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Epidemiology

Risk of stillbirth in low-risk singleton term pregnancies following fertility treatment: a national cohort study

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Objective To assess the risk of stillbirth in low-risk in vitro fertilisation (IVF) pregnancies.

Design Register-based national cohort study.

Setting Denmark 2003–2013.

Population Cohort of 425 732 singleton pregnancies including 10 235 conceived following IVF/intracytoplasmic sperm injection (ICSI), 4521 conceived following intrauterine insemination (IUI), and 410 976 spontaneously conceived.

Methods Information on pregnancy, obstetrical risk factors, stillbirth, and fertility treatment was obtained from the Danish national health registers for all pregnancies after gestational week 21^{+6}. We estimated the overall and gestational age-specific risk of stillbirth in low-risk term pregnancies following IVF, ICSI, and IUI. Further, we estimated the association between stillbirth and IVF and ICSI respectively as well as fresh or frozen-thawed embryo transfer.

Main outcome measures Risk of stillbirth.

Results The number of stillbirths in spontaneously conceived and IVF/ICSI low-risk term pregnancies was 525 (0.1%) and 35 (0.3%), respectively. In multivariate analysis, the risk of stillbirth in pregnancies following IVF/ICSI was increased (odds ratio 2.1, 95% CI 1.4–3.1). The risk of stillbirth was correspondingly increased in time-to-event analyses taking risk time for each fetus into account from gestational week 37 and onwards (hazard ratio 2.4, 95% CI 1.6–3.6). In sub-analyses, the risk of stillbirth was increased for pregnancies following ICSI (odds ratio 2.2, 95% CI 1.2–3.1), but not IVF (odds ratio 1.7, 95% CI 0.9–3.1).

Conclusion We found a systematically increased risk of stillbirth in low-risk term pregnancies following IVF/ICSI. Whether the risk was related to the treatment or to underlying subfertility is uncertain. The results may indicate a need for obstetrical surveillance for these pregnancies when reaching term.

Keywords Fertility treatment, in vitro fertilisation, intracytoplasmic sperm injection, stillbirth.

Tweetable abstract Increased risk of stillbirth in low-risk term pregnancies following fresh cycle IVF/ICSI.

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Introduction

Fertility treatment offers unique possibilities for otherwise infertile couples to become parents. While the procedures are generally considered safe for the woman, there is substantial evidence of a higher risk of pregnancy complications. Compared with spontaneous conception, in vitro fertilisation (IVF) has been associated with increased risk of pre-eclampsia, intrauterine growth restriction, preterm birth, and low birthweight.[1–3] A few studies have suggested an overall higher risk of stillbirth compared with spontaneously conceived pregnancies,[4–6] but recently a multinational cohort study showed a comparable risk of stillbirth after gestational week 28^{+0}.[7]

Due to the risk of pregnancy complications, doctors may be prone to induce labour in pregnancies following IVF at an

earlier gestation than in spontaneously conceived pregnancies. Moreover, the presence of obstetrical risk factors triggering induction of labour is more frequent in pregnancies following IVF (i.e. maternal age above 40 years). Correspondingly, IVF has been associated with increased risk of induction of labour.[2,8] When evaluating the risk of stillbirth at a given gestational age associated with IVF, failure to account for induction of labour, or the reason hereof, may lead to underestimation of the true association, as it may give rise to comparison of pregnancies following spontaneous conception with the remaining on-going uncomplicated IVF pregnancies. Thus, for the uncomplicated majority of IVF pregnancies, the risk of stillbirth at term is still controversial.

With this large nationwide cohort study, we aimed to investigate the risk of stillbirth in low-risk IVF pregnancies at term taking obstetrical risk factors and induction of labour into account. These results are important for the future obstetrical management of uncomplicated IVF pregnancies in terms of whether to induce labour or not.[9]

Methods

Design and population

We designed a historical cohort study including all births in Denmark from 1 January 2003 to 31 December 2013. We established the cohort based on data from the Danish Medical Birth Register[10] and the Danish IVF register.[11] By using the mother's Danish personal identification number (CPR number) we were able to ensure accurate individual-level linkage between national health registers on all pregnancies in Denmark after gestational week 21^{+6}. The study was conducted without patient involvement.

