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a Danish national retrospective cohort study**

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*Published in:*  
American Journal of Obstetrics & Gynecology

*DOI:*  
10.1016/j.ajog.2022.10.028

*Publication date:*  
2023

*Document version:*  
Final published version

*Document license:*  
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*Citation for pulished version (APA):*  
Kristensen, S. E., Ekelund, C. K., Sandager, P., Jørgensen, F. S., Hoseth, E., Sperling, L., Balaganeshan, S. B., Hjortshøj, T. D., Gadsbøll, K., Wright, A., Wright, D., McLennan, A., Sundberg, K., & Petersen, O. B. (2023). Risks and pregnancy outcome after fetal reduction in dichorionic twin pregnancies: a Danish national retrospective cohort study. *American Journal of Obstetrics & Gynecology*, 228(5), 590.e1-590.e12. <https://doi.org/10.1016/j.ajog.2022.10.028>

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## OBSTETRICS

# Risks and pregnancy outcome after fetal reduction in dichorionic twin pregnancies: a Danish national retrospective cohort study



Steffen Ernesto Kristensen, MD; Charlotte Kvist Ekelund, PhD; Puk Sandager, PhD; Finn Stener Jørgensen, DMSc; Eva Hoseth, MD; Lene Sperling, PhD; Sedrah Butt Balaganeshan, MD; Tina Duelund Hjortshøj, PhD; Kasper Gadsbøll, MD; Alan Wright, PhD; David Wright, PhD; Andrew McLennan, MD; Karin Sundberg, DMSc; Olav Bjørn Petersen, PhD

**BACKGROUND:** Twin pregnancies carry a higher risk of congenital and structural malformations, and pregnancy complications including miscarriage, stillbirth, and intrauterine fetal death, compared with singleton pregnancies. Carrying a fetus with severe malformations or abnormal karyotype places the remaining healthy fetus at an even higher risk of adverse outcome and pregnancy complications. Maternal medical conditions or complicated obstetrical history could, in combination with twin pregnancy, cause increased risks for both the woman and the fetuses. To our knowledge, no previous studies have evaluated and compared the outcomes of all dichorionic twin pregnancies and compared the results of reduced twins with those of nonreduced and primary singletons in a national cohort. These data are important for clinicians when counseling couples about fetal reduction and its implications.

**OBJECTIVE:** This study aimed to describe and compare the risks of adverse pregnancy outcomes, including the risk of pregnancy loss, in a national cohort of all dichorionic twins—reduced, nonreduced, and primary singletons. In addition, we examined the implications of gestational age at fetal reduction on gestational age at delivery.

**STUDY DESIGN:** This was a retrospective cohort study of all Danish dichorionic twin pregnancies, including pregnancies undergoing fetal reduction and a large proportion of randomly selected primary singleton pregnancies with due dates between January 2008 and December 2018. The primary outcome measures were adverse pregnancy outcomes (defined as miscarriage before 24 weeks, stillbirth from 24 weeks, or single intrauterine fetal death in nonreduced twin pregnancies), preterm delivery, and obstetrical pregnancy complications. Outcomes after fetal reduction were compared with those of nonreduced dichorionic twins and primary singletons.

**RESULTS:** In total, 9735 dichorionic twin pregnancies were included, of which 172 (1.8%) were reduced. In addition, 16,465 primary singletons were included. Fetal reductions were performed between 11 and 23 weeks by transabdominal needle-guided injection of potassium chloride, and outcome data were complete for all cases. Adverse pregnancy

outcome was observed in 4.1% (95% confidence interval, 1.7%–8.2%) of reduced twin pregnancies, and 2.4% (95% confidence interval, 0.7%–6.1%) were delivered before 28 weeks, and 4.2% (95% confidence interval, 1.7%–8.5%) before 32 weeks. However, when fetal reduction was performed before 14 weeks, adverse pregnancy outcomes occurred in only 1.4% (95% confidence interval, 0.0%–7.4%), and delivery before 28 and 32 weeks diminished to 0% (95% confidence interval, 0.0%–5.0%) and 2.8% (95% confidence interval, 0.3%–9.7%), respectively. In contrast, 3.0% (95% confidence interval, 2.7%–3.4%) of nonreduced dichorionic twins had an adverse pregnancy outcome, and 1.9% (95% confidence interval, 1.7%–2.1%) were delivered before 28 weeks, and 7.3% (95% confidence interval, 6.9%–7.7%) before 32 weeks. Adverse pregnancy outcomes occurred in 0.9% (95% confidence interval, 0.7%–1.0%) of primary singletons, and 0.2% (95% confidence interval, 0.1%–0.3%) were delivered before 28 weeks, and 0.7% (95% confidence interval, 0.6%–0.9%) before 32 weeks. For reduced twins, after taking account of maternal factors and medical history, it was demonstrated that the later the fetal reduction was performed, the earlier the delivery occurred ( $P < .01$ ). The overall risk of pregnancy complications was significantly lower among reduced twin pregnancies than among nonreduced dichorionic twin pregnancies ( $P = .02$ ).

**CONCLUSION:** In a national 11-year cohort including all dichorionic twin pregnancies, transabdominal fetal reduction by needle guide for fetal or maternal indication was shown to be safe, with good outcomes for the remaining co-twin. Results were best when the procedure was performed before 14 weeks.

**Key words:** adverse pregnancy outcome, chance of liveborn, co-twin, Danish national cohort, embryo reduction, multifetal pregnancies, multifetal pregnancy, multifetal pregnancy reduction, multiples, pregnancy complications, reproductive autonomy, selective feticide, selective fetocide, selective termination

**Cite this article as:** Kristensen SE, Ekelund CK, Sandager P, et al. Risks and pregnancy outcome after fetal reduction in dichorionic twin pregnancies: a Danish national retrospective cohort study. *Am J Obstet Gynecol* 2023;228:590.e1–12.

