Ultrasound Obstet Gynecol 2019; **54**: 452–457
Published online 6 September 2019 in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.20293

Procedure-related risk of miscarriage following chorionic villus sampling and amniocentesis

J. BETA[1], W. ZHANG[1], S. GERIS[1], V. KOSTIV[1] and R. AKOLEKAR[1,2]

[1]*Fetal Medicine Unit, Medway Maritime Hospital, Gillingham, UK;* [2]*Institute of Medical Sciences, Canterbury Christ Church University, Chatham, UK*

KEYWORDS: amniocentesis; chorionic villus sampling; CVS; fetal demise; miscarriage; procedure-related risk

CONTRIBUTION

What are the novel findings of this work?
The procedure-related risks of miscarriage following chorionic villus sampling and amniocentesis are not significantly different from those in women who did not undergo an invasive procedure.

What are the clinical implications of this work?
The procedure-related risks of miscarriage following chorionic villus sampling and amniocentesis carried out by expert operators in specialist fetal medicine centers are considerably lower than currently quoted to women. The information provided to women who are considering these procedures for prenatal diagnosis should be revised and made uniform across all recommendations and guidelines.

ABSTRACT

Objectives *To estimate the procedure-related risks of miscarriage following chorionic villus sampling (CVS) and amniocentesis in a large unselected screened population, and to determine whether these risks are consistent with those reported in systematic reviews and meta-analyses.*

Methods *This was a retrospective cohort study carried out on data obtained from a large fetal medicine unit in the UK between January 2009 and May 2018. We included all women with singleton pregnancy who booked for pregnancy care at our unit before 20 weeks' gestation, after excluding those with multiple pregnancy, major fetal defect, pregnancy termination and loss to follow-up. We estimated the risk of miscarriage in women who underwent a CVS or amniocentesis as well as in those who did not have an invasive procedure. The procedure-related risk of miscarriage was estimated as risk difference (95% CI) between the two groups. Univariate and multivariate regression analyses were used to derive odds ratios (95% CI) and determine which maternal and pregnancy characteristics provided a significant contribution in the prediction of miscarriage and whether CVS or amniocentesis provided a significant independent contribution.*

Results *During the study period, 45 120 singleton pregnancies were booked for pregnancy care at our hospital, of which 1546 had an invasive procedure. We excluded 1429 (3.2%) pregnancies due to fetal defects, termination of pregnancy or missing outcomes. Of the 43 691 pregnancies included in the study population, 861 underwent CVS and 375 amniocentesis. In pregnancies that underwent CVS, the risk of miscarriage was 1.5% (13/861), compared with 1.2% (476/39 152) in pregnancies that had first-trimester combined screening and did not have an invasive procedure (*$P = 0.437$*). In pregnancies that underwent an amniocentesis, the risk of miscarriage was 0.8% (3/375), compared with 1.2% (491/42 463) in those that did not undergo an invasive procedure (*$P = 0.520$*). Univariate and multivariate regression analysis demonstrated that there was no significant contribution in the prediction of the risk of miscarriage from CVS (*$P = 0.399$ *and* $P = 0.592$*, respectively) or amniocentesis (*$P = 0.543$ *and* $P = 0.550$*, respectively). The risk of procedure-related loss attributed to CVS was 0.29% (95% CI, −0.53 to 1.12%) and that following amniocentesis was −0.36% (95% CI, −1.26 to 0.55%), which was not significantly different from the risk in women who did not have any procedure.*

Conclusions *The procedure-related risks of miscarriage following CVS and amniocentesis in our study are considerably lower than those currently quoted and are consistent with the estimates of such risks reported by systematic reviews and meta-analyses. Copyright © 2019 ISUOG. Published by John Wiley & Sons Ltd.*

Correspondence to: Prof. R. Akolekar, Institute of Medical Sciences, Canterbury Christ Church University, Rowan Williams Court, Chatham ME4 4UF, UK (e-mail: ranjit.akolekar@canterbury.ac.uk)

