICD-8 during the period of interest. We used ICD-8 codes 400–404 and 637.00 (essential and gestational hypertension) and 637.03, 637.04, 637.09, 637.19, and 637.99 (pre-eclampsia, eclampsia, and toxemia). Prevalence of hospital admission due to maternal diabetes was below 1%, therefore maternal diabetes as measured by hospitalization was not a strong confounder in our analysis.

From the baseline questionnaire we obtained data on participants' own reproductive history, including age at menarche, cycle regularity, gravidity, parity, and history of unsuccessful pregnancy attempts ≥12 months. At baseline, participants also reported their weight (in kilograms) and height (in centimeters) and we calculated their body mass index (BMI) as (weight (kilograms)/height squared (m^2)). Further, data on participants' age, number of cycles of pregnancy attempt at study entry, intercourse frequency, mother's and father's educational level, and mother's smoking during pregnancy were reported in the baseline questionnaire.

Ethics statement

The "Snart-Gravid" study was approved by the Danish Data Protection Board (journal no. 2013-41-1922) and the Institutional Review Board at Boston University. Consent was obtained from the participants before completion of the first questionnaire. Data from the DMBR and the DNRP were retrieved from Statens Serum Institut (http://www.ssi.dk/Sundhedsdataotit.aspx). Data from the "Snart-Gravid" study are hosted by the Department of Clinical Epidemiology, Aarhus University Hospital; as this study is still in progress, access to the data is not yet freely available. All data were anonymized after retrieval and no CPR numbers were included in the dataset that was the basis of our analyses.

Missing values

The proportion of missing values for the variables birth weight, birth order, mother's lifetime parity, mother's age at delivery, mother's marital status, and mother's smoking during pregnancy ranged from 4.8% to 8.4%. For 17.2% of the participants, values were missing on gestational age at birth, which was partly attributable to procedural changes instituted in 1978 in reporting this variable to the DMBR [46]. For 17.2% and 20.4% of participants, there were missing observations on mother's history of difficulty conceiving and mother's history of spontaneous abortion, respectively, most likely due to participants not knowing this information. For 30.4% and 35.0% of participants, there were missing observations on mother's and father's educational level, respectively. These missing data resulted from random assignment of half of the early study participants to a short-form baseline questionnaire that did not include questions on parental educational level.

On the assumption that data were missing at random, we imputed missing values using multiple imputation by chained equations (MICE program in Stata version 12.0). We included 36 variables in the imputation, including all variables used in the substantive analyses, and imputed five data sets. Distributions of continuous variables were examined by histograms and box plots. Variables that diverged from the normal distribution were transformed to the log-scale before imputation.

Data analysis

We calculated Kaplan-Meier estimates to assess the cumulative probability of conception within 3, 6, and 12 menstrual cycles, accounting for delayed entry using left-truncation, and losses to follow-up and other reasons for censoring (e.g., no longer trying to conceive or initiation of fertility treatment). We described the distribution of participants' characteristics (for women lost to follow-up, women who completed the study, and for all of the 2,773 women in the study cohort) according to weight at birth. Using a proportional probabilities model, we then estimated fecundability ratios (FR) and 95% confidence intervals (CI) for categories of birth weight (<2,500, 2,500–2,999, and ≥4,000 grams, with 3,000–3,999 grams as the reference category), using TTP measured in cycles. The FR of any two groups was calculated as the ratio of their cycle-specific probabilities [47]. Participants contributed cycles at risk from entry into the study until report of pregnancy, receipt of fertility treatment, discontinuation of pregnancy attempt, loss to follow-up, or end of observation (maximum 12 cycles). Distinct intercept parameters were included for each of the 12 cycles of follow-up, to allow for decline in the baseline conception rate over follow-up time.

We examined potential interaction between weight and gestational age at birth by including product terms for gestational age as a continuous variable in the regression model, and found no evidence of interaction. Adjustments were made in three steps: first, we adjusted for year of birth and gestational age as a continuous variable with values 28–44 weeks only (model 1); second, we included parental socio-demographic and medical characteristics (mother's age, mother's marital status, mother's and father's educational level, mother's smoking during pregnancy, and mother's history of hypertension and pre-eclampsia) (model 2); and third, we included markers of the participant's mother's fecundability in the regression model (mother's lifetime parity, participant's birth order, mother's history of difficulty conceiving, and mother's history of spontaneous abortion) (model 3). Variables included in the three models were chosen a priori because they have previously been associated with offspring weight at birth [13,15,33–38,48–51], and may influence the daughter's fecundability [13,15,27–32,52,53]. Not much is known about the potential influence of maternal reproductive health on the fecundability of daughters. Based on evidence of familial clustering of other reproductive health outcomes [21–32], it is plausible that proxy markers of the mother's fecundability, e.g., mother's history of difficulty conceiving, might be causally associated with daughters' fecundability. On this basis, we investigated the potential confounding effect of maternal socio-demographic, medical and reproductive characteristics. We repeated the analyses restricted to women born at term, i.e., at 37–41 weeks of gestation, to restrict the influence of gestational age at birth. To evaluate sensitivity of the study result to inclusion of women who had tried to conceive for up to 11 cycles at study entry, we repeated the analyses restricted to women with only up to 6 cycles of attempt time. Previous reports indicate that accelerated weight gain in infancy, which is often exhibited by infants with a low birth weight, is associated with overweight or obesity later in life [54,55], and obesity has been linked with reduced fecundability [56]. Thus, we also considered the potential mediating influence of pre-pregnancy BMI on an association between weight at birth and fecundability.

In addition to considering gestational age at birth by adjustment and restriction to term births, we also examined the association

between weight at birth and fecundability by z-scores of birth weight, to compare infants of differing relative weights by using weight estimates that were adjusted for gestational age at birth [43]. We estimated fecundability ratios by categories of z-score (≤-2, -2-≤-1, -1-≤0, 1-≤2, and >2, with 0-≤1 as the reference category), using the same proportional probabilities regression model as in the initial analyses.

Analyses were performed using Stata version 12.0 (StataCorp., TX, USA) and SAS version 9.2 (Cary, NC, USA).

Results

Among the 2,773 women included in our analyses, 245 (8.8%) were lost to follow-up. Women lost to follow-up contributed cycles at risk for as many cycles as they were observed in the study, and were censored at the time of non-response. Among women lost to follow-up, mean birth weight overall was 3,281 grams (95% CI: 3,209;3,353 grams), which was slightly lower than among women with complete follow-up. The distribution of gestational age at birth among women lost to follow-up was similar to that for women who completed the study (data not shown). Women with low birth weight that were lost to follow-up were more likely to have a mother who was divorced or widowed, and had a lifetime parity of ≥4 children, more likely to have a high birth order and irregular cycles, and more had only attempted to become pregnant for 0–1 cycles at study entry, compared with women with low birth weight who completed the study (data not shown).

Mean birth weight overall among the 2,773 women in the study cohort was 3,315 grams (95% CI: 3,295;3,334 grams), and mean birth weight among those born at term was 3,326 grams (95% CI: 3,307;3,345 grams). There were 2,432 (87.7%) participants who had been born at term, 102 (3.7%) who had been born preterm, and 239 (8.6%) who had been born post-term.

Kaplan-Meier estimates for the cumulative probability of conception among the 2,773 participants were 47% within 3 cycles, 67% within 6 cycles, and 83% within 12 cycles. Characteristics of participants according to their weight at birth are presented in Table 1. Participants with a birth weight <2,500 grams were more likely to have been exposed to maternal smoking in pregnancy, have a mother who had hypertension or pre-eclampsia during pregnancy with the participant, have a mother with a history of difficulty conceiving or spontaneous abortion, have a mother with a lifetime parity of at least 4 children, and to be first-born. They were also more likely to be obese (BMI≥30), to have a history of unsuccessful pregnancy attempts ≥12 months, longer pregnancy attempt time at study entry, and intercourse ≥4 times a week, compared with participants with a birth weight of 3,000–3,999 grams.

Crude and adjusted FRs according to weight at birth are presented in Table 2. After adjustment for all covariates except BMI and measures of maternal fecundability (model 2), FRs for birth weight categories <2,500 grams, 2,500–2,999 grams and ≥4,000 grams, compared with the reference category, were 0.99 (95% CI: 0.73;1.34), 0.99 (95% CI: 0.87;1.12), and 1.08 (95% CI: 0.94;1.24), respectively. When we added markers of maternal fecundability to the regression analysis (mother's lifetime parity, participant's birth order, mother's history of difficulty conceiving, and mother's history of spontaneous abortion) (model 3), we obtained almost identical results; FRs were 0.98 (95% CI: 0.72;1.32), 0.99 (95% CI: 0.87;1.13), and 1.07 (95% CI: 0.93;1.24) for birth weights <2,500 grams, 2,500–2,999 grams, and ≥4,000 grams, respectively.

Table 2 shows that results changed little after restricting the analysis to women born at term. Relative to women with a birth weight of 3,000–3,999 grams, FRs in the fully adjusted model were 1.00 (95% CI: 0.69;1.45), 0.97 (95% CI: 0.84;1.12), and 1.08 (95% CI: 0.93;1.26) for women with a birth weight <2,500 grams, 2,500–2,999 grams, and ≥4,000 grams, respectively. Repeating these analyses among women with up to 6 cycles of pregnancy attempt at study entry yielded similar results (data not shown). Results were also consistent when we controlled for pre-pregnancy BMI via stratification or adjustment (data not shown). As shown in Table 3, when we examined the association between weight at birth and fecundability using z-scores, we obtained results similar to those based on absolute measures of weight at birth, i.e., FRs suggested little association.

Discussion

In our study of 2,773 pregnancy planners, we found little evidence supporting a relation between weight at birth and fecundability. Results were similar when we restricted the cohort to women born at term, and when we considered relative measures of weight at birth using z-score transformation. Further, we found no indication that markers of maternal fecundability confounded the association between weight at birth and women's own fecundability.

To our knowledge, this is the first prospective study to examine the association between weight at birth and fecundability in a cohort of pregnancy planners. Our data allowed for a more accurate estimate of TTP, based on women with and without successful conceptions, in contrast to data retrospectively obtained from women who were already pregnant. A validation study of retrospective data on TTP, using prospective data as the gold standard, reported a mean difference in TTP of −1.4 months among women with a recall period of 3–20 months [57], suggesting that misclassification of TTP may be present in retrospective studies, even for recent pregnancies. While the "Snart-Gravid" study may appeal more to women who anticipate that their fecundability may be impaired, it is unlikely that participation would be related to weight at birth, as participants had no knowledge that these associations would be investigated when they entered the study. When we restricted our analysis to women with a maximum of 6 cycles of pregnancy attempt time at study entry to assess the potential influence of excluding women who may have had reduced fecundability, our findings were similar. The proportion of women with low birth weight was slightly higher among those lost to follow-up. In addition, among women with low birth weight who were lost to follow-up, more had irregular cycles, and more had only attempted to become pregnant for 0–1 cycles at study entry, compared with women with low birth weight who completed the study. However, differential loss to follow-up is unlikely to have attenuated our findings, as there was little association with fecundability for any category of birth weight.

Data on birth weight were not recorded in a uniform manner in the DMBR during the birth years of the participants in our cohort [42]. The resulting non-differential misclassification of birth weight may have diluted the association if there was one. Nevertheless, by using registry-based data on weight and gestational age at birth, we avoided the possibility of differential misclassification. It is known that preterm birth was underreported to the DMBR during the birth years of our cohort [41]; however, there was little association of low birth weight with fecundability before adjustment for gestational age. Small numbers precluded us from examining the association of fecundability with very low birth weight (<1,500 grams), which has been associated with prolonged TTP and reduced probability of reproducing in similar

Table 1. Characteristics of 2,773 women according to categories of birth weight, ''Snart-Gravid'' study, Denmark, 2007–2012.

