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# Chronic Villus Sampling and the Risk of Hypertensive Disorders of Pregnancy: A Case Control Study

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# CHORIONIC VILLUS SAMPLING AND THE RISK OF HYPERTENSIVE DISORDERS OF PREGNANCY: A CASE CONTROL STUDY

A Thesis Submitted to the

Yale University School of Medicine

in Partial Fulfillment of the Requirements for the

Degree of Doctor of Medicine

By

Sanaz Ghazal

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# CHORIONIC VILLUS SAMPLING AND THE RISK OF HYPERTENSIVE DISORDERS OF PREGNANCY: A CASE CONTROL STUDY

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The purpose of this study was to determine whether there is an association between chorionic villus sampling for prenatal diagnosis and the development of hypertensive disorders of pregnancy. This study is a single-site retrospective case control study using medical records of patients seen at Yale-New Haven Hospital. A total of 448 patients in three groups (first trimester aneuploidy screening with nuchal translucency assessment, genetic amniocentesis, and chorionic villus sampling) were included and data on maternal characteristics, delivery outcomes, risk factors, and hypertensive outcomes were recorded. Unadjusted odds ratios and odds ratios adjusted for maternal age and race were calculated to compare the probability of gestational hypertension and preeclampsia between the groups using the nuchal translucency group as the control.

In the genetic amniocentesis group, the adjusted odds ratio for gestational hypertension was 1.9 (95% CI 0.2 – 170.1) and the ratio for preeclampsia was 1.4 (95% CI 0.19-5.80), both statistically not significant. In the chorionic villus sampling group, the adjusted odds ratio for gestational hypertension was 0.4 (95% CI 0.03 – 4.7) and the ratio for preeclampsia was 0.93 (95% CI 0.8 – 1.07), again both statistically not significant.

This study concluded that there is no association between chorionic villus sampling and the development of hypertensive disorders of pregnancy.

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## Introduction

*Prenatal Diagnosis:*

The advent of prenatal diagnostic techniques grew out of a desire on the part of many mothers to be reassured that their unborn baby is healthy and without genetic abnormalities. Various screening programs designed to provide reassurance of fetal health differ in the amount of time needed to obtain results, rate of false positive results, level of invasiveness, and safety for both mother and baby (1). Prenatal diagnosis of structural, functional, or genetic abnormalities in the developing fetus provides valuable information to both clinicians and patients during the pregnancy. This information may lead to modifications in surveillance, the initiation of fetal therapy to optimize delivery, or, in some cases, the consideration of pregnancy termination (2). It is important to select a screening modality that will yield accurate results as early in the pregnancy as possible in order to allow the option of pregnancy termination to be considered at a safe and more discreet stage in the pregnancy.

Ultrasound can be used to detect anatomic malformation and maternal serum screening can help detect an increased risk of trisomy and other fetal anomalies. However, fetal cells are needed for the definitive diagnosis of chromosomal abnormalities. These fetal cells can be obtained from the amniotic fluid surrounding the fetus (amniocentesis) or from the placenta (chorionic villus sampling). These two modes of invasive prenatal diagnosis will be discussed here.

On average, about 5-10% of pregnant women in the United States decide to undergo invasive prenatal testing (3). Indications for invasive prenatal diagnostic testing include maternal age greater than or equal to 35, family history of genetic disorders, prior

history of a fetus with a chromosomal abnormality, a positive screening test, or a fetal anomaly suspected on ultrasound.

The risks associated with invasive prenatal diagnostic techniques such as amniocentesis and chorionic villus sampling have been widely studied. In light of the increased risks associated with invasive procedures, many women opt for less invasive ways to obtain genetic information about their fetus. This has led to a surge in the number of women who are pursuing first trimester aneuploidy screening and nuchal translucency assessment.

*First Trimester Aneuploidy Screening:*

First Trimester Aneuploidy Screening (FTAS) was introduced in the 1990s as an alternative to invasive diagnostic testing (4). First trimester screening protocols consist of maternal serum analyte screening, ultrasound evaluation, or a combination of both in addition to the assessment of maternal age (2). In the second trimester, maternal age can be combined with levels of alpha-fetoprotein, human chorionic gonadotropin, and unconjugated estriol to estimate the risk of fetal aneuploidy. This method identifies about 65 percent of fetuses with trisomy 21 with a 4.5 to 5.0 percent false positive rate. When levels of inhibin A are added (quadruple screen), the detection rate increases to approximately 75 percent (5).