0002-9378

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<https://doi.org/10.1016/j.ajog.2022.10.028>



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## Introduction

Twin pregnancies account for 2% of all pregnancies. Compared with singleton pregnancies, twins are associated with increased maternal and fetal risks. Twin pregnancies are at increased risk of miscarriage, preeclampsia, and preterm birth, affecting both fetuses, whereas other conditions, such as congenital malformations and chromosomal anomalies, typically only affect 1 fetus.<sup>1–4</sup> Discordant fetal disease is a risk

factor for adverse outcomes in the healthy co-twin as a consequence of increased preterm delivery rates and perinatal morbidity that are closely correlated to the type and severity of the anomaly.<sup>5–8</sup>

Fetal reduction (FR) in dichorionic (DC) twin pregnancies, discordant for fetal anomalies or severe maternal medical conditions, has been advocated to mitigate risks and improve overall outcome of pregnancy.<sup>5,7,9,10</sup> However,

## AJOG at a Glance

**Why was this study conducted?**

To the best of our knowledge, there have been no studies on fetal reduction conducted in a national cohort of all dichorionic twins, comparing reduced, nonreduced, and primary singleton pregnancies.

**Key findings**

Fetal reduction performed for fetal or maternal indication in dichorionic twin pregnancies is a safe procedure with low risk of miscarriage or stillbirth, especially when performed before 14 weeks. Fetal reduction also reduces the risk of obstetrical complications and could improve outcome for the remaining co-twin.

**What does this add to what is known?**

Our results support fetal reduction performed at the earliest possible gestational age. Therefore, early diagnosis is crucial for offering treatment at the lowest risks.

all invasive procedures during pregnancy, including FR, carry a risk of adverse outcomes such as miscarriage, intrauterine death, and preterm birth.<sup>11–18</sup> Previously reported rates of adverse outcomes related to FR are inconsistent because most studies suffer from selection bias and lack appropriate comparators.<sup>12,13,15,17–19</sup> Very few studies included both maternal and fetal risk factors, and hitherto none have reported on national data.

In Denmark, FR of twin pregnancies is legally restricted to pregnancies with a severe fetal anomaly or maternal medical condition, and requires approval by board consultation.

This national study aimed to estimate the risk of pregnancy complications and adverse outcomes related to all FRs performed in DC twin pregnancies in Denmark over 11 years and to compare those results with data from the same study period for all nonreduced DC twin pregnancies and a large cohort of singleton pregnancies.

**Materials and Methods****Study population and design**

We conducted a Danish nationwide retrospective register-based study between January 2008 and December 2018, in accordance with the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement.<sup>20</sup> The data were prospectively collected

from women undertaking combined first-trimester risk assessment at 11 to 14 weeks' gestation. The Danish Fetal Medicine Database (DFMD) contains data on all pregnancies seen for a first-trimester ultrasound scan. In Denmark, most women decide to have a combined first-trimester trisomy risk assessment and a second-trimester fetal anomaly scan.<sup>21</sup> All participants' baseline characteristics and clinical data were obtained from DFMD, and missing data were obtained from electronic medical files.

Following national guidelines, DC twin pregnancies had an ultrasound assessment and routine obstetrician visit every 4 weeks from the second-trimester anomaly scan at approximately 20 weeks' gestation until delivery. In addition, all twin pregnancies had 2 cervical length measurements performed routinely, at approximately 20 and 24 weeks, and routine visits with a midwife and a general practitioner. Delivery was recommended at 37 to 38 weeks for DC twin pregnancies and before 42 weeks for singleton pregnancies. Pregnancy outcomes were retrieved from DFMD because each pregnancy is linked to the Danish National Birth Register and the National Patient Register by a unique personal identification number (CPR number), which is given to all citizens at birth or immigration.<sup>22</sup> Moreover, the CPR number system is used to identify

and document every contact in the public healthcare system.

**Inclusion and exclusion criteria**

The inclusion criteria for this study were DC twin pregnancies with 2 viable fetuses at the combined first-trimester risk assessment between 11 and 14 weeks' gestation. Dichorionicity was confirmed by the presence of 2 separate placentas or the presence of a "lambda sign" of the intertwin membrane. For comparison, a cohort of singleton pregnancies from the same national cohort and study period were randomly selected by computer. Quantitative variables were checked for consistency, and in the case of extreme outliers or doubts, a correction was made with details from electronic medical files, where available, or otherwise excluded from further analysis. All DC twin pregnancies were included, irrespective of discordancy for fetal anomalies or the calculated risk from the combined first-trimester risk assessment. We excluded all higher-order multifetal pregnancies, monochorionic twins, and all terminated pregnancies. Singletons and nonreduced DC twins with unknown outcomes were excluded from analyses (Figure 1).

**Fetal reduction cohort**

DC twin pregnancies undergoing FR were identified using the local fetal medicine databases (Astraia GmbH, Ismaning, Germany) of the 4 tertiary centers performing FR in Denmark (Copenhagen University hospitals Rigshospitalet and Hvidovre, Aalborg University Hospital, and Aarhus University Hospital, Skejby). In Denmark, all FRs are performed as outpatient procedures according to the same protocol, involving a transabdominal approach, mandatory use of a needle guide, and intracardiac injection of 2 mmol/mL potassium chloride to induce asystole. Prophylactic antibiotics were not used. The procedure was performed by or under the supervision of fetal medicine consultants, all experienced in invasive prenatal diagnosis techniques. All women had an ultrasound examination shortly after the procedure and after 1

week to demonstrate the viability of the remaining fetus.

### Outcome measures

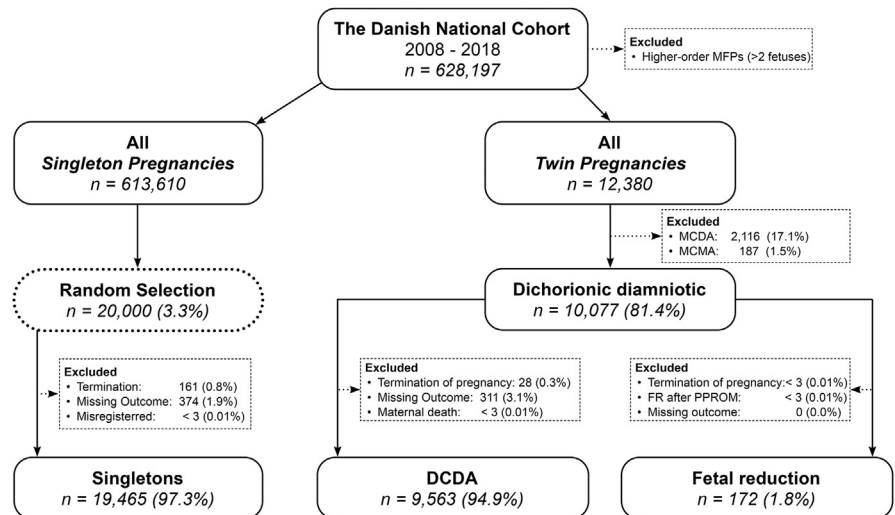
Primary outcome measures were adverse pregnancy outcome (defined as miscarriage before 24<sup>+</sup> weeks, stillbirth from 24<sup>+</sup> weeks, or single intrauterine fetal death in the nonreduced twin pregnancies), preterm delivery before 28<sup>+</sup>, 32<sup>+</sup>, or 37<sup>+</sup> weeks, rate of live-born children, and gestational age at delivery. Moreover, pregnancy complications defined as preterm prelabor rupture of membranes (PPROM), preeclampsia, placenta previa, and placental abruption, and birthweight z-scores (adjusted for gender and gestational age at delivery) were included as secondary outcomes. Z-scores were calculated using the birthweight reference by Marsál et al,<sup>23</sup> recommended for both singletons and twins by the Danish national guideline.

