Infertility and preterm delivery, birthweight, and Caesarean section: a study within the Danish National Birth Cohort

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BACKGROUND: More than 10% of babies are born to couples taking >1 year to conceive (a common definition of infertility). Some evidence indicates that such pregnancies are at increased risk of preterm delivery and other adverse birth outcomes, but the problem has rarely been addressed in large, longitudinal studies enrolling couples irrespective of infertility treatment. METHODS: We used data from the Danish National Birth Cohort: 55 906 singleton live births from women who reported their waiting time to pregnancy (TTP) and other covariates in an interview during the 2nd trimester of pregnancy. RESULTS: A TTP >1 year was associated with an increased risk of all outcomes studied, including preterm birth [odds ratios and 95% confidence intervals were 1.5 (1.2, 1.8) among primiparas and 1.9 (1.5, 2.4) among multiparas]. Odds ratios for preterm remained elevated after adjustment for covariates. Among couples with a TTP >1 year, infertility treatment was associated with added risk only among multiparas. CONCLUSION: Infertile women are at higher risk of adverse birth outcomes even if they conceive without treatment. With >10% of babies born to infertile couples, it is important to consider this group as potentially high risk when providing prenatal care.

Key words: birthweight/Caesarean section/infertility/preterm delivery/time to pregnancy

Introduction

Infertility is a common reproductive problem. Ten to 20% of pregnant women report a time to pregnancy (TTP) of >1 year (Juul *et al.*, 1999), which is a commonly used clinical definition of infertility. Infertile couples who conceive via IVF appear to be at increased risk of preterm birth (Olivennes *et al.*, 1993; Dhont *et al.*, 1999; Koudstaal *et al.*, 2000; Wang *et al.*, 2002), raising speculation about possible adverse effects of infertility treatments. However, the underlying causes of infertility may also contribute to problems during pregnancy. Studies have suggested that women with a TTP of >1 year are at a higher risk of pre-eclampsia (Basso et al., 2003), low birthweight (Williams *et al.*, 1991) and preterm delivery (Joffe *et al.*, 1994; Henriksen *et al.*, 1997) independently of treatment.

Infertility can be caused by disruption in any of several reproductive processes. Some of these problems, such as reproductive tract infections, hormonal disorders or poor placentation, could also plausibly contribute to adverse birth outcomes. Despite the high proportion of babies born to infertile couples, surprisingly little research has considered the relationship between infertility and pregnancy outcome. If infertility is a risk factor for poor pregnancy outcome, identifying such pregnancies as high risk so that they can be closely monitored might reduce adverse events.

In this paper we use data on live births within a large Danish pregnancy cohort to examine whether infertile couples, identified as those taking >1 year to conceive, have an elevated risk of preterm delivery, decreased birthweight, or delivery by Caesarean section. We adjust for several possible risk factors that might affect both infertility and birth outcome, and we compare infertile couples who conceived with and without treatment.

Materials and methods

Women in the Danish National Birth Cohort are enrolled early in pregnancy. Participants are interviewed by telephone four times, twice during pregnancy and twice after delivery. Approximately 60% of all eligible pregnant women in Denmark are contacted (based upon whether the doctors and midwives collaborate) and ~60% of those contacted chose to participate (Olsen *et al.*, 2001).

