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Quadruplet pregnancy outcome with and without fetal reduction: Danish national cohort study (2008–2018) and comparison with dichorionic twins

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KEYWORDS: birth weight; fetal reduction; higher order; multifetal pregnancy; multifetal pregnancy reduction; pregnancy outcome; preterm delivery; quadruplet

CONTRIBUTION

What are the novel findings of this work?
Fetal reduction in quadrichorionic quadriamniotic quadruplet pregnancies is a safe procedure with a low risk of miscarriage. Fetal reduction decreases the risk of adverse pregnancy outcome, preterm delivery and low birth weight, which are common complications seen in non-reduced quadruplets and are associated with neonatal mortality and morbidity.

What are the clinical implications of this work?
This study delivers pivotal insights for healthcare practitioners advising couples on managing a quadruplet pregnancy. The data support fetal reduction as a safe intervention for improving pregnancy outcome. This research underscores the importance of personalized care and informed decision-making in the management of quadruplet pregnancy.

ABSTRACT

Objectives *To perform a nationwide study of quadrichorionic quadriamniotic (QCQA) quadruplet pregnancies and to compare the pregnancy outcome in those undergoing fetal reduction with non-reduced quadruplets and dichorionic diamniotic (DCDA) twin pregnancies from the same time period.*

Methods *This was a retrospective Danish national register-based study performed using data from the national Danish Fetal Medicine Database, which included all QCQA quadruplets and all non-reduced DCDA twin pregnancies with an estimated due date between 2008 and 2018. The primary outcome measure was a composite of adverse pregnancy outcomes, including pregnancy loss or intrauterine death of one or more fetuses. Secondary outcomes included gestational age at delivery, the number of liveborn children, preterm delivery before 28, 32 and 37 gestational weeks and birth weight. Data on pregnancy complications and baseline characteristics were also recorded. Outcomes were compared between reduced and non-reduced quadruplet pregnancies, and between DCDA pregnancies and quadruplet pregnancies reduced to twins. A systematic literature search was performed to describe and compare previous results with our findings.*

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Results *Included in the study were 33 QCQA quadruplet pregnancies, including three (9.1%) non-reduced pregnancies, 28 (84.8%) that were reduced to twin pregnancy and fewer than three (6.1%) that were reduced to singleton pregnancy, as well as 9563 DCDA twin pregnancies. Overall, the rate of adverse pregnancy outcome was highest in non-reduced quadruplets (66.7%); it was 50% in quadruplets reduced to singletons and 10.7% in quadruplets reduced to twins. The proportion of liveborn infants overall was 91.1% of the total number expected to be liveborn in quadruplet pregnancies reduced to twins. This was statistically significantly different from 97.6% in non-reduced dichorionic twins (*$P = 0.004$*), and considerably higher than 58.3% in non-reduced quadruplets. The rates of preterm delivery < 28, < 32 and < 37 weeks were decreased in quadruplets reduced to twins compared with those in non-reduced quadruplet pregnancies. Quadruplets reduced to twins did not achieve equivalent pregnancy outcomes to those of DCDA twins.*

Conclusion *This national study of QCQA quadruplets has shown that multifetal pregnancy reduction improves pregnancy outcome, including a decreased rate of preterm delivery and higher proportion of liveborn children.*

INTRODUCTION

The use of assisted reproductive technology, including ovulation induction and *in-vitro* fertilization, has increased the prevalence of multifetal pregnancy (MFP), including quadruplet pregnancy[1–4]. However, most countries have implemented guidelines to minimize the number of MFP, mainly due to the increased risk of maternal, fetal and neonatal complications[4]. Preterm delivery is the most frequent complication in MFP[5]. In non-reduced quadruplets, studies have reported a pregnancy loss rate of 25%, for example the study conducted by Evans *et al.* in 2002[6]. Furthermore, fetal growth restriction (FGR) affects approximately half of all quadruplets, predisposing these fetuses to low birth weight and long-term complications[7].

MFP reduction is a procedure that was developed in the 1980s, initially for single feticide of an affected fetus in a twin pregnancy, and later implemented in MFP to reduce the number of fetuses[8]. However, there are risks associated with this procedure, including miscarriage, intrauterine fetal death (IUFD) and preterm delivery < 37 weeks (see Table S1). Unfortunately, there is considerable variation among published risk data, which makes it challenging when providing information and counseling to expectant parents.