Even though second trimester screening has been shown to be accurate and effective, delaying screening until the second trimester can limit decision-making about prenatal diagnosis and pregnancy termination. Chorionic villus sampling is an option for prenatal diagnosis that is available to patients in the first trimester. Delayed screening until the second trimester precludes the use of chorionic villus sampling for early definitive genetic diagnosis and decisions about pregnancy termination must also be delayed (5). Thus, an emphasis was placed on developing adequate first trimester screening protocols that would provide pregnant women with more options for prenatal diagnosis, including chorionic villus sampling in the first trimester, and would allow for earlier and safer pregnancy termination.

In first trimester screening, the most useful maternal serum analytes are pregnancy-associated plasma protein A (PAPP-A) and free beta subunit of human chorionic gonadotropin (free beta-hCG) (6). Using maternal age in combination with

levels of PAPP-A and free beta-hCG has resulted in Down syndrome detection rates of 60 to 65 percent (7)(8). Nuchal translucency (NT) assessment in the first trimester is another method used to evaluate the risk of fetal aneuploidy. Nuchal translucency is obtained by measuring the maximum thickness of the subcutaneous translucency between the skin and the soft tissues behind the cervical spine in the midsagittal plane (9). This hypoechoic region is thought to represent mesenchymal edema and, when enlarged, is often associated with fetal aneuploidy (10). Ultrasound measurement of nuchal translucency in combination with maternal age has been reported to independently detect 77 percent of Down syndrome cases with a false positive rate of 5 percent (11).

When the ultrasound measurement of nuchal translucency is combined with biochemical evaluation of PAPP-A and free beta-hCG, the sensitivity of predicting risk of fetal aneuploidy, particularly trisomy 21, is greatly enhanced. The combination of first trimester ultrasound assessment and maternal serum screening was evaluated by two large trials and was shown to be effective (2)(12)(13). In the First Trimester Maternal Serum Biochemistry and Fetal Nuchal Translucency Screening Study (BUN study) by Wapner et al., 8514 women underwent screening for trisomy 21 and trisomy 18 between 74 and 97 days of gestation using maternal age, maternal levels of free beta-hCG and PAPP-A, and ultrasound measurement of nuchal translucency (12). Using a Down syndrome risk cutoff of 1:270, this combined screening method detected 85.2 percent of Down syndrome cases with a false positive rate of 9.4 percent. This study also reported that screening identified 90.9 percent of trisomy 18 cases with a 2 percent false positive rate.

The First and Second Trimester Evaluation of Risk (FASTER) trial reported by Malone et al. was another large multi-center trial that studied 33,546 women. Study subjects underwent both first trimester screening, which included assessment of nuchal translucency, levels of PAPP-A, and free beta-hCG as well as second trimester quadruple screening, which included measuring levels of maternal alpha-fetoprotein, total hCG, unconjugated estriol, and inhibin A (13). If either the first or second trimester screening test was positive, the patient was offered fetal karyotyping. The authors compared the detection rates of first trimester screening, second trimester screening, and combined first and second trimester screening (fully integrated screening). Using a Down syndrome risk cutoff value of 1:270 and a 5 percent false positive rate, the authors reported Down syndrome detection rates for first trimester screening of 87 percent, 85 percent, and 82 percent for testing done at 11, 12, and 13 weeks, respectively. The second trimester quadruple screen detection rate for Down's syndrome was 81 percent. The fully integrated screening (single risk result provided) yielded the best results and detected 96 percent of Down syndrome cases.

First trimester aneuploidy screening does have a few drawbacks. There is a relatively narrow window of time to perform the screening, usually between 11 and 14 weeks gestation depending on crown-rump length. Additionally, the accurate assessment of gestational age is an essential element of calculating risk. It was also noted by the authors of the FASTER trial that nuchal translucency measurements performed as part of the screening protocol can be difficult to perform accurately (13). Nuchal translucency measurements can vary from operator to operator based on experience and technique and they can also vary by a single operator over time. Other factors that can complicate

accurate measurements include suboptimal fetal position and poor visibility (2). Despite these drawbacks, the data shows that first trimester aneuploidy screening is a safe and accurate testing modality that can be used as an alternative to invasive prenatal diagnosis or as a tool to help clinicians determine which patients should be offered definitive genetic testing.