We had 64 167 records of responders to the first interview between December 12, 1997 and July 31, 2001. As shown in Figure 1, we excluded pregnancies ending in other than singleton live births as well as those with critical missing data. We focused on live births because
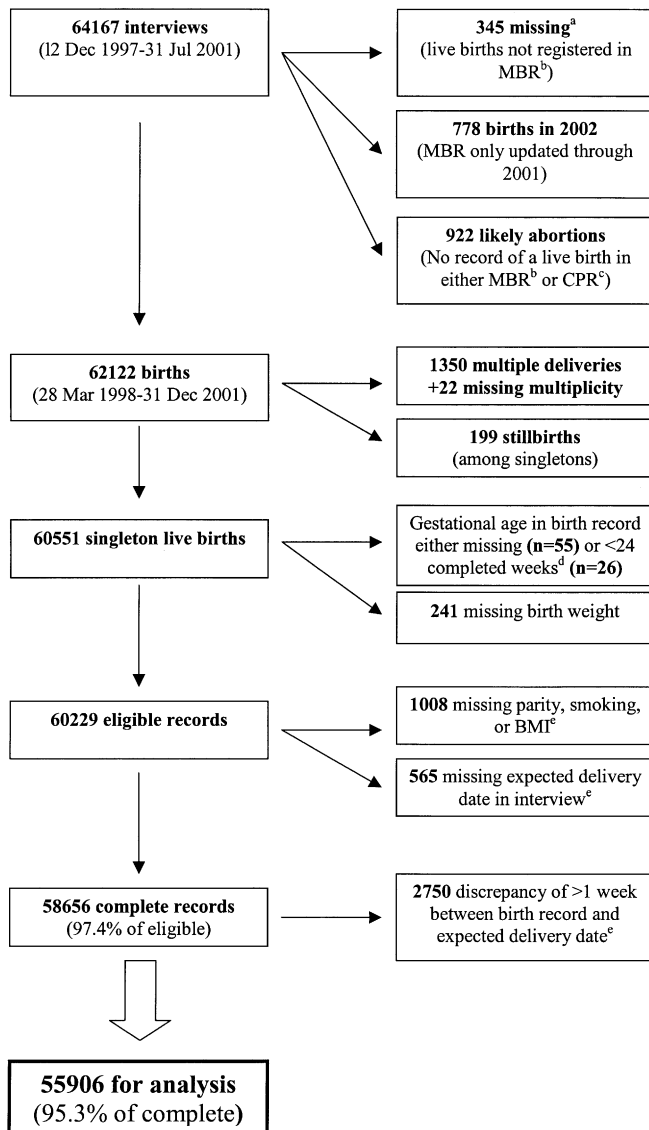
Figure 1. Steps in identification of the analysis sample. [a]Reasons for missing might be a delivery abroad, in the home, error in the personal identifier number, or delay in reporting to the Danish National Board of Health. [b]Medical Birth Registry. [c]Central Person Registry. [d]Before 24 completed weeks it is in some cases left to the obstetrician's judgement whether to classify as a live birth or a late abortion a foetus that shows ambiguous signs of life at birth and is dead shortly after. [e]Except for 45 pregnancies with missing parity, women excluded because of missing values or inconsistencies in gestational age (n = 4278) were reintroduced in an additional analysis.

both preterm delivery and reduced growth may have long-term consequences. We used two sources of information on gestational age: one was based on the woman's estimated date of delivery provided at the first interview, and the other was gestational age from the birth record. Because we needed good quality information on gestational age at delivery, we identified records with data from both sources (58 656, 99% of the available records). Of these, we included 45 519 (77.6%) that had the same estimated week of delivery reported in both instances and 10 387 (17.7%) that differed by ≤1 week. When sources differed, we used the gestation reported in the birth record. We thus had 55 906 births for analysis. Data on mother's age at delivery, sex of

the baby, Caesarean sections and birth outcomes were taken from the hospital birth record obtained from the Danish National Board of Health. The other analysis variables were derived from the first interview. Median time of interview among women in this analysis was the 16th week, and 95% of interviews were completed by the 25th week.

The questions concerning pregnancy planning and waiting TTP were phrased as follows: 'Was this pregnancy planned?' (possible answers were: 'planned', 'partly planned', 'not planned', 'don't know', 'do not wish to answer'). If the pregnancy was planned or partly planned, the participant was asked 'How long did you try to become pregnant before you succeeded?' (possible answers were 'did not try to become pregnant', 'became pregnant right away', '1–2 months', '3–5 months', '6–12 months', 'more than 12 months', 'don't know', 'do not wish to answer'). Those who had not planned their pregnancy were asked whether they had conceived despite contraception, and two categories were used for analysis: 'conceived despite contraception' and 'not planned', which included the women who had not planned their pregnancies but had not conceived while using contraception. Of the 6755 women who responded that they had partly planned this pregnancy, 72.7% reported a TTP. However, since we were not sure what 'partly planning' implied concerning the ability to reconstruct TTP, we included in one separate category all women reporting that they had partly planned their pregnancy (without taking into consideration their TTP). Of the 39 801 women who reported having planned their pregnancy, 350 did not report a TTP and we categorized them with 'part planners'. A total of 2884 women reported infertility treatment. Most of these were planners who took >1 year to conceive, but 417 were planners who waited between 6 and 12 months. The 57 others who reported infertility treatment were in the 'partly planned' (n = 52) and 'not planned' (n = 5) groups.

