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Risk of fetal loss after chorionic villus sampling in twin pregnancy derived from propensity score matching analysis

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KEYWORDS: adverse pregnancy outcome; chorionic villus sampling; CVS; first-trimester screening; invasive procedure; invasive testing; miscarriage; pregnancy complications; prenatal diagnosis

CONTRIBUTION

What are the novel findings of this work?
In women with twin pregnancy, the risk of fetal loss following chorionic villus sampling (CVS) depends on a series of maternal and pregnancy characteristics and, to a lesser extent, on the procedure itself. The risk factors for spontaneous fetal loss are similar to those that lead to CVS being performed, and, in women with a high background risk of fetal loss, the risk of fetal loss following the invasive test could paradoxically be lower than if they did not have the invasive test, for the simple reason that prenatal diagnosis often converts spontaneous loss of a chromosomally abnormal fetus into pregnancy termination.

What are the clinical implications of this work?
The true procedure-related risk of fetal loss from CVS in twin pregnancy can be derived only by examining women with a low background risk of fetal loss, and in such women, the risk of fetal loss may increase by about 3.5% after CVS.

ABSTRACT

Objective *To estimate the risk of fetal loss associated with chorionic villus sampling (CVS) in twin pregnancy, using propensity score analysis.*

Methods *This was a multicenter cohort study of women with twin pregnancy undergoing ultrasound examination at 11–13 weeks' gestation, performed in eight fetal medicine units in which the leadership were trained at the Harris Birthright Research Centre for Fetal Medicine in London, UK, and in which the protocols for screening, invasive testing and pregnancy management are similar. The risk of death of at least one fetus was compared between pregnancies that had and those that did not have CVS, after propensity score matching (1:1 ratio). This procedure created two comparable groups by balancing the maternal and pregnancy characteristics that lead to CVS being performed, similar to how randomization operates in a randomized clinical trial.*

Results *The study population of 8581 twin pregnancies included 445 that had CVS. Death of one or two fetuses at any stage during pregnancy occurred in 11.5% (51/445) of pregnancies in the CVS group and in 6.3% (515/8136) in the non-CVS group (*$P < 0.001$*). The propensity score algorithm matched 258 cases that had CVS with 258 non-CVS cases; there was at least one fetal loss in 29 (11.2%) cases in the CVS group and in 35 (13.6%) cases in the matched non-CVS group (odds ratio (OR), 0.81; 95% CI, 0.48–1.35;* $P = 0.415$*). However, there was a significant interaction between the risk of fetal loss after CVS and the background risk of fetal loss; when the background risk was higher, the risk of fetal loss after CVS decreased (OR, 0.46; 95% CI, 0.23–0.90), while, in pregnancies with a lower background risk of fetal loss, the risk of fetal loss after CVS increased (OR, 2.45; 95% CI, 0.95–7.13). The effects were statistically significantly different (P-value of the interaction =* 0.005*). For a pregnancy in which the background risk of fetal loss was about 6% (the same as in our non-CVS population),*

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there was no change in the risk of fetal loss after CVS, but, when the background risk was more than 6%, the posterior risk was paradoxically reduced, and when the background risk was less than 6%, the posterior risk increased exponentially; for example, if the background risk of fetal loss was 2.0%, the relative risk was 2.8 and the posterior risk was 5.6%.

Conclusion *In twin pregnancy, after accounting for the risk factors that lead to both CVS and spontaneous fetal loss and confining the analysis to pregnancies at lower prior risk, CVS seems to increase the risk of fetal loss by about 3.5% above the patient's background risk.*
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INTRODUCTION

The procedure-related risk of fetal loss following chorionic villus sampling (CVS) in twin pregnancy has not been investigated in a randomized controlled trial. Four small studies reported contradictory results concerning the risk of CVS-related miscarriage, as compared to controls that did not undergo invasive testing[1–4]. The issue of the CVS-related risk of fetal loss was addressed by a recent multicenter study of 8581 twin pregnancies undergoing ultrasound examination at 11–13 weeks' gestation, including 445 twin pregnancies that had CVS[5]. Multivariable logistic regression analysis with backward stepwise elimination was used to examine whether CVS provided a significant independent contribution to the prediction of the risk of fetal loss after adjusting for maternal and pregnancy characteristics. The study reported that, in twin pregnancies undergoing CVS, compared to those that did not have CVS, there was a 2-fold increased risk of fetal loss at any stage in pregnancy, and the factors providing a significant independent contribution to the prediction of fetal loss were increased maternal weight, black racial origin, monochorionicity, large intertwin discordance in crown–rump length (CRL), high fetal nuchal translucency thickness (NT) and low serum pregnancy-associated plasma protein-A (PAPP-A). There was a trend for an increased risk of fetal loss from CVS after adjustment for maternal and pregnancy characteristics, but this did not reach statistical significance[5].