Due to their rarity, there are only a small amount of published data available regarding quadruplet pregnancy and the interventions used. This nationwide study aimed to compare the pregnancy outcome and perinatal mortality of quadrichorionic quadriamniotic (QCQA) quadruplet pregnancies undergoing fetal reduction with those of non-reduced quadruplets, in a Danish national cohort with complete follow-up.

METHODS

Study population and design

The Danish Fetal Medicine Database (DFMD), which contains data on all pregnancies undergoing prenatal ultrasound examination in Denmark from week 11 onwards, was the primary source of data and pregnancy outcomes. In Denmark, the public healthcare system offers all women a combined first-trimester ultrasound scan and aneuploidy risk assessment at 11–14 weeks and a second-trimester anomaly scan at 18–22 weeks. DFMD and local data (Astraia, GmbH, Germany) from the four Danish departments performing fetal reduction procedures were used to identify reduced and non-reduced quadruplet pregnancies with an estimated due date between January 2008 and December 2018.

In the DFMD, each pregnancy and associated children are linked to the Danish National Birth Register and the Danish National Patient Register by a unique personal identification number (CPR number) that is provided to all citizens at birth or immigration[9]. Furthermore, every encounter with the public healthcare system is identified and documented using the CPR number system. Due to the confidentiality of the CPR number system regarding personally identifiable information, outcomes in our data with low numbers are given as < 3 or as a percentage rather than actual numbers.

Fetal reduction procedure

All fetal reductions performed in Denmark are carried out as outpatient procedures using the same technique, which involves a transabdominal approach, the use of a needle guide, a 20-gauge needle and intracardiac injection of a few mL of 2 mmol/mL potassium chloride to induce asystole. Prophylactic antibiotics were not administered routinely. Fetal medicine specialists performed the procedure themselves or supervized it. To determine the viability of the remaining fetuses, all women underwent an ultrasound examination shortly after the procedure and again 1 week later. Due to their rarity in Denmark, there is no national guideline for managing quadruplet pregnancies or recommended timing of delivery. However, uncomplicated quadruplet pregnancies typically result in delivery at around 32–34 weeks of gestation. These pregnancies undergo bi-weekly growth assessments, with increased monitoring if complications or concerns arise, given their high-risk nature.

Outcome measures

The primary outcome measure was a composite of the following adverse pregnancy outcomes: miscarriage before 24 weeks, stillbirth from 24 weeks, and single, double and triple IUFD. In addition, the number of

liveborn children, gestational age (GA) at delivery, preterm delivery before 28, 32 and 37 weeks and birth weight were assessed. Birth weight *Z*-scores were calculated according to the reference of The Fetal Medicine Foundation (FMF)[10]. Birth weight < 10th percentile was classified as small-for-gestational age (SGA) and < 3rd percentile was defined as FGR. Secondary outcome measures were the following clinically meaningful pregnancy complications: preterm prelabor rupture of membranes (PPROM), pre-eclampsia, placenta previa and placental abruption. Baseline characteristics included maternal age, body mass index, parity and method of conception.

Literature search and systematic review

This systematic review was conducted following PRISMA guidelines[11]. We performed a systematic literature search with the help of an information specialist from the Royal Library of Copenhagen University. Using the terms: "Quadruplet"[MeSH], Quadruplet*[Title/Abstract], Multiple pregnanc*[Title/Abstract], Multifetal [Title/Abstract], Multifetal pregnanc*[Title/Abstract], "Pregnancy Reduction, Multifetal"[MeSH], MFPR[Title/Abstract], Multifetal Pregnancy Reduction*[Title/Abstract], Multifetal Reduction*[Title/Abstract], Embryo Reduction*[Title/Abstract], Selective Fetal Termination*[Title/Abstract], Fetal Reduction*[Title/Abstract], Selective feticide[Title/Abstract] and combinations of these terms, the medical database, PubMed, was searched on 16 April 2023 to access international studies on quadruplets (Figure 1). Two reviewers conducted the systematic review, using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia; www.covidence.org) to screen the results by title and abstract, yielding 47 articles for full-text review, of which 43 could be retrieved. Of these, 13 studies included appropriate outcome data for reduced and/or non-reduced quadruplet pregnancies. All of these studies were also assessed by two reviewers using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE)[12] system, through which the quality of evidence and strength of recommendation are systematically rated, summarized and categorized as being high, moderate, low or very low. The main results are presented in an evidence table, generated using GRADEpro[13] (see Table S1).