The social status variable was based on the self-reported job title of the current or most recent job (if the women worked in the last 6 months). If participants were in school, even if working part time, the social status was based on the type of education. We included in the high social status all those in management and requiring higher education, generally ≥4 years beyond the compulsory level of 9 years. Office workers, service workers, skilled manual workers, and women in the military constituted the middle category, and unskilled workers were classified in the lowest social class. Job titles had been categorized according to Denmark's job classification scheme (Danmarks Statistiks Fagklassifikation, 1996).

We estimated the association between a TTP of >1 year and dichotomous birth outcomes (preterm delivery and very preterm delivery, which was defined as a gestation ending before the completion of the 34th week, planned Caesarean section and emergency Caesarean section) using logistic regression models. We modelled in one variable with eight levels all five categories of TTP (right away, which was the reference category, 1–2 months, 3–5 month, 6–12 months and >12 months) and the three categories of unplanned pregnancy (partly planned, conceived despite contraception and not planned) We stratified all analyses by parity (primiparas versus multiparas), and we adjusted for maternal age at delivery, pre-pregnancy body mass index (BMI, kg/m^2), smoking in pregnancy, social status of the mother and sex of the baby. Menstrual cycle characteristics may influence the estimate of both TTP and gestational age and thus we adjusted for menarche and cycle length/regularity in the models where gestational age was not included as a covariate. All variables were categorized as reported in Table I and Table II. When examining multiparas, we further adjusted for parity (2nd birth versus 3rd or higher). The decision on which factors to include was made *a priori*.

Table I. Primiparas: pregnancy characteristics by planning/time to pregnancy (TTP)

	≤1 year[a]	>1 year		Partly planned	Not planned[b]
		Untreated	Treated		
n (%)	15 302 (60.0)	1968 (7.7)	1931 (7.6)	3480 (13.7)	2794 (11.0)
Mother's age (years)					
≤25	22.9	15.1	5.9	29.5	45.6
26–30	56.1	49.2	37.2	47.1	32.9
31–35	18.1	29.1	40.5	19.5	15.6
≥35	2.9	6.5	16.4	3.9	5.9
Pre-pregnancy BMI (kg/m^2)					
<21	30.1	28.3	27.8	33.0	35.8
21–24.9	45.1	39.8	40.3	43.8	41.2
25–29.9	18.3	20.2	20.9	16.3	16.4
≥30	6.5	11.7	11.0	6.9	6.6
Smoking in pregnancy					
No	76.5	69.7	77.4	65.3	52.9
Quit before interview	11.4	11.8	8.2	15.8	15.9
Smoked at interview	12.1	18.5	14.4	18.9	31.2
Age at menarche (years)					
7–11	7.5	9.2	8.0	8.5	10.1
12–14	72.9	71.2	71.4	71.7	73.1
≥15	15.1	15.3	17.1	15.6	13.3
Missing	4.6	4.3	3.6	4.2	3.5
Cycle length					
Irregular	11.2	21.0	24.5	15.9	16.5
14–24	4.2	2.5	1.4	3.5	5.3
25–27	10.0	12.7	12.6	10.5	11.8
28–30	66.3	55.7	52.0	62.6	59.1
≥31	6.1	7.3	9.2	5.5	4.8
Missing	2.1	0.8	0.3	2.1	2.6
Mother's social status					
High	54.5	44.3	49.5	50.7	39.1
Middle	33.3	40.9	37.2	33.9	37.7
Low	9.7	12.2	10.8	11.8	17.9
Missing	2.5	2.6	2.5	3.6	5.3
Reported infertility treatment	1.4	0.0	100.0	1.3	0.1
Proportion of boys	51.3	50.7	51.3	50.3	51.1
Birth at <37 weeks	5.4	7.4	7.6	5.1	5.5
Birth at <34 weeks	1.3	2.2	2.4	1.2	1.5
Mean gestation (days)	279.6	278.9	277.8	279.9	279.2
Mean birthweight (g)	3505.4	3451.7	3427.3	3500.4	3440.2
Low birthweight among term	1.1	1.6	2.1	1.0	2.2
Planned Caesarean section	4.2	5.2	6.5	4.0	3.9
Acute Caesarean section	12.3	15.0	16.3	12.7	11.6

Values are percentages unless otherwise indicated.
[a]Includes women who conceived right away and with TTP of 1–2 months, 3–5 months and 6–12 months.
[b]Includes women becoming pregnant despite contraception and those reporting not having planned the pregnancy.
BMI = body mass index.