An alternative to multivariable logistic regression analysis for assessment of the CVS-related risk of fetal loss is propensity score analysis, in which an attempt is made to emulate a randomized controlled trial by matching each CVS case to a similar non-CVS control, adjusting for those maternal and pregnancy characteristics that are known to be risk factors for subsequent fetal loss[5–11]. This approach of propensity score analysis was carried out in singleton pregnancies to estimate the CVS-related risk of miscarriage[12]. The study reported that, although there was no significant difference in the rate of miscarriage between the CVS and non-CVS groups, there was an interaction between the estimated risk of aneuploidy and the risk of miscarriage; the risk of miscarriage following the procedure in patients at higher risk of aneuploidy and who therefore presented the worst profile for spontaneous pregnancy loss, was reduced, whilst the opposite effect was seen in the group of patients at lower risk of aneuploidy, in whom the risk of miscarriage following CVS was increased[12]. The authors concluded that the true effect of CVS could be examined only in low-risk pregnancies; in the high-risk group, there were many aneuploid pregnancies that resulted in termination, thereby masking potential spontaneous miscarriages that would have occurred had the pregnancies not been terminated.

The objective of this study was to investigate the risk of CVS-related fetal loss in twin pregnancy, using propensity score analysis in the same dataset in which we previously examined the risk using multivariable logistic regression analysis[5].

METHODS

Study design and population

This was a multicenter cohort study of women with twin pregnancy from eight fetal medicine units in the UK, Spain, Italy, Bulgaria and Portugal, in which the leadership were trained at the Harris Birthright Research Centre for Fetal Medicine in London, UK, and in which the protocols for screening, invasive testing and pregnancy management are similar[5]. At 11–13 weeks, we recorded maternal demographic characteristics and carried out ultrasound examination for, first, determination of gestational age from the measurement of CRL of the larger twin[13], second, determination of chorionicity from the number of placentae and the presence or absence of the lambda sign at the intertwin membrane–placental junction[14], third, exclusion of vanishing twin[15], fourth, diagnosis of major fetal abnormalities[16], fifth, assessment of intertwin discordance in CRL (difference between the two fetuses expressed as a percentage of the larger one), because a large discordance is associated with adverse pregnancy outcome[10], and, sixth, measurement of NT in each fetus for assessment of risk for trisomy and determination of whether the NT in one or both fetuses was $\geq 95^{th}$ percentile of our reference range for CRL[17], because high NT is associated with adverse pregnancy outcome[11]. In most, but not all, pregnancies, maternal serum free β-human chorionic gonadotropin (β-hCG) and PAPP-A were measured using automated machines (DelfiaXpress system, PerkinElmer Life and Analytical Sciences, Waltham, MA, USA; Brahms Kryptor system, Thermo Fisher Scientific, Berlin, Germany; or Cobas e411 system, Roche Diagnostics, Penzberg, Germany) and the values were expressed as multiples of the median (MoM) after adjustment for maternal weight, height, racial origin, parity, smoking status, method of conception and machine used for the measurement[18,19].

In each center, details of maternal characteristics and the findings at the 11–13-week assessment were recorded in a fetal database. Data on pregnancy outcome were obtained from the maternity computerized records or the general medical practitioners of the women and were also

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recorded in the database. Anonymized data from each center were provided to K.H.N. for further analysis. This study constitutes a retrospective analysis of data derived from a routine clinical service and did not require ethics committee approval.

Chorionic villus sampling

All CVS procedures were carried out transabdominally under ultrasound guidance. In cases of monochorionic twins, only one sample was obtained, whereas, in cases of dichorionic twins, it was generally aimed to obtain a sample from both placentae. Most operators used separate needle entries to sample each placenta, but a few used a double-needle system. In this system, the outer needle with a stylet was inserted across both placentae, the stylet was removed and an inner needle was used to sample the most distant placenta, then the stylet was reinserted into the outer needle which was withdrawn to within the proximal placenta, and, after removal of the stylet, a sample was obtained through the outer needle.

Inclusion and exclusion criteria

The inclusion criteria for this study were dichorionic, monochorionic diamniotic or monochorionic monoamniotic twin pregnancy with two live fetuses at 11–13 weeks' gestation and known pregnancy outcome. In cases in which CVS was carried out, only those with a normal result were included. We excluded pregnancies with a chromosomal abnormality or major defect diagnosed prenatally or postnatally, those with twin reversed arterial perfusion sequence or conjoined twins and those in which amniocentesis, embryo reduction or termination was carried out.