	Birth weight, grams			
Characteristic	**<2,500**	**2,500–2,999**	**3,000–3,999**	**≥4,000**
No. of women	119	488	1,866	300
Age, years (mean)	26.1	26.4	26.5	26.5
Born at term (%)	54.6	89.8	90.5	80.3
Mother's age at time of delivery (median)	25	25	26	26
Mother's marital status (%):				
Married	61.3	62.1	65.1	71.7
Unmarried	31.1	34.4	31.2	24.7
Divorced/widowed	7.6	3.5	3.7	3.7
Mother's education, less than Upper Secondary School (%)	69.8	60.9	57.2	59.0
Father's education, less than Upper Secondary School (%)	74.0	64.6	67.3	71.7
Mother smoked during pregnancy (%)	57.1	51.8	31.4	22.0
Mother had hypertension (%)*	3.4	0.4	0.8	1.0
Mother had pre-eclampsia (%)*	7.6	3.3	1.6	2.7
Mother had difficulty conceiving (%)	19.3	18.9	13.3	15.0
Mother had spontaneous abortion (%)	42.0	28.9	24.5	18.3
Mother's lifetime parity (%):				
1	10.9	12.1	9.4	6.3
2–3	68.9	74.6	76.9	76.0
≥4	20.2	13.3	13.7	17.7
Birth order of participant (%):				
First-born	54.6	56.4	45.2	32.0
Second-born	27.7	29.7	37.1	47.0
>Second-born	17.7	13.9	17.7	21.0
Age at menarche, years (mean)	12.6	12.7	12.9	12.9
Irregular cycles (%)	26.1	25.0	28.7	27.7
Gravidity ≥1 (%)	32.8	37.3	33.1	33.0
Parity ≥1 (%)	21.0	21.7	20.0	20.3
History of unsuccessful pregnancy attempts ≥12 months (%)	16.8	11.9	7.8	6.3
Pre-pregnancy BMI, kg/m^2 (%):				
<18.5	5.9	5.9	4.0	3.0
18.5–24.9	53.8	60.5	64.6	62.0
25.0–29.9	21.9	18.0	20.3	22.7
≥30	18.5	15.6	11.1	12.3
No. of cycles of pregnancy attempt at study entry (%):				
0–1	41.2	48.6	47.7	46.7
2–3	23.5	22.8	21.9	27.0
4–6	21.0	16.4	17.3	17.7
7–11	14.3	12.3	13.1	8.7
Intercourse frequency ≥4 times/week (%)	26.1	22.8	21.1	23.0

*Mother diagnosed with hypertension or pre-eclampsia during pregnancy with the participant.

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studies [13,15,16,18]. Therefore, our inability to differentiate birth weights of <1,500 grams from those <2,500 grams may have obscured an association for very low birth weight.

In agreement with our results, a French prospective study of 403 women who had attempted to conceive found nearly no association between being born SGA and later TTP, relative to women whose size at birth was appropriate for gestational age [17]. Similarly, a registry-based prospective study of 148,281 Swedish women found little association between being born SGA and the probability of giving birth, when SGA was defined as 3 standard deviations below the mean weight for the length of gestation [13]. Likewise, a registry-based study of 494,692 Swedish women (including women from the other Swedish study [13]) found little association between being born SGA and the probability of giving birth. This study also reported a hazard ratio for giving birth of 0.95 (95% CI: 0.93; 0.97) among women

Table 2. Fecundability by categories of birth weight.

					Unadjusted model		Adjusted model[1]		Adjusted model[2]		Adjusted model[3]	
	Birth weight, grams	No. of women	No. of cycles	No. Of pregnancies	FR	95% CI	FR	95% CI	FR	95% CI	FR	95% CI
All women,												
N = 2,773	<2,500	119	504	66	0.89	0.71;1.12	1.01	0.75;1.36	0.99	0.73;1.34	0.98	0.72;1.32
	2,500–2,999	488	1,979	314	0.97	0.86;1.09	1.00	0.88;1.13	0.99	0.87;1.12	0.99	0.87;1.13
	3,000–3,999	1,866	7,461	1,176	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
	≥4,000	300	1,131	201	1.10	0.96;1.26	1.07	0.94;1.23	1.08	0.94;1.24	1.07	0.93;1.24
Born at term,												
N = 2,432	<2,500	65	230	36	0.98	0.69;1.38	1.01	0.70;1.46	1.01	0.69;1.46	1.00	0.69;1.45
	2,500–2,999	452	1,786	277	0.96	0.84;1.09	0.97	0.85;1.11	0.96	0.84;1.10	0.97	0.84;1.12
	3,000–3,999	1,814	6,782	1,069	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
	≥4,000	279	947	166	1.11	0.95;1.29	1.10	0.94;1.28	1.09	0.93;1.27	1.08	0.93;1.26

Model[1]: Adjusted for participant's gestational age and year of birth.
Model[2]: Model 1 + mother's age, mother's marital status, mother's and father's educational level, mother's smoking during pregnancy, mother's hypertension, and mother's pre-eclampsia during pregnancy with the participant.
Model[3]: Model 2 + mother's lifetime parity, participant's birth order, mother's history of difficulty conceiving, and mother's history of spontaneous abortion.
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with a birth weight <2,500 grams [15]. These results appear to support our findings, though we recognize that actual reproduction cannot be equated to fecundability; thus, the Swedish studies do not necessarily convey information on potential differences in the ability to conceive according to weight at birth.

Our findings differ from those of Nohr et al., who conducted a retrospective TTP study of 21,786 Danish women and reported an OR for a TTP of 6–12 months of 1.2 (95% CI: 0.9;1.5) and OR for a TTP >12 months of 1.2 (95% CI: 1.0;1.5) among women born at term with a birth weight ≤2,500 grams, compared with women born at term with a weight of 3,001–4,000 grams [18]. The study by Nohr et al. was conducted in a cohort of pregnant women who reported their weight and gestational age at birth, as well as retrospective data on TTP leading to their ongoing pregnancy. As such, results are not directly comparable with ours. Our data indicated that weight at birth is not meaningfully associated with a reduced fecundability; however, even a weak association would be easier to distinguish from a null association in

Table 3. Fecundability by z-scores of birthweight for gestational age.

					Unadjusted model		Adjusted model[1]		Adjusted model[2]		Adjusted model[3]	
	Z-score of birthweight	No. of women	No. of cycles	No. of pregnancies	FR	95% CI	FR	95% CI	FR	95% CI	FR	95% CI
All women,												
N = 2,773	≤-2	28	99	17	1.23	0.78;1.92	1.19	0.76;1.87	1.17	0.74;1.85	1.17	0.74;1.86
	-2-≤-1	379	1,523	246	1.07	0.92;1.24	1.06	0.91;1.23	1.04	0.89;1.21	1.04	0.89;1.22
	-1-≤0	1,127	4,512	713	1.03	0.92;1.14	1.02	0.92;1.14	1.02	0.91;1.13	1.02	0.91;1.13
	0-≤1	915	3,693	566	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
	1-≤2	298	1,143	199	1.12	0.96;1.30	1.11	0.96;1.29	1.11	0.95;1.29	1.10	0.95;1.28
	>2	26	105	16	0.98	0.62;1.55	0.95	0.60;1.51	0.95	0.59;1.52	0.95	0.59;1.51
Born at term,												
N = 2,432	≤-2	27	96	16	1.17	0.72;1.88	1.15	0.71;1.85	1.14	0.70;1.85	1.13	0.69;1.85
	-2-≤-1	325	1,348	208	0.98	0.84;1.14	0.97	0.83;1.14	0.97	0.83;1.14	0.97	0.82;1.14
	-1-≤0	1,011	4,042	642	0.99	0.88;1.11	0.99	0.88;1.11	0.99	0.88;1.11	0.99	0.88;1.11
	0-≤1	776	3,092	487	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
	1-≤2	268	1,063	180	1.05	0.89;1.23	1.05	0.89;1.23	1.04	0.88;1.22	1.03	0.88;1.21
	>2	25	104	15	0.91	0.57;1.44	0.89	0.56;1.41	0.89	0.56;1.42	0.89	0.56;1.41

Model[1]: Adjusted for participant's year of birth.
Model[2]: Model 1 + mother's age, mother's marital status, mother's and father's educational level, mother's smoking during pregnancy, mother's hypertension, and mother's pre-eclampsia during pregnancy with the participant.
Model[3]: Model 2 + mother's lifetime parity, participant's birth order, mother's history of difficulty conceiving, and mother's history of spontaneous abortion.
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a larger cohort. We do not know whether the associations observed in the other Danish study were causal or due to shared risk factors that were uncontrolled.

In conclusion, the present study indicates that infant weight at birth does not appear to have a meaningful influence on female fertility in adult life. If correct, this finding implies that even if gonadal development and function are compromised in adolescents with a small size at birth, such anomalies may not persist to influence fecundability in adult women attempting to conceive.

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Author Contributions

Conceived and designed the experiments: CW AHR VE BLH EEH LAW KJR HTS EMM. Analyzed the data: CW AHR. Wrote the paper: CW AHR VE BLH EEH LAW KJR HTS EMM.

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Paper II

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human reproduction

ORIGINAL ARTICLE ***Reproductive epidemiology***

A prospective cohort study of a woman's own gestational age and her fecundability

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STUDY QUESTION: What is the magnitude of the association between a woman's gestational age at her own birth and her fecundability (cycle-specific probability of conception)?

SUMMARY ANSWER: We found a 62% decrease in fecundability among women born <34 weeks of gestation relative to women born at 37–41 weeks of gestation, whereas there were few differences in fecundability among women born at later gestational ages.

WHAT IS KNOWN ALREADY: One study, using retrospectively collected data on time-to-pregnancy (TTP), and self-reported data on gestational age, found a prolonged TTP among women born <37 gestational weeks (preterm) and with a birthweight ≤1500 g. Other studies of women's gestational age at birth and subsequent fertility, based on data from national birth registries, have reported a reduced probability of giving birth among women born <32 weeks of gestation.

STUDY DESIGN, SIZE, DURATION: We used data from a prospective cohort study of Danish pregnancy planners ('Snart-Gravid'), enrolled during 2007–2011 and followed until 2012. In all, 2814 women were enrolled in our study, of which 2569 had complete follow-up.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Women eligible to participate were 18–40 years old at study entry, in a relationship with a male partner, and attempting to conceive. Participants completed a baseline questionnaire and up to six follow-up questionnaires until the report of pregnancy, discontinuation of pregnancy attempts, beginning of fertility treatment, loss to follow-up or end of study observation after 12 months.

MAIN RESULTS AND THE ROLE OF CHANCE: Among women born <34 gestational weeks, the cumulative probability of conception was 12, 28 and 48% within 3, 6 and 12 cycles, respectively. Among women born at 37–41 weeks of gestation, cumulative probability of conception was 47, 67 and 84% within 3, 6 and 12 cycles, respectively. Relative to women born at 37–41 weeks' gestation, women born <34 weeks had decreased fecundability (fecundability ratio (FR) 0.38, 95% confidence interval (CI): 0.17–0.82). Our data did not suggest reduced fecundability among women born at 34–36 weeks of gestation or at ≥42 weeks of gestation (FR 1.03, 95% CI: 0.80–1.34, and FR 1.13, 95% CI: 0.96–1.33, respectively).

LIMITATIONS, REASONS FOR CAUTION: Data on gestational age, obtained from the Danish Medical Birth Registry, were more likely to be based on date of last menstrual period than early ultrasound examination, possibly leading to an overestimation of gestational age at birth. Such overestimation, however, would not explain the decrease in fecundability observed among women born <34 gestational weeks. Another limitation is that the proportion of women born before 34 weeks of gestation was low in our study population, which reduced the precision of the estimates.

WIDER IMPLICATIONS OF THE FINDINGS: By using prospective data on TTP, our study elaborates on previous reports of impaired fertility among women born preterm, suggesting that women born <34 weeks of gestation have reduced fecundability.