Emergency and planned Caesarean section deliveries were identified from ICD-10 diagnoses (O82.0 for planned and O82.1 for emergency). Thirty-eight of the 8066 Caesarean sections were classified as neither planned nor emergency, and were not considered as an outcome in the analysis of either planned or emergency Caesarean sections. These analyses were adjusted for the same confounders as for preterm delivery.

We examined the association between TTP and birthweight by fitting linear regression models using covariates as described above, but we excluded menarche and menstrual cycle characteristics and included gestational age at birth (in 15 categories) to explore whether the growth of the baby was affected independently of gestational age. We also estimated the association between a TTP >1 year and low birthweight at term, restricting the analyses to births occurring from week 37 onward. We used logistic regression and adjusted for the

same covariates as in the birthweight models but with the narrowed gestational age range.

For all outcomes we estimated the association with a TTP >1 year among all women and we repeated the analyses excluding all women who reported having received infertility treatment, regardless of the duration of their TTP. For the sake of brevity, we only present tables including the estimates for a TTP >1 year.

There might be adverse effects of infertility treatment or differences in the severity of infertility between women who conceive with and without treatment. We therefore estimated the odds ratio (OR) of adverse birth outcomes associated with treatment restricting the analysis to women taking >1 year to conceive. We adjusted for the same covariates as in the TTP analyses and stratified on parity.

Couples planning a pregnancy may include an excess of infertile couples, so we repeated all analyses using as a reference category the

Table II. Multiparas: pregnancy characteristics by planning/time to pregnancy (TTP)

	≤1 year[a]	>1 year		Partly planned	Not planned[b]
		Untreated	Treated		
n (%)	20280 (66.6)	1858 (6.1)	653 (2.1)	3985 (13.1)	3655 (12.0)
Mother's age (years)					
≤25	6.1	3.6	1.1	7.4	7.9
26–30	38.4	25.3	16.2	33.9	29.7
31–35	43.8	47.0	49.8	42.3	40.0
≥35	11.8	24.1	32.9	16.5	22.5
Pre-pregnancy BMI					
<21	28.9	25.5	26.6	31.0	31.1
21–24.9	43.5	40.0	36.9	41.9	41.0
25–29.9	20.0	22.1	23.1	19.6	19.1
≥30	7.6	12.4	13.3	7.5	8.8
Smoking in pregnancy					
No	78.8	68.9	79.5	70.9	64.3
Quit before interview	6.4	8.0	4.7	8.0	8.0
Smoked at interview	14.8	23.1	15.8	21.1	27.7
Age at menarche					
7–11	7.7	7.1	8.1	8.9	9.8
12–14	71.1	69.1	72.4	70.2	69.7
≥15	16.3	18.6	16.4	16.6	15.7
Missing	4.9	5.2	3.1	4.4	4.8
Cycle length					
Irregular	9.7	17.7	24.8	14.0	15.9
14–24	4.1	4.2	1.5	4.0	3.8
25–27	11.4	12.4	12.7	11.5	10.9
28–30	67.5	57.7	52.1	62.8	61.8
31+	6.0	7.1	8.6	6.3	6.1
Missing	1.2	0.9	0.3	1.5	1.5
Mother's social status					
High	46.6	40.5	44.0	45.2	41.3
Middle	34.9	39.6	38.4	34.6	32.3
Low	12.6	15.3	12.3	12.9	17.1
Missing	5.9	4.6	5.4	7.3	9.3
Reported infertility treatment	1.1	0.0	100.0	0.9	0.1
2nd birth	73.6	75.4	87.9	65.6	46.2
3rd birth or higher	26.4	24.6	12.1	34.4	53.8
Proportion of boys	51.0	50.1	54.1	52.4	51.9
Birth before 37 weeks	2.9	4.8	7.0	3.1	3.8
Birth before 34 weeks	0.7	1.0	1.8	0.8	1.1
Mean gestation (days)	280.3	279.3	277.2	280.2	279.3
Mean birthweight (g)	3693.4	3613.9	3579.0	3671.8	3642.0
Low birthweight among term	0.6	0.9	2.3	0.5	1.1
Planned Caesarean section	5.9	7.6	10.1	6.4	6.6
Acute Caesarean section	5.6	6.7	12.1	5.4	6.1

Values are percentages unless otherwise indicated.
[a]Includes women who conceived right away and with TTP of 1–2 months, 3–5 months and 6–12 months.
[b]Includes women becoming pregnant despite contraception and those reporting not having planned the pregnancy.
BMI = body mass index.

combination of couples who conceived right away, the part planners, those who conceived despite birth control, and the non-planners.