Information on fertility treatment

Exposure information on fertility treatment was obtained from the Danish IVF register.[11] In Denmark, it is mandatory by law for clinicians in private and public clinics to report each initiated treatment cycle independently of pregnancy outcome to the register. Since the start of the register in 1994, information has been collected on specific type of treatment, i.e. IVF, intracytoplasmic sperm injection (ICSI), fresh or frozen cycle, and gamete donation. From 2006, information on intrauterine insemination (IUI) was included in the register. Further, the register collects information on the CPR number of the woman along with the outcome of the treatment cycle and the CPR numbers of any liveborn children resulting from the treatment. For this study, fertility treatment was divided into three groups: pregnancies following IVF with or without intracytoplasmic sperm injection (ICSI), pregnancies after IUI (from 2006), and pregnancies following spontaneous conception (i.e. all births after gestational week 21^{+6} not registered in the IVF register).

Information on pregnancy and stillbirth

Information on pregnancy, obstetrical risk factors, and stillbirth was obtained from the Danish medical birth register.[10] In this register, all information on pregnancy, delivery, and newborns is registered by the attending physicians and midwives to be used for the electronical report to the Danish health authorities. The healthcare system in Denmark ensures that all healthcare cost are free of charge, so besides possibilities for nationwide register-based research, the registration of healthcare activities are used for reimbursement of the hospital by the Danish government, ensuring complete coverage. Using the CPR numbers, we cross-linked information as registered in the medical birth register with information in the IVF register to ensure accurate individual-level exposure and outcome information.

Statistical analyses

We aimed to investigate the risk of stillbirth in low-risk term pregnancies following IVF in order to contribute evidence on the obstetrical handling of such pregnancies. Hence, we excluded all preterm births, multiple pregnancies, all pregnancies of women 40 years or older, women with a body mass index (BMI) of 35 or more, induced labour (except if the indication was stillbirth), and women having pregnancy complications known to trigger induction of labour or acute caesarean section, such as pre-existing or gestational hypertension, pre-eclampsia, eclampsia, HELLP (haemolysis, elevated liver enzymes, and low platelet count), pre-existing or gestational diabetes, intrahepatic cholestasis of pregnancy, and immunisation.

First, using multiple logistic regressions we compared the estimated overall risk of stillbirth in low-risk term pregnancies following IVF/ICSI or IUI, respectively, with that of spontaneously conceived pregnancies. Secondly, we estimated the risk of stillbirth from a given gestational age (i.e. the risk from week 37^{+0}, the risk from week 38^{+0}, the risk from weeks 39^{+0}, etc.) while accounting for the time at risk for each fetus. Each pregnancy contributed with time at risk of stillbirth beginning at the day of fulfilling the Danish liveborn criteria at gestational age 22^{+0} weeks and ending on the first coming date of a registered stillbirth, live birth or end of follow up on 31 December 2014 (1 year after the end of the study period). We estimated the risk of stillbirth associated with conception mode using standard Cox regression analyses; to account for correlations between siblings, all analyses were performed using robust standard errors. Further, we estimated the association between stillbirth and subtypes of procedures (IVF and ICSI, respectively) as well as type of embryo transfer (fresh or frozen-thawed embryo transfer).

In all analyses, we adjusted for *a priori* determined potentially confounding variables including maternal age

(continuous), parity (nulliparous/parous), smoking in pregnancy (yes, no), and child sex (male/female). To assess the extent to which unmeasured confounding may have affected the associations, we calculated the *E*-value.[12] The proportional hazards assumption was evaluated by graphical assessment of log-log plots, and the assumption was met. In reporting the results we refer to the risks as odds ratio (OR) or hazard ratios (HR) with 95% confidence intervals (CI). *P*-values <0.05 were considered statistically significant. All statistical analyses were based on an *a priori* specified analysis plan and were performed using complete case analyses with STATA/SE 12.[13]