Inclusion and exclusion criteria

Included in this study were all QCQA quadruplet pregnancies, either reduced or non-reduced, with four viable fetuses at the 11–14-week ultrasound examination and available pregnancy outcome. As multifetal pregnancy reduction of quadruplet to twin pregnancy (4–2 reduction) is the most frequent intervention in QCQA pregnancies in Denmark, all non-reduced dichorionic diamniotic (DCDA) pregnancies with two viable fetuses at the combined first-trimester risk assessment were included for comparison of their outcome.

Triamniotic or diamniotic quadruplet pregnancies were excluded, as were those with higher-order multiples (≥ five fetuses) in order to provide some uniformity for the data comparison.

Statistical analysis

Data are summarized as percentage with 95% CI for categorical variables and median with interquartile range

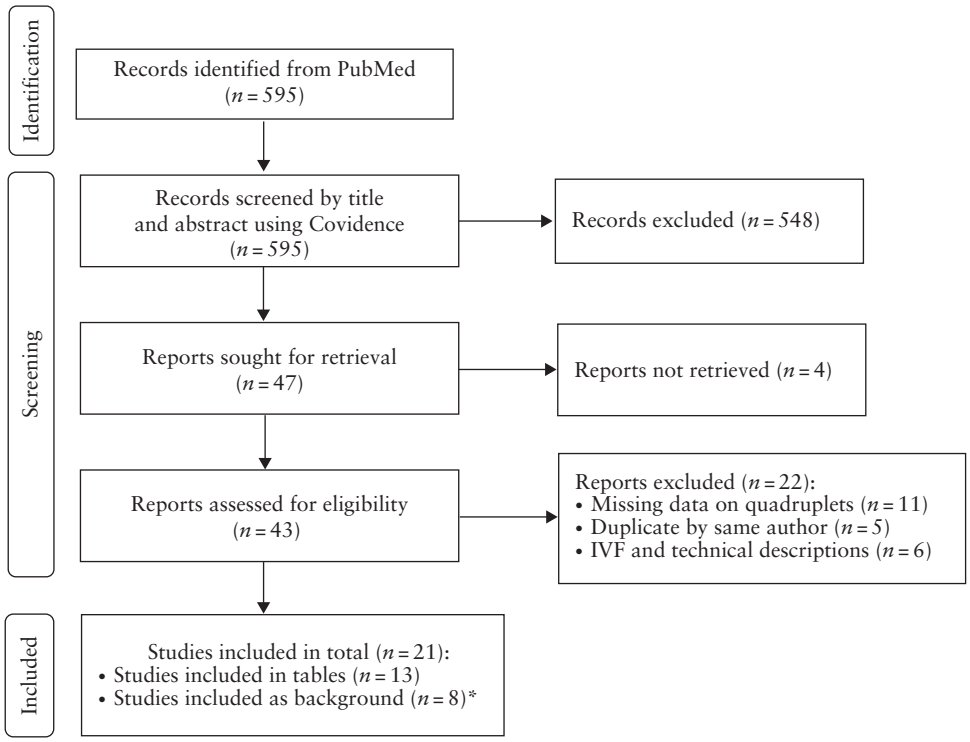

Figure 1 PRISMA flow diagram summarizing inclusion of studies. *Although not meeting all criteria for inclusion in the study, these articles contributed important background information. IVF, *in-vitro* fertilization.

for continuous variables. Statistical tests for differences were performed only between QCQA pregnancies with 4–2 reduction and DCDA pregnancies, due to the small numbers of pregnancies reduced to a singleton (4–1) and non-reduced QCQA pregnancies. The Wilcoxon rank-sum test was performed for continuous variables and Fisher's exact test for categorical variables. A Kaplan–Meier curve was used to illustrate the cumulative incidence of delivery according to GA. All data were analyzed using the statistical software RStudio[14] (version 2023.03.0 + 386 for Mac).

For both reduced and non-reduced quadruplets in the systematic review, included studies were searched for details of pregnancy type and the number of pregnancies, loss (defined as miscarriage and/or IUFD), preterm delivery before 28, 32 and 37 weeks and mean GA at delivery. These data are presented as fractions (*n*/*N*) and percentages when possible. For non-reduced pregnancies, data on spontaneous reduction were also included as an outcome measure, and for reduced pregnancies, the type of reduction was included due to possible effect on outcome measures.