Outcome measure

The primary outcome was the rate of fetal loss (pregnancies with one or two miscarriages or fetal deaths) at any stage following CVS or the first-trimester scan.

Statistical analysis

Descriptive data were expressed as median and interquartile range (IQR) or as *n* (%). Comparisons between treatment groups were performed using the Mann–Whitney *U*-test or Fisher's exact test, as appropriate. Analyses were run on a complete-case basis, and the number of pregnancies included in each analysis was reported wherever necessary. The level of significance was set at 0.05.

Propensity score matching analysis was performed to assess the effect of CVS on the risk of fetal loss, adjusting for the confounding bias caused by the different maternal and pregnancy characteristics in the two study groups. The propensity score was defined as the conditional probability of having CVS given the measured covariates in order to balance covariates in the two groups. To obtain the propensity score, we fitted a logistic regression model with CVS as the dependent variable and then modeled the conditional probability of having CVS as a function of baseline and those clinical characteristics associated with having CVS. We used the propensity score to match, without replacement, each complete CVS case with the non-CVS case that had the closest propensity score at a 1:1 ratio in order to optimize the precision of the estimate of the association and limit bias. Additionally, we accepted cases only if the difference in propensity score between the matched cases was small (caliper of 0.1), resulting in excellent balance between the CVS and non-CVS cases as matched samples[20]. We computed standardized differences for all variables included in the propensity score before and after matching to assess the effect of matching on the imbalance. We deemed a 10% standardized difference to be the limit for a correct balance. After matching, we compared the fetal-loss rate between CVS and non-CVS cases as matched groups. Finally, we calculated an odds ratio (OR) to quantify the association between CVS and fetal loss using univariable logistic regression fitted by generalized estimating equations to account for matched data. To assess the possible interaction between propensity score and CVS (i.e. whether the effect on the risk of fetal loss differed when CVS was performed in pregnancies with different propensity-score profiles), we divided the matched cases into those with a propensity score lower than its median (50% of cases) and those with a propensity score higher than its median (50% of cases). We then calculated the OR for each group using logistic regression analysis and assessed the significance of the difference by calculating the *P*-value of the interaction.

The statistical software package R was used for data analyses[21]. The R package MatchIt[22] was used for matching with the propensity score and calculating the standardized differences. Analysis of matched cases was performed using the R package Geepack[23].

RESULTS

Study population

The study population of 8581 twin pregnancies that fulfilled the inclusion criteria was comprised of 445 pregnancies that underwent CVS and 8136 that did not have CVS. Patient and pregnancy characteristics of the two groups are summarized in Table 1[5]. Measurement of CRL, NT and heart rate in each fetus was carried out in all pregnancies, but serum free β-hCG and PAPP-A were measured in only 90.6% (7776/8581) of pregnancies. In the CVS group, compared to the non-CVS group, median maternal age, intertwin discordance in CRL, maximum fetal NT, serum free β-hCG MoM and minimum fetal heart rate were significantly higher, and maternal weight and PAPP-A MoM were significantly lower. The incidence of black racial origin, conception by *in-vitro* fertilization and dichorionic twins was lower in the CVS group compared to the non-CVS group. The only parameters that were not significantly different between the groups were smoking status, parity and gestational age at the time of the ultrasound assessment.

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In monochorionic twin pregnancies, an 18-G or 20-G needle was used to sample the placenta. In dichorionic twin pregnancies, either a 17-G or 19-G double needle system was used to obtain a sample from both placentae through a single uterine insertion, two separate 18-G or 20-G needles were introduced twice into the uterus to obtain a sample from each placenta, or an 18-G or 20-G needle was used to sample only one of the placentae.

Death of one or two fetuses at any stage during pregnancy occurred in 11.5% (51/445) of pregnancies in the CVS group and in 6.3% (515/8136) of those in the non-CVS group ($P < 0.001$).

Propensity score matching

We calculated the propensity score for each case in the study population based on the probability of having CVS. The predictive model included maternal age, method of conception, maternal weight, smoking status, race, parity, chorionicity, gestational age at the time of the ultrasound assessment, intertwin CRL discordance, maximum NT, minimum fetal heart rate and serum free β-hCG and PAPP-A (Table 2). The propensity score algorithm matched 258 CVS cases with 258 non-CVS cases, largely reducing the initial imbalance between women who had and those who did not have CVS, with between-group standardized differences for all variables being lower than the recommended 10% limit (Figure 1, Table 3). The number of cases with any fetal loss was 29 (11.2%) in the CVS group and 35 (13.6%) in the matched non-CVS group. Overall, propensity score analysis did not identify a significant association between CVS and fetal loss (OR, 0.81; 95% CI, 0.48–1.35; $P = 0.415$).