### Statistical analyses

Data were summarized by percentages with 95% confidence intervals for categorical variables and medians with interquartile range (IQR) for continuous variables across singleton, nonreduced twins and reduced twins. The 3 groups were compared using Fisher exact tests for categorical variables and Wilcoxon rank-sum tests for continuous variables. Rates of adverse pregnancy outcomes, live-born children, preterm deliveries, and pregnancy complications are graphically presented as forest plots. The cumulative incidence of preterm delivery before 37 weeks was plotted against gestational age at delivery for singletons, twins reduced before 14 weeks, twins reduced from 14 weeks, and nonreduced twins. To explore the possible effect of the indication for FR, a subgroup analysis of adverse pregnancy outcomes and risk of preterm delivery was performed by grouping reduced pregnancies by fetal or maternal indication.

For reduced twins, the distributional properties of gestational age at delivery were investigated by plotting histograms and gestational age at delivery against gestational age at FR, whereby the division at 14 weeks was determined.

**FIGURE 1**  
Flowchart of included pregnancies



Flowchart of the national Danish study population, with numbers of included and excluded pregnancies.

DCDA, dichorionic-diamniotic; FR, fetal reduction; MCDA, monochorionic-diamniotic; MCMA, monochorionic-monoamniotic; MFP, multifetal pregnancy; PPROM, preterm prelabor rupture of membranes.

Kristensen. A Danish national study of fetal reduction in dichorionic twins. *Am J Obstet Gynecol* 2023.

**TABLE 1**  
Baseline maternal characteristics

Characteristics	Singleton <sup>a</sup> N=19,465		Fetal reduction <sup>a</sup> N=172		Dichorionic twin <sup>a</sup> N=9563	
Maternal age	30	(26–33)	34	(30–39) <sup>b,c</sup>	32	(29–35)
BMI	23	(20–26)	22	(20–25) <sup>c</sup>	23	(21–27)
(Missing)	683	(3.5%)	21	(12.2%)	392	(4.1%)
Nulliparity	6397	(32.8%)	57	(33.1%)	2794	(29.2%)
(Missing)	4899	(25.2%)	52	(30.2%)	3548	(37.1%)
Conception						
Natural	17,589	(90.3%)	85	(49.4%) <sup>b</sup>	4846	(50.7%)
OI	138	(0.7%)	7	(4.1%) <sup>b</sup>	422	(4.4%)
IUI	326	(1.7%)	16	(9.3%) <sup>b</sup>	942	(9.9%)
IVF	820	(4.2%)	53	(30.8%) <sup>b</sup>	2974	(31.1%)
(Missing)	592	(3.0%)	11	(6.4%)	379	(4.0%)
Current smoker	1786	(9.2%)	11	(6.4%)	660	(6.9%)
(Missing)	390	(2.0%)	18	(10.5%)	351	(3.7%)
White ethnicity	17,506	(89.9%)	145	(84.3%) <sup>b,c</sup>	8526	(89.2%)
(Missing)	691	(3.5%)	22	(12.8%)	579	(6.1%)

BMI, body mass index; IUI, intrauterine insemination; IVF, in vitro fertilization; OI, ovulation induction.

<sup>a</sup> Continuous variables: median (interquartile range) and Wilcoxon rank-sum test; categorical variables: number (percentage) and Fisher exact test; <sup>b</sup> Significantly ( $P < .05$ ) different from singletons; <sup>c</sup> Significantly ( $P < .05$ ) different from nonreduced dichorionic twins.

Kristensen. A Danish national study of fetal reduction in dichorionic twins. *Am J Obstet Gynecol* 2023.

**TABLE 2**  
**Pregnancy outcomes**

Outcomes	Singleton N=19,465 <sup>a</sup>		FR: GA <14 wk N=73 <sup>a</sup>		FR: GA ≥14 wk N=99 <sup>a</sup>		Dichorionic twin N=9563 <sup>a</sup>	
GA at delivery (d)	281	(273–287)	277	(269–284) <sup>b,c</sup>	272	(260–281) <sup>b,c</sup>	262	(248–266)
Adverse pregnancy outcome	0.9%	(0.7–1.0)	1.4%	(0.0–7.4)	6.1%	(2.3–12.7) <sup>b</sup>	3.1%	(2.7–3.4)
Miscarriage <24 wk	0.6%	(0.5–0.8)	1.4%	(0.0–7.4)	5.1%	(1.7–11.4) <sup>b,c</sup>	1.7%	(1.5–2.0)
Stillbirth ≥24 wk	0.2%	(0.2–0.3)	0.0%	(0.0–4.9)	1.0%	(0.0–5.5)	0.1%	(0.0–0.1)
Single intrauterine fetal death	—	—	—	—	—	—	1.3%	(1.1–1.5)
At least one live-born	99.1%	(99.0–99.3)	98.6%	(92.6–100.0)	93.9%	(87.3–97.7) <sup>b,c</sup>	98.2%	(97.9–98.5)
Two live-born	—	—	—	—	—	—	96.9%	(96.6–97.3)
Preterm delivery								
Live-born <28 wk	0.2%	(0.1–0.3)	0.0%	(0.0–5.0)	4.3%	(1.2–10.6) <sup>b</sup>	1.9%	(1.7–2.1)
Live-born <32 wk	0.7%	(0.6–0.9)	2.8%	(0.3–9.7)	5.4%	(1.8–12.1) <sup>b</sup>	7.3%	(6.9–7.7)
Live-born <37 wk	4.9%	(4.6–5.2)	6.9%	(2.3–15.5) <sup>c</sup>	19.4%	(11.9–28.9) <sup>b,c</sup>	39.1%	(38.3–39.8)
Term delivery	95.1%	(94.8–95.4)	93.1%	(84.5–97.7) <sup>c</sup>	80.6%	(71.1–88.1) <sup>b,c</sup>	60.9%	(60.2–61.7)

FR, fetal reduction; GA, gestational age.