Results

Eleven per cent of the study sample tried for >1 year to conceive (15% of primiparas and 8% of multiparas). In Table I and Table II we report, for primiparas and multiparas respectively, the characteristics of treated and untreated women with a TTP of >1 year compared with planners conceiving within 1 year, part planners and non-planners.

Table III shows estimates for the association between a TTP of >1 year and the outcomes of interest. Among both primiparas and multiparas, infertile women had an increased risk of all adverse study outcomes, although the crude estimates were higher than the adjusted ones. Notably, the adjusted ORs of preterm birth were significantly elevated even after excluding couples reporting infertility treatment.

Among primiparas, infertility was associated with a very small decrease in the mean birthweight after adjustment for gestational age and a slight increase in the risk of weighing <2500 g at term. Both associations weakened when excluding women reporting treatment. Among multiparas, infertility was associated with a reduction in the mean birthweight of ~50 grams, and, when restricted to term babies, the OR for low birthweight was also significantly elevated. When treated

Table III. Estimated effect of time to pregnancy (TTP) of >12 months on pregnancy outcomes[a]: multiple regression models

	Crude estimates (95% CI)	Adjusted estimates (95% CI)	
Outcome	All women	All women	Untreated only[b]
Primiparas			
Birth before 37 weeks (OR)	1.46 (1.20, 1.76)	1.38 (1.14, 1.69)[c]	1.36 (1.08, 1.71)[c]
Birth before 34 weeks (OR)	1.64 (1.16, 2.33)	1.51 (1.05, 2.16)[c]	1.48 (0.97, 2.26)[c]
Birthweight deviation (g)	−68.9 (−94.6, −43.3)	−20.3 (−40.2, −0.4)[d]	−16.2 (−39.9, 7.6)[d]
Low birthweight at term (OR)[e]	1.82 (1.20, 2.74)	1.44 (0.94, 2.21)[f]	1.27 (0.76, 2.10)[f]
Planned Caesarean section (OR)	1.32 (1.07, 1.63)	1.14 (0.92, 1.41)[c]	1.05 (0.81, 1.36)[c]
Emergency Caesarean section (OR)	1.40 (1.22, 1.60)	1.15 (1.00, 1.32)[c]	1.15 (0.98, 1.36)[c]
Multiparas			
Birth before 37 weeks (OR)	1.93 (1.53, 2.43)	1.79 (1.41, 2.26)[c]	1.57 (1.20, 2.05)[c]
Birth before 34 weeks (OR)	1.70 (1.06, 2.71)	1.45 (0.90, 2.35)[c]	1.15 (0.66, 2.02)[c]
Birthweight deviation (g)	−110.0 (−135.3, −84.7)	−47.3 (−68.1, −26.5)[d]	−47.5 (−70.5, −24.4)[d]
Low birthweight at term (OR)[e]	2.59 (1.55, 4.33)	1.92 (1.13, 3.28)[f]	1.33 (0.71, 2.51)[f]
Planned Caesarean section (OR)	1.55 (1.30, 1.86)	1.30 (1.08, 1.56)[c]	1.21 (0.98, 1.48)[c]
Emergency Caesarean section (OR)	1.47 (1.23, 1.76)	1.23 (1.02, 1.47)[c]	1.01 (0.81, 1.25)[c]

[a]Reference category: pregnant right away.
[b]Analysis restricted to women who did not report treatment.
[c]Variables in the model: TTP/planning, mother's age, pre-pregnancy body mass index, smoking, social status, sex of the baby, age at menarche, cycle regularity and length, parity (if applicable).
[d]As in [c], but including gestational age (15 categories), excluding menarche and cycle regularity and length.
[e]Analysis restricted to term births (24 027 among primiparas, 29 447 among multiparas).
[f]Adjusted as in [d] (with six categories of gestational age).
OR = odds ratio; CI = confidence interval.