To investigate whether the effect of CVS on fetal loss was the same in women at higher risk of having CVS as compared to those at lower risk, we divided the 516 matched cases into two equal groups based on the median of the propensity score, considering the propensity score as a proxy for the prior risk of fetal loss (i.e. the variables increasing the risk of having CVS are those increasing the risk of spontaneous fetal loss). The median propensity score was 0.209 (IQR, 0.141–0.358) in the higher-risk group ($n = 258$) and 0.037 (IQR, 0.019–0.061) in the lower-risk group ($n = 258$). In the higher-risk group, fetal loss occurred in 11.7% (15/128) of cases in the CVS group and in 22.3% (29/130) of cases in the non-CVS group (OR, 0.46; 95% CI, 0.23–0.90). In contrast, in the lower-risk group, fetal loss occurred in 10.8% (14/130) of cases in the CVS group and in 4.7% (6/128) of cases in the non-CVS group (OR, 2.45; 95% CI, 0.95–7.13); these effects were statistically different (*P*-value of the interaction = 0.005). These results suggest that CVS has

Table 1 Maternal and pregnancy characteristics of the study population of 8581 twin pregnancies, according to whether chorionic villus sampling (CVS) was performed

Variable	*No CVS (n = 8136)*	*CVS (n = 445)*	P
Age (years)	33.6 (29.9–36.8)	35.7 (32.2–38.6)	< 0.001
Method of conception			< 0.001
Spontaneous	5077 (62.4)	308 (69.2)	0.004
In-vitro fertilization	2848 (35.0)	119 (26.7)	< 0.001
Ovulation drugs	211 (2.6)	18 (4.0)	0.070
Weight (kg)	66.0 (59.0–76.6)	64.0 (57.8–72.0)	< 0.001
Active smoker			0.078
No	7448 (91.5)	418 (93.9)	
Yes	688 (8.5)	27 (6.1)	
Racial origin			< 0.001
Non-black	7458 (91.7)	432 (97.1)	
Black	678 (8.3)	13 (2.9)	
Parity			0.961
Nulliparous	4442 (54.6)	242 (54.4)	
Parous	3694 (45.4)	203 (45.6)	
Chorionicity			0.004
Dichorionic	6314 (77.6)	316 (71.0)	0.002
Monochorionic diamniotic	1749 (21.5)	122 (27.4)	0.004
Monochorionic monoamniotic	73 (0.9)	7 (1.6)	0.195
Gestational age at scan (weeks)	12.9 (12.5–13.3)	12.9 (12.4–13.4)	0.545
Crown–rump length discordance (%)	3.57 (1.57–6.47)	4.74 (1.98–8.45)	< 0.001
Maximum nuchal translucency thickness (mm)	1.90 (1.64–2.10)	2.60 (1.92–3.40)	< 0.001
β-human chorionic gonadotropin MoM*	1.01 (0.70–1.46)	1.16 (0.74–1.77)	< 0.001
Pregnancy-associated plasma protein-A MoM*	1.10 (0.78–1.50)	0.84 (0.54–1.19)	< 0.001
Minimum fetal heart rate (bpm)	157 (152–161)	158 (153–162)	0.012
Outcome			< 0.001
Both fetuses alive	7621 (93.7)	394 (88.5)	
One or two fetal deaths	515 (6.3)	51 (11.5)	

Data are given as median (interquartile range) or *n* (%). *Measurements of serum free β-human chorionic gonadotropin and pregnancy-associated plasma protein-A were missing for 689 (8.4%) cases in the no-CVS group and 116 (26.1%) in the CVS group. MoM, multiples of the median.

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Table 2 Propensity score model used to calculate the probability of chorionic villus sampling being performed in twin pregnancy, using logistic regression analysis