<sup>a</sup> Continuous variables: median (interquartile range) and Wilcoxon rank-sum test; categorical variables: percentage (95% confidence interval) and Fisher exact test; <sup>b</sup> Significantly ( $P<.05$ ) different from singletons; <sup>c</sup> Significantly ( $P<.05$ ) different from nonreduced dichorionic twins.Kristensen. A Danish national study of fetal reduction in dichorionic twins. *Am J Obstet Gynecol* 2023.

Multivariate linear regression models were fitted, with appropriately transformed gestational age at delivery as the dependent variable, and gestational age at reduction, indication for the reduction, maternal weight and height, ethnicity, method of conception, smoking status, and parity as independent variables. Backward elimination was used for model selection.

All statistical analyses were performed using the statistical software R (version 4.0.4 for Mac; R Core Team, Vienna, Austria).

### Ethical consideration

This study was approved by the regional data security management authority (approval number: P-2019-696). Access to the requested data was approved by the national clinical quality control database (DFMD: RKKP-case number: FØTO-2019-11-12). Furthermore, approval was given by the Danish Patient Safety Authority to retrieve missing or supplementary data from electronic files of the departments where the participants delivered (case number: 31-1521-26). Because direct contact with the study participants was not required, the authors were given legal approval to

perform the study without consent from the participants.

### Results

In total, 12,683 twin pregnancies were identified in the DFMD between January 2008 and December 2018, of which 10,077 (79.5%) were DC; 342 pregnancies were excluded, leaving 9735 DC twins in the cohort, 172 (1.8%) of which were reduced. Indications for FR were fetal malformation in 92 (53.5%) pregnancies, fetal genetic disease in 57 (33.1%), maternal medical condition in 21 (12.2%), and maternal obstetrical history in 2 (1.2%) pregnancies. In addition, 19,465 (97.3%) of the randomly selected primary singletons met the inclusion criteria (Figure 1 includes details of inclusions and exclusions).

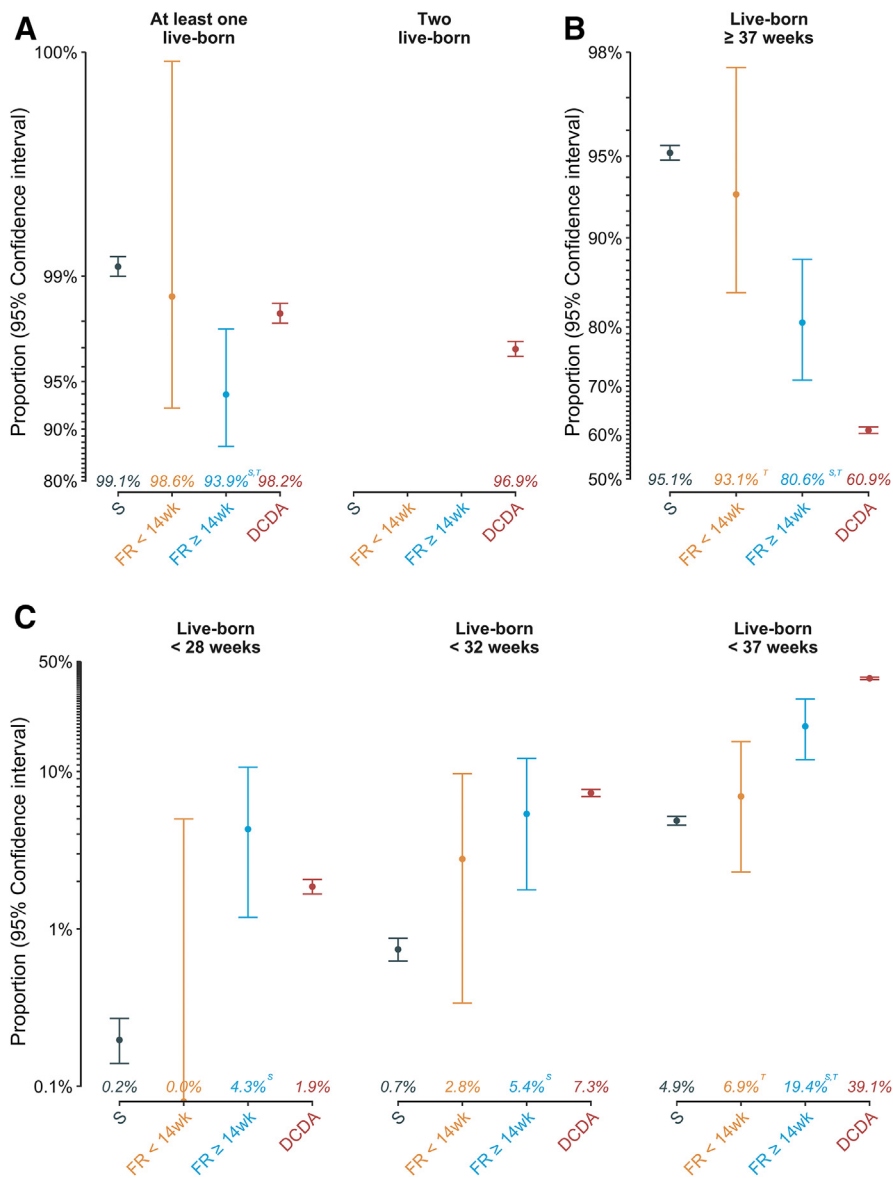
Table 1 summarizes maternal characteristics and pregnancy history across the 3 groups (singletons, nonreduced twins, and FRs). Women in the reduced-twin group were older than those in the nonreduced twin and singleton groups, and the use of assisted reproductive technology was more frequent in women with twin pregnancies than in those with singleton pregnancies.