RESULTS

During the study period (2008–2018) in Denmark, the prevalence of QCQA quadruplets was 0.5 per 10 000 pregnancies and that of DCDA twins was 150 per 10 000 pregnancies, with a total of 33 QCQA pregnancies and 9563 DCDA twin pregnancies included in this study.

Among the QCQA pregnancies, three (9.1%) were non-reduced, 28 (84.8%) were reduced 4–2, and fewer than three (6.1%) were reduced 4–1. Fetal reductions were performed by one of 15 operators, at a median GA of 11 + 6 (range, 11 + 3 to 14 + 3) weeks. We found no significant between-group differences in maternal age, body mass index or nulliparity across QCQA quadruplet and DCDA twin pregnancies. Baseline maternal characteristics are summarized in Table 1.

Table 1 Baseline maternal characteristics for study population of quadrichorionic quadriamniotic (QCQA) quadruplet and dichorionic diamniotic (DCDA) twin pregnancies

Characteristic	*QCQA quadruplets*	*DCDA twins*
Pregnancies (*n*)	33	9563
Maternal age (years)	29 (26–32)*	32 (29–35)
BMI (kg/m^2)	22 (19–26)	23 (21–27)
Nulliparous	9/16 (56.3)	2794/6012 (46.5)
Conception		
Spontaneous	1/30 (3.3)*	4846/9184 (52.8)
Ovarian induction	6/30 (20.0)	422/9184 (4.6)
Intrauterine insemination	19/30 (63.3)*	942/9184 (10.3)
In-vitro fertilization	4/30 (13.3)*	2974/9184 (32.4)
Current smoker	0/24 (0)	660/9212 (7.2)
Caucasian ethnicity	21/22 (95.5)	8526/8984 (94.9)

Data are given as median (interquartile range) or *n*/*N* (%), unless stated otherwise. *Significantly different ($P < 0.05$) from DCDA twins. BMI, body mass index.

Pregnancy outcomes for all included QCQA quadruplet pregnancies, according to whether they were reduced, and DCDA twin pregnancies are detailed in Table 2. Outcome data were available for all reduced and non-reduced QCQA pregnancies. Of the non-reduced quadruplets, 66.7% had an adverse pregnancy outcome, of either double or triple IUFD, these being equal in number. Miscarriage < 24 weeks, stillbirth from 24 weeks and single IUFD each contributed equally to the 10.7% composite risk of an adverse pregnancy outcome among 4–2 reductions. Among DCDA twin pregnancies, 3.1% had an adverse outcome, comprising 1.7% due to miscarriage and 1.3% to single IUFD. There was a significantly higher risk of stillbirth from 24 weeks among 4–2-reduced quadruplets (3.6%) compared with DCDA twins (0.1%) ($P < 0.001$).

Non-reduced quadruplets were delivered 2 weeks earlier than 4–2-reduced quadruplets (median GA at delivery, 33 + 0 weeks and 35 + 0 weeks, respectively), whereas DCDA twins were delivered approximately 2.5 weeks later (median GA, 37 + 3 weeks) ($P < 0.001$). The cumulative incidence of delivery is depicted as an inverse Kaplan–Meier curve in Figure 2, displaying how GA at delivery seems to be improved in 4–2-reduced pregnancies compared with non-reduced ones. However, GA at delivery was not extended in the 4–2-reduced pregnancies to that of DCDA pregnancies.

The risk of extreme preterm delivery (< 28 weeks) was 28.6% for non-reduced QCQA quadruplets, 11.8% among 4–2-reduced quadruplet pregnancies and 1.9% in DCDA twin pregnancies ($P < 0.001$). Similarly, preterm delivery rates before 32 and 37 weeks in the 4–2-reduced quadruplet pregnancies were lower than those in the non-reduced quadruplets but higher than those in the DCDA twin pregnancies. However, the relative difference between the 4–2-reduced quadruplet pregnancies and the DCDA twin pregnancies decreased as the GA at delivery increased.

The chance of at least one or two liveborn children was no different or only marginally significantly different between 4–2-reduced QCQA quadruplet pregnancies and DCDA twin pregnancies ($P = 0.050$ and $P = 0.030$, respectively). All non-reduced quadruplet pregnancies resulted in at least one liveborn baby. However, only one-third of non-reduced quadruplets resulted in four liveborn children, delivered on average at 33 gestational weeks. There was a considerable difference in the risk of having no liveborn children across all groups.

