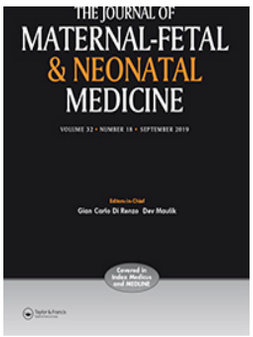

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ORIGINAL ARTICLE

Risk of preeclampsia in of women who underwent chorionic villus sampling

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ABSTRACT

Objective: To assess the risk of preeclampsia in women who underwent chorionic villus sampling (CVS).

Study design: This is a retrospective, single-center, cohort study. All consecutive singleton gestations who underwent chorionic villus sampling from January 2014 to January 2016 were included in the study. The primary outcome was the incidence of preeclampsia. Subgroup analysis in women with beta thalassemic trait was performed. Logistic regression, presented as adjusted odds ratio (aOR) with the 95% of confidence interval (CI), was performed.

Results: Five hundred forty-seven women who underwent CVS, and 1532 women who did not were analyzed. Women who underwent CVS had a significantly lower risk of preeclampsia (4.4 versus 8.0%; aOR 0.53, 95%CI 0.34–0.83), and late-onset preeclampsia (3.3 versus 6.1%; aOR 0.52, 95%CI 0.31–0.87). No statistically significant differences were found in preeclampsia with severe features, early-onset preeclampsia, and preterm birth (PTB). Women who underwent CVS due to thalassemic trait had a lower incidence of preeclampsia compare to those women who did not undergo CVS (3.3 versus 8.0%; aOR 0.39, 95%CI 0.14–0.87), while no differences were found comparing women who underwent CVS due to thalassemic trait with women who underwent CVS due to other reasons.

Conclusions: Women who underwent first trimester CVS had a lower risk of preeclampsia compared to those who did not.

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CVS; preeclampsia; hypertension

Introduction

Preeclampsia is a leading cause of maternal and neonatal mortality and morbidity, complicating up to 5–10% of all pregnancies [1]. The etiology of preeclampsia is unknown [1], as well as the associated risk factors [1–10]. Although much of the literature has focused on the degree of trophoblastic invasion by the placenta, also local environmental factors and iron deficiency are associated [11]. Placental disruption during early pregnancy may enhance abnormal placentation, and invasive prenatal diagnosis, including chorionic villus sampling (CVS) has been suggested to increase the risk of hypertensive complications and preeclampsia in some studies, while others showed a decrease in these complications [12–14].

Thus, the aim of this study was to estimate the risk of preeclampsia after first trimester CVS.

Materials and methods

This was a retrospective cohort study. Clinical records of all consecutive singleton pregnancies who underwent CVS at the University of Naples "Federico II" (Naples, Italy) from January 2014 to August 2016 were collected in a dedicated merged database. Women with multiple gestations, and those with chronic hypertension were excluded.

In our institution, routine procedure during the study period was that CVS was performed by MFM attendings transabdominally using a single-needle technique under ultrasound guidance between 12 and 15 weeks of gestation with a 20- or 22-ga needle.

The primary outcome was the incidence of preeclampsia [15]. The secondary outcomes were intrauterine growth restriction (i.e. ultrasound estimated fetal weight <10th centile), preeclampsia with severe features, early-onset (i.e. preeclampsia requiring delivery

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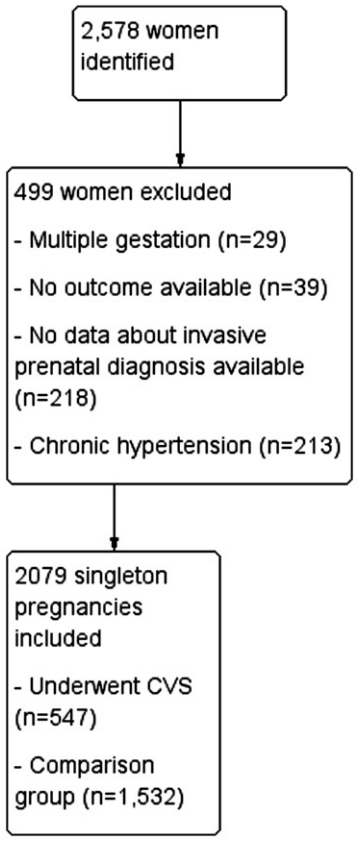

Figure 1. Study flow chart.

before 34 weeks) and late-onset preeclampsia (i.e. preeclampsia requiring delivery at or after 34 weeks), and preterm birth (PTB) <37 weeks. The comparison group included women with singleton gestations who did not undergo CVS. Comparison group included all consecutive singleton gestations without chronic hypertension referred to our Department in the same period (January 2014 to August 2016).