STUDY FUNDING/COMPETING INTEREST(S): The study was supported by the National Institute of Child Health and Human Development (R21-050264), the Danish Medical Research Council (271-07-0338), and the Health Research Fund of Central Denmark Region (1-01-72-84-10). The authors have no competing interests to declare.

Key words: fecundability / female infertility / gestational age / preterm birth / cohort study

Introduction

Improvements in neonatal care during the 1980s have led to increasing numbers of preterm born infants (birth <37 weeks of gestation) surviving to reach reproductive age (Villadsen, 2008). Survivors of preterm birth may have an elevated risk of long-term adverse health outcomes, including chronic respiratory symptoms (Anand *et al.*, 2003; Jaakkola *et al.*, 2006; Saigal *et al.* 2007; Harju *et al.*, 2014), neurodevelopmental disorders (Hack *et al.*, 2002; Saigal *et al.*, 2007; Moster *et al.*, 2008), higher blood pressure (de Jong et al., 2012; Parkinson *et al.*, 2013) and insulin resistance and diabetes (Hofman *et al.*, 2004; Kaijser *et al.*, 2009; Crump *et al.*, 2011). Abbreviated gestation may also be associated with poor fertility. Infant girls born preterm have increased levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) up to 3 months after birth, as well as delayed follicular development, compared with girls born at term. This phenomenon is thought to indicate an insufficient maturation of the hypothalamic–pituitary–ovarian axis at preterm birth (Tapanainen *et al.*, 1981; Kuiri-Hanninen *et al.*, 2011). Among women aged 23–37 years, reduced fertility (measured as registered births of the woman in national birth registries) has been reported for those born before 32 gestational weeks compared with women born at term (Swamy *et al.*, 2008; deKeyser et al., 2012). A Danish cross-sectional analysis of 21 786 women who gave birth did not find prolonged time-to-pregnancy (TTP) among women born preterm compared with women born at term, except for women born preterm with a birthweight ≤1500 g. The authors suggested that the longer TTP among such women might be attributable to very preterm birth (Nohr *et al.*, 2009). The study did not estimate fecundability (i.e. the cycle-specific probability of conception).

Reproductive history tends to recur within families, as shown for preterm birth (Swamy *et al.*, 2008; Boyd *et al.*, 2009; Shah et al., 2009; Bhattacharya *et al.*, 2010), low birthweight (Shah *et al.*, 2009), spontaneous abortion (Zhang *et al.*, 2010; Kolte *et al.*, 2011) and parity (Murphy and Knudsen, 2002; Goodman and Koupil, 2009). Thus, it is reasonable to hypothesize the existence of familial recurrence of decreased fecundability. With this hypothesis, reproductive outcomes of a woman's mother may be markers of the mother's fecundability, with a possible influence on the fecundability of her daughter. Thus, maternal reproductive history may confound the association between gestational age at birth and fecundability in the daughter. These factors were not controlled in previous studies.

We conducted a prospective cohort study among pregnancy planners in Denmark to examine the association between gestational age at birth and fecundability, while controlling for potential confounding by maternal reproductive history.

Subjects and Methods

Study population

Data for this study originated from a population-based prospective cohort study of Danish pregnancy planners ('Snart-Gravid'), initiated in 2007 (Mikkelsen *et al.*, 2009). Women eligible to participate were Danish residents, 18–40 years old at study entry, in a relationship with a male partner, attempting to conceive, and not receiving fertility treatment. Eligible participants completed a baseline questionnaire and bi-monthly follow-up questionnaires for an observational period of up to 12 months. Participants were enrolled during 2007–2011 and follow-up concluded in 2012.

There were 5512 potential participants for this study. We excluded women who provided only baseline data, had already entered the study once, had implausible or insufficient information on date of last menstrual period (LMP), had been adopted or with missing data on adoptive status, or were born after a non-singleton gestation or with missing data on multiplicity of gestation. We also excluded women born before 1 January 1978, because information about the specific gestational age at birth was not recorded in the Danish Medical Birth Registry (DMBR) until this date. The final study population comprised 2814 women (Fig. 1).

Assessment of gestational age at birth

After giving consent, participants provided their Civil Personal Registration (CPR) number, a unique personal identifier assigned to all Danish citizens at birth or time of immigration, enabling linkage of persons in national health registries (Pedersen, 2011). We collected data on participants' gestational age at birth from the DMBR, which contains computerized health records of over 99% of hospital-based or home live births and stillbirths in Denmark since 1973. Data are reported to the registry by midwives attending the birth (Kristensen *et al.*, 1996; Knudsen and Olsen, 1998). In the DMBR, gestational age at birth was recorded in full weeks (since 1978) and estimated from the woman's LMP, adjusted by results of an ultrasound examination, if performed. Use and results of ultrasound examinations were not recorded in the DMBR. To our knowledge, the earliest report on the use of prenatal ultrasound examination in Denmark considered the years 1989–1990 (Jorgensen, 1993). At that time, around 20% of pregnant women did not receive an ultrasound examination, suggesting that a non-negligible proportion of values of gestational age were determined solely by LMP during the birth years of our cohort (Jorgensen, 1993). The participants' gestational ages at birth ranged from 28 to 44 completed weeks. We defined gestational age <37 weeks as preterm, 37–41 weeks as term, and ≥42 weeks as post-term (Wilcox, 2010).

Assessment of time-to-pregnancy

The event of interest was pregnancy, regardless of outcome. At baseline, participants reported the number of months that they had already attempted to become pregnant and the date of the LMP. In each follow-up questionnaire, participants reported the date of their LMP and whether they were currently pregnant or had experienced a pregnancy termination (spontaneous abortion, therapeutic abortion or ectopic pregnancy) since the last follow-up. TTP, defined as the number of menstrual cycles at risk for pregnancy, was estimated using the following formula: (days of pregnancy attempt at study entry/days of usual cycle length) + (((LMP date from the most recent follow-up questionnaire − date of study entry)/days of usual cycle length) + 1) (Wise *et al.*, 2010). Participants contributed cycles at risk until they reported a pregnancy, started fertility treatment, gave up pregnancy attempts, were lost to follow-up, or until the end of the observation period of 12 months, whichever came first. Women with an unknown reason for not completing the study were considered lost to follow-up and censored at the time of last follow-up questionnaire completion.

Assessment of covariates

Measures of maternal reproductive health such as history of difficulty conceiving, spontaneous abortion, preterm birth and lifetime parity

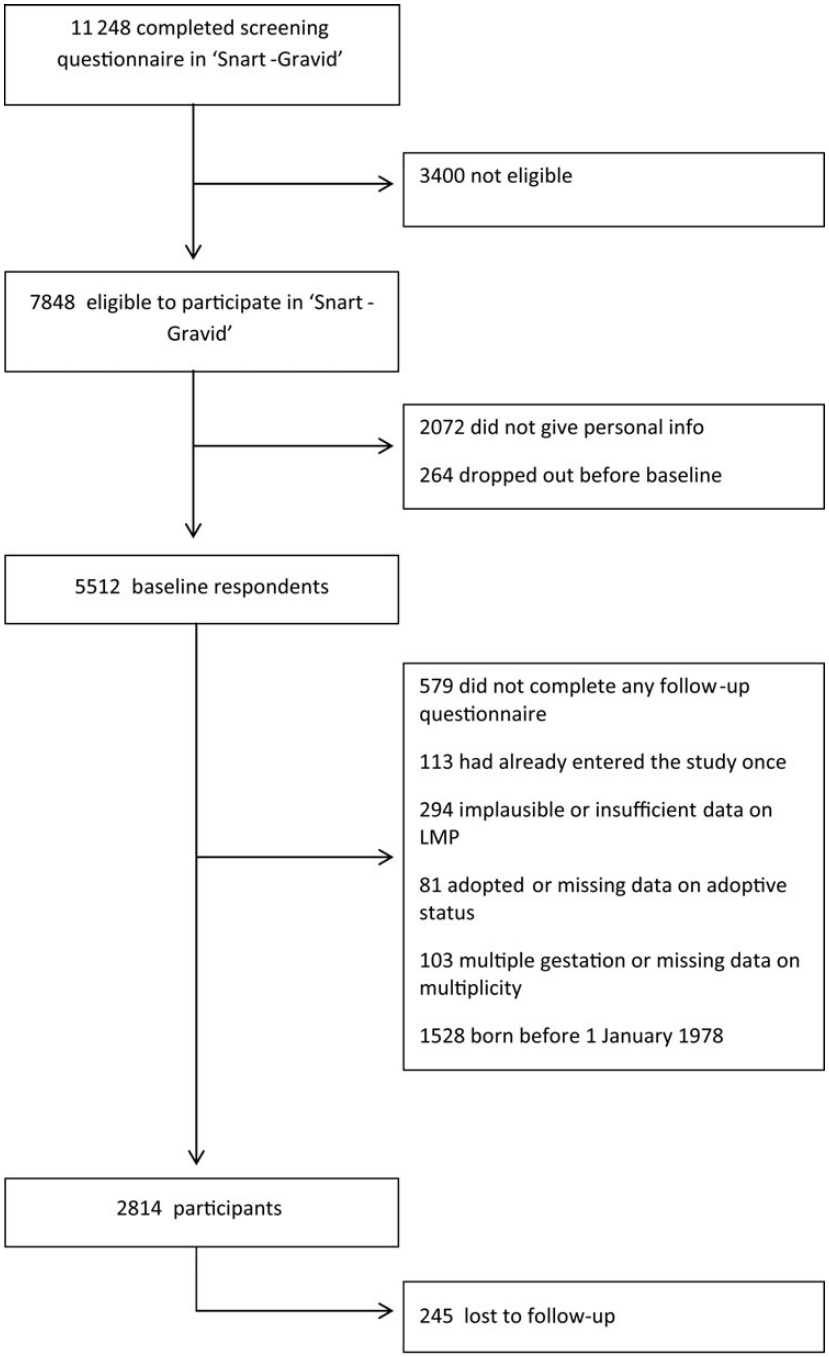

Figure 1 Study flow chart.

were considered to be markers of the participant's mother's fecundability. Data on participant's mother's age and marital status at time of the participant's delivery, history of preterm birth, and lifetime parity were obtained from the DMBR via linkage with the participant's CPR number. Data on mother's history of preterm birth included siblings born since 1973 at a gestational age <37 completed weeks. Mother's lifetime parity was assessed by combining mother's parity recorded in the DMBR with number of children identified in the registry and using the maximum value in the analyses. From the DMBR we also obtained data on the participant's weight at birth. From the Danish National Registry of Patients (DNRP), we obtained data on mother's hospital diagnoses of hypertension (diagnosis codes 400–404 and 637.00), pre-eclampsia (637.03, 637.04, 637.09, 637.19 and 637.99) and diabetes (249, 250 and 634.74) during pregnancy with the participant. The diagnoses were coded according to the International Classification of Diseases, 8th revision. From the 'Snart-Gravid' baseline questionnaire we obtained data from each participant on her mother's and father's educational level, mother's smoking status during pregnancy with the participant, mother's

history of difficulty conceiving and spontaneous abortion, and the following information on the participant: age at study entry, age at menarche, menstrual cycle regularity, gravidity, parity, history of ≥12 months attempting a pregnancy, and number of cycles of attempted pregnancy at the time of study entry.

Ethical approval

The 'Snart-Gravid' study was approved by the Danish Data Protection Board (record no. 2013-41-1922) and by the Institutional Review Board at Boston University. Consent was obtained from all participants before completion of questionnaires.