The lowest median birth weight of liveborn children of pregnancies starting as QCQA quadruplets was seen in the non-reduced quadruplets (1560 g; FMF *Z*-score, −2.51), then the 4–1-reduced quadruplets (1648 g; FMF *Z*-score −3.37) and the highest was among the 4–2-reduced ones (2200 g; FMF *Z*-score, −1.33). DCDA twin pregnancies reached significantly higher birth weights (median, 2600 g; FMF *Z*-score, −0.97) compared with 4–2-reduced quadruplets ($P < 0.001$). However, the proportion of SGA and FGR children was not significantly different between these two groups ($P = 0.18$ and $P = 0.41$, respectively).

Table 2 Pregnancy outcome of quadrichorionic quadriamniotic (QCQA) quadruplet pregnancies, according to whether they were reduced, and non-reduced dichorionic diamniotic (DCDA) twin pregnancies

	*QCQA quadruplets**			*DCDA twins**	*QCQA 4–2 reduction* vs *DCDA*	
Outcome	*Non-reduced*	*Reduction: 4–1*	*Reduction: 4–2*	*Non-reduced*	*Estimate*†‡	P‡
Pregnancies (*n*)	3	< 3	28	9563		
Expected liveborn infants (*n*)	12	< 3	56	19 126		
GA at delivery (days)	231 (181–268)	187 (160–214)	245 (236–261)	262 (248–266)	255 (254 to 255)	< 0.001
Adverse pregnancy outcome	66.7 (9.4–99.2)	50.0 (1.3–98.7)	10.7 (2.3–28.2)	3.1 (2.7–3.4)	3.80 (0.90–10.9)	0.030
Miscarriage < 24 weeks	0.0 (0.0–70.8)	50.0 (1.3–98.7)	3.6 (0.1–18.3)	1.7 (1.5–2.0)	2.11 (0.12–9.99)	0.46
Stillbirth ≥ 24 weeks	0.0 (0.0–70.8)	0.0 (0.0–84.2)	3.6 (0.1–18.3)	0.1 (0.0–0.1)	70.8 (3.63–459)	< 0.001
Single IUFD	0.0 (0.0–70.8)	—	3.6 (0.1–18.3)	1.3 (1.1–1.5)	2.84 (0.16–13.5)	0.31
Double IUFD	33.3 (0.8–90.6)	—	—	—	—	—
Triple IUFD	33.3 (0.8–90.6)	—	—	—	—	—
One liveborn	33.3 (0.8–90.6)	50.0 (1.3–98.7)	3.6 (0.1–18.3)	1.3 (1.1–1.5)	2.84 (0.16–13.5)	0.31
Two liveborn	33.3 (0.8–90.6)	—	89.3 (71.8–97.7)	96.9 (96.6–97.3)	0.26 (0.09–1.11)	0.030
Three liveborn	0.0 (0.0–70.8)	—	—	—	—	—
Four liveborn	33.3 (0.8–90.6)	—	—	—	—	—
At least one liveborn	100.0 (29.2–100.0)	50.0 (1.3–98.7)	92.9 (76.5–99.1)	98.2 (97.9–98.5)	0.24 (0.07–1.47)	0.050
At least two liveborn	66.7 (9.4–99.2)	—	89.3 (71.8–97.7)	96.9 (96.6–97.3)	0.26 (0.09–1.11)	0.030
At least three liveborn	33.3 (0.8–90.6)	—	—	—	—	—
No liveborn	0.0 (0.0–70.8)	50.0 (1.3–98.7)	7.1 (0.9–23.5)	1.8 (1.5–2.1)	4.25 (0.68–14.4)	0.050
Liveborn children§	58.3 (27.7–84.8)	50.0 (1.3–98.7)	91.1 (80.4–97.0)	97.6 (97.4–97.8)	0.25 (0.11–0.73)	0.004
Preterm delivery						
Liveborn < 28 weeks	28.6 (3.7–71.0)	0.0 (0.0–97.5)	11.8 (4.4–23.9)	1.9 (1.7–2.1)	7.06 (2.69–15.4)	< 0.001
Liveborn < 32 weeks	28.6 (3.7–71.0)	0.0 (0.0–97.5)	15.7 (7.0–28.6)	7.3 (6.9–7.7)	2.36 (1.03–4.77)	0.026
Liveborn < 37 weeks	85.7 (42.1–99.6)	100.0 (2.5–100.0)	68.6 (54.1–80.9)	39.1 (38.3–39.8)	3.41 (1.92–6.34)	< 0.001
Term delivery: liveborn ≥ 37 weeks	14.3 (0.4–57.9)	0.0 (0.0–97.5)	31.4 (19.1–45.9)	60.9 (60.2–61.7)	0.29 (0.16–0.52)	< 0.001
Birth weight of liveborn						
Birth weight (g)	1560 (1130–1573)	1648¶	2200 (1720–2598)	2600 (2218–2900)	2516 (2508 to 2525)	< 0.001
Birth weight (FMF *Z*-score)	−2.51 (−2.56 to −0.59)	−3.37¶	−1.33 (−1.94 to −0.74)	−0.97 (−1.72 to −0.28)	−1.1 (−1.1 to −1.0)	< 0.001
SGA (*Z*-score < 10th centile)	33.3 (9.9–65.1)	50.0 (1.3–98.7)	46.4 (33.0–60.3)	37.6 (36.9–38.3)	1.44 (0.84–2.43)	0.18
FGR (*Z*-score < 3rd centile)	33.3 (9.9–65.1)	50.0 (1.3–98.7)	25.0 (14.4–38.4)	20.6 (20.0–21.1)	1.29 (0.68–2.30)	0.41