Subgroup analysis for the primary outcome (i.e. incidence of preeclampsia) in women who underwent CVS due to beta thalassemic trait was performed.

Diagnosis and management of preeclampsia and preeclampsia with severe features were based on 2013 ACOG guidelines [15]. Preeclampsia (i.e. preeclampsia without severe features) was defined as a blood pressure elevation (≥140/90 on two occasions 4 h apart or ≥160/110 once), after 20 weeks of gestation, with proteinuria (≥300 mg on 24-h protein or >0.3 protein/creatinine ratio) or any of the following if proteinuria not present: platelets <100,000; creatinine >1.1 (or doubling of creatinine in absence of other renal disease); doubled of AST or ALT. Preeclampsia with severe features was defined as preeclampsia with any of the following: blood pressure ≥160/110 4 h apart on bed rest (unless on antihypertensive); platelets <100,000; doubling of AST or ALT; creatinine >1.1 (or doubling of creatinine in absence of other renal disease); pulmonary edema; new cerebral or visual disturbances.

Table 1. Characteristics of the included women.

	CVS $n = 547$	Control group $n = 1532$	p value
Age			
Mean ± SD (years)	27.4 ± 4.5	28.2 ± 9.3	.11
Nulliparous *n* (%)	450 (82.3%)	1200 (72.3%)	.17
Ethnicity			
Caucasian *n* (%)	498 (91.0%)	1379 (90.0%)	.14
NonCaucasian *n* (%)	49 (9.0%)	153 (10.0%)	
BMI			
Mean ± SD (kg/m^2)	25.3 ± 12.4	25.8 ± 11.2	.74
Smoking *n* (%)	57 (10.4%)	150 (9.8%)	.47
Diabetes mellitus (including GDM) *n* (%)	28 (5.1%)	80 (5.2%)	.93

Data are presented as number (percentage) or as mean ± standard deviation.
SD: standard deviation; BMI: body mass index; CVS: chorionic villus sampling; GDM: gestational diabetes mellitus.

Statistical analysis was performed using statistical package for social sciences (SPSS) v. 19.0 (IBM Inc, Armonk, NY). Data are shown as means ± SD, or as number (percentage). Univariate comparisons of dichotomous data were performed with the use of the chi-square or Fisher's exact test. Comparisons between groups were performed with the use of the *t*-test to test group means with SD. Primary and secondary outcomes were estimated with multivariate analyses.

Logistic regression, presented as unadjusted odds ratio (crude odds ratio (OR)) or adjusted odds ratio (aOR) with the 95% of confidence interval (CI), was performed. Adjusted analysis was performed to correct data for relevant baseline characteristics. Adjusted analysis was performed including all potentially relevant baseline characteristics to the model as covariates.

We calculated two sided *p*-values. A *p*-value <.05 was considered to indicated statistical significance.

Results

Five hundred forty-seven women who underwent CVS, and 1532 women who did not were analyzed (Figure 1). Characteristics of women are shown in Table 1. All women were singleton pregnancies without chronic hypertension.

Table 2 shows primary and secondary outcomes. Women who underwent CVS had a significantly lower risk of preeclampsia (4.4 vs. 8.0%; aOR 0.53, 95%CI 0.34–0.83), and late-onset preeclampsia (3.3 vs. 6.1%; aOR 0.52, 95%CI 0.31–0.87). No statistically significant differences were found in preeclampsia with severe features, early-onset preeclampsia, and PTB.

Women who underwent CVS due to thalassemic trait had a lower incidence of preeclampsia compared to those women who did not undergo CVS (3.3 vs.

Table 2. Primary and secondary outcomes.

	CVS n = 547	Control group *n* = 1532	Crude OR (95%CI)	aOR (95%CI)[a]
Preeclampsia	24 (4.4%)	122 (8.0%)	**0.48 (0.44–0.74)**	**0.53 (0.34–0.83)**
Preeclampsia with severe features	7 (1.3%)	33 (2.2%)	**0.52 (0.34–0.98)**	0.59 (0.26–1.34)
Early-onset preeclampsia	6 (1.1%)	28 (1.8%)	0.54 (0.34–1.12)	0.60 (0.25–1.45)
Late-onset preeclampsia	18 (3.3%)	94 (6.1%)	**0.50 (0.41–0.79)**	**0.52 (0.31–0.87)**
PTB <37 weeks	41 (7.5%)	133 (8.7%)	**0.82 (0.60–0.99)**	0.85 (0.59–1.23)
IUGR <10th	57 (10.4%)	300 (19.6%)	**0.53 (0.41–0.69)**	**0.56 (0.40–0.72)**
IUGT <5th	31 (5.7%)	105 (6.9%)	0.83 (0.56–1.22)	0.85 (0.50–1.37)

Data are presented as number (percentage) or as mean ± standard deviation.
SD: standard deviation; BMI: body mass index; CVS: chorionic villus sampling; GDM: gestational diabetes mellitus; OR: odds ratio; CI: confidence interval; aOR: adjusted odds ratio; IUGR: intrauterine growth restriction; PTB: preterm birth.
[a]Adjusted for all variables reported in Table 1.
Boldface data, statistically significant.