Variable	*aOR (95% CI)*	P
Age (in years)	1.096 (1.068–1.126)	< 0.001
Method of conception		
Spontaneous	Reference	—
In-vitro fertilization	0.534 (0.381–0.743)	< 0.001
Ovulation drugs	1.438 (0.717–2.661)	0.273
Weight (in kg)	0.984 (0.975–0.994)	0.001
Active smoker		
No	Reference	—
Yes	0.801 (0.469–1.293)	0.388
Racial origin		
Non-black	Reference	—
Black	0.529 (0.266–0.958)	0.049
Parity		
Nulliparous	Reference	—
Parous	1.068 (0.810–1.408)	0.641
Chorionicity		
Dichorionic	Reference	—
MCDA	1.031 (0.747–1.409)	0.851
MCMA	1.246 (0.289–3.686)	0.727
GA at scan (in weeks)	0.703 (0.550–0.898)	0.005
CRL discordance (in %)	1.025 (0.998–1.050)	0.059
Maximum NT (in mm)	7.328 (5.988–9.030)	< 0.001
β-hCG MoM	1.518 (1.340–1.712)	< 0.001
PAPP-A MoM	0.263 (0.195–0.351)	< 0.001
Minimum FHR (in bpm)	1.019 (0.999–1.041)	0.067

β-hCG, β-human chorionic gonadotropin; aOR, adjusted odds ratio; CRL, crown–rump length; FHR, fetal heart rate; GA, gestational age; MCDA, monochorionic diamniotic; MCMA, monochorionic monoamniotic; MoM, multiples of the median; NT, nuchal translucency thickness; PAPP-A, pregnancy-associated plasma protein-A.

a different effect on the risk of fetal loss when the risk of aneuploidy is high compared to when it is low.

To assess the increase in the risk of fetal loss after CVS according to patient and pregnancy characteristics, we used our previously published model (Table S1)[5] to calculate the background risk of pregnancy loss for each case. We then calculated the relative risk after CVS using propensity score analysis (Figure 2). For a pregnancy in which the background risk of fetal loss was about 6% (the same as in our non-CVS population), there was no change in the risk of fetal loss after CVS; however, when the background risk was more than 6%, the posterior risk was paradoxically reduced, and when the background risk was less than 6%, the posterior risk increased exponentially; for example, if the background risk was 5.0%, 4.0%, 3.0% or 2.0%, the relative risks were 1.2, 1.5, 1.9 and 2.8 and the posterior risks were 6.0%, 6.0%, 5.7% and 5.6%, respectively (Figure 2).

DISCUSSION

Principal findings

The main finding of this study is that the CVS-related risk of fetal loss in twin pregnancy is not constant, but rather it depends mainly on the prior risk of fetal loss. In women with patient and pregnancy characteristics suggesting a high risk of fetal loss, the posterior risk of fetal loss after CVS is paradoxically reduced, whereas, in women with a low background risk of fetal loss, there may be a 3.5% increase in risk following CVS.

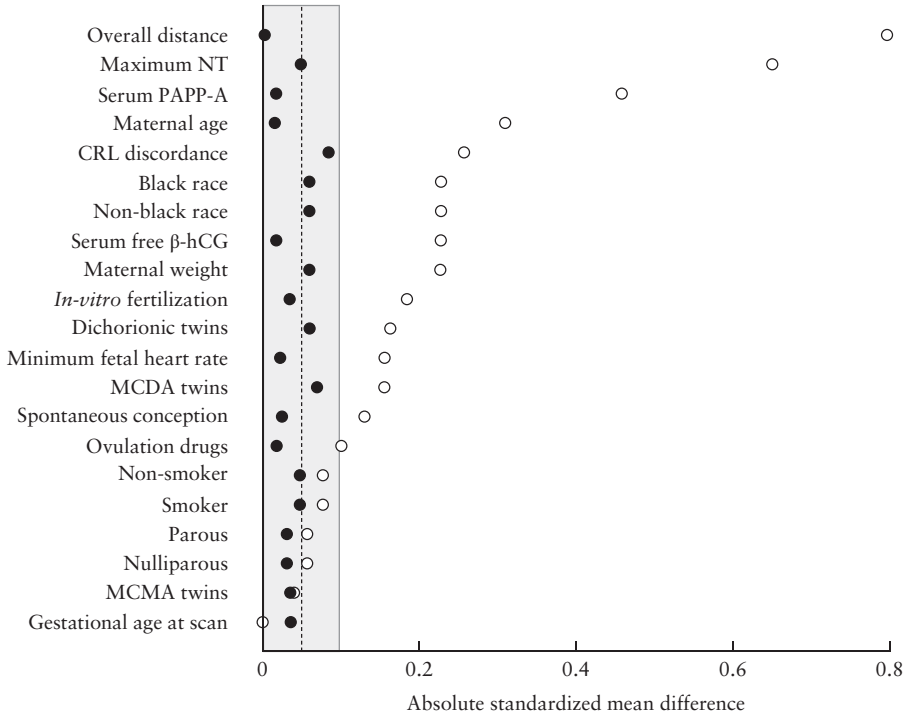

Figure 1 Propensity score matching of twin pregnancies that had chorionic villus sampling (CVS) with those that did not have CVS. Shaded area represents 10% standardized difference between covariates. ○, unmatched; ●, matched; β-hCG, β-human chorionic gonadotropin; CRL, crown–rump length; MCDA, monochorionic diamniotic; MCMA, monochorionic monoamniotic; NT, nuchal translucency thickness; PAPP-A, pregnancy-associated plasma protein-A.