Data analysis

According to the World Health Organization, birth before 32 full gestational weeks is defined as very preterm, birth at 32–33 weeks as moderately preterm and birth at 34–36 weeks as late preterm (March of Dimes, PMNCH, Save the Children, WHO, 2012). Based on these standards and the conventional definitions of preterm birth (<37 gestational weeks), term birth (37–41 gestational weeks) and post-term birth (≥42 gestational weeks) (Wilcox, 2010), we examined the distribution of baseline characteristics according to categories of gestational age at birth (<34, 34–36, 37–41 and ≥42 weeks) among women lost to follow-up and compared it with the distribution among women with complete follow-up. We also examined the distribution of characteristics among all women included in our analyses. To examine the cumulative probability of conception by gestational age, we calculated Kaplan–Meier estimates, allowing for delayed entry and censoring at loss to follow-up, discontinuation of pregnancy attempts, initiation of fertility treatment, or reaching the end of the observation period (Hosmer et al., 2008). We examined fecundability according to the predefined categories of gestational age as well as 1-week categories of gestational age at birth (<32, each completed week 32–42, and ≥43 weeks, with 40 gestational weeks as the reference group) by calculating fecundability ratios (FR) with 95% confidence intervals (CI). FRs were calculated by proportional probabilities regression modeling, and represent ratios of cycle-specific probabilities of conception comparing exposed with unexposed women (Weinberg and Wilcox, 2008). To account for women whose pregnancy attempts started before study entry, cycles before study entry were left-truncated. Thus, a woman contributed cycles observed only after study entry, but these were corrected for the number of cycles attempting pregnancy before study entry (Wise et al., 2010).

Potential confounders were selected based on available literature of associations with gestational age at birth (Mercer et al., 1999; Shah and Bracken, 2000; Sibai et al., 2000; Kallen 2001; Ray et al., 2001; Buchmayer et al., 2004; Ekholm et al., 2005; Fadl et al., 2010; Eidem et al., 2011; Weintraub et al., 2011; deKeyser et al., 2012; Yanit et al., 2012; Messerlian et al., 2013), and their potential effect on fecundability (Weinberg et al., 1989; Ekholm et al., 2005; Ye et al., 2010; deKeyser et al., 2012). Considering that other reproductive outcomes tend to cluster in families, markers of mothers' fecundability, i.e. history of difficulty conceiving, history of spontaneous abortion, history of preterm birth, and lifetime parity, may be causally associated with daughters' fecundability. In addition, medical conditions such as hypertension, pre-eclampsia and diabetes may be associated with maternal impaired fertility (Basso et al., 2003; Trogstad et al., 2009; Whitworth et al., 2011), and thus, may influence the fecundability of the daughter. On this basis, we adjusted for participant's year of birth (continuous); mother's age (<20, 20–24, 25–29 and ≥30 years), marital status (married, unmarried or divorced/widowed), smoking status during pregnancy with the participant (yes/no), hypertension (yes/no), pre-eclampsia (yes/no), and diabetes during pregnancy with the participant (yes/no); and mother's and father's educational level (9th–10th grade or Upper Secondary School/equivalent) in Model 1. We further adjusted for mother's history of difficulty conceiving (yes/no), spontaneous abortion (yes/no), preterm birth (yes/no) and lifetime parity (1, 2–3 or ≥4) in Model 2.

We assessed the potential non-linear relation between gestational age at birth and fecundability using restricted cubic splines. Measures of gestational age that are determined from the LMP may be overestimated, compared with measures based on ultrasound examination (Tunon et al., 1996; Savitz et al., 2002). To assess the potential influence of misclassification of gestational age in the DMBR, we subtracted 1 week from each value of gestational age and repeated the analyses for 1-week categories of gestational age (<34, each gestational week 34–42, and ≥43 weeks, with 40 weeks' gestation as the reference group). Finally, in other sensitivity analyses, we restricted to women with no more than three cycles of attempted pregnancy at study entry to assess associations among participants with the highest fecundability.

The proportion of missing values ranged from 4.8 to 17.1% for the variables obtained from registries, and from 0.1 to 35.2% for variables from the self-administered questionnaires (Supplementary Table SI). On the premise that data were missing at random, we used multiple imputation by chained equations (MICE, Stata version 12.0) to impute missing values. This approach included all substantive variables used in the analyses, and generated five data sets. Because there were over 35% missing values of one variable included in the study (father's educational level), we generated forty imputed datasets and repeated the main analysis, yielding results that were close to those based on five datasets (White et al., 2011). For this reason, we considered using five imputed datasets to be sufficient for this and other analyses.

Analyses were conducted using Stata version 12.0 (StataCorp., TX, USA), and SAS version 9.2 (Cary, NC, USA).

Results

During the observation period, 245 women (8.7%) were lost to follow-up. These women were slightly younger (mean age at study start 25.7 years versus 26.6 years), but had a similar distribution of gestational age at birth as women with complete follow-up. Among women born <34 gestational weeks and lost to follow-up, a greater proportion had attempted to become pregnant for more than three cycles at study entry, and a greater proportion had a mother or a father with a maximum of 10 years of education, and a mother who was 20–24 years old, or unmarried at time of delivery of the participant. Fewer had a mother with a history of difficulty conceiving and a history of preterm birth, compared with women born <34 gestational weeks who completed the study.

Among the 2814 participants, 19 (0.7%) had been born <34 weeks, 89 (3.2%) at 34–36 weeks, 2463 (87.5%) at 37–41 weeks and 243 (8.6%) at ≥42 weeks of gestation. The proportion of women born preterm was similar to those reported in other studies of preterm birth in Scandinavia in the period, which ranged from 4.4 to 4.7%

(Swamy *et al.*, 2008; Boyd *et al.*, 2009; deKeyser *et al.*, 2012). Compared with women born at 37–41 weeks, women born <34 weeks of gestation were less likely to have irregular cycles, to have been pregnant or to be parous, more likely to have a history of ≥12 months attempting a pregnancy, and more likely to have attempted pregnancy for more than three cycles at study entry. They were also more likely to have a mother who was 20–24 years old at delivery, married, who smoked during pregnancy, was diagnosed with pre-eclampsia, had a history of difficulty conceiving, spontaneous abortion, or preterm birth, and a parity of at least four children (Table I).

Kaplan–Meier estimates for the cumulative probability of conception were 12% (95% CI: 0–31%), 28% (95% CI: 0–50%), and 48% (95% CI: 11–69%) within 3, 6, and 12 cycles, respectively, for women born <34 weeks of gestation, and 47% (95% CI: 43–49%), 67% (95% CI: 65–70%), and 84% (95% CI: 82–85%) within 3, 6, and 12 cycles, respectively, for women born at 37–41 weeks of gestation. Crude FRs, presented in Table II, were 0.37 (95% CI: 0.17–0.81) for women born <34 weeks, 1.05 (95% CI: 0.82–1.34) for women born at 34–36 weeks and 1.11 (95% CI: 0.94–1.30) for women born at ≥42 weeks of gestation, relative to women born at 37–41 weeks' gestation. Results were similar after

Table I Characteristics of 2814 participants and their mothers according to four categories of gestational age.

Characteristic	Gestational age, weeks			
	<34	34–36	37–41	≥42
No. of women, *n* (%)	19 (0.7)	89 (3.2)	2463 (87.5)	243 (8.6)
Mean age in years (s.e.)	25.1 (0.6)	26.6 (0.3)	26.5 (0.1)	26.3 (0.2)
Mean weight at birth in grams (s.e.)	1572 (102.5)	2476 (51.8)	3326 (9.6)	3638 (29.4)
Mean age at menarche in years (s.e.)	12.8 (0.4)	12.5 (0.1)	12.9 (0.0)	12.8 (0.1)
Irregular menstrual cycles, %	21.1	14.6	28.2	27.6
Gravidity ≥1, %	15.8	37.1	33.4	39.1
Parity ≥1, %	10.5	24.7	20.0	24.7
History of ≥12 months attempting a pregnancy, %	31.6	11.2	8.9	5.4
No. of cycles of attempted pregnancy at study entry, %				
0–1	42.1	46.1	47.2	49.0
2–3	21.1	20.2	23.3	18.5
4–11	36.8	33.7	29.5	32.5
Mother's age at time of delivery, %				
<20	0.0	5.6	4.1	3.3
20–24	47.4	37.1	32.5	38.7
25–29	26.3	25.8	38.9	38.3
≥30	26.3	31.5	24.5	19.8
Mother's marital status at time of delivery, %				
Married	73.7	57.3	65.3	63.4
Unmarried	21.1	40.5	30.9	33.3
Divorced/widowed	5.3	2.3	3.8	3.3
Mother's education, 9th–10th grade, %	57.9	60.7	57.9	60.9
Father's education, 9th–10th grade, %	79.0	70.8	67.3	69.1
Mother smoked during pregnancy, %	52.6	49.4	34.7	26.8
Mother had hypertension, %	0.0	1.1	0.9	0.8
Mother had pre-eclampsia, %	10.5	10.1	2.0	1.2
Mother had diabetes, %	0.0	4.5	0.5	0.0
Mother's history of difficulty conceiving, %	26.3	14.6	14.6	15.2
Mother's history of spontaneous abortion, %	42.1	37.1	24.5	25.1
Mother's history of preterm birth, older sibs, %	26.3	16.9	3.7	2.1
Mother's history of preterm birth, all sibs, %	42.1	22.5	6.1	3.7
Mother's lifetime parity, %				
1	5.3	14.6	10.6	8.6
2–3	68.4	73.0	76.9	78.2
≥4	26.3	12.4	12.5	13.2

s.e., standard error.

adjusting for year of birth and mothers' socio-demographic and medical characteristics, and when we further adjusted for the markers of mothers' reproductive health. Adjusted FRs for each completed gestational week at birth, presented in Table III, did not indicate a material association with fecundability for any category of gestational age, except for women born <34 weeks of gestation. Within the category of <34 weeks of gestation, we found similar effect estimates for women born in the three subcategories <32, 32 and 33 weeks of gestation. The smaller numbers within these subcategories gave broader confidence intervals than the combined category, and these confidence intervals individually included a wider range of parameter values. Nonetheless, the pattern of effect estimates was similar for the categories below 34 weeks of gestation, indicating that the observed effect was not limited to either subcategory. The smoothed relation between fecundability and gestational age at birth, throughout the range from 28 to 44 completed weeks, was modeled using restricted cubic splines, and is shown in Fig. 2. Using 40 weeks as the reference point, the smoothed curve indicates increasing fecundability with increasing gestational age at birth from 28 weeks until about 35 weeks, and is then nearly level with only small fluctuations from the reference value through the highest gestational ages.

In a sensitivity analysis, we subtracted 1 week from each value of gestational age, assuming that it was overestimated in the registry. The adjusted FR for women born <34 weeks according to this categorization was 0.64 (95% CI: 0.40–1.04), thus still markedly reduced compared with women born at 40 weeks of gestation (Supplementary Table SII).

To examine whether our results were influenced by having included women with up to 11 cycles of pregnancy attempt time at study entry,

Table II Fecundability by four categories of gestational age, *N* = 2814.

Gestational age, weeks	No. of women	No. of cycles	No. of pregnancies	Unadjusted model		Adjusted Model 1		Adjusted Model 2	
				FR	95% CI	FR	95% CI	FR	95% CI
<34	19	109	6	0.37	0.17–0.81	0.39	0.18–0.84	0.38	0.17–0.82
34–36	89	371	60	1.05	0.82–1.34	1.04	0.80–1.34	1.03	0.80–1.34
37–41	2463	9845	1571	1	Reference	1	Reference	1	Reference
≥42	243	877	150	1.11	0.94–1.30	1.13	0.96–1.33	1.13	0.96–1.33

Model 1: Adjusted for participant's year of birth, mother's age, mother's marital status, mother's and father's educational level, mother's smoking during pregnancy, mother's hypertension, mother's pre-eclampsia, and mother's diabetes during pregnancy with the participant.
Model 2: Model 1 + mother's history of difficulty conceiving, mother's history of spontaneous abortion, mother's history of preterm birth and mother's lifetime parity.
FR, fecundability ratio; CI, confidence interval.

Table III Fecundability according to gestational age in weeks, *N* = 2814.