*Continuous variables are expressed as median (interquartile range) and categorical variables as % (95% CI). †Continuous variables are expressed by simple linear regression (Intercept α + slope β (95% CI)); categorical variables are expressed by univariate logistic regression (odds ratio (95% CI)). ‡Unadjusted. §As a percentage of expected liveborn infants. ¶$n = 1$. FGR, fetal growth restriction; FMF, Fetal Medicine Foundation; GA, gestational age; IUFD, intrauterine fetal death; SGA, small-for-gestational age.

PPROM was the most common pregnancy complication among 4–2-reduced QCQA quadruplets (14.3%), followed by pre-eclampsia (10.7%). The frequency of PPROM was slightly but non-significantly higher among the 4–2-reduced QCQA quadruplet compared with DCDA twin pregnancies, while the rates for pre-eclampsia were similar among the two groups ($P = 0.92$). Complications of pregnancy are summarized in Table 3.

Literature review

The 13 studies included in the systematic review and their evidence profiles regarding non-reduced and reduced quadruplet pregnancies are summarized in Table S1. A pooled analysis of 11 observational studies[1,6,8,15–22], including 2084 quadruplet pregnancies, showed that quadruplet pregnancies undergoing 4–2 fetal reduction were at increased risk of miscarriage < 24 weeks compared with those undergoing expectant management (odds ratio (OR), 2.17 (95% CI, 1.09–4.31)). A pooled analysis of eight observational studies[1,6,16–19,21,23], including 5317 quadruplet pregnancies, showed that pregnancies undergoing 4–2 fetal reduction were at decreased risk for IUFD (OR, 0.0315 (95% CI, 0.0157–0.0635)).

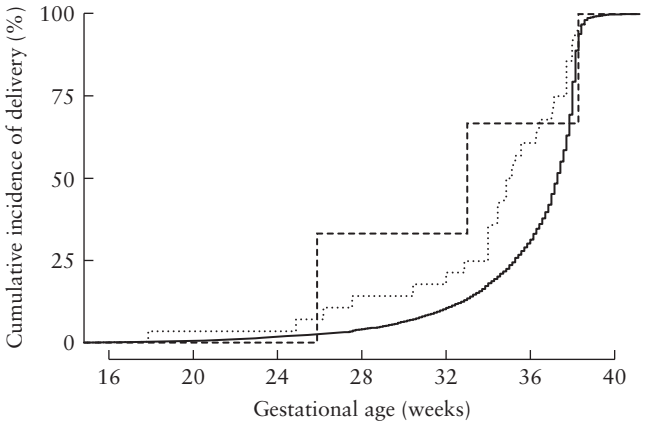

Figure 2 Inverse Kaplan–Meier curve showing cumulative incidence of delivery as a function of gestational age in 28 quadrichorionic quadriamniotic (QCQA) quadruplet pregnancies reduced to twins (·····), three non-reduced QCQA quadruplet pregnancies (----) and 9563 non-reduced dichorionic diamniotic twin pregnancies (——).