Table IV. Estimated effect of reported infertility treatment on pregnancy outcomes among women with time to pregnancy (TTP) >12 months[a]: multiple regression models

	Primiparas		Multiparas	
Outcome	n[b]	Estimate (95% CI)	n[b]	Estimate (95% CI)
Birth before 37 weeks (OR)[c]	1931	1.08 (0.84, 1.39)	653	1.70 (1.15, 2.51)
Birth before 34 weeks (OR)[c]	1931	1.10 (0.71, 1.70)	653	2.48 (1.12, 5.47)
Birthweight deviation (g)[d]	1931	−9.5 (−38.5, 19.5)	653	−1.9 (−43.9, 40.2)
Low birthweight at term (OR)[e]	1746	1.27 (0.76, 2.11)	593	2.48 (1.14, 5.38)
Planned Caesarean section (OR)[c]	1931	1.13 (0.85, 1.49)	653	1.29 (0.94, 1.79)
Emergency Caesarean section (OR)[c]	1931	0.99 (0.83, 1.19)	653	1.86 (1.37, 2.54)

[a]Analysis restricted to women with time to pregnancy (TTP) >12 months, reference category: women not reporting treatment.
[b]Number of women who reported treatment.
[c]Adjusted for mother's age, pre-pregnancy body mass index, smoking, social status, sex of the baby, age at menarche, cycle regularity and length, parity (if applicable).
[d]As in [c], but including gestational age (15 categories), excluding menarche and cycle regularity and length.
[e]Analysis restricted to term births, adjusted as in [d] (with six categories of gestational age).
OR = odds ratio; CI = confidence interval.

multiparas were excluded, the decrease in mean birthweight did not change, but the risk of low birthweight at term was no longer as high. The risk of having an emergency Caesarean section was slightly higher among infertile women compared with women who conceived right away. When treated women were excluded, the elevated risk persisted in primiparas but not in multiparas. Infertile primiparas also had a slightly higher risk of planned Caesarean section, but the elevated risk did not persist after excluding couples treated for infertility.

Table IV shows the relationship between treatment and the same outcomes shown in Table III among women with a TTP >1 year. Among primiparas there were no substantial differences between treated and untreated. However, among multiparas, the risks were consistently elevated for the treated women with the exception of mean birthweight, which was very similar for treated and untreated women.

We further explored our strongest finding, the association between infertility and preterm birth, by examining the relationship in various subsets of the study population, after combining data for primiparas and multiparas. When we excluded women aged >30 years, those who might have age-related infertility, the results were similar to those prior to the exclusion. The association remained also when the sample was restricted to women with a BMI of 20–24.99 and to non-smokers. Finally, gestational age may be inaccurate for women with particularly short, long or irregular menstrual cycles, but when we restricted the analysis to women with regular menstrual cycles of 27–31 days, we again saw little change.

When we used a reference category of the combination of couples who conceived right away, the part planners, those who conceived despite birth control, and the non-planners the results were virtually the same (data not shown).

Finally, we reintroduced into the analyses women who had been excluded because of missing data in pre-pregnancy BMI, smoking, or the estimate of the expected date of delivery, or because of discrepancies in the two values of gestational age (*n* = 4278). Missing values for BMI and smoking were coded in separate categories in the models. Compared with the adjusted estimates among all women in Table III, the differences concerned only the estimates of a delivery before 34 completed weeks, as primiparas had a weaker estimate (OR: 1.36; 95% confidence interval: 0.96, 1.91), and multiparas a stronger one (1.68; 1.09, 2.59).

Discussion

Based on data from singleton live births in the Danish Birth Cohort, we found that infertile women were at increased risk for preterm delivery, low birthweight babies (adjusted for gestational age) and Caesarean section. The OR ranged from 1.3 to 2.6. Risk estimates remained elevated even after adjusting for several factors that might potentially affect both infertility and birth outcome, and most elevated risks were seen even among the untreated infertile group. Infertility treatment was associated with significant additional risk (above that for the untreated infertile group) only among multiparas.

Adverse birth outcomes have previously been described for singleton babies born after IVF (MRC Working Party, 1990; Tan *et al*., 1992; Olivennes *et al*., 1993; Wang *et al*., 1994, 2002; Dhont *et al*., 1999; Koudstaal *et al*., 2000). Less is known about the general population of infertile couples, though increased adverse birth outcomes have been reported (Bhalla *et al*., 1992; Olivennes *et al*., 1993; Joffe *et al*., 1994; Sundstrom *et al*., 1997; Henriksen *et al*., 1997).