Gestational age, weeks	No. of women	No. of cycles	No. of pregnancies	Unadjusted model		Adjusted Model 1		Adjusted Model 2	
				FR	95% CI	FR	95% CI	FR	95% CI
<34	19	109	6	0.37	0.17–0.81	0.39	0.18–0.85	0.38	0.17–0.83
<32	*11*	*70*	*4*	*0.38*	*0.15–0.98*	*0.40*	*0.15–1.03*	*0.40*	*0.15–1.04*
32	*4*	*24*	*1*	*0.31*	*0.05–2.09*	*0.32*	*0.05–2.21*	*0.30*	*0.04–2.08*
33	*4*	*15*	*1*	*0.42*	*0.06–2.79*	*0.43*	*0.06–2.82*	*0.39*	*0.06–2.54*
34	15	61	11	1.14	0.65–2.02	1.15	0.63–2.11	1.12	0.61–2.06
35	24	94	19	1.19	0.78–1.82	1.18	0.77–1.82	1.17	0.75–1.80
36	50	216	30	0.94	0.62–1.42	0.93	0.61–1.42	0.94	0.62–1.42
37	134	566	80	0.96	0.77–1.20	0.97	0.77–1.22	0.97	0.76–1.22
38	267	1083	159	0.91	0.74–1.11	0.91	0.74–1.12	0.90	0.74–1.11
39	472	1836	308	1.04	0.91–1.17	1.05	0.93–1.20	1.05	0.92–1.19
40	1105	4481	711	1	Reference	1	Reference	1	Reference
41	485	1879	313	1.01	0.89–1.15	1.02	0.90–1.16	1.02	0.90–1.16
42	209	765	128	1.11	0.92–1.32	1.14	0.95–1.36	1.14	0.95–1.37
≥43	34	112	22	1.09	0.71–1.66	1.12	0.74–1.70	1.11	0.73–1.69

Model 1: Adjusted for participant's year of birth, mother's age, mother's marital status, mother's and father's educational level, mother's smoking during pregnancy, mother's hypertension, mother's pre-eclampsia, and mother's diabetes during pregnancy with the participant.
Model 2: Model 1 + mother's history of difficulty conceiving, mother's history of spontaneous abortion, mother's history of preterm birth and mother's lifetime parity.
FR, fecundability ratio; CI, confidence interval.

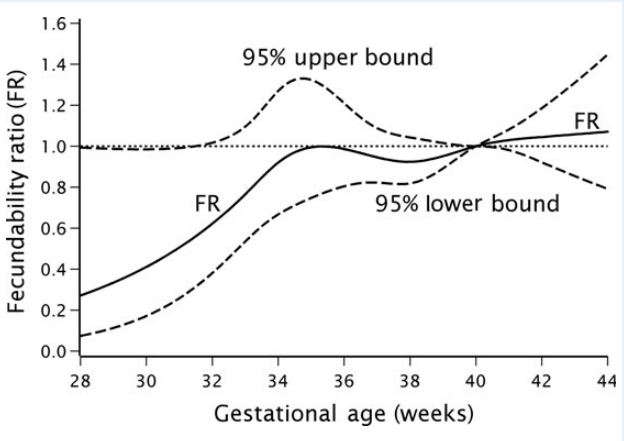

Figure 2 Association between gestational age at birth and fecundability, fitted by restricted cubic splines. The dashed lines indicate the 95% confidence interval (CI). The reference level for the fecundability ratio (FR) was 40 weeks of gestation. The curves were adjusted for participant's year of birth; mother's age, marital status, smoking status, hypertension, pre-eclampsia, diabetes, history of difficulty conceiving, spontaneous abortion, preterm birth and lifetime parity; and mother's and father's educational level. Five knot points were located at 33, 34, 38, 40 and 42 weeks' gestation.

we repeated the analysis after restricting to women with ≤3 cycles of attempt time ($n = 1971$). The fully adjusted FRs in this analysis were 0.33 (95% CI: 0.13–0.86) for women born <34 weeks, 1.06 (95% CI: 0.78–1.45) for women born at 34–36 weeks and 1.17 (95% CI: 0.98–1.41) for women born ≥42 weeks of gestation.

Discussion

In this study of 2814 Danish pregnancy planners, fecundability was 62% lower among women born <34 weeks than women born at 37–41 weeks of gestation. This result was not explained by measured maternal characteristics, including markers of reproductive health. Fecundability did not appear to be different among women born at 34–36 weeks or ≥42 weeks of gestation.

Data on gestational age at birth, obtained from the DMBR for women born during 1978–1992, inevitably have a degree of measurement error. In a study based on 1662 Danish births occurring in the period 1982–1987, the level of agreement between data on gestational age in the DMBR and the medical record was estimated to be 43% (Kristensen *et al.*, 1996). For the majority of discrepancies, gestational age at birth was recorded as 1 week later in the DMBR than evaluated by the investigators from the medical record, indicating an underreporting of preterm birth in the registry. In the medical records, determination of gestational age at birth was based on date of LMP in 64% of cases, on ultrasound examination in 35% of cases, and on clinical examination in 1% (Kristensen *et al.*, 1996). This suggests that in our study, gestational age was likely to have been determined primarily by the LMP-based method, which moves the distribution of gestational age toward higher values compared with ultrasound examination (Tunon *et al.*, 1996; Savitz *et al.*, 2002). When we re-defined the categories of gestational age by subtracting 1 week from each value, the adjusted FR for women born <34 gestational weeks was 0.64 (95% CI: 0.40–1.04). Thus, measurement error of gestational age may have contributed to a decrease in FR, but even after considering this, our data indicated that women born <34 weeks had a 36% reduction in fecundability compared with women born at 40 weeks of gestation. Misclassification of gestational age in a woman's birth record would be unlikely to be related to subsequent TTP, implying that such misclassification would be non-differential. More than 96% of pregnancies in our study were detected by home pregnancy tests (Wise *et al.*, 2011), suggesting that our results were not influenced by differential recognition of pregnancy by gestational age of the women.

It is plausible that our study of pregnancy planners attracted women who were already struggling to conceive. If women born <34 weeks' gestation and with previous reproductive problems entered the study out of concern for their fecundability, the FR for such women would be biased downward (Rothman, 2002). Nonetheless, participation was unlikely to be associated with gestational age at birth, because studying gestational age was not a stated objective of the 'Snart-Gravid' study, nor was there much information in the literature about an association of gestational age with infertility.

Our study included pregnancy planners only, thus excluding women with high fecundability who had an unintended pregnancy. To examine whether our results were partly attributable to a selection of women with prolonged pregnancy attempts, we restricted to women with ≤3 cycles of pregnancy attempt time at study entry, and obtained similar results, suggesting that inclusion of women trying to conceive for >3 cycles did not introduce substantial bias.

A greater proportion of women born <34 gestational weeks and lost to follow-up had tried to become pregnant for >3 cycles at study entry than women born <34 gestational weeks with complete follow-up. This difference implies that fecundability among women born <34 weeks may be lower than what we observed. This result, however, was based on only five women born <34 weeks and lost to follow-up. Finally, small numbers of women at the extreme ends of the distribution of gestational age reduced the precision of the associated estimates.

Overall, our results correspond to findings from previous studies. Based on the Danish National Birth Cohort, Nohr *et al.* reported an OR for a TTP >12 months versus <6 months of 1.8 (95% CI: 1.1–3.1) among women born preterm with a birthweight ≤1500 g, compared with women born at term with birthweights of 3001–4000 g (Nohr *et al.*, 2009). There were no substantial differences in probability of prolonged TTP among women born preterm or term with approximately the same birthweights, suggesting that preterm birth was not associated with prolonged TTP. Preterm birth, however, was merely defined as birth <37 weeks' gestation; because a birthweight ≤1500 g is likely to be related to very preterm birth, the possibility that very preterm birth influenced later TTP was not ruled out.

Further, Norwegian and Swedish historical registry based cohort studies have examined associations between a woman's gestational age and her later pregnancy resulting in a birth, as recorded in national birth registries. Ekholm *et al.* reported a hazard ratio (HR) for reproducing of 0.89 (95% CI: 0.74–1.07) for women born <32 weeks; when stratifying by women's age at the time of delivering their first child, HR decreased to 0.71 (95% CI: 0.50–1.01) for women ≥25 years old, whereas there was little association among women who gave birth at younger ages (Ekholm *et al.*, 2005). DeKeyser *et al.* found a HR for reproducing of 0.69 (95% CI: 0.45–1.05) among women born <27 completed weeks, and HR of 0.81 (95% CI: 0.75–0.88) among women

born <32 completed weeks of gestation (deKeyser et al., 2012). This study included women from the other Swedish study (Ekholm et al., 2005). Swamy et al. reported a relative risk (RR) for reproducing of 0.78 (95% CI: 0.65–0.93) among women born at 22–27 gestational weeks, and RR of 0.89 (95% CI: 0.86–0.93) among women born at 28–32 gestational weeks (Swamy et al., 2008). Finally, Moster et al. reported a RR for reproducing of 0.9 (95% CI: 0.6–1.2) among women born at 23–<28 gestational weeks, and RR of 0.9 (95% CI: 0.8–1.0) among women born at 28–<31 weeks (Moster et al., 2008). This study included women from the other Norwegian study (Swamy et al., 2008). Lower fertility among women born preterm, as suggested by these studies, may not entirely reflect decreased fecundability; it could be partly attributed to altered mating patterns, since individuals born preterm are less likely than those born at term to be cohabiting or married (Lindstrom et al., 2007; Moster et al., 2008). In contrast, our results cannot be explained by mating patterns related to preterm birth, since we only considered women in stable relationships. Further, these studies considered the number of registered births, which is not a sensitive indicator of fecundability; e.g. conceptions ending in a miscarriage will not contribute to such a measure of fertility. In contrast to previous studies, we assessed fecundability in 1-week categories of gestational age, from <32 to ≥43 weeks. The FRs for the gestational weeks <32, 32 and 33 were imprecise due to a low number of women in these categories, however, the effect estimates all ranged from 0.30 to 0.40, consistent with a deleterious effect of early gestational age on fecundability of approximately the same magnitude. On this basis, we chose to combine these categories into one category (<34 gestational weeks). Our data did not indicate a notable decrease in fecundability among women born after 34 weeks.

It is biologically plausible that preterm birth is associated with subsequent impaired fecundability, although the underlying pathways remain difficult to disentangle. At delivery, the infant is separated from its sources of maternal and placental hormones, leading to large increases in infant gonadotrophin levels (i.e. FSH and LH) and increased ovarian follicular maturation, particularly during the first 3–6 months of life (Speroff et al., 1999). However, FSH levels are 10–20 times higher, and LH levels 3–4 times higher in the first post-natal weeks among girls born preterm compared with girls born at term (Tapanainen et al., 1981; Kuiri-Hanninen et al., 2011). This increase is prolonged and follicular development is delayed relative to full-term girls (Kuiri-Hanninen et al., 2011), suggesting immaturity of reproductive organs and the hypothalamic–pituitary–ovarian axis at preterm birth. Although speculative, it seems plausible that such abnormalities may be related to impaired fecundability.

The link between preterm birth and later fecundability also could be established in fetal life. According to the 'developmental origins of health and disease' hypothesis, adverse environmental stimuli during the prenatal or early post-natal period may induce permanent alterations in physiology, metabolism and the functioning of endocrine axes, predisposing the individual to adult diseases (Gluckman and Hanson, 2004, Gluckman et al., 2008). Preterm birth may be a fetal response to an adverse intrauterine environment (Impey and Child, 2012); hence, factors operating in the prenatal period may explain the relation between preterm birth and later fecundability. Adolescent girls born small-for-gestational age (a different measure of a suboptimal intrauterine milieu) have reduced uterine and ovarian size, and anovulation or lower ovulation rate compared with girls with an appropriate weight for their gestational age at birth (Ibanez et al., 2000, 2002), indicating a relation between early life events and later fertility. To consider the potential influence of maternal environmental factors, we controlled for mother's smoking and medical conditions during pregnancy; however, controlling for these factors did not materially alter our estimates of association. We also considered whether potential hereditary factors, i.e. markers of maternal fecundability with a possible influence on fecundability of the daughter, might contribute to the observed association, but we found no evidence of this.