Accepted: 30 March 2019

INTRODUCTION

Amniocentesis and chorionic villus sampling (CVS) are invasive procedures carried out for prenatal diagnosis. It is essential that women are provided with accurate evidence-based information regarding the risk of miscarriage following these invasive procedures. However, there is still considerable variation in recommendations from professional bodies regarding procedure-related risk of miscarriage quoted to women, with some reporting that the additional risk following CVS is up to 1–2% and that following amniocentesis is 1%[1–5]. Recent systematic reviews and meta-analyses, as well as large population and cohort studies, have shown that the procedure-related risk of miscarriage following invasive procedures carried out by specialists in fetal medicine centers is much lower than that currently reported[6–11]. There is a need to update and standardize the information provided to women, to allow them to make informed decisions based on accurate data.

The objectives of our study were to estimate the procedure-related risks of miscarriage following CVS and amniocentesis in a large unselected population screened in a specialist fetal medicine unit, and to determine whether these risks are consistent with those reported in systematic reviews and meta-analyses.

PATIENTS AND METHODS

Study population

This was a retrospective cohort study of data obtained at the Fetal Medicine Centre at Medway NHS Foundation Trust, UK, during the period of 1 January 2009 to 31 May 2018. In our unit, all women booking their pregnancy care prior to 14 weeks' gestation are offered an appointment at 11–13 weeks' gestation for dating of the pregnancy by measurement of fetal crown–rump length, assessment of fetal anatomy and combined screening for trisomies 13, 18 and 21. The assessment of risk for aneuploidy from combined screening is based on maternal age, measurement of fetal nuchal translucency (NT) thickness and maternal serum free β-human chorionic gonadotropin (β-hCG) and pregnancy-associated plasma protein-A (PAPP-A)[12–14]. Women booking after 14 weeks' gestation are offered an ultrasound scan for dating of the pregnancy, assessment of fetal anatomy and assessment of risk of fetal aneuploidy from second-trimester serum biochemical testing[15]. At each of these visits, maternal demographic characteristics and medical history are recorded on an electronic database (Viewpoint version 5.6; GE Medical Systems, Zipf, Austria).

Invasive procedures

Women who were deemed to be at high risk for fetal aneuploidy and those with major fetal defects diagnosed on ultrasound were offered the option of invasive prenatal diagnosis. CVS is offered as the procedure of choice up to 15 weeks' gestation and amniocentesis is offered after this gestational age. All procedures were carried out by either a specialist in fetal medicine or a trainee under direct supervision of a specialist. All procedures were carried out transabdominally under direct ultrasound guidance with a free-hand technique and using standard antiseptic precautions for outpatient procedures with no routine use of antibiotic prophylaxis before or after the procedure. The CVS procedures were carried out using a 17 G × 17 cm linear echo CVS needle (Rocket® LX™ Chorionic Villus Sampling Set, Rocket Medical PLC, Watford, UK). The amniocentesis procedures were carried out using 22 G × 15 cm EchoTip® amniocentesis needle (Cook Medical, Bloomington, IN, USA).

Inclusion criteria

We included all singleton pregnancies that were booked during the study period at our hospital and Fetal Medicine Centre for pregnancy care before 20 weeks' gestation. We excluded multiple pregnancies, pregnancies with major fetal defects, terminations of pregnancy and cases lost to follow-up. All pregnancies meeting the inclusion criteria were divided into two groups: the invasive group that included women who underwent a CVS or an amniocentesis procedure, and the control group comprising women who did not have any invasive procedure. Miscarriage was defined as a pregnancy loss prior to 24 weeks' gestation. We compared the risks of miscarriage in pregnancies that underwent CVS and amniocentesis to those in pregnancies that did not have an invasive procedure. The procedure-related risk of pregnancy loss following any invasive procedure was calculated as a risk difference between the two groups.

Statistical analysis

Comparison of the maternal and pregnancy characteristics in the outcome groups was performed using the χ^2-square test and Fisher's exact test for categorical variables and the Mann–Whitney *U*-test for continuous variables. Significance was assumed at 5% and *post-hoc* Bonferroni correction was used to adjust for multiple comparisons where necessary.