*Genetic Amniocentesis:*

Amniocentesis is a technique in which amniotic fluid is aspirated from the uterine cavity for both diagnostic and therapeutic purposes. One of the main diagnostic indications for the procedure is prenatal genetic testing and fetal karyotyping. In 1956, Fuchs and Riis were the first to report on the use of amniocentesis for genetic diagnosis when they discovered that cells from amniotic fluid could be used to determine fetal sex (14). Over 50 years later, amniocentesis has become a standard tool used by obstetricians and gynecologists for the diagnosis of fetal malformations and genetic abnormalities. Other diagnostic indications include the assessment of fetal lung maturity and evaluation of the fetus for infection, degree of hemolytic anemia, hemoglobinopathy, neural tube defects, and coagulopathy. The most common therapeutic indication of amniocentesis is the removal of excess amniotic fluid.

Amniocentesis is usually performed between 14 and 20 weeks gestation, typically around 16 weeks. The procedure is done during this time because there is believed to be enough amniotic fluid surrounding the fetus to extract an adequate amount for sample without significant technical difficulties (1). Early amniocentesis, which is typically performed between 11 and 14 weeks gestation, has been widely studied in comparison to second trimester amniocentesis. The technique for early amniocentesis is the same as midtrimester amniocentesis, however, early amniocentesis requires greater technical skill by the operator and a smaller volume of fluid is removed (2). The accuracy of the cytogenetic findings between early amniocentesis and second trimester amniocentesis is similar (> 99%), however there is a higher rate of culture failure with early versus midtrimester amniocentesis (15)(16). Furthermore, studies have shown an increased risk

of fetal loss with early amniocentesis compared to midtrimester amniocentesis. In the Canadian Early and Mid-trimester Amniocentesis Trial (CEMAT), researchers studied 4374 women randomized to undergo early amniocentesis before 13 weeks gestation or midtrimester amniocentesis after 15 weeks gestation and found a significant difference in the rate of fetal loss in the early amniocentesis group compared to the midtrimester amniocentesis group (7.6% vs. 5.9%, $p = 0.012$). They also noted a higher incidence of talipes equinovarus, a congenital deformity of the foot, in the early amniocentesis group than in the midtrimester amniocentesis group (1.3% vs. 0.1%, $p = 0.0001$)(10). Because midtrimester amniocentesis is considered safer and less technically demanding, many centers no longer perform early amniocentesis. Performing genetic amniocentesis beyond 20 weeks is possible, but can be problematic if pregnancy termination is a consideration in the setting of abnormal findings.

Amniocentesis is typically done in an outpatient or ambulatory setting. The procedure begins with the patient in the supine position and a sterile preparation. An ultrasound assessment is performed first to confirm fetal viability, fetal position, and placental location. An anatomic survey and biometry are also usually performed at this time. Using continuous ultrasound guidance to avoid the placenta, umbilical cord, fetus, and maternal bowel and bladder, a 20- to 22-gauge spinal needle is inserted through the maternal abdominal wall and into the amniotic sac. Approximately 20 to 30 milliliters of amniotic fluid is collected and sent for cell culture and fetal karyotyping. The needle is then removed, the puncture site is observed for bleeding, and the fetal heart rate is assessed and documented. Side effects immediately after the procedure are rare and

generally mild, however, patients may experience uterine cramping, transient vaginal spotting, and amniotic fluid leakage after the procedure (2).

Potential complications of genetic amniocentesis that should be discussed with patients prior to the procedure include direct fetal injury, indirect fetal injury, leakage of fluid, infection, and pregnancy loss. The risk of direct fetal injury with the needle is rare, particularly since the vast majority of procedures are now performed with continuous ultrasound guidance and visualization of the needle tip throughout the procedure. In a randomized study of ultrasound-guided amniocentesis by Tabor et al. there was no evidence of direct fetal injury in 2239 pregnancies (17). There have been isolated case reports of fetal injuries such as skin dimples, ocular injury, and intracranial and bowel abnormalities that have been associated with amniocentesis, however, there is no direct evidence to support these associations (18)(19). A few studies have reported an increased prevalence of indirect fetal injury secondary to amniocentesis, such as orthopedic malformations and respiratory complications, however, the data has been inconsistent (17). Several case reports have described mother to infant transmission of infection by amniocentesis, particularly in women who are infected chronically (20). The Pediatric AIDS Clinical Trials Group reported an increased rate of vertical transmission to infants in HIV-infected women who underwent amniocentesis compared to HIV-infected women who did not undergo amniocentesis (36% vs. 14%). However, they also showed that the rate of vertical transmission of HIV is reduced in treated versus untreated women (21).