Results

A total of 662 739 singletons were born in Denmark by 432 938 mothers during the study period from 1 January 2003 to 31 December 2013. We excluded all preterm births (n = 33 259) and all pregnancies of women 40 years or older (n = 19 942), with a BMI of 35 or more (n = 23 482), or women having pre-existing or gestational hypertension, pre-eclampsia, eclampsia, or HELLP (n = 30 072), pre-existing or gestational diabetes (n = 18 908), intrahepatic cholestasis of pregnancy (n = 5388) or immunisation (n = 2745). Except for immunisation, all these obstetrical risk factors were more prevalent in pregnancies following IUI and IVF/ICSI compared with those spontaneously conceived (Supporting Information Table S1). Baseline characteristics for the remaining 548 908 singleton pregnancies are shown in Table 1 according to conception methods. To explore the risk of stillbirth in pregnancies with expectant spontaneous delivery, we excluded all induced deliveries unless the induction of labour was performed due to antenatal diagnosed stillbirth. Hence, for the analyses of an association between mode of conception and stillbirth, the study population comprised 425 732 pregnancies. Of these, a total of 10 235 (2.4%) were conceived following IVF/ICSI, 4521 (1.1%) were conceived following IUI, and the remaining 410 976 (96.5%) were conceived spontaneously.

In the study period, a total of 2180 stillbirths (0.3%) occurred. When only considering the included low-risk term pregnancies, the crude number of stillbirths was reduced to 572 (0.1%), of whom 525 (0.1%) were born following spontaneous conception, 35 (0.3%) were born following IVF/ICSI, and 12 (0.3%) were born following IUI. The median gestational age at stillbirth was 277 days (25th/75th percentile 269/284 days, respectively) with no statistical difference between the conception groups.

Risk of stillbirth associated with conception mode

The overall risk of stillbirth is presented in Table 2. Compared with spontaneously conceived low-risk term pregnancies, the risk of stillbirth in pregnancies conceived following IVF/ICSI was increased (OR 2.1, 95% CI 1.4–3.1). The risk of stillbirth in pregnancies following IUI was comparably increased, although just short of statistical significance (OR 1.8, 95% CI 1.0–3.5).

Using gestational age-specific Cox regression, we analysed the risk of stillbirth from a given gestational age and onwards (Table 2). Compared with spontaneously conceived pregnancies, IVF/ICSI was associated with an increased hazard of stillbirth from gestational week 37^{+0} (HR 2.4, 95% CI 1.6–3.6), from gestational week 38^{+0} (HR

Table 1. Baseline characteristics among women with uncomplicated* pregnancies following in vitro fertilisation/Intracytoplasmic sperm injection (IVF/ICSI), intrauterine insemination (IUI), and spontaneous conception (SC), Denmark 2003–2013

Characteristics	SC *n* = 527 881	IVF/ICSI *n* = 14 630	IUI *n* = 6397	*P*
Child sex, male, n (%)	269 635 (51.1)	7307 (50.0)	3241 (50.7)	0.01
Maternal age at birth in years, mean (± SD)	30.3 (4.5)	33.1 (3.7)	32.6 (4.0)	<0.001
Paternal age at birth in years, mean (± SD)	32.9 (5.4)	35.9 (5.4)	34.9 (5.3)	<0.001
Parity, nulliparous, *n* (%)	225 354 (43.3)	9637 (66.8)	4144 (65.6)	<0.001
Maternal smoking in pregnancy, *n* (%)	75 699 (14.7)	1033 (7.2)	349 (5.5)	<0.001
Maternal BMI, kg/m^2, median (25th/75th percentile)	22.8 (20.8/25.6)	22.8 (20.8/25.4)	23.0 (20.9/25.8)	<0.001
Caesarean section				
Emergency, *n* (%)	50 517 (9.6)	1962 (13.4)	867 (13.6)	<0.001
Planned, *n* (%)	40 894 (7.8)	1554 (10.6)	633 (9.9)	<0.001
Previous, *n* (%)	51 597 (9.8)	1077 (7.4)	512 (8.0)	<0.001
Induction of labour, *n* (%)	75 919 (14.4)	2860 (19.6)	1252 (19.6)	<0.001

BMI, body mass index.
*Defined as singleton pregnancies without hypertension, pre-eclampsia, eclampsia, HELLP, immunisation, intrahepatic cholestasis of pregnancy, diabetes, gestational diabetes or preterm labour (<37^{+0}) in women <40 years old with a BMI ≥35.