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Table 3 Maternal and pregnancy characteristics of 516 twin pregnancies, according to whether chorionic villus sampling (CVS) was performed, matched by propensity score

Variable	*No CVS* (n = *258*)	*CVS* (n = *258*)	P
Age (years)	35.5 (31.7–38.5)	35.7 (31.7–38.4)	0.765
Method of conception			0.881
Spontaneous	172 (66.7)	167 (64.7)	0.711
In-vitro fertilization	73 (28.3)	79 (30.6)	0.629
Ovulation drugs	13 (5.0)	12 (4.7)	1
Weight (kg)	63.0 (56.3–71.9)	64.0 (57.1–74.0)	0.525
Active smoker			0.712
No	244 (94.6)	241 (93.4)	
Yes	14 (5.4)	17 (6.6)	
Racial origin			0.693
Non-black	243 (94.2)	246 (95.3)	
Black	15 (5.8)	12 (4.7)	
Parity			0.660
Nulliparous	130 (50.4)	136 (52.7)	
Parous	128 (49.6)	122 (47.3)	
Chorionicity			1
Dichorionic	189 (73.3)	188 (72.9)	1
Monochorionic diamniotic	66 (25.6)	66 (25.6)	1
Monochorionic monoamniotic	3 (1.2)	4 (1.6)	1
Gestational age at scan (weeks)	12.9 (12.6–13.3)	12.9 (12.4–13.4)	0.875
Crown–rump length discordance (%)	4.81 (2.76–8.09)	4.16 (1.94–8.23)	0.115
Maximum nuchal translucency thickness (mm)	2.30 (1.90–2.80)	2.30 (1.80–3.00)	0.674
β-human chorionic gonadotropin MoM	1.16 (0.76–1.74)	1.21 (0.74–1.73)	0.667
Pregnancy-associated plasma protein-A MoM	0.88 (0.63–1.18)	0.84 (0.50–1.26)	0.182
Minimum fetal heart rate (bpm)	158 (153–162)	157 (153–162)	0.779
Outcome			0.505
Both fetuses alive	223 (86.4)	229 (88.8)	
One or two fetal deaths	35 (13.6)	29 (11.2)	

Data are given as median (interquartile range) or *n* (%). MoM, multiples of the median.

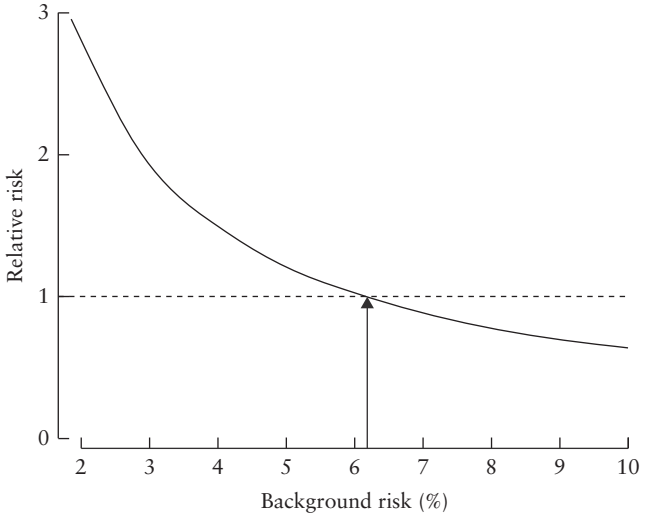

Figure 2 Estimated relative risk of fetal loss after chorionic villus sampling in twin pregnancy, for a modeled prior risk of fetal loss of between 2% and 10%.

Interpretation of results and comparison with findings of previous studies

In our previous study attempting to estimate the CVS-related risk of fetal loss in twin pregnancies, we used multivariable logistic regression analysis to adjust for maternal and pregnancy characteristics and found that, after such adjustment, CVS did not provide a significant independent contribution to the prediction of the risk of fetal loss[5].