Table 3. Primary outcome in subgroup analyses.

	CVS thalasemic trait *n* = 123	CVS other reasons *n* = 424	Crude OR (95%CI)	aOR (95%CI)[a]
CVS for thalassemic trait versus CVS for other reasons				
Preeclampsia	4 (3.3%)	20 (4.7%)	0.62 (0.34–1.42)	0.68 (0.23–2.03)
		n = 1532		
CVS for thalassemic trait versus no CVS				
Preeclampsia	4 (3.3%)	122 (8.0%)	**0.34 (0.33–0.74)**	**0.39 (0.14–0.87)**

Data are presented as number (percentage).
OR: odds ratio; CI: confidence interval; aOR: adjusted odds ratio; CVS: chorionic villus sampling.
[a]Adjusted for all variables reported in Table 1.
Boldface data, statistically significant.

8.0%; aOR 0.39, 95%CI 0.14–0.87), while no differences were found comparing women who underwent CVS due to thalassemic trait with women who underwent CVS due to other reasons (Table 3).

Discussion

Main findings

This study, including 547 women who underwent CVS, and 1532 women who did not, showed that women who underwent first trimester CVS had lower risk of preeclampsia.

Comparison with the prior literature

Our data concur with prior studies, but are at odds with others. Sotiriadis et al. showed that CVS was not associated with fetal growth impairment, while it was associated with a decrease in the rate of preeclampsia [16]. Silver et al. concluded that the focal disruption of the placenta in the first trimester following 13–14 weeks CVS may increase the risk of hypertension and preeclampsia [12]. Cederholm et al. in a population-based study showed that among women aged 35–49 years, amniocentesis and CVS were not associated with important adverse outcomes, such as preeclampsia or abruption [13].

Strengths and limitations

Our study has several strengths. The number of women included was high. We performed subgroup analysis in women with beta thalassaemic trait to explore the role of anemia to the developing of preeclampsia. We used the new ACOG guidelines for the diagnosis and management of preeclampsia. However, the retrospective approach of the study is the major shortcoming. Because of its retrospective nature, it was not possible to separate the importance of CVS versus possible other confounders. Because this was not a randomized comparison, the findings were subjective to bias. We evaluated the effect of only transabdominal CVS as a technique, and therefore the possible effect of other CVS technical aspects (eg trancervical CVS) was not studied.

Implications

The possible association between CVS and placenta related complications was first highlighted by Silver et al. [12]. They concluded that the focal disruption of the placenta in the first trimester following 13–14 weeks CVS may increase the risk of hypertension and preeclampsia. However, other published evidence showed that it is very likely that first trimester placenta is compliant enough to overcome the damage cause by CVS. Our study provides evidence that this overcome may decrease the risk of preeclampsia by

better reconstruction of the villi; a local injury of trophoblast because the needle's passage in the chorion may activates mechanisms of remodeling and reorganization of the architecture of chorionic plate with increased trophoblast invasion into spiral arteries. In a past letter [17], we described a lower rate of preeclampsia in women who underwent CVS because of thalassaemic trait; the hypothesis was a sum of two effects: (1) the mechanic effect with the repair of villi after the injury of the chorion, (2) the hypoxemic effect induced by maternal anemia. Tissue hypoxia induced by maternal anemia may stimulate an adaptive response designed to increase oxygen transfer towards the placenta. In pregnancies with a low maternal hemoglobin concentration, trophoblast invasion into the spiral arteries is increased leading to increased spiral artery lumina [18]. These mechanisms of compensation may explain the lower rate of preeclampsia in our population even if the mayor effect seems to be the mechanic one since no differences of incidence of PE were found comparing women who underwent CVS due to thalassemic trait with women who underwent CVS due to other reasons. However, it is important to highlight that most women with beta-thalassemia may not have a degree of anemia that would translate in a hypoxia-induced improved trophoblast invasion.

Conclusions

In summary, women who underwent first trimester CVS had a lower risk of preeclampsia compared to those who did not.

Disclosure statement

The authors report no conflict of interest.

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