FR was performed between 11<sup>+0</sup> and 23<sup>+0</sup> weeks at a median gestational age of 14<sup>+3</sup> (IQR, 13<sup>+3</sup>–17<sup>+3</sup>). Seventy-three reductions were performed before 14<sup>+0</sup> weeks, and the remaining 99 reductions occurred from week 14<sup>+0</sup>. The procedure was performed at 4 different centers by 15 different operators, with a median of 10 procedures per operator (range, 1–41).

Pregnancy outcomes across singletons, FRs before 14 weeks, FRs from 14 weeks, and nonreduced twins are shown in Table 2 and Figure 2. Reduced twins were delivered earlier than singletons ( $P<.01$ ); those reduced before 14 weeks were delivered, on average, 4 days earlier and those reduced after 14 weeks were delivered, on average, 9 days earlier than singletons. Nonreduced twins were delivered significantly earlier than reduced twins ( $P<.01$ ), by on average 15 days for twins reduced before 14 weeks and 10 days for twins reduced from 14 weeks. Figure 3 shows the cumulative incidence of delivery before 37 weeks for singletons, twins reduced before 14 weeks, twins reduced from 14 weeks, and nonreduced twins.

The median (IQR) birthweight was slightly higher among live-born infants



**FIGURE 2**  
Rates of live-born children and preterm deliveries

Rates of liveborn children and preterm deliveries are illustrated as plots showing percentages with error bars of 95% confidence intervals. Superscript letter *S* denotes significantly ( $P < .05$ ) different from singletons; Superscript letter *T* denotes significantly ( $P < .05$ ) different from nonreduced dichorionic twins.

DC, nonreduced dichorionic twin pregnancies; FR < 14, fetal reduction before 14 weeks; FR ≥ 14, fetal reduction from 14 weeks; S, singletons.

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(from 24<sup>+0</sup> weeks) after FR compared with nonreduced twins (Z-score, -0.6 [-1.2 to 0.1] vs -1.1 [-1.7 to -0.4]). Singletons had the highest birthweights (Z-score, -0.1 [-0.8 to 0.6]) (Supplemental Figure 1). Adverse pregnancy outcome, defined as miscarriage before 24<sup>+0</sup> weeks, stillbirth from 24<sup>+0</sup>

weeks, or single intrauterine fetal death in nonreduced twins, was observed in 4.1% of reduced twins vs 0.9% of singletons ( $P < .01$ ) and 3.1% of nonreduced twins ( $P = .4$ ). In twins reduced before 14 weeks, 1.4% had an adverse pregnancy outcome, and in those reduced from 14 weeks, 6.1% had an adverse pregnancy

outcome (Table 2; Supplemental Figure 2). The chance of at least 1 live-born child did not differ between pregnancies with singletons (99.1%), twins reduced before 14 weeks (98.6%), and nonreduced twins (98.2%). However, in twins reduced from 14 weeks, this rate was significantly lower (93.9%) compared with nonreduced twins ( $P < .01$ ) and singletons ( $P < .01$ ).

By multivariate linear regression analysis, gestational age at reduction was found to be the only significant predictor for gestational age at delivery for reduced twins. The later the reduction was performed, the earlier the delivery occurred, on average. The relationship is given by  $GA_{delivery} = 42 - 10^{0.0424 + 0.0036 \times GA_{reduction}}$  ( $P < .01$ ), as shown in Supplemental Figure 3.

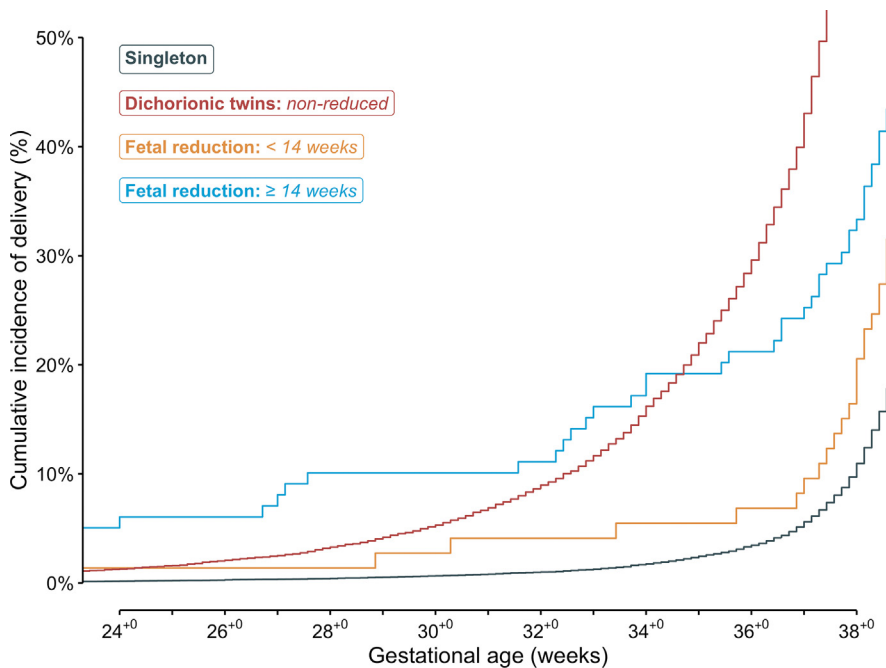
Because of the small sample size, comparison of the risk of adverse pregnancy outcomes according to the indication for the procedure, fetal indication ( $n = 149$ ), and maternal indication ( $n = 23$ ) did not achieve significance (3.4% vs 8.7%;  $P = .2$ ). Similarly, subgroup analysis found no significant differences in risk of preterm delivery before 28, 32, or 37 weeks, although substantial differences could not be ruled out because of the small sample sizes.

Pregnancy complications across singletons, twins reduced before 14 weeks, twins reduced from 14 weeks, and nonreduced twins are shown in Table 3 and Figure 4. The highest proportion of pregnancy complications was in DC twin pregnancies (21.7%), followed by twins reduced before 14 weeks (11%), and singletons (5.8%). For a narrated presentation of the study and results, see Video 1.