Pooled analyses of five[1,6,15,19,24], seven[1,6,15,19,21,22,24] and six[1,6,15,21,22,24] observational studies, including 1720, 1864 and 1856 quadruplet pregnancies, respectively, showed that pregnancies undergoing 4–2 fetal reduction were at decreased risk for preterm delivery < 28 weeks (OR, 0.0477 (95% CI, 0.0094–0.2400)), preterm delivery < 32 weeks (OR, 0.0644 (95% CI, 0.0117–0.3537)) and preterm delivery < 37 weeks (OR, 0.2792 (95% CI, 0.0253–3.0851)). A pooled analysis of seven observational studies[6,8,15,16,19,21,22], including 879 quadruplet pregnancies, found a mean GA at delivery of 30.0 weeks for non-reduced quadruplets, and a mean difference of +5.4 weeks (95% CI, +4.2 to +6.6 weeks) in 4–2-reduced quadruplets. Finally, a pooled analysis of four observational studies[8,16,19,22], including 251 quadruplet pregnancies, found a mean birth weight of 932 g for non-reduced quadruplets, with a mean difference of +1348 g (95% CI, +1134 to +1561) in 4–2-reduced quadruplets.

Overall, the quality of the evidence (according to the GRADE system[12,13]) for all of the included studies and outcomes were rated as very low due to serious/very serious limitations identified during the certainty assessment. It is important to note that all the included studies were observational in nature, which inherently provides low-quality evidence. Further details and the certainty assessment can be found in the evidence table (Table S1). Missing outcome data were reported only in three of the 13 included studies.

DISCUSSION

Principal findings

Multifetal pregnancy reduction was performed in 90.9% of all QCQA quadruplet pregnancies in Denmark between 2008 and 2018. Most quadruplets were reduced to twins (4–2). The overall rate of adverse pregnancy outcome was considerably lower (10.7% *vs* 66.7%) in the 4–2-reduced compared with the non-reduced pregnancies. The rate of adverse pregnancy outcome was higher in 4–2-reduced QCQA quadruplet compared with DCDA twin pregnancies but the difference only just reached statistical significance ($P = 0.030$). Additionally, the 4–2-reduced quadruplets had the highest birth weight among pregnancies starting as QCQA, followed by the

Table 3 Pregnancy complications of quadrichorionic quadriamniotic (QCQA) quadruplet pregnancies, according to whether they were reduced, and non-reduced dichorionic diamniotic (DCDA) twin pregnancies

	*QCQA quadruplets**			*DCDA twins**	*QCQA 4–2 reduction* vs *DCDA*	
Outcome	*Non-reduced*	*Reduction: 4–1*	*Reduction: 4–2*	*Non-reduced*	*Estimate*†‡	P‡
Pregnancies (*n*)	3	< 3	28	9563		
PPROM	0.0 (0.0–70.8)	0.0 (0.0–84.2)	14.3 (4.0–32.7)	10.4 (9.8–11.1)	1.43 (0.42–3.71)	0.51
Pre-eclampsia	0.0 (0.0–70.8)	0.0 (0.0–84.2)	10.7 (2.3–28.2)	10.1 (9.5–10.8)	1.06 (0.25–3.04)	0.92
Placenta previa	0.0 (0.0–70.8)	0.0 (0.0–84.2)	0.0 (0.0–12.3)	1.1 (0.9–1.4)	0.00 (0.00 to ∞)	0.98
Placental abruption	0.0 (0.0–70.8)	0.0 (0.0–84.2)	0.0 (0.0–12.3)	1.0 (0.9–1.3)	0.00 (0.00 to ∞)	0.98

*Expressed as % (95% CI) unless stated otherwise. †Expressed by univariate logistic regression (odds ratio (95% CI)). ‡Unadjusted. ∞, infinite value; PPROM, preterm prelabor rupture of membranes.

4–1-reduced quadruplets, with the lowest birth weight observed in non-reduced quadruplets. DCDA twins had significantly higher birth weights compared with the 4–2-reduced QCQA quadruplet babies. However, there was no significant difference in the proportion of SGA and FGR children between these two groups ($P = 0.18$ and 0.41, respectively).

Comparison with other studies

To our knowledge, no recent systematic reviews have been published comparing reduced and non-reduced quadruplet pregnancies. The primary outcome results from relevant published studies[1,6,8,15–24] are summarized in Table S1. The results from our present study generally agree with those from the previous publications. However, Table S1 highlights that the current literature on quadruplets reports a wide range of risk figures that may be biased by various factors, an issue that we aimed to address in the current study.