In conclusion, using prospective data on TTP, we found a pronounced decrease in fecundability among women born <34 weeks of gestation. We hesitate to infer a causal relation between early birth and lower fecundability, but our finding does augment results from previous studies that reported reduced fertility among women born preterm.

Supplementary data

Supplementary data are available at http://humrep.oxfordjournals.org/.

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Authors' roles

All authors contributed to the design of the study. C.W. wrote the drafts of the paper, and C.W. and A.H.R. performed the statistical analyses. All authors contributed to the interpretation of the study results, and reviewed and approved the final manuscript.

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Conflict of interest

None declared.

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SUPPLEMENTARY DATA

Supplementary Table SI Proportions of missing values of characteristics of 2814 participants and their mothers, and data sources.

Variable	Proportion of missing values (%)	Data source
Mother's lifetime parity	4.8	DMBR
Mother's age at time of delivery	4.8	DMBR
Mother's marital status at time of delivery	4.8	DMBR
Weight at birth	5.1	DMBR
Gestational age at birth[a]	17.1	DMBR
History of ≥12 months attempting a pregnancy	0.1	'Snart-Gravid'
Gravidity	0.1	'Snart-Gravid'
Age at menarche	0.1	'Snart-Gravid'
Parity	0.2	'Snart-Gravid'
Irregular menstrual cycles	0.3	'Snart-Gravid'
Mother's smoking during pregnancy	8.5	'Snart-Gravid'
Mother's history of difficulty conceiving[b]	17.2	'Snart-Gravid'
Mother's history of spontaneous abortion[b]	20.5	'Snart-Gravid'
Mother's educational level[c]	30.6	'Snart-Gravid'
Father's educational level[c]	35.2	'Snart-Gravid'

DMBR, Danish Medical Birth Registry.
[a]Missing values of participant's gestational age at birth were primarily attributable to the years 1978–1981 after an administrative change in the reporting of gestational age was implemented in the DMBR in 1978 (Knudsen and Olsen, 1998).
[b]These values were likely to be missing due to participants not knowing this information.
[c]For the first 6 months of the 'Snart-Gravid' study, 50% of participants were randomized to receive a short-form version of the questionnaire, which did not include the question about parental educational level.

Supplementary Table SII **Fecundability according to gestational age in weeks, assuming that gestational age is overestimated by 1 week in the Danish Medical Birth Registry, *N* = 2814.**

Gestational age, weeks	No. of women	No. of cycles	No. of pregnancies	Unadjusted model		Adjusted Model 1		Adjusted Model 2	
				FR	95% CI	FR	95% CI	FR	95% CI
<34	34	170	17	0.65	0.41–1.04	0.66	0.41–1.07	0.64	0.40–1.04
34	24	94	19	1.18	0.77–1.80	1.16	0.75–1.80	1.14	0.73–1.77
35	50	216	30	0.93	0.61–1.41	0.92	0.59–1.41	0.91	0.59–1.40
36	134	566	80	0.94	0.74–1.21	0.95	0.73–1.23	0.94	0.72–1.22
37	267	1083	159	0.90	0.73–1.11	0.90	0.72–1.11	0.88	0.71–1.09
38	472	1836	308	1.02	0.88–1.19	1.04	0.89–1.20	1.02	0.88–1.19
39	1105	4481	711	0.99	0.87–1.12	0.98	0.86–1.12	0.98	0.86–1.11
40	485	1879	313	1	Reference	1	Reference	1	Reference
41	209	765	128	1.09	0.89–1.34	1.12	0.91–1.37	1.11	0.90–1.37
42	29	98	20	1.02	0.63–1.66	1.05	0.65–1.69	1.03	0.64–1.68
≥43	5	14	2	1.71	0.50–5.87	1.79	0.51–6.33	1.75	0.48–6.41

Model 1: Adjusted for participant's year of birth, mother's age, mother's marital status, mother's and father's educational level, mother's smoking during pregnancy, mother's hypertension, mother's pre-eclampsia, and mother's diabetes during pregnancy with the participant.
Model 2: Model 1 + mother's history of difficulty conceiving, mother's history of spontaneous abortion, mother's history of preterm birth and mother's lifetime parity.
FR, fecundability ratio; CI, confidence interval.

Paper III

Fecundability among women with a history of miscarriage

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ABSTRACT

Objective: To examine the association between history of miscarriage and fecundability.

Subjects and methods: Data originated from a Danish prospective cohort study of pregnancy planners ("Snart-Gravid"). Eligible women were 18-40 years old at study entry, attempting to conceive, and not using fertility treatment. Participants were followed for up to 12 months or until they reported a pregnancy, stopped trying to conceive, or started fertility treatment, whichever came first. Information on previous pregnancy outcomes, including miscarriage, came from self-report or from relevant registries. We used Kaplan-Meier methods to estimate cumulative probabilities of conception for women whose reproductive history included only miscarriage or only live birth. Using data on time-to-pregnancy, we computed fecundability ratios (FR) with 95% confidence intervals (CI) comparing women with a history of only miscarriage with women with a history of only live birth.

Results: After adjustment for potential confounders, the cumulative probabilities of conception within 12 cycles of follow-up were 85% (95% CI: 81%-89%) for women with a history of 1 miscarriage, 85% (95% CI: 73%-92%) for women with a history of ≥2 miscarriages, and 88% (95% CI: 87%-89%) for women whose reproductive history included only live birth. Adjusted FRs were 0.87 (95% CI: 0.71-1.07) and 0.65 (95% CI: 0.36-1.17) for women with a history of 1 and ≥2 miscarriages, respectively.

Conclusions: Our results indicate that women with a history of miscarriage may have slightly reduced fecundability compared with women with a history of only live birth. The reduction in fecundability was greater for women with repeated miscarriages, although the estimates were imprecise. Despite a potential delay in conception, women with previous miscarriage may have similar probability of pregnancy by 12 cycles of attempts to women with proven fertility.

BACKGROUND

Miscarriage, defined as a spontaneous loss of an embryo or a fetus, affects up to 20% of pregnancies.[1] Approximately 30% of biochemically detected conceptions, including early losses occurring before a pregnancy is clinically recognized, fail to survive.[2, 3] Miscarriage is associated with an increased risk of obstetric and perinatal complications in the subsequent pregnancy, including repeated miscarriage,[4, 5] threatened miscarriage, preterm birth, and perinatal death,[6, 7] and may also be associated with impaired fecundity. The probability of conception among women with previous miscarriage ranges from 60% to 80% within 12 months of pregnancy attempts,[8-12] in contrast to 83% to 92% in the general population of women attempting to conceive.[13, 14]

Relative to women who had a live birth, longer time-to-pregnancy (TTP) in the subsequent pregnancy attempt was reported among women with miscarriage in their most recent pregnancy.[15] This finding was based on retrospectively self-reported TTP, raising concerns about differential recall of TTP by previous pregnancy outcome. A prospective cohort study of pregnancy planners reported a subsequently longer TTP within 12 months of a pregnancy loss, but this was primarily limited to losses occurring early in gestation (median gestation at time of loss: 35 days).[16] Contrary to these results, another prospective cohort study of pregnancy planners reported that early pregnancy loss (pregnancy loss before 6 weeks after onset of the last menstrual period [LMP]) in a preceding cycle was associated with increased odds of clinical pregnancy in a subsequent cycle.[3]

Given the lack of conclusive evidence, we examined the association between history of miscarriage and fecundability using prospectively collected data on TTP in a cohort of Danish women attempting to become pregnant.

SUBJECTS AND METHODS

Study population

Data for this study originated from a population-based prospective cohort study of Danish pregnancy planners ("Snart-Gravid"), initiated in 2007. The study has been described in detail elsewhere.[17] Eligible participants were Danish female residents, 18-40 years old at study enrollment, in a relationship with a male partner, attempting to conceive, and not receiving fertility treatment. Study enrollment was sought using advertisement on a health-related Danish

website, and in various Danish media.[17] Consenting participants completed a web-based baseline questionnaire and bimonthly follow-up questionnaires for up to 12 months after enrollment. At baseline, participants also provided their Civil Personal Registration (CPR) number, which is a unique 10-digit personal number assigned to Danish citizens at birth or immigration, enabling identification of persons in national health registries.[18] Participants were randomized to completion of either a short or a long version of the baseline questionnaire during the first 6 months of the study.[19] Subsequently, all new participants received the long version of the questionnaire. Study enrollment continued until 2011, and follow-up for all participants ended in 2012.

From among the 6,033 potential participants for the study, we initially excluded 1,824 women according to the criteria shown in Figure 1. From the remaining 4,209 women, we excluded women who were nulligravid, women with a history of only stillbirth, induced abortion or ectopic pregnancy, and women with gravidity >1 with heterogeneous pregnancy outcomes (e.g., both live births and miscarriages). The final study population comprised 977 women who had been pregnant at least once, with pregnancies ending only in at least one miscarriage (n=191), or only in at least one live birth (n=786). Women who had experienced only live birth served as the reference group; these women had no history of fetal loss (stillbirth, ectopic pregnancy or miscarriage) and had demonstrated their fertility by having had a live birth.

Some women did not complete the entire 12 months of observation and did not provide a reason for non-response; in all, 9 of 191 (4.7%) women with history of miscarriage and 57 of 786 (7.3%) women with history of live birth had only partial follow-up. Women with a history of miscarriage who had partial follow-up were more likely to have a body mass index (BMI) ≥30 kg/m^2 and a history of having attempted pregnancy for ≥12 months, than women with previous miscarriage who had complete follow-up. There were no appreciable differences in other baseline characteristics. Women who had partial follow-up contributed cycles at risk to the analyses until the date of completion of their last follow-up questionnaire.

Assessment of miscarriage and other pregnancy outcomes

We obtained data on participants´ history of miscarriage and other birth outcomes from the baseline questionnaire, and also from the Danish National Patient Registry (DNPR)

(miscarriage, induced abortion, and ectopic pregnancy), and the Danish Medical Birth Registry (DMBR) (stillbirth and live birth) by linkage with participants´ CPR numbers. Pregnancy outcomes observed in a hospital setting are assigned a diagnosis code according to the International Classification of Diseases; the 8th revision (ICD-8) was in use through 1993, and the 10th revision (ICD-10) thereafter.[20] Miscarriage was defined as the loss of an embryo or fetus before 22 gestational weeks.[21]

On the baseline questionnaire, participants reported previous pregnancies and the outcome of each pregnancy (live birth, stillbirth, miscarriage, induced abortion, ectopic pregnancy, or other), with dates. We combined self-reported and registry data on pregnancy outcomes to reconstruct women's reproductive histories. Cases of discordance between the two sources of data were solved as follows: if a woman did not report any pregnancy outcomes on the baseline questionnaire, but had a record of ≥1 miscarriage(s) in the DNPR, and no record of other types of pregnancy outcomes, she was considered to have had miscarriage(s) as her only pregnancy outcome. Similarly, if a woman reported miscarriage as her only type of pregnancy outcome at baseline, and had no records of miscarriage or of other types of pregnancy outcomes in the registries, she was considered to have had a history of miscarriage only. In cases of discrepancy between self-report and registry, the woman was considered to have had heterogeneous outcomes, unless her gravidity was one, in which case the registry record was considered to represent the true outcome. Using this approach, miscarriages that did not lead to a hospital encounter were also included in the analyses. We identified women who had only given live birth by the same strategy. Supplementary Table 1 shows ICD-8 and ICD-10 diagnosis codes for the pregnancy outcomes.