Data for risks of miscarriage were entered into contingency tables and absolute risks were estimated by determining the prevalence of miscarriage in the study groups. Univariate and multivariate logistic regression analysis was used to determine which of the maternal and pregnancy characteristics provided a significant contribution in the prediction of miscarriage. To determine whether either CVS or amniocentesis had any significant independent prediction of miscarriage, we estimated unadjusted and adjusted odds from univariate and multivariate regression analysis to derive the odds ratio (OR) (95% CI). The estimates of procedure-related risks of miscarriage from CVS or amniocentesis were calculated as a risk difference (95% CI).

The statistical package SPSS Statistics for Windows version 24.0 (IBM Corp., Armonk, NY, USA) was used for data analyses.

RESULTS

Study population

During the study period (1 January 2009 to 31 May 2018), 45 120 singleton pregnancies were booked for pregnancy care at our hospital. Of these, 43 574 (96.6%) women did not undergo an invasive procedure and 1546 (3.4%) had invasive prenatal diagnosis, including 1127 (72.9%) who had CVS, 404 who had amniocentesis (26.1%) and 15 (1.0%) who underwent both procedures. We excluded a total of 1429 (3.2%) pregnancies, due to major fetal defects or because they ended in termination of pregnancy ($n = 475$), and due to missing follow-up data ($n = 954$). Therefore, the study population included 43 691 singleton pregnancies with complete outcome data, comprising 507 (1.2%) that ended in miscarriage prior to 24 weeks' gestation and 43 184 (98.8%) that delivered a phenotypically normal neonate. In the study population of 43 691 pregnancies, 40 013 (91.6%) underwent first-trimester combined screening and 3678 (8.4%) pregnancies were booked for pregnancy care late, at between 14 and 24 weeks' gestation. In the study cohort, we carried out a total of 1236 invasive procedures in 1228 patients (eight underwent both CVS and amniocentesis), including 861 (69.7%) CVS and 375 (30.3%) amniocentesis procedures.

The maternal and pregnancy characteristics of the study cohort according to incidence of miscarriage are compared in Table 1. In pregnancies that ended in miscarriage compared with those that did not, the median maternal height was smaller, more women were of Afro-Caribbean, South Asian, East Asian or mixed racial origin, more women had conceived following assisted conception, and there was higher prevalence of chronic hypertension. Maternal characteristics in pregnancies that underwent CVS or amniocentesis compared with those that did not are presented in Tables S1 and S2.

Table 1 Maternal and pregnancy characteristics of 43 691 singleton pregnancies included in study cohort, according to whether they ended in miscarriage prior to 24 weeks' gestation

Characteristic	*No miscarriage (n = 43 184)*	*Miscarriage (n = 507)*
Age (years)	28.1 (24.3–32.0)	28.0 (24.1–33.0)
Weight (kg)	68.8 (59.7–81.1)	69.6 (59.1–85.0)
Height (cm)	164 (160–169)	163 (159–167)*
Racial origin		
Caucasian	39 615 (91.7)	427 (84.2)
Afro-Caribbean	1342 (3.1)	26 (5.1)†
South Asian	1860 (4.3)	40 (7.9)*
East Asian	147 (0.3)	6 (1.2)*
Mixed	220 (0.5)	8 (1.6)†
Conception		
Spontaneous	42 497 (98.4)	489 (96.4)
Assisted	687 (1.6)	18 (3.6)*
Cigarette smoker	6558 (15.2)	86 (17.0)
History of medical disorder		
Chronic hypertension	375 (0.9)	14 (2.8)*
Diabetes mellitus	316 (0.7)	6 (1.2)
Connective-tissue disorder	63 (0.1)	0
Thrombophilia	43 (0.1)	0
Asthma	2223 (5.1)	33 (6.5)
Epilepsy	254 (0.6)	3 (0.6)
Nulliparous	20 104 (46.6)	209 (41.2)†

Data are given as median (interquartile range) or *n* (%).
Significance level: *$P < 0.0001$; †$P < 0.01$.