Table 2. Odds ratio (OR) or Hazard ratio (HR) and 95% confidence intervals (CI) of stillbirth in uncomplicated term pregnancies following in vitro fertilisation/Intracytoplasmic sperm injection (IVF/ICSI), intrauterine insemination (IUI), and spontaneous conception (SC) with non-induced intended vaginal labour, Denmark 2003–2013

	SC *n* = 410 976	IVF/ICSI *n* = 10 235		IUI *n* = 4521	
	Reference group, *n* (%)	*n* (%)	OR (95% CI)	*n* (%)	OR (95% CI)
Overall risk of stillbirth from gestational week 37^{+0}, logistic regression	525 (0.1)	35 (0.3)	2.1 (1.4–3.1)	12 (0.3)	1.8 (1.0–3.5)
	Reference group, *n* (%)	***n* (%)**	**HR (95% CI)**	***n* (%)**	**HR (95% CI)**
Gestational age-specific hazard ratio of stillbirth (time to event)					
Gestational week[a] $\geq 37^{+0}$	525 (0.1)	35 (0.3)	2.4 (1.6–3.6)	12 (0.3)	1.9 (1.0–3.6)
Gestational week[b] $\geq 38^{+0}$	453 (0.1)	31 (0.3)	2.3 (1.5–3.6)	10 (0.2)	1.7 (0.8–3.5)
Gestational week[c] $\geq 39^{+0}$	351 (0.1)	24 (0.3)	2.5 (1.5–4.1)	7 (0.2)	1.3 (0.5–3.4)
Gestational week[d] $\geq 40^{+0}$	234 (0.1)	19 (0.3)	3.0 (1.7–5.2)	7 (0.3)	2.0 (0.7–5.4)
Gestational week[e] $\geq 41^{+0}$	124 (0.1)	10 (0.4)	2.4 (0.9–5.9)	5 (0.4)	3.7 (1.2–11.6)
Gestational week[f] $\geq 42^{+0}$	18 (0.2)	2 (1.0)	6.8 (1.3–36.6)	0 (0.0)	n/a

Adjusted for child sex, maternal age, parity, smoking during pregnancy, and year of birth.
[a]SC (410 976), IVF/ICSI (10 235), and IUI (4521).
[b]SC (394 504), IVF/ICSI (9745), and IUI (4330).
[c]SC (352 360), IVF/ICSI (8609), and IUI (3870).
[d]SC 253 585), IVF/ICSI (6022), and IUI (2792).
[e]SC (108 322), IVF/ICSI (2443), and IUI (1145).
[f]SC (10 993), IVF/ICSI (192), and IUI (40).

2.3, 95% CI 1.5–3.6), from gestational week 39^{+0} (HR 2.5, 95% CI 1.5–4.1), from gestational week 40^{+0} (HR 3.0, 95% CI 1.7–5.2), from gestational week 41^{+0} (HR 2.4, 95% CI 0.9–5.9), and from gestational week 42^{+0} (HR 6.8, 95% CI 1.3–37). For pregnancies following IUI, the hazard ratios were also increased, although slightly less so, and without reaching statistical significance except for pregnancies beyond gestational week 41^{+0} (HR 3.7, 95% CI 1.8–11.6).

From the hazard ratio of stillbirth from gestational week 37^{+0} (HR 2.4, 95% CI 1.6–3.6), an *E*-value of 4.2 was obtained, indicating that the observed risk ratio of 2.4 could potentially be explained by an unmeasured confounder that was associated with both the treatment and the outcome by a risk ratio of 4.2; however, weaker confounding could not do so.

Hazards associated with IVF, ICSI, and with fresh or frozen-thawed embryo transfer

Based on the information in the IVF register, the group of IVF/ICSI consisted of 4858 pregnancies conceived following standard IVF, and 4661 pregnancies conceived after IVF with ICSI. The remaining 716 pregnancies were conceived following IVF/ICSI without specification (frozen embryo transfer or egg donation with no information on the preceding IVF or ICSI). Compared with spontaneously conceived pregnancies, the hazard risk of stillbirth was increased for pregnancies following ICSI, but not for pregnancies following IVF. The overall odds ratio of stillbirth was 2.2 (95% CI 1.2–3.1) and 1.7 (95% CI 0.9–3.1) for pregnancies following ICSI and IVF, respectively. Similarly, the gestational age-specific risk was increased for pregnancies following ICSI, but not for after IVF (Table 3).

Among the 10 235 pregnancies conceived following IVF/ICSI, a total of 874 treatments were performed as frozen-thawed embryos, 6027 were categorised as fresh IVF/ICSI treatment, and for the remaining 3334 IVF/ICSI pregnancies, no information on fresh or frozen-thawed treatment was available and thus these were excluded from this analysis. Compared with spontaneously conceived pregnancies, the hazard risk of stillbirth was increased for pregnancies following fresh IVF/ICSI treatment (OR 2.1, 95% CI 1.2–3.5), but not for pregnancies following frozen-thawed embryo transfer (OR 1.0, 95% CI 0.2–6.2). The number of stillbirths was too low to explore the gestational age-specific risk of stillbirth (Table 3).