Assessment of fecundability

We measured fecundability, i.e., the cycle-specific probability of conception, using data on TTP, defined as the number of menstrual cycles at risk of pregnancy.[22] At study entry, participants reported the number of months of attempted pregnancy, the date of their LMP, and usual cycle length. In the follow-up questionnaires, they reported the date of their LMP and whether they were currently pregnant or had had a pregnancy termination (miscarriage, induced abortion, or ectopic pregnancy) since the previous follow-up. The event of interest in our study was pregnancy. Over 96% of the participants used a home pregnancy test to determine

pregnancy.[23] TTP was estimated using the following formula: (days of pregnancy attempt at study entry/days of usual cycle length)+((LMP date from the most recent follow-up questionnaire – date of study entry)/days of usual cycle length)+1.[24] Participants contributed cycles at risk until report of pregnancy or until censoring by failing to respond to follow-up questionnaires, discontinuation of pregnancy attempts, initiation of fertility treatment, or reaching the end of the 12-month observation period, whichever came first. To account for left-truncation, i.e., of women initiating their pregnancy attempts one or more cycles before study entry, we defined observed cycles at risk as those contributed after study entry.[24] The number of cycles of pregnancy attempts at study entry considered only the cycles following the most recent miscarriage or live birth.

Assessment of covariates

At baseline, participants reported their age, educational level, height and weight, menstrual cycle regularity, frequency of intercourse, and history of fertility problems (history of attempting pregnancy ≥12 months, and history of consultation with a physician due to difficulty conceiving). We estimated participants´ BMI as weight (kg) divided by height squared (m^2).

Familial predisposition to miscarriage has been associated with history of at least one miscarriage[25] and recurrent miscarriage (≥3 consecutive miscarriages[26]).[27, 28] Considering a mother´s history of miscarriage as an indicator of her own fertility, with a potential influence on the fertility of her daughters, we hypothesized that the miscarriage-fecundability association may vary by maternal history of miscarriage. We also considered whether the participants´ sisters had a history of miscarriage, as a proxy measure of familial characteristics. Data on miscarriage were available since 1977 in the DNPR,[20] thus, for the participants´ mothers, we supplemented with data on history of miscarriage from the DMBR. These data were available since 1978 and are reported by the woman to the midwife at a prenatal visit, thus including some of the miscarriages experienced by the participants´ mothers before 1977.[29, 30]

Ethical approval

The “Snart-Gravid” study was approved by the Danish Data Protection Agency (record no. 2013-41-1922) and by the Institutional Review Board at Boston University. Participants provided informed consent before completing study questionnaires.

Data analysis

We first assessed the distribution of baseline characteristics for women with 1 miscarriage, ≥2 miscarriages, or with live birth. We used the Kaplan-Meier method to estimate crude and adjusted cumulative probabilities of conception with 95% confidence intervals (CI), allowing for left-truncation and censoring.[31] We fitted a proportional probabilities regression model to estimate fecundability ratios (FR) and 95% CI, comparing fecundability among women with a history of miscarriage with that among women with a history of live birth.[32] A FR <1 indicates lower relative fecundability (longer TTP), and a FR >1 indicates higher relative fecundability (shorter TTP). We examined the effect of miscarriage in categories of 1 or ≥2 miscarriages, and repeated the analysis with a restriction to women with a gravidity of 1. In another sensitivity analysis, we computed FRs with a restriction to women with ≤3 cycles of pregnancy attempts at study enrollment. To assess the effect of miscarriage recency on fecundability, we calculated FRs for women who had their miscarriage <1 year or ≥1 year before initiation of their current pregnancy attempts; this analysis was restricted to women with a gravidity of 1. In a subanalysis, we stratified the FR estimates by participants´ mothers´ or sisters´ history of miscarriage (yes/no).

Based on published evidence[4, 5, 13, 24, 33-37] and on available data, we adjusted the FR estimates for age at first miscarriage or live birth (continuous), calendar year at first miscarriage or live birth (<2003; 2003-2007; >2007), higher education (none; <3 years; 3-4 years; >4 years), BMI (<18.5; 18.5-24.9; 25.0-29.9; ≥30.0 kg/m^2), history of pregnancy attempts ≥12 months (yes; no), and history of consultation with a physician due to difficulty conceiving (yes; no). At baseline, participants also reported levels of caffeine and alcohol consumption, smoking status and physical activity. These lifestyle factors may be associated with miscarriage[34, 38, 39] and with impaired fecundability,[36, 40-43] thus qualifying as potential confounders. Even though these lifestyle exposures could have changed from the time of miscarriage to the time of attempting to conceive again, possibly as a result of the earlier miscarriage, we examined potential confounding by these factors. As we found that adjustment did not affect the estimates, we did not include these variables in the analyses presented here.

Analyses were conducted using Stata version 12.0 (StataCorp., College Station, TX, USA), and SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

Missing observations

The proportions of missing observations were below 2% for most variables. For the variable on participant's history of consultation with a physician due to difficulty conceiving, data were missing for 26% of the participants. This variable was not included in the short version of the baseline questionnaire, contributing to the high proportion of missing values. We estimated the missing covariate values using multiple imputation by chained equations, and included all variables considered in the analyses in the imputation procedure.[44]

RESULTS

Of 977 women in the study population at the start of follow-up, 786 women had a history of live birth only, and 191 women had a history of miscarriage only; 168 had had 1 miscarriage, and 23 women had ≥2 miscarriages. Table 1 shows the baseline characteristics of the women according to previous pregnancy outcome. Women with a history of miscarriage tended to be younger, more likely to have had their first pregnancy event after 2007, have no higher education, to have intercourse ≥4 times/week, and more likely to have attempted to become pregnant for at least 4 cycles at study entry than women with live births. Among women with ≥2 miscarriages, there was a lower prevalence of irregular menstrual cycles, and an elevated prevalence of BMI ≥30 kg/m^2, history of pregnancy attempts ≥12 months and having consulted a physician due to difficulty conceiving, as well as familial history of miscarriage.

Crude Kaplan-Meier estimates for the cumulative probability of conception within 6 and 12 cycles of pregnancy attempts were 69% (95% CI: 62%-75%) and 85% (95% CI: 80%-88%) for women with a history of 1 miscarriage, 46% (95% CI: 21%-63%) and 69% (95% CI: 49%-82%) for women with a history of ≥2 miscarriages, and 76% (95% CI: 74%-79%) and 89% (95% CI: 87%-90%) for women with previous live birth. The corresponding adjusted estimates were similar except for women with ≥2 miscarriages; the adjusted cumulative probabilities of conception were 71% (95% CI: 52%-82%) within 6 cycles and 85% (95% CI: 73%-92%) within 12 cycles. Figure 2 shows that the differences in the adjusted cumulative probabilities of conception associated with miscarriage were largest during the first 6 cycles of pregnancy attempts, gradually tapering off by 12 cycles.

Table 2 shows that the adjusted FRs were 0.87 (95% CI: 0.71-1.07) for women with a history of 1 miscarriage, and 0.65 (95% CI: 0.36-1.17) for women with a history of ≥2 miscarriages.

When we restricted to women with gravidity of 1 at entry into the study, the result for 1 miscarriage was similar (FR 0.85 [95% CI: 0.69-1.05]). The adjusted FRs for women with a pregnancy attempt time of ≤3 cycles at study enrollment were 0.95 (95% CI: 0.73-1.22) for women with a history of 1 miscarriage, and 0.55 (95% CI: 0.22-1.38) for women with a history of ≥2 miscarriages. Among women with gravidity of 1, the adjusted FR for women who had their miscarriage <1 year before initiating their current pregnancy attempts was 0.86 (95% CI: 0.68-1.08), and 0.82 (95% CI: 0.52-1.29) for women with miscarriage ≥1 year before current attempts (Table 3). The FRs did not vary appreciably by history of miscarriage among the mothers and sisters of the participants (results not shown).

DISCUSSION

We found that women with a previous miscarriage had a 13% decrease, and women with at least 2 previous miscarriages, a 35% decrease, in fecundability compared with women who had only had a live birth. However, the estimates were imprecise and the confidence intervals were consistent with a broad range of values, from strong effects to little or no association. The cumulative probability of conception was lower among women with miscarriage, but this difference gradually diminished and had disappeared by 12 cycles of pregnancy attempts.

In a recent prospective study of women with ≥2 previous miscarriages who were attempting to conceive, Kaandorp *et al.* reported crude 6- and 12-month cumulative incidences of conception to be 56% and 74%,[8] which was marginally higher than our respective estimates of 46% and 69%. This difference may be partly attributable to the fact that 13% of women in the study by Kaandorp *et al.* conceived with fertility treatment. After adjustment for confounding, we found that the probability of conception within 12 cycles increased to 85% and was comparable with that for women with 1 previous miscarriage (85%), previous live birth (88%), and general populations of women attempting to conceive (83%-92%).[13, 14]

In comparison with our findings, Wang *et al.* observed that early pregnancy loss in a preceding cycle was associated with increased odds of clinical pregnancy in a subsequent cycle (odds ratio [OR] 2.0 [95% CI: 1.3-3.0]).[3] That study considered pregnancy losses occurring before 6 weeks post-LMP. In our study, we were not able to distinguish between early and later pregnancy

losses, as we did not have data on gestational length at the time of miscarriage. Further, the study by Wang *et al.* considered nulliparous women who were younger than women in our cohort (mean age 25 years vs. 30 years), and excluded those with a history of pregnancy attempts ≥12 months, suggesting that they were reproductively healthier than women in our study. Thus, those results are difficult to compare with our findings. In contrast, in a cross-sectional study of pregnant women, Hassan *et al.* compared self-reported TTP before and after a miscarriage in the previous pregnancy with TTP before and after a previous live birth.[15] Women with a miscarriage in their previous pregnancy had longer TTP after miscarriage than before miscarriage (risk ratio [RR] 2.1 [95% CI: 1.4-3.0]) and longer TTP than women with a previous live birth (OR 2.1 [95% CI: 1.6-2.6]). The retrospective ascertainment of TTP in that study may have created a spurious association because of recall bias. Still, in a prospective study of women attempting to conceive, Sapra *et al.* found that TTP after an early miscarriage (median gestation at pregnancy loss: 35 days [5%: 26 days, 95%: 81 days]) was longer than before miscarriage. Relative to the first attempt (before the miscarriage), fecundability was reduced in the second pregnancy attempt (fecundability odds ratio [FOR] 0.42 [95% CI: 0.28-0.65]), and in the third pregnancy attempt (FOR 0.56 [95% CI: 0.11-2.79]).[16] Despite differences in the measurement of miscarriage and TTP across studies, our results corroborate these previous reports of a small delay in conception among women with miscarriage.

If women with co-occurring previous miscarriages and impaired fecundability were more likely to enroll in our study, the FRs that we observed might overestimate the deleterious effect of previous miscarriage. Still, fecundability did not appear to be appreciably different among women with only up to 3 cycles of pregnancy attempts at study enrollment, suggesting that such a mechanism was not of substantial concern.

One advantage of our study is that we were able to combine registry and self-reported data on previous pregnancy outcomes, improving the completeness of miscarriage ascertainment when compared with each data source alone. Prevalence of pregnancies ending in a miscarriage is 11%-16%, based on data from Danish national health registries, and 21% based on self-report.[1, 33] Entry errors and incorrect assignment of diagnosis codes are potential sources of information bias when using data from registries. However, the positive predictive value of miscarriage diagnoses in the DNPR was 93%-100% in the period 1980-2008, regardless of the ICD

classification used.[21] The proportion of self-reported miscarriages that cannot be identified in the DNPR has been estimated to be 30%.[1] On the other hand, recall of prior miscarriages may depend on duration of the pregnancy and time since the event, with losses occurring at an early gestation and several years ago less likely to be recalled.[45-47] Since we supplemented women´s self-reports with registry-based data, the number of women with unidentified miscarriages is likely to be minor. Importantly, data on previous pregnancy outcomes were retrieved independently of outcome information, implying that differential misclassification is an unlikely explanation for our results. Further, as over 96% of participants in "Snart-Gravid" confirmed their pregnancy using a home pregnancy test, it is plausible that recognition of pregnancy was unrelated to the woman´s previous pregnancy outcome.