Factors predicting risk of miscarriage in study population

The maternal and pregnancy characteristics associated with risk of miscarriage were examined using univariate and multivariate regression analysis (Table 2). After adjustment for confounding factors in multivariate analysis, the maternal characteristics associated with a subsequent risk of miscarriage following a first-trimester scan at 11–14 weeks' gestation were advanced maternal age, weight, height, racial origin, method of conception and chronic hypertension, but not cigarette smoking or other medical disorders such as diabetes mellitus, epilepsy or asthma. These maternal characteristics providing a significant contribution in the multivariate analysis formed the *a-priori* risk for miscarriage. The components of first-trimester combined screening that provided a significant contribution in prediction of miscarriage were $\log_{10}$ *a-priori* risk, an increased fetal NT $\geq 95^{th}$ percentile, serum PAPP-A multiples of the median (MoM) ≤ 0.3 and reversed a-wave in the ductus venosus, but not serum free β-hCG MoM ($P = 0.913$).

Procedure-related risk of miscarriage after CVS and amniocentesis

In the study population, the risk of miscarriage following invasive prenatal diagnostic procedures was 1.3% (16/1228) compared with 1.2% (491/42 463) in pregnancies that did not have an invasive procedure ($P = 0.636$). Univariate regression analysis demonstrated that there was no significant prediction for the risk of miscarriage from invasive procedures ($P = 0.636$). Multivariate regression analysis demonstrated that the addition of invasive procedures to the combination of $\log_{10}$ *a-priori* risk from maternal factors and components of first-trimester combined screening, including fetal NT, serum PAPP-A MoM and flow in the ductus venosus, did not provide any significant contribution ($P = 0.415$) to the prediction of miscarriage. The risk of procedure-related loss attributed to any invasive procedure was 0.1% (95% CI, −0.5% to 0.8%), which was not significantly different from the risk in women who did not undergo an invasive procedure.

In pregnancies that underwent CVS, the risk of miscarriage was 1.5% (13/861) compared with 1.2% (476/39 152) in pregnancies that had first-trimester

Table 2 Univariate and multivariate regression analysis to assess contribution from maternal and pregnancy characteristics and independent contribution of chorionic villus sampling and amniocentesis in prediction of miscarriage

	Univariate		*Multivariate*	
Variable	*OR (95% CI)*	P	*OR (95% CI)*	P
Maternal characteristic				
Age ≥ 40 years	2.48 (1.65–3.74)*	< 0.001	1.92 (1.26–2.93)†	0.001
Weight in kg	1.00 (1.00–1.01)	0.225	1.01 (1.00–1.01)†	0.005
Height in cm	0.96 (0.95–0.98)*	< 0.001	0.96 (0.95–0.98)*	< 0.001
Racial origin				
Caucasian (reference)	1.00		1.00	
Afro-Caribbean	2.00 (1.35–2.97)†	0.001	1.74 (1.16–2.60)†	0.006
South Asian	2.07 (1.49–2.89)*	< 0.001	1.80 (1.28–5.54)†	0.001
East Asian	4.11 (1.80–9.37)†	0.001	3.31 (1.43–7.65)†	0.006
Mixed	3.83 (1.88–7.82)*	< 0.001	3.77 (1.84–7.73)*	< 0.001
Method of conception				
Spontaneous (reference)	1.00		1.00	
Assisted	2.06 (1.27–3.37)	0.004	1.92 (1.16–3.19)†	0.023
Cigarette smoker	1.20 (0.95–1.52)	0.128	—	—
History of medical disorder				
Chronic hypertension	3.34 (1.95–5.74)*	< 0.001	2.70 (1.55–4.71)*	< 0.001
Diabetes mellitus	1.40 (0.57–3.39)	0.462	—	—
Asthma	1.31 (0.92–1.87)	0.137	—	—
Epilepsy	1.03 (0.33–3.23)	0.960	—	—
Maternal/pregnancy characteristic				
Maternal characteristics ($\log_{10}$ *a priori)*	10.61 (6.94–16.23)*	< 0.001	10.56 (6.66–16.64)*	< 0.001
Fetal NT ≥ 95th percentile	3.34 (2.18–5.11)*	< 0.001	2.91 (1.75–4.86)*	< 0.001
Reversed a-wave in ductus venosus	2.58 (1.53–4.35)*	< 0.001	2.22 (1.24–4.00)†	0.008
Serum free β-hCG ≤ 0.3 MoM	1.59 (0.82–3.10)	0.171	—	—
Serum PAPP-A ≤ 0.3 MoM	2.63 (1.70–4.06)*	< 0.001	2.46 (1.59–3.81)*	< 0.001
Invasive procedure				
Chorionic villus sampling	1.27 (0.73–2.21)	0.399	—	—
Amniocentesis	0.69 (0.22–2.16)	0.543	—	—