Table 3. Hazard ratio (HR) and 95% confidence intervals (CI) of stillbirth in uncomplicated term pregnancies and non-induced intended vaginal labour following in vitro fertilisation (IVF), intracytoplasmic sperm injection (ICSI) including fresh or frozen-thawed cycles, and spontaneous conception (SC) non-induced intended vaginal labour, Denmark 2003–2013

	SC *n* = 410 976	IVF *n* = 4858		ICSI *n* = 4661	
	Reference group, *n* (%)	***n* (%)**	**OR (95% CI)**	***n* (%)**	**OR (95% CI)**
Overall risk of stillbirth (logistic regression)	525 (0.1)	15 (0.3)	1.7 (0.9–3.1)	16 (0.3)	2.2 (1.2–3.8)
	Reference group, *n* (%)	***n* (%)**	**HR (95% CI)**	***n* (%)**	**HR (95% CI)**
Gestational age-specific risk of stillbirth (time to event)					
Gestational week[a] $\geq 37^{+0}$	525 (0.1)	15 (0.3)	1.9 (0.9–3.6)	16 (0.3)	2.4 (1.4–4.4)
Gestational week[b] $\geq 38^{+0}$	453 (0.1)	12 (0.3)	1.5 (0.7–3.3)	15 (0.3)	2.6 (1.4–4.7)
Gestational week[c] $\geq 39^{+0}$	351 (0.1)	8 (0.2)	1.2 (0.4–3.1)	12 (0.3)	3.1 (1.6–5.9)
Gestational week[d,e] $\geq 40^{+0}$	234 (0.1)	6 (0.2)	1.3 (0.4–4.2)	10 (0.4)	3.9 (1.9–7.9)
	SC *n* = 410 976	Fresh cycles IVF/ICSI *n* = 6027		Frozen-thawed cycles IVF/ICSI *n* = 874	
	Reference group, *n* (%)	***n* (%)**	**OR (95% CI)**	***n* (%)**	**OR (95% CI)**
Overall risk of stillbirth (logistic regression)	525 (0.1)	22 (0.4)	2.1 (1.2–3.5)	1 (0.1)	1.0 (0.2–6.2)

Adjusted for child sex, maternal age, parity, smoking during pregnancy, and year of birth.
[a]SC (410 976), IVF (4858), and ICSI (4661).
[b]SC (394 504), IVF (4584), and ICSI (4471).
[c]SC (352 360), IVF (4053), and ICSI (3940).
[d]SC (253 585), IVF (2824), and ICSI (2774).
[e]Numbers to few to evaluate the risk after gestational week 41^{+0}.

Discussion

Main findings

In this large cohort study of low-risk term pregnancies conceived after IVF, ICSI, and IUI, we found an increased risk of stillbirth in pregnancies following IVF/ICSI compared with spontaneously conceived pregnancies. When considering the specific type of treatment, the increased risk of stillbirth was related to ICSI, but not IVF, and increased in pregnancies following fresh-embryo cycles, but not frozen-embryo transfer cycles.

The increased risk of stillbirth following after ART could potentially be secondary to ovarian stimulation, the invasive procedure of ICSI where a single sperm is introduced into the oocyte by micro-insemination or because men with low sperm quality are more likely to have chromosomal abnormalities that they may pass on to the offspring.[14]

Strengths and limitations

The main strength of the present study includes a large sample size of an unselected cohort of all pregnancies that during the study period lead to the birth of a singleton after gestational week 21^{+6}. Using the unique Danish CPR number, we were able to crosslink the information in different Danish national health registers and to control for a wide range of potential confounding factors in the multivariable analyses. Additionally, this comprehensive information made it possible to perform subgroup analyses on the risk following fresh- and frozen-embryo transfer cycles. However, residual confounding cannot be excluded. However, based on the calculated *E*-value of 4.2, it is unlikely that residual confounding could explain the findings of this study.