Our data show that infertile couples are at significantly elevated risk of adverse birth outcomes, and the risks cannot be attributed solely to the effects of infertility treatment. A long waiting time to pregnancy is a proxy for conditions in both the male and female, and a number of these conditions may share one or more causal paths with the adverse birth outcomes. When we adjusted for factors such as age and smoking, the associations between infertility and birth outcomes decreased in magnitude, indicating that these factors may explain some of the association. However, significant associations still remained, probably due to further overlapping aetiological paths for which we could not adjust. For example, *Chlamydia* infection is known to cause infertility (Toye *et al*., 1993; Land and Evers, 2002) and is also associated with preterm delivery (Johns Hopkins Study, 1989; Kovacs *et al*., 1998; Andrews *et al*., 2000). Other possible common causes of infertility and preterm birth are prenatal diethylstilbestrol exposure (Senekjian *et al*., 1988), solvent exposure (Lindbohm 1995; Sallmen *et al*., 1995) and psychological stress (Copper *et al*., 1996).

We conducted a series of exclusion analyses to try to identify possible mediators in the TTP–preterm birth relationship. A long waiting time was associated with pre-eclampsia in a previous study conducted on women enrolled in the Danish National Birth Cohort (Basso et al., 2003), but the association with preterm delivery reported in the present study is not a consequence of pre-eclampsia; the association was essentially unchanged when we excluded pre-eclamptic pregnancies. If abnormal hormonal factors were the mediator, the association might be weaker if women with irregular menstrual cycles were excluded, but the effect was essentially unchanged. Nor did excluding women with a high BMI change the association. There was also no evidence that age-related changes in ovarian and uterine function were important mediators, because when older women were excluded, the magnitude of the association actually increased somewhat, though not significantly.

We had anticipated that couples undergoing infertility treatment would show higher risks than untreated infertile couples because treated couples may have more severe infertility than those who conceive without treatment, and the treatment procedures may have adverse effects. For example, ovulation induction results in increased endometrial thickness, and this might be detrimental to implantation and placentation (Weissman *et al*., 1999). Our observation that treated and untreated primiparas have similar risks provides some reassurance that treatments *per se* may not be a major factor in adverse birth outcomes. However, the underlying causes of infertility are likely to differ between treated and untreated individuals. Without taking these differences into account, the effect of treatment cannot be definitively evaluated.

Our study is limited in other ways beyond our inability to ascertain causes of infertility. The data on infertility, treatment and most of the covariates were obtained by self-report. Since TTP was categorized in the questionnaire, all couples who took >1 year to conceive were in one group, so we were unable to control for duration of infertility. Finally, the relatively low participation rate in the cohort could be a source of bias. Unplanned pregnancies may be under-represented. This could create a spurious association if fertile women with a higher risk of adverse birth outcome were systematically under-represented. An examination of selection in the cohort within one geographical area (Northern Jutland: Nøhr, 2001) revealed somewhat higher rates of deliveries before 32 weeks in the general population compared with the cohort (1.0 versus 0.6%), but similar overall preterm birth rates (5.0 versus 4.4%). Thus, at least our findings regarding preterm birth are unlikely to be explained by selection bias. We also evaluated bias from unplanned pregnancies (Weinberg at al., 1994; Olsen *et al*., 1998) within our study by including partly planned and unplanned pregnancies within the reference group with which the infertile group were compared, and by adding back the women who had been excluded because of missing data or differences in the two sources of gestational age. In both analyses the findings were essentially unchanged.

The study had numerous strengths. Our sample was large, which allowed us to evaluate effects for primiparas and multiparas separately. Data on waiting time to pregnancy and planning status were collected before the outcome, so knowledge of the outcome did not influence reporting. Infertility treatment is free of charge in Denmark, at least for a limited number of attempts, so treatment is not limited to high-income couples. We had data on several potential risk factors, and results were adjusted for these. Our data on gestational age were reliable, and this increased the accuracy of our determin-

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ation of preterm births and allowed us to adjust appropriately for gestational age when looking for effects on birthweight.

Adverse birth outcomes are important causes of infant and maternal morbidity. With >10% of babies born to infertile couples, it is important to consider this group as potentially high risk when providing prenatal care. In addition, research aimed at understanding the biological basis of the association between infertility and adverse birth outcomes is needed. Such research may suggest new approaches for preventing adverse events.

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