Impaired fertility after a miscarriage may be related to tubal damage from infection, or to intrauterine adhesions, which may occur as a consequence of e.g., infection or dilatation and curettage procedures, performed to manage miscarriage.[48] Although several studies have reported similar probabilities of conception after miscarriage irrespective of medical, surgical or expectant management,[10-12, 49] a recent meta-analysis found the prevalence of intrauterine adhesions among women with previous miscarriage was 19%, with women having multiple miscarriages being more likely to have adhesions than women with a single miscarriage (OR 1.99 [95% CI: 1.32-3.00]), which was mainly attributed to recurrent curettage procedures performed in the former group.[50] This finding might contribute to explain why women with ≥2 miscarriages had lower fecundability than women with 1 miscarriage. We did not have data on gynecologic complications associated with miscarriage or medical conditions with a potential influence on miscarriage and fecundability, which limited our ability to examine plausible biological mechanisms. Some studies suggest that women with infertility are more likely to experience miscarriage.[4, 5, 15, 35] We controlled for pre-existing subfertility by adjusting for previous pregnancy attempts ≥12 months and having consulted a physician due to difficulty conceiving. This adjustment did not appreciably change our estimates.

In conclusion, our results suggest a decreased fecundability among women with a history of miscarriage, most prominent among women with repeated miscarriages, although the estimates were imprecise. The delay in conception was most evident during the first cycles of

pregnancy attempts, still, by 12 cycles, the probability of conception was similar to that of women with proven fertility, suggesting that although women with miscarriage may experience a lower average probability of conception, such delay may be transient.

AUTHORS´ ROLES

CW, VE, EMM and HTS developed the hypothesis and analytic plan. CW and AHR analyzed the data. CW performed the literature review and took the lead on drafting the paper, and AHR, VE, EEH, LAW, KJR, HTS and EMM contributed in revising the work. All authors gave their final approval of the manuscript, and agree to be accountable for all aspects of the work.

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CONFLICT OF INTEREST

The authors have no competing interests to declare.

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Table 1. Characteristics of 977 participants who experienced only miscarriage or only live birth

Characteristic	Only ever 1 miscarriage	Only ever ≥2 miscarriages	Only ever live birth
No. of women	168	23	786
Age at study entry, mean (s.e.), years	27.9 (0.3)	27.5 (0.9)	30.6 (0.1)
Age at first pregnancy event, mean (s.e.), years*	26.3 (0.3)	25.0 (1.0)	27.1 (0.1)
Calendar year of first pregnancy event, %*			
<2003	10.1	17.4	20.0
2003-2007	53.0	60.9	75.5
>2007	36.9	21.7	4.6
Higher education, %			
None	14.3	17.4	8.5
<3 years	33.9	30.4	30.7
3-4 years	31.6	30.4	38.4
>4 years	20.2	21.7	22.4
BMI, kg/m^2, %			
<18.5	1.8	4.4	3.4
18.5-24.9	67.9	39.1	58.5
25.0-29.9	17.9	26.1	23.2
≥30.0	12.5	30.4	14.9
Irregular menstrual cycles, %	24.4	13.0	22.4
Intercourse frequency ≥4 times/week, %	17.3	26.1	11.8
No. of cycles of attempted pregnancy at study entry, %			
0-1	34.5	30.4	55.6
2-3	28.0	17.4	20.6
4-6	26.2	21.7	12.7
7-11	11.3	30.4	11.1
History of pregnancy attempts ≥12 months, %	13.7	30.4	19.0
History of consultation with a physician due to difficulty conceiving, %	15.5	30.4	21.0
Miscarriage in mother or sister, %	26.8	30.4	22.0

Abbreviations: s.e., standard error; BMI, body mass index.
*First pregnancy event=first miscarriage or first live birth.

Table 2. Fecundability among women who have only had miscarriage, gravidity≥1

				Unadjusted model		Adjusted model*	
Pregnancy outcome	No. of women	No. of cycles	No. of pregnancies	FR	95% CI	FR	95% CI
Only miscarriage							
Total	191	727	121	0.87	0.73-1.04	0.85	0.70-1.03
1	168	632	111	0.91	0.76-1.09	0.87	0.71-1.07
≥2	23	95	10	0.60	0.33-1.07	0.65	0.36-1.17
Only live birth	786	2,796	565	1	Reference	1	Reference

Abbreviations: FR, fecundability ratio; CI, confidence interval.

*Adjusted for age at first miscarriage or live birth, calendar year of first miscarriage or live birth, higher education, body mass index, history of pregnancy attempts ≥12 months, and history of consultation with a physician due to difficulty conceiving.

Table 3. Fecundability among women who have only had miscarriage according to recency of miscarriage*, gravidity=1

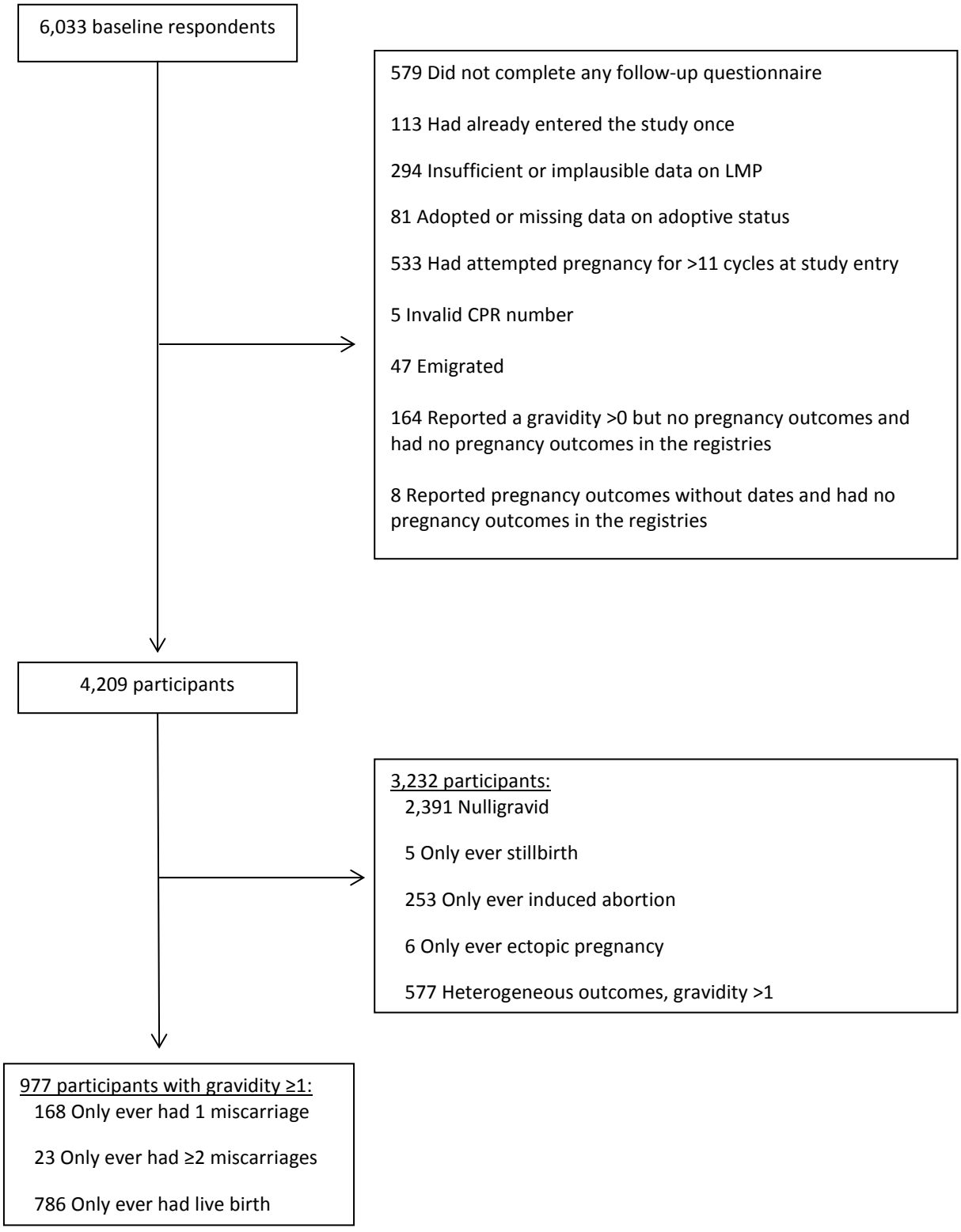
				Unadjusted model		Adjusted model‡	
Pregnancy outcome	No. of women	No. of cycles	No. of pregnancies	FR	95% CI	FR	95% CI
Miscarriage							
<1 year	136	509	93	0.91	0.74-1.11	0.86	0.68-1.08
≥1 years	32	123	18	0.72	0.47-1.11	0.82	0.52-1.29
Live birth	607	2,105	442	1	Reference	1	Reference

Abbreviations: FR, fecundability ratio; CI, confidence interval.

*Number of years before initiation of current pregnancy attempts.

‡Adjusted for age at first miscarriage or live birth, calendar year of first miscarriage or live birth, higher education, body mass index, history of pregnancy attempts ≥12 months, and history of consultation with a physician due to difficulty conceiving.

Figure 1. Study flow chart



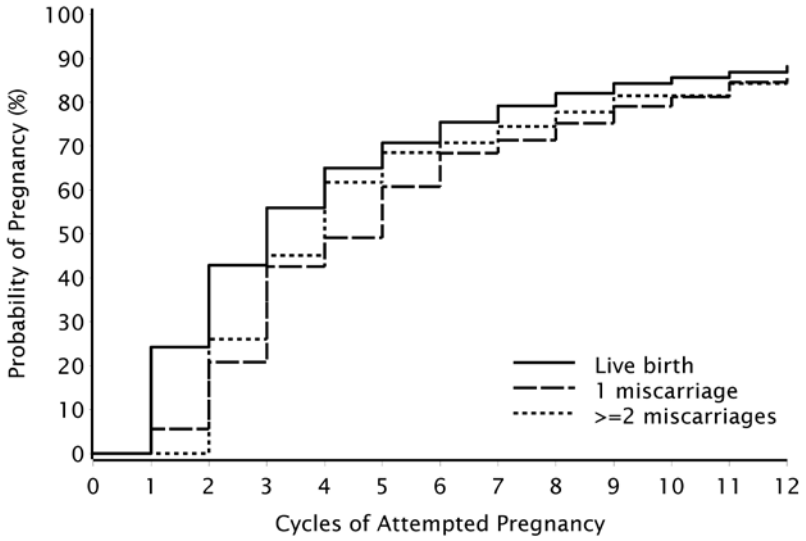


Figure 2. Adjusted cumulative probabilities of conception after miscarriage or live birth*

*Adjusted for age at first miscarriage or live birth, calendar year of first miscarriage or live birth, higher education, body mass index, history of pregnancy attempts ≥12 months, and history of consultation with a physician due to difficulty conceiving.

Adjusted cumulative probability of conception with 95% confidence intervals (CI), 6 cycles:
1 miscarriage: 68% (62%-74%); ≥2 miscarriages: 71% (52%-82%); live birth: 75% (74%-77%)

Adjusted cumulative probability of conception with 95% CI, 12 cycles:
1 miscarriage: 85% (81%-89%); ≥2 miscarriages: 85% (73%-92%); live birth: 88% (87%-89%)

Supplementary Table 1. ICD-8 and ICD-10 diagnosis codes for pregnancy outcomes in the Danish National Patient Registry*

Pregnancy outcome	ICD-8 diagnosis code	ICD-10 diagnosis code
Miscarriage	634.61, 643, 645.1	DO021, DO03, DN969
Induced abortion	640, 641, 642	DO04, DO05, DO06
Ectopic pregnancy	631, excluding 631.90	DO00

*Live births and stillbirths were identified in the Danish Medical Birth Registry by CPR numbers, and not by diagnosis codes.

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