Significance level: *$P < 0.0001$; †$P < 0.01$. β-hCG, β-human chorionic gonadotropin; MoM, multiples of the median; NT, nuchal translucency thickness; OR, odds ratio; PAPP-A, pregnancy-associated plasma protein-A.

combined screening and no invasive procedure ($P = 0.437$). Univariate regression analysis demonstrated that there was no significant contribution from CVS in the prediction of the risk of miscarriage ($P = 0.399$). Multivariate regression analysis demonstrated that the addition of CVS to the combination of $\log_{10}$ *a-priori* risk from maternal factors and components of first-trimester combined screening, including fetal NT, serum PAPP-A MoM and flow in the ductus venosus, did not provide any significant contribution ($P = 0.592$) to the prediction of miscarriage. The risk of procedure-related loss attributed to CVS was 0.29% (95% CI, −0.53 to 1.12%; $P = 0.483$), which was not significantly different from the risk in women who did not have an invasive procedure.

In pregnancies that underwent an amniocentesis, the risk of miscarriage was 0.8% (3/375), compared with 1.2% (491/42 463) in women who did not have an invasive procedure during their pregnancy ($P = 0.520$). Univariate regression analysis demonstrated that there was no significant contribution from amniocentesis in the prediction of miscarriage ($P = 0.543$). Multivariate regression analysis demonstrated that the addition of amniocentesis to the combination of $\log_{10}$ *a-priori* risk from maternal factors, did not provide any significant contribution ($P = 0.550$) to the prediction of miscarriage. The risk of procedure-related loss attributed to amniocentesis was −0.36% (95% CI, −1.26 to 0.55%; $P = 0.442$), which was not significantly different from that in women who did not undergo an invasive procedure.

DISCUSSION

Principal findings

The findings of our study demonstrate that, first, there was no significant increase in the risk of miscarriage following CVS or amniocentesis compared with that in pregnancies that did not undergo an invasive procedure; second, miscarriage is associated with maternal and pregnancy characteristics; and third, the estimate of procedure-related risk of miscarriage from CVS is 0.29% (95% CI, −0.53 to 1.12%) and that from amniocentesis is −0.36% (95% CI, −1.26 to 0.55%).

Strengths and limitations

The strengths of the study are, first, examination of a large unselected cohort of consecutively screened pregnancies in a specialist fetal medicine unit; second, procedures were either carried out or directly supervised by specialist fetal medicine consultants; and third, accurate ascertainment

of maternal and pregnancy characteristics along with pregnancy outcomes to ensure valid estimation of the risk of miscarriage.

The limitations of our study relate to its retrospective design, but we accounted for the potential biases arising from this by ensuring that the study population was an unselected screened cohort over a fixed period of time, thus avoiding selection bias in choosing cases or controls. Similarly, the possibility of recall bias was unlikely in our study as the risk factors associated with the adverse outcome were recorded systematically in our database before the occurrence of the invasive procedure and pregnancy outcome. Thirdly, all invasive procedures were carried out transabdominally, and therefore, the estimates of risks only relate to procedures carried out transabdominally.