Propensity score analysis creates homogeneous groups that are suitable for comparison and has emerged as a robust methodology that is well suited to estimating causal effects from observational data while accounting for a greater number of confounder effects than for which classical multivariable analysis is able to adjust[24,25]. In our matching approach, we used a 1:1 ratio and considered only matched cases with a small difference in propensity score to ensure that the CVS and non-CVS groups had a very similar risk profile. The most likely explanation for the finding that CVS appears to be protective against fetal loss in cases with a high background risk is that invasive testing leads to the diagnosis of major aneuploidy followed by elective pregnancy termination in cases that would have otherwise resulted in spontaneous miscarriage. To try to avoid this selection bias, we studied separately the effect of CVS on fetal loss in cases with a lower probability of having CVS and in those with a higher probability. Contrary to high-risk cases, CVS increases the risk of fetal loss by about 3.5% in low-risk women.

Our findings in twin pregnancies are consistent with those of a previous study investigating the risk of miscarriage after CVS in singleton pregnancies in which propensity score analysis was used to match 2122 CVS cases with 2122 non-CVS cases[12]. Overall, there was no significant difference between groups in the risk of miscarriage following CVS (OR, 0.72; 95% CI, 0.48–1.10), but, after dividing the matched population into two equal groups based on the median of the propensity score (with one group having a higher risk of aneuploidy than

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the other), there was a significant decrease in the risk of miscarriage after CVS in the higher risk group (OR, 0.47; 95% CI, 0.28–0.76) and a significant increase in the lower risk group (OR, 2.87; 95% CI, 1.13–7.30)[12].

Strengths and limitations

The main strength of this study is the large study population, which made it possible to match 258 CVS cases with 258 controls that had a very similar risk profile, allowing fair comparisons between groups and even subgroup analysis. Moreover, the multicenter and multioperator nature of the study makes the results generalizable to other experienced fetal medicine units.

The main limitation of the study is the non-randomized design. Although propensity score analysis is a well-accepted method to emulate randomized trials when they are not feasible, we could balance only those maternal and pregnancy characteristics that had been recorded; therefore, we cannot disregard the possibility of some residual confounding. Finally, since it is impossible to define all potential factors that contribute to fetal loss, it is likely that the inclusion and exclusion criteria of the study may have introduced bias resulting in a higher rate of fetal loss in pregnancies that did not have CVS. For example, fetuses with a chromosomal abnormality are at increased risk of fetal death, and, in the CVS group, all such cases were excluded, whereas, in the non-CVS group, some of the fetal losses may have been the consequence of an undiagnosed chromosomal abnormality.

Conclusions

The risk of fetal loss following CVS in twin pregnancy depends on a series of maternal and pregnancy characteristics and, to a lesser extent, on the procedure itself. The risk factors for fetal loss are similar to those that make CVS necessary and, in women at high prior risk of fetal loss, the risk of fetal loss following the invasive test could paradoxically be lower than if they did not have the invasive test, for the simple reason that prenatal diagnosis often converts spontaneous loss of a chromosomally abnormal fetus into pregnancy termination. As shown in this study, the CVS-related risk of fetal loss can become apparent by examining women at low risk of fetal loss, and, in such cases, there may be up to an approximately 3.5% increase in the risk of fetal loss following CVS.

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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 Model for prediction of fetal loss from maternal and pregnancy characteristics in twin pregnancy[5]

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Riesgo de muerte fetal tras una biopsia de vellosidades coriónicas en el embarazo de gemelos derivado del análisis de pareamiento por puntaje de propensión

RESUMEN

Objetivo. Estimar el riesgo de muerte fetal asociado a la biopsia de vellosidades coriónicas (BVC) en el embarazo de gemelos, mediante un análisis de pareamiento por puntaje de propensión.

Métodos. Este fue un estudio de cohortes multicéntrico de mujeres con embarazo de gemelos que se sometieron a un examen ecográfico a las 11–13 semanas de gestación, realizado en ocho unidades de medicina fetal en las que la gerencia se formó en el Harris Birthright Research Centre for Fetal Medicine de Londres (Reino Unido), en las cuales los protocolos de cribado, pruebas agresivas y la atención médica al embarazo son similares. Se comparó el riesgo de muerte de al menos un feto entre los embarazos a los que se les practicó la BVC y los que no se les practicó, tras un pareamiento por puntaje de propensión (relación 1:1). Este procedimiento creó dos grupos comparables en los que las características de la madre y el embarazo que se asocian con la BVC estaban equilibradas, de manera similar a cómo funciona la aleatorización en un ensayo clínico aleatorizado.