## Comments

Since it was first described in 1978,<sup>9</sup> FR has been used as a method to mitigate risks of adverse outcomes in multifetal pregnancies discordant for fetal disease or in severe maternal conditions. Counseling couples with twin pregnancies at risk is complex and should be based on reliable data. Randomized studies are not available for obvious ethical reasons. Therefore, we present

**FIGURE 3**  
**Cumulative incidence of delivery**



Kaplan—Meier curve illustrating the cumulative incidence of delivery according to gestational age. Kristensen. A Danish national study of fetal reduction in dichorionic twins. *Am J Obstet Gynecol* 2023.

our data on adverse pregnancy outcomes and pregnancy complications in a nationwide cohort of all reduced DC twin pregnancies in Denmark. Furthermore, we compared the results with all nonreduced DC twin pregnancies and a representative cohort of singleton pregnancies.

### Principal findings

FR was performed in 1.8% of all included DC twin pregnancies in

Denmark between 2008 and 2018. The overall rate of pregnancy complications was reduced by 50% in reduced twin pregnancies compared with nonreduced twin pregnancies. The risk of an adverse pregnancy outcome in reduced DC twin pregnancies was 4.1%, and the rate of preterm delivery before 28<sup>+</sup>0 and 32<sup>+</sup>0 weeks was low, with the overall preterm delivery rate being significantly lower than that of nonreduced twin pregnancies ( $P<.01$ )

and similar to that of singleton pregnancies ( $P=.4$ ). The rate of adverse pregnancy outcome for reductions before 14 weeks was approximately a quarter of that for reductions performed from 14 weeks ( $P=.2$ ). There was a significant inversely proportional relationship between gestational age at reduction and gestational age at delivery ( $P<.01$ ).

### Results in the context of what is known

Several studies have reported pregnancy loss and preterm delivery rates after FR in DC twin pregnancies. A multicenter study from 1999 by Evans et al<sup>24</sup> reported a 7.9% risk of fetal loss and preterm delivery rates before 28 and 32 weeks of 4.6% and 12.4%, respectively. In 2015, van de Mheen et al<sup>25</sup> reported an 11.9% risk of pregnancy loss and a preterm delivery rate before 32 weeks of 18.6%, which is 3 to 4 times higher than our results. In a large single-center study from 2019 with FRs performed before 15 weeks, Vieira et al<sup>26</sup> reported a total loss rate of 4.0% and a preterm delivery rate before 32 weeks of 4.1%, which are comparable to or higher than what we found in this study, but outcome data were missing in 20% of their cases. Other studies have reported diverging results regarding pregnancy loss and preterm delivery, often with a large or undescribed proportion of missing outcome data.<sup>18,19,27</sup>

The effect of the residual placenta on birthweight is supported by studies on

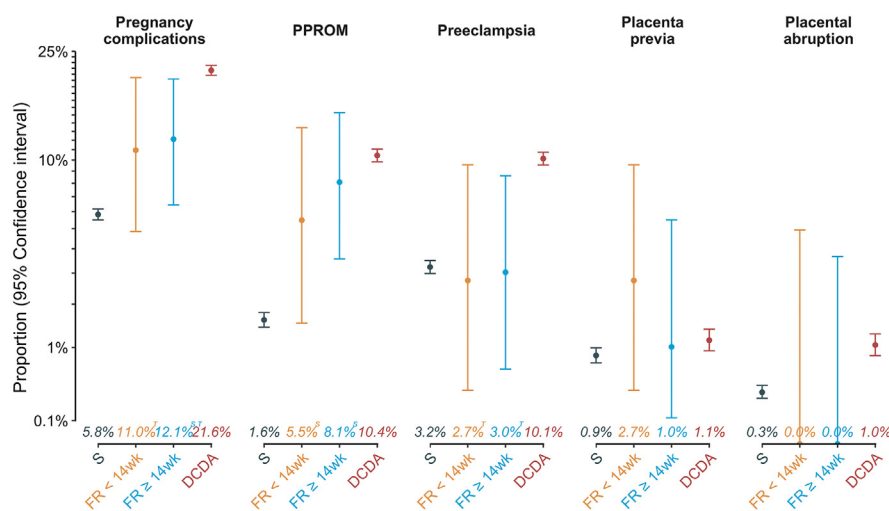
**TABLE 3**  
**Pregnancy complications**

Type of complication	Singletons N=19,465 <sup>a</sup>	FR: GA <14 wk N=73 <sup>a</sup>	FR: GA ≥14 wk N=99 <sup>a</sup>	Dichorionic twins N=9563 <sup>a</sup>
Pregnancy complications	5.8% (5.5–6.2)	11.0% (4.9–20.5) <sup>b</sup>	12.1% (6.4–20.2) <sup>b,c</sup>	21.7% (20.8–22.5)
PPROM	1.6% (1.4–1.8)	5.5% (1.5–13.4) <sup>b</sup>	8.1% (3.6–15.3) <sup>b</sup>	10.4% (9.8–11.1)
Preeclampsia	3.2% (3.0–3.5)	2.7% (0.3–9.5) <sup>c</sup>	3.0% (0.6–8.6) <sup>c</sup>	10.1% (9.5–10.8)
Placenta previa	0.9% (0.7–1.0)	2.7% (0.3–9.5)	1.0% (0.0–5.5)	1.1% (0.9–1.4)
Placental abruption	0.3% (0.2–0.4)	0.0% (0.0–4.9)	0.0% (0.0–3.7)	1.0% (0.9–1.3)

FR, fetal reduction; GA, gestational age; PPRM, preterm prelabor rupture of membranes.

<sup>a</sup> Percentage (95% confidence interval) and Fisher exact test; <sup>b</sup> Significantly ( $P<.05$ ) different from singletons; <sup>c</sup> Significantly ( $P<.05$ ) different from nonreduced dichorionic twins.

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**FIGURE 4**  
**Pregnancy complications**

Rates of obstetrical pregnancy complications are illustrated as plots showing percentages with error bars of 95% confidence intervals. Superscript letter *S* denotes significantly ( $P < .05$ ) different from singletons; Superscript letter *T* denotes significantly ( $P < .05$ ) different from nonreduced dichorionic twins.

DC, nonreduced dichorionic twin pregnancies; FR < 14, fetal reduction before 14 weeks; FR ≥ 14, fetal reduction from 14 weeks; PPROM, preterm prelabor rupture of membranes; S, singletons.

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vanishing twin pregnancies,<sup>28,29</sup> and suggests that the remaining twin's placenta is somehow adversely affected by the initial sharing of the intrauterine environment.