Comparison with existing literature

Our findings are consistent with results of systematic reviews and meta-analyses that report that the procedure-related risk of miscarriage from invasive procedures is much lower than that currently quoted to women[6–11]. A large Danish nationwide population-based study of 147 987 singleton pregnancies, which included 5072 women who underwent CVS and 1809 who underwent amniocentesis, reported that the procedure-related risk of miscarriage at 21 days following CVS was −0.21% and that at 28 days following amniocentesis was 0.56%[7]. A recent meta-analysis of large controlled studies, which took into account the results of the Danish population-based study, reported that there were 623 losses in 64 901 women who underwent amniocentesis and 327 losses in 19 000 women who underwent CVS, and the procedure-related risks of miscarriage, after taking into account the miscarriage rate in controls that did not have an invasive procedure, was about 0.35% and 0.30%, respectively[8]. The findings of our study are also consistent with a previous study reporting that the characteristics that are significantly associated with risks of miscarriage, such as increased fetal NT, decreased serum PAPP-A and reversed a-wave in the ductus venosus, are the very factors that are associated with increased risk for aneuploidy, and therefore, the uptake of CVS[9]. Thus, in estimation of the procedure-related risk of invasive procedures, it is necessary to adjust for these confounding factors. The findings of our study, based on a large unselected cohort of more than 45 000 pregnancies, are consistent with the results from systematic reviews and meta-analyses, confirming that the procedure-related risks of miscarriage from invasive procedures are considerably lower than those currently advocated by professional bodies[6,8].

Implications for clinical practice

The main clinical implication of our study is that the procedure-related risk of miscarriage is considerably lower than that currently stated to women, and therefore, in view of these results, as well as those from recent meta-analyses[6,8,16], the procedure-related risks associated with CVS and amniocentesis should be revised and made uniform across all recommendations and guidelines. It is important to note that the results from our study are those from a specialist fetal medicine center, so all the procedures in the study were either undertaken or directly supervised by fetal medicine specialists. This point is also emphasized in the meta-analyses as the studies that were included in the analysis were those performed by experts in large specialist centers; thus, the reported procedure-related risks are those from expert operators[6]. There is evidence highlighting the fact that the risk of miscarriage from invasive procedures is related to the skill and experience of the operator[17–19]. It may be worthwhile considering that invasive prenatal diagnostic procedures should be undertaken by skilled operators in specialist centers to minimize procedure-related complications, rather than by operators who do these procedures infrequently, and for whom the procedure-related risks may well be higher.

Conclusion

The procedure-related risks of miscarriage following CVS and amniocentesis in our study are considerably lower than those currently quoted and consistent with the estimates of such risks reported by systematic reviews and meta-analyses.