We aimed to assess the risk of stillbirth in low-risk pregnancies following IVF/ICSI. Therefore, the results cannot be generalised to all pregnancies following IVF/ICSI. If any prespecified obstetrical risk factors or pregnancy complication was present, the pregnancy was excluded from the present study. As the proportions of obstetrical risk factors were more prevalent among pregnancies following IUI and IVF/ICSI, the exclusion of at-risk pregnancies may have affected the results of this study, most likely with an

attenuation of a higher risk of stillbirth among pregnancies following IVF/ICSI.

The analyses were conditional on gestational age, as we only included term pregnancies. Preterm delivery is associated with the risk of stillbirth and occurs more frequently following IVF/ICSI.[1,15] Hence, gestational age may be considered on the causal pathway between IVF/ICSI and stillbirth, which could have led to bias in this study, most likely towards null.[16]

Most studies investigating the risk of stillbirth following ART were relatively small and often had stillbirth as a secondary outcome. Fortunately, stillbirth is a very rare event, which may cause insufficient statistical power when studying this outcome. Assuming a background risk of stillbirth of 0.1%, the sample sizes in the exposed and reference group should be at least 2500 to test the hypothesis of a doubling of the risk with a power of 80% and a significance level of 0.05. Hence, most studies reporting stillbirth as an outcome following IVF have been underpowered.[17–19] Additionally, besides multiplicity, previous studies have only lightly accounted for the increased prevalence of obstetrical risk factors among women undergoing ART, and no study has taken into account the management of these pregnancies with a considerable increased incidence of induced labour. Independent of risk factors, induction of labour in IVF pregnancies at no later than 41 weeks of gestation has been standard in Denmark until recently. Further, obstetrical risks such as maternal age above 40 years, pre-existing medical conditions, and pre-eclampsia often leading to induction of labour are more frequent in pregnancies following IVF. Therefore, any risk of bias could be reduced if obstetrical risk factors and induction of labour were taken into account, as in the case of the present study.

Interpretation

In line with our results, Wisborg et al. drew comparable conclusions while evaluating the overall risk of stillbirth from gestational age 22 weeks among Danish singleton pregnancies in fertile and sub-fertile parents and parents conceiving following IVF/ICSI and non-ART treatments. Compared with pregnancies achieved spontaneously within 12 months, pregnancies following IVF/ICSI had a higher risk of stillbirth (OR 4.08, 95% CI 2.11–7.93), while pregnancies following non-ART had a comparable risk of stillbirth (OR 0.53, 95% CI 0.13–2.18).[4] Similarly, a large Australian study found an increased risk of stillbirth following any assisted conception treatment (OR 1.82, 95% CI 1.34–2.48), IVF with fresh-embryo cycles (OR 2.35, 95% CI 1.34–4.11), and ICSI with fresh-embryo cycles (OR 2.46, 95% CI 1.29–4.68), but not following less invasive fertility treatment (ovulation induction OR 0.52, 95% CI 0.07–4.18).[5] Further supporting the results of present study, those authors showed that the risk of stillbirth was more pronounced following fresh-embryo cycles than following frozen-embryo cycles. Moreover, results from a Belgian matched case-control study on 6096 singleton pregnancies demonstrated that IVF/ICSI was associated with a higher risk of stillbirth compared with spontaneously conceived pregnancies (OR 2.51, 95% CI 1.24–5.20).[6] However, none of the above-mentioned studies conducted analyses stratified by gestational age.

In contrast, the largest study to date on the risk of stillbirth showed a comparable risk beyond gestational week 28 when comparing pregnancies following ART with spontaneously conceived pregnancies. In that well-conducted multinational Nordic cohort study, Henningsen et al.[7] compared the risk of stillbirth between 62 485 singleton pregnancies following ART with that of 362 798 spontaneously conceived controls. Although the definition of stillbirth varied among the participating countries, they were able to appropriately evaluate the gestational age-specific risk of stillbirth using 'fetuses-at-risk' estimates. Unlike the present study, they did not find an increased risk of stillbirth among ART singletons in the third trimester. This discrepancy may partly be explained by differences in methodological approach. As opposed to our study, the Nordic collaborative study did not account for difference in maternal smoking or BMI. As potentially modifiable risk factors, maternal obesity and smoking in pregnancy has, together with fetal growth restriction, been estimated to account for more than half of all stillbirths.[20] Hence, this may have caused a considerable underestimation in the Nordic study. Additionally, the study did not account for variations in obstetrical management. Compared with spontaneously conceived pregnancies, labour following ART pregnancies is more frequently induced,[2,8] which again may be explained by increased prevalence of obstetrical risk factors or complications, or as a consequence of anxiety or maternal request. However, if unaccounted for, it may introduce survivorship bias and underestimation of the true risk of stillbirth, as it may lead to comparison of pregnancies following spontaneous conception with the remaining ongoing uncomplicated IVF pregnancies.