Our data on preeclampsia show that the 3-fold increase in risk observed in twin pregnancies reverts to singleton risk levels after FR, which is in agreement with other studies.<sup>18,30</sup> The pathophysiological mechanism is not fully understood but is supported by case series demonstrating recovery from second-trimester preeclampsia after FR.<sup>31</sup>

### Clinical implications

Our results and the latest published reports support performing FR as early as possible after first-trimester ascertainment of fetal health to reduce the risk of fetal loss and preterm birth.<sup>12,15,17,18,25,32</sup>

Technological advances in diagnostic equipment, improvements in sonographer training, and image capture standardization have pushed screening and diagnosis of fetal anomalies toward the late first and early second trimester of pregnancy. This allows identification of

fetal structural and genetic abnormalities in twin pregnancies before 14 weeks, when parents can be adequately counseled and opt for earlier reduction with better outcomes, which has implications for long-term prognosis. Certain fetal anomalies remain undetectable at 11 to 14 weeks, and later FRs will still be necessary. We found a 4-fold increase in risk of adverse pregnancy outcome in reductions performed from 14 weeks. However, the risk remains low in absolute terms.

Our results could also be viewed in a health-policy perspective: in Denmark, FR in twin pregnancies on maternal request is not allowed, but termination of the whole pregnancy is a legal right until 12 weeks. Therefore, abortion of healthy twin pregnancies occurs in Denmark because of the current legislation. The evidence provided in this paper shows that FR on maternal request could be an option. A recent Norwegian medical ethical assessment supported this policy, concluding that "on the same conditions as we allow for abortions, we should also allow FR."<sup>33</sup> The decision

whether to offer FR to all or a subgroup of women with twin pregnancies could also include other aspects not addressed in our study.

### Research implications

The adverse outcome figures from this study are among the best published. We can only speculate on the reason for this, but a contributing factor could be adherence to a national procedural protocol, without prophylactic antibiotics and with the mandatory use of a needle guide. Although the utility of this device is a matter of ongoing international debate, the low rate of PPROM in our study may provide further support for its use.

### Strengths and limitations

The major strength of this study is the national cohort database with complete follow-up for all reduced cases and little missing outcome data for nonreduced DC twins and singletons. The inclusion of all DC twin pregnancies and a large, randomly selected cohort of singleton pregnancies provides valuable background information for clinicians and parental counseling because risks of adverse pregnancy outcomes or preterm delivery should always be interpreted against background risks.

This study was retrospective and register-based, which inherently carries risk of bias owing to incomplete or incorrect data registration. The Danish public healthcare system and medical registries have universally high standards, and >94% of women with singleton pregnancies and virtually all women with twin pregnancies elect to undertake a combined first-trimester risk assessment and second-trimester anomaly ultrasound, which limits these risks and the risk of bias caused by unequal access to medical care. Finally, we were unable to report neonatal outcomes of reduced cases, but others have not found any direct adverse neonatal effects related to the procedure.<sup>18,34</sup>

### Conclusions

This national study indicates that FR is performed in 1 of 63 of all DC twin pregnancies in Denmark, and is a safe



procedure that improves the outcome of the remaining co-twin and reduces the risk of pregnancy complications when 1 fetus is anomalous or in case of a complicated maternal history. The risk of adverse pregnancy outcome and preterm delivery is lowest when the reduction is performed before 14 weeks, which results in the reduced pregnancy having approximately the same chance of at least 1 live-born infant as pregnancies with singleton or nonreduced twins. ■

## Acknowledgments

The authors would like to acknowledge the Danish Fetal Medicine Study Group for their collaboration in data extraction and important work in verifying questions related to the data.

The authors would also like to thank Professor Emerita, Ann Tabor, MD, DMSc (Department of Obstetrics, Center for Fetal Medicine and Ultrasound, Copenhagen University Hospital—Rigshospitalet, Copenhagen, Denmark) for her support and critical review during the design, analysis, and reporting of our results.

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Received June 28, 2022; revised Sept. 27, 2022; accepted Oct. 22, 2022.

The authors report no conflict of interest.

O.B.P. was financially supported by a grant from the Novo Nordisk Foundation (grant: NNFS170030576), which did not participate in any

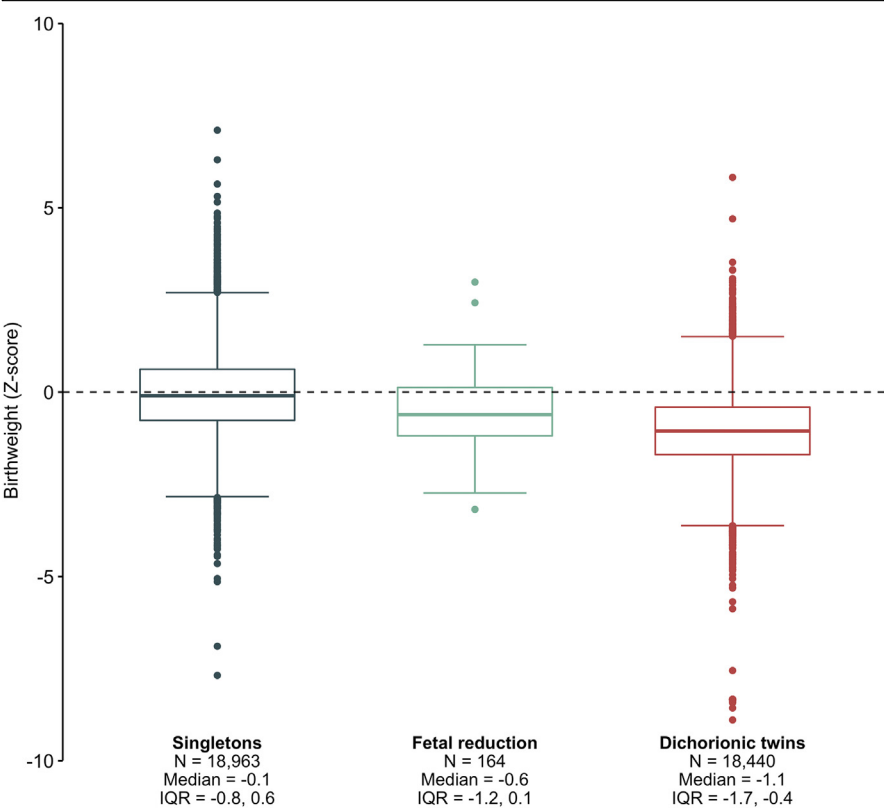
part of the planning, conduct, or preparation of the manuscript.