The improvements in outcome were most significant following 4–2 reduction[1,8,15,16]. In a retrospective review in 1993, Benshushan *et al.*[25] found that 4–2 reduction was associated with higher rates of liveborn children (92.6%) compared with non-reduced pregnancies (83.0%). We found similar results, although there was only a small number of non-reduced quadruplets in our study. In our study, there was a 92.9% chance of at least one liveborn following 4–2 reduction.

Two studies by Evans *et al.*[2,6], in 2004 and 2002, found a decrease in the risk of fetal demise in reduced quadruplets compared with the risk before reduction. Our results showed a very low rate (3.6%) of single IUFD in 4–2-reduced pregnancies, whilst two of the three non-reduced quadruplets had either double or triple IUFD. A single-center study from 2002 by Strauss *et al.*[5] reported that limitations to the intrauterine environment inherent in MFP cause FGR. Torok *et al.*[24], in 1998, and Depp *et al.*[26], in 1996, found that quadruplets reduced to twins had a greater risk of FGR than did non-reduced twins. These results are different from ours: we did not see a difference in FGR between 4–2 reduced quadruplets and non-reduced DCDA twins. The risk of spontaneous pregnancy reduction in couples deciding to continue without fetal reduction in quadruplet pregnancy has been reported in a few studies[6,17,18,27]. Although our cohort lacks directly comparable data due to missing GA data in reports of single, double and triple IUFD, this is crucial information when counseling couples about the risks of continuing a quadruplet pregnancy without fetal reduction.

Clinical implications

Considering our results alongside those reported in the literature, multifetal pregnancy reduction in quadruplets is supported as a safe procedure. Our data on adverse pregnancy outcomes in reduced quadruplets are generally lower than those reported in the literature, which might reflect the generally low-risk nature of the population in Denmark. Also, the adherence to a national procedural protocol and the use of a needle guide could have influenced our results, but this is speculative since we cannot address these effects directly due to the retrospective study design. Better outcomes are generally achieved in quadruplet pregnancies which undergo fetal reduction than in non-reduced pregnancies, but these benefits come at the expense of a small increase in the risk of miscarriage, stillbirth and IUFD in the remaining fetuses, considered to be due to procedure-related complications, although the numbers in our study were too small for meaningful comparison, particularly in the non-reduced quadruplet group. Our findings will provide valuable information for clinicians and parents considering the risks and benefits of multifetal pregnancy reduction.

Strengths, limitations and external validity

The national DFMD, which contains data on all quadruplet pregnancies in Denmark, both reduced and non-reduced, provides valuable data relevant in counseling couples about the risks and possible benefits associated with quadruplet pregnancy and the option of fetal reduction. By using nationwide Danish data, we limited the risk of selection bias, due to the high standards of the Danish national registries combined with free and equal access to healthcare in the Danish public healthcare system, which might contribute to pregnant women's compliance and willingness to undergo ultrasound scans and risk assessments in the first and second trimesters. Our results indicate a low degree of missing data, which minimizes the risk of bias and increases the validity of our findings. Another strength of this study is our reporting of pregnancy outcomes in terms of liveborn children and at least one, two, three or four liveborn children, ensuring transparency of our results. These outcomes were chosen to address the issues seen in previous studies, which did not specify rates of different numbers of liveborn children.

There are also some limitations associated with our study. The retrospective register-based design increases the possibility of bias due to incomplete or incorrect recording of data. Despite being a national study, the rarity of quadruplets in Denmark and the small study population is a limitation, particularly the 4–1 reductions and the non-reduced quadruplets, which is also reflected in the corresponding wide-ranging 95% CIs.

Conclusions

The risk of an adverse pregnancy outcome is high in quadrichorionic quadruplets with no intervention, and most couples in Denmark chose fetal reduction. Quadrichorionic quadruplet reduced to twin pregnancies had a decreased risk of adverse pregnancy outcome, preterm delivery and low birth weight, which could potentially reduce fetal mortality and morbidity in these high-risk pregnancies. However, the degree of these decreases did not bring the rates down to the levels in dichorionic twin

pregnancies. The rate of miscarriage in quadrichorionic quadruplets reduced to twins was low, supporting fetal reduction in these quadruplets as a safe procedure.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Comparison of 4–2 fetal reduction with expectant management for quadruplet pregnancy, based on the literature