REFERENCES

1. NHS Fetal Anomaly Screening Programme. Chorionic villus sampling (CVS) and amniocentesis: information for parents. FASP88, 2017. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/805913/Chorionic_villus_sampling_and_amniocentesis_information_for_parents.pdf
2. Royal College of Obstetricians and Gynaecologists (RCOG). *Amniocentesis and Chorionic Villus Sampling*. Green Top Guideline No. 8. RCOG: London, 2010.
3. Royal College of Obstetricians and Gynaecologists (RCOG). Chorionic villus sampling and amniocentesis. Information for you. RCOG Press: London, 2011. https://www.rcog.org.uk/globalassets/documents/patients/patient-information-leaflets/pregnancy/pi-chorionic-villus-sampling-and-amniocentesis.pdf
4. Invasive prenatal testing for aneuploidy. ACOG Practice Bulletin No. 88, December 2007. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2007; **110**: 1459–1467.
5. Wilson RD, Langlois S, Johnson JA. Mid-trimester amniocentesis fetal loss rate: Society of Obstetricians and Gynaecologists of Canada. *J Obstet Gynaecol Can* 2007; **29**: 586–595.
6. Akolekar R, Beta J, Picciarelli G, Ogilvie C, D'Antonio F. Procedure-related risk of miscarriage following amniocentesis and chorionic villus sampling: a systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2015; **45**: 16–26.
7. Wulff CB, Gerds TA, Rode L, Ekelund CK, Petersen OB, Tabor A; Danish Fetal Medicine Study Group. Risk of fetal loss associated with invasive testing following combined first-trimester screening for Down syndrome: a national cohort of 147 987 singleton pregnancies. *Ultrasound Obstet Gynecol* 2016; **47**: 38–44.
8. Beta J, Lesmes-Heredia C, Bedetti C, Akolekar R. Risk of miscarriage following amniocentesis and chorionic villus sampling: a systematic review of the literature. *Minerva Ginecol* 2018; **70**: 215–219.
9. Akolekar R, Bower S, Flack N, Bilardo CM, Nicolaides KH. Prediction of miscarriage and stillbirth at 11-13 weeks and the contribution of chorionic villus sampling. *Prenat Diagn* 2011; **31**: 38–45.
10. Odibo AO, Gray DL, Dicke JM, Stamilio DM, Macones GA, Crane JP. Revisiting the fetal loss rate after second-trimester genetic amniocentesis: a single center's 16-year experience. *Obstet Gynecol* 2008; **111**: 589–595.
11. Odibo AO, Dicke JM, Gray DL, Oberle B, Stamilio DM, Macones GA, Crane JP. Evaluating the rate and risk factors for fetal loss after chorionic villus sampling. *Obstet Gynecol* 2008; **112**: 813–819.
12. Robinson HP, Fleming JE. A critical evaluation of sonar crown rump length measurements. *Br J Obstet Gynaecol* 1975; **182**: 702–710.
13. Snijders RJ, Noble P, Sebire N, Souka A, Nicolaides KH; Fetal Medicine Foundation First Trimester Screening Group. UK multicentre project on assessment of risk of trisomy 21 by maternal age and fetal nuchal-translucency thickness at 10-14 weeks of gestation. *Lancet* 1998; **352**: 343–346.

14. Kagan KO, Wright D, Baker A, Sahota D, Nicolaides KH. Screening for trisomy 21 by maternal age, fetal nuchal translucency thickness, free beta-human chorionic gonadotropin, and pregnancy associated plasma protein-A. *Ultrasound Obstet Gynecol* 2008; **31**: 618–624.
15. NHS England. *NHS Fetal Anomaly Screening Programme Handbook*. PHE Publications, 2018. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/749742/NHS_fetal_anomaly_screening_programme_handbook_FINAL1.2_18.10.18.pdf
16. Salomon LJ, Sotiriadis A, Wulff CB, Odibo A, Akolekar R. Risk of miscarriage following amniocentesis or chorionic villus sampling: systematic review of literature and updated meta-analysis. *Ultrasound Obstet Gynecol* 2019; **54**: 442–451.
17. Wijnberger LDE, van der Schouw YT, Christiaens GCML. Learning in medicine: chorionic villus sampling. *Prenat Diagn* 2000; **20**: 241–246.
18. Tabor A, Vestergaard CH, Lidegaard O. Fetal loss rate after chorionic villus sampling and amniocentesis: an 11-year national registry study. *Ultrasound Obstet Gynecol* 2009; **34**: 19–24.
19. Bakker M, Birnie E, Robles de Medina P, Sollie KM, Pajkrt E, Bilardo CM. Total pregnancy loss after chorionic villus sampling and amniocentesis: a cohort study. *Ultrasound Obstet Gynecol* 2017; **49**: 599–606.

SUPPORTING INFORMATION ON THE INTERNET

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

Table S1 Maternal and pregnancy characteristics in singleton pregnancies undergoing chorionic villus sampling compared with those that did not have an invasive procedure

Table S2 Maternal and pregnancy characteristics in singleton pregnancies undergoing amniocentesis compared with those that did not have an invasive procedure