Resultados. La población del estudio fue de 8581 embarazos de gemelos e incluyó 445 a los que se les practicó una BVC. La muerte de uno o dos fetos en cualquier fase del embarazo se produjo en el 11,5% (51/445) de los embarazos en el grupo con BVC y en el 6,3% (515/8136) en el grupo sin BVC (P<0,001). El algoritmo del puntaje de propensión emparejó 258 casos a los que se les practicó una BVC con 258 casos sin BVC; hubo al menos una muerte fetal en 29 (11,2%) casos del grupo con BVC y en 35 (13,6%) casos del grupo emparejado sin BVC (razón de momios [RM], 0,81; IC 95%, 0,48–1,35; P=0,415). Sin embargo, hubo una interacción significativa entre el riesgo de muerte fetal después de la BVC y el riesgo previo de muerte fetal; cuando el riesgo previo era mayor, el riesgo de muerte fetal después de la BVC disminuyó (RM, 0,46; IC 95%, 0,23–0,90), mientras que en los embarazos con un riesgo previo de muerte fetal menor, el riesgo de muerte fetal después de la BVC aumentó (OR, 2,45; IC 95%, 0,95–7,13). Los efectos fueron significativamente diferentes desde el punto de vista estadístico (valor P de la interacción=0,005). Para un embarazo en el que el riesgo previo de muerte fetal era de aproximadamente el 6% (el mismo que en la población sin BVC), no hubo ningún cambio en el riesgo de muerte fetal tras la BVC, pero, cuando el riesgo previo era superior al 6%, el riesgo posterior se redujo, paradójicamente, y cuando el riesgo previo era inferior al 6%, el riesgo posterior aumentó exponencialmente; por ejemplo, si el riesgo previo de muerte fetal era del 2,0%, el riesgo relativo era del 2,8 y el riesgo posterior fue del 5,6%.

Conclusión. En los embarazos de gemelos, después de tener en cuenta los factores de riesgo que conducen tanto a la BVC como a la pérdida espontánea del feto y limitando el análisis a los embarazos con un riesgo previo menor, la BVC parece aumentar el riesgo de pérdida del feto en aproximadamente un 3,5% por encima del riesgo previo de la paciente.

从倾向度匹配分析获得双胎妊娠中绒膜绒毛取样后妊娠丢失的风险

摘要

目的采用倾向度分析，估计双胎妊娠中绒膜绒毛取样（CVS）相关的妊娠丢失风险。

方法这是一项多中心人群队列研究，研究对象包含在八家胎儿医学中心进行超声检查的孕 11-13 周双胎妊娠妇女。这些医学中心的领导层都曾在英国伦敦的哈里斯胎儿医学出生权利研究中心（Harris Birthright Research Centre for Fetal Medicine）接受过培训，其筛查、侵入性检查及妊娠管理医疗方案均类似。至少一胎死亡的风险在倾向度匹配（1：1 比率）后在进行和未进行 CVS 的妊娠之间进行了比较。通过比较致使进行 CVS 的产妇特征及妊娠特征，类似于随机化在随机临床试验中操作，该程序创建了两个可比组。

结果 本研究人群共 8581 例双胎妊娠，含进行过 CVS 的 445 例。在妊娠期任何阶段有一胎或双胎死亡的，在 CVS 组中有 11.5%（51/445），在未进行 CVS 组中有 6.3%（515/8136）（P<0.001）。倾向度算法配对了进行过 CVS 的 258 例和未进行过 CVS 的 258 例；在 CVS 组中至少一胎妊娠丢失的有 29 例（11.2%），而在配对的未进行 CVS 组中有 35 例（13.6%）（比值比（OR），0.81；95%CI，0.48 – 1.35，P=0.415）。然而，在 CVS 之后妊娠丢失风险与妊娠丢失的背景风险之间有显著的相互影响；当背景风险较高时，CVS 后妊娠丢失的风险下降（OR，0.46；95%CI，0.23 – 0.90），而在妊娠丢失背景风险较低的妊娠中，妊娠丢失风险在 CVS 后增加（OR，2.45；95%CI，0.95 – 7.13）。该影响在统计学上有显著差异（相互影响的 P 值=0.005）。对于妊娠丢失背景风险在 6%左右的妊娠（在我们未进行 CVS 的人群中也是一样），CVS 后妊娠丢失风险没有变化，但是当妊娠丢失背景风险在 6%以上时，事后风险反常地减少了，而当妊娠丢失背景风险小于 6%时，事后风险却成倍增加；例如，如妊娠丢失的背景风险是 2.0%，相对风险为 2.8，事后风险为 5.6%。

结论 在双胎妊娠中，在解释了导致 CVS 和自然妊娠丢失的风险因素之后，并将分析局限在先前风险较低的妊娠，CVS 似乎将妊娠丢失风险在患者的背景风险之上增加了 3.5%左右。

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