The findings of this study were presented at the annual meeting of the Nordic Network of Fetal Medicine, Stockholm, Sweden, May 4–5, 2022. The preliminary findings were presented as a virtual poster at the 30th world congress on Ultrasound in Obstetrics and Gynecology of the International Society of Ultrasound in Obstetrics and Gynecology, held virtually, October 16–18, 2020.

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Appendix

**SUPPLEMENTAL FIGURE 1**  
**Birthweight of live-born children**

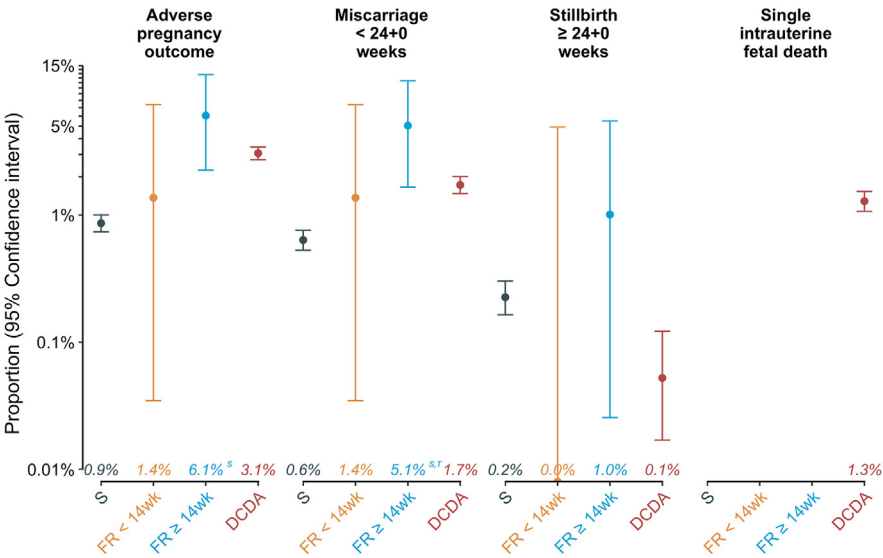


The birthweight of live-born children in z-scores illustrated as bar plots with error bars.

IQR, interquartile range.

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SUPPLEMENTAL FIGURE 2  
Risk of adverse pregnancy outcome

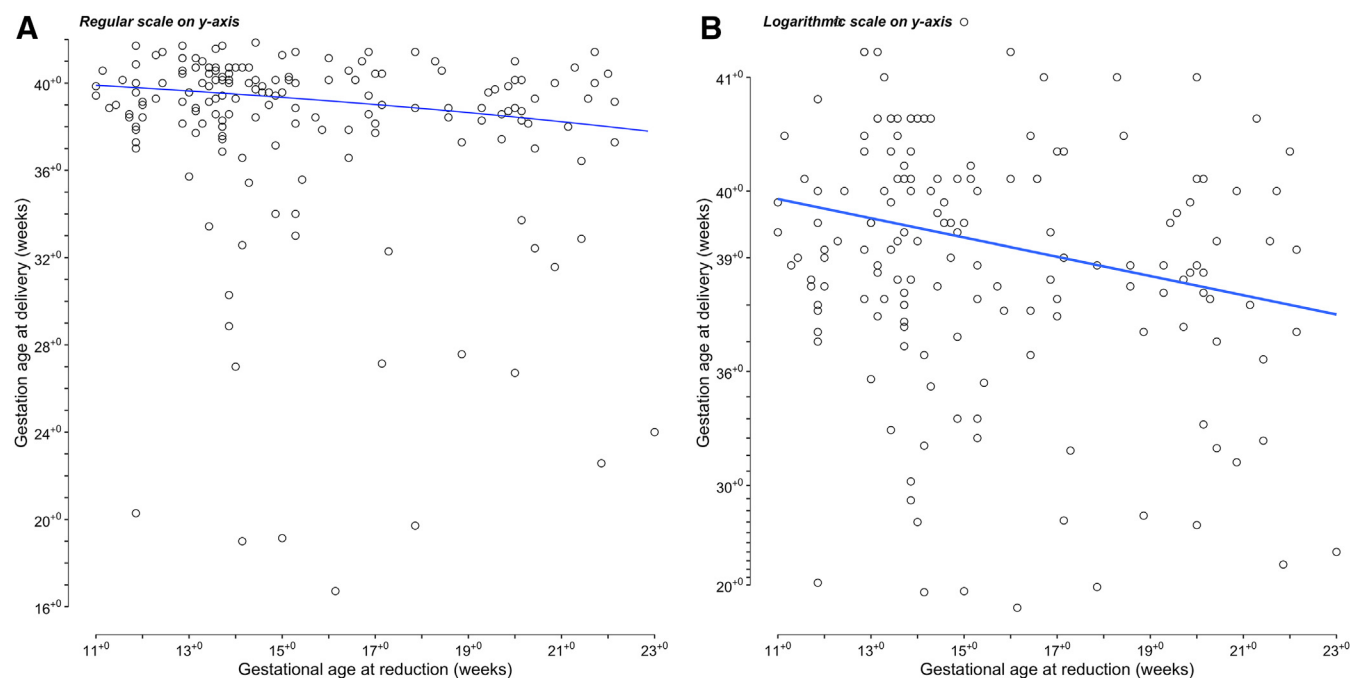


Rates of adverse pregnancy outcomes are illustrated as plots showing percentages with error bars of 95% confidence intervals. Superscript letter S denotes significantly ( $P < .05$ ) different from singletons; Superscript letter T denotes significantly ( $P < .05$ ) different from nonreduced dichorionic twins. DC, nonreduced dichorionic twin pregnancies; FR < 14, fetal reduction before 14 weeks; FR ≥ 14, fetal reduction from 14 weeks; S, singletons.

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## SUPPLEMENTAL FIGURE 3

## Gestational age at delivery according to gestational age at fetal reduction



The association between gestational age at fetal reduction and gestational age at delivery illustrated as a scatterplot on (A) a regular scale on the y-axis, and (B) logarithmic scale on the y-axis, with the linear regression (blue line) illustrated on both scales.

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