Whereas the study by Henningsen et al. aimed to evaluate the risk in different categories of gestational age, the aim of this study was to estimate the risk from a given gestational age until birth using time-to-event analyses, which may mimic the everyday clinical setting in a slightly more appropriate was. When advising parents to reach a specific gestational age, the cumulative hazard of stillbirth may be easier to communicate, as the exact time of birth is hard to predict regardless of whether the physician chooses to advise on induction or to await spontaneous onset of labour.

Similar to the Nordic collaborative study, a few other studies have concluded that the risk of stillbirth among

ART pregnancies is comparable to that of spontaneously conceived pregnancies. A Norwegian study including 998 pregnancies reported no significant difference in the number of stillbirths with an incidence of 19.7‰ in a study group of pregnancies following various procedures of assisted reproduction and 12.4‰ in the control group matched for age and parity.[17] Similarly, a Chinese study found no significant association between IVF and stillbirth among 870 IVF pregnancies and 3433 spontaneously conceived pregnancies matched for maternal age and parity (OR 1.96, 95% CI 0.84–4.57).[18] Nevertheless, the risk estimates in these studies were quite similar to those in the present study. As these studies were rather small with <1000 exposed pregnancies, there is a considerable risk of a type II statistical error with failure to reach statistical significance due to low number of participants.

Although the majority of the existing literature reports an increased incidence of stillbirth following ART, it remains uncertain whether the increased risk is related to a causal association with the IVF procedures or with factors related to the underlying sub-fertility. In a Norwegian study, Romundstad et al.[21] found an increased risk of perinatal mortality following assisted conceptions, but this association diminished when analyses were repeated in sibling-pair analyses among siblings born to women who had conceived both spontaneously and after assisted fertilisation. Hence, the differences could not be attributed to the reproductive technology but most likely to factors related to the underlying subfertility. Additionally, the authors noted that women who had had a perinatal death in a spontaneously conceived pregnancy were three times more likely to seek fertility treatment afterwards than those who had not.

Only a few other studies have investigated the risk of stillbirth following fresh- and frozen-embryo transfer cycles. Similar to our results, these studies found any risk of stillbirth related to IVF to be lower and comparable to that of spontaneously conceived pregnancies among the subgroup conceiving after frozen-embryo cycles.[5,22] This is in line with several other studies finding a significantly lower risk of other perinatal complications following frozen-embryo cycles than following fresh-embryo cycles.[1] Nevertheless, the results of the subgroup analyses in this study showing a reduced risk of stillbirth following frozen-embryo transfers must be interpreted with caution, given the lower numbers of participants.

Conclusion

In this large national register-based cohort study we found an increased risk of stillbirth following IVF/ICSI. Although the study was designed to assess the risk of stillbirth in low-risk IVF pregnancies at term, the results must be interpreted with caution for the whole population of IVF pregnancies. Whether the risk is related to the treatment itself or to the underlying sub-fertility of women seeking IVF treatment is uncertain. Nevertheless, the results may indicate a need for closer obstetrical surveillance of these pregnancies when reaching term.

Disclosure of interests

UK has received payment for teaching of nurses in legal issues and statistics (MSD and Ferring Pharmaceuticals). The other authors declare no competing interests. Completed disclosure of interest forms are available to view online as supporting information.

Contribution to authorship

BB, SB, and USK contributed substantially to the conception and design of the study and acquisition of data. BB and SB contributed to the analyses of data. BB, SB, and USK contributed to interpretation of data, reviewed the first and subsequent drafts of the article, revised it critically for intellectual content, and approved the final version before submission.

Details of ethics approval

The study was approved by the Danish Data Protection Agency 6 October 2015 (File number 1-16-02-298-15). Register-based studies do not require approval from ethical committees or institutional review boards in Denmark.

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None.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Numbers and proportions [*n* (%)] of excluded pregnancies following in vitro fertilisation/intracytoplasmic sperm injection (IVF/ICSI), intrauterine insemination (IUI), and spontaneous conception (SC), Denmark 2003–2013. ■

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