Perhaps the most widely studied complication of amniocentesis is the risk of fetal loss. In 2006, the First And Second Trimester Evaluation of Risk for Aneuploidy Trial (FASTER trial) studied the procedure-related pregnancy loss rate after second trimester

amniocentesis (22). A total of 35,003 unselected patients were enrolled in the study, where 3,096 patients underwent midtrimester amniocentesis and 31,907 did not and were considered the control group. This study showed that the spontaneous fetal loss rate prior to 24 weeks gestation in the amniocentesis group was not statistically significant from the background loss rate in the control group (1.0% vs. 0.94%, $p = 0.74$). They also determined that the procedure-related loss rate after amniocentesis was 0.06 percent (1.0 percent minus the 0.94 percent background loss rate in controls) and concluded that there was no significant difference in fetal loss rate between women undergoing amniocentesis and those who did not. There were several pitfalls with this study, such as the low background loss rate for the control group, which called into question the applicability of the results. To date, the randomized study performed by Tabor et al. in 1986 provides the best estimate of the risk of fetal loss after amniocentesis (1)(17). In a low risk population with a background pregnancy loss rate of 2 percent, midtrimester amniocentesis increases the risk of pregnancy loss by another 1 percent.

The main advantage of midtrimester amniocentesis is that it can provide accurate information regarding genetic or chromosomal abnormalities in a fetus and in the hands of a skilled operator the procedure is safe. The results of the test are generally available in two to three weeks. This long waiting period for results is one of the major disadvantages of midtrimester amniocentesis, particularly when pregnancy termination is desired based on abnormal test results. The need for genetic information earlier in the pregnancy prompted clinicians to explore other forms of prenatal diagnostic testing, such as chorionic villus sampling.

*Chorionic Villus Sampling:*

Chorionic villus sampling (CVS) is a procedure used for the prenatal diagnosis of genetic abnormalities, which involves sampling the placenta for chromosome or DNA analysis. CVS was first introduced in the late 1960s when Scandinavian researcher Jan Mohr performed a transcervical biopsy of the chorion. Chorionic villi are the precursor of the placenta and can be used for genetic testing of the fetus. The adoption of chorionic villus sampling into standard practice wavered in light of studies showing the relative safety and accuracy of amniocentesis compared to CVS. However, with advancements in ultrasound technology and molecular genetics, the desire for earlier prenatal diagnosis increased and the demand for chorionic villus sampling slowly increased.

CVS is typically performed in the first trimester after 10 weeks gestation compared to second trimester amniocentesis, which is generally performed between 15 and 17 weeks gestation. Thus, CVS provides mothers with genetic information earlier in the pregnancy, which is imperative to many mothers who would consider pregnancy termination in the setting of abnormal results. Performing CVS prior to 10 weeks gestation has been shown to be associated with an increased frequency of oromandibular defects and limb-reduction defects, with the incidence of defects reported to be as high as 1 to 2 percent (23)(24). Researchers have found that the incidence of limb-reduction defects is about 6 per 10,000 when CVS is performed after 9 weeks, which is the same as the background incidence (25). Thus, clinicians recommend waiting until after 10 weeks to undergo the procedure.

CVS is generally performed as an ambulatory or outpatient procedure. An ultrasound is performed before the procedure to document fetal viability, confirm the

number of embryos, detect any fetal structural abnormalities, and to locate the placenta. The procedure may be performed using either a transabdominal or transcervical approach. The transabdominal approach begins with placing the woman in the supine position, locating the placenta with a transabdominal ultrasound, and prepping the lower abdomen in a sterile fashion. Under continuous ultrasound guidance, a 20-gauge needle is inserted transabdominally and advanced until it penetrates the long axis of the placenta. A syringe containing medium for the tissue sample is mounted and attached to the needle hub. The needle tip is oscillated back and forth within the placenta in order to aspirate an adequate sample of tissue. After the needle is removed, ultrasound is used to document fetal movement. The tissue sample in medium is then sent for cell culture and fetal karyotyping.

If a transcervical approach is planned, cervicovaginal cultures should be obtained to identify any potential infection that may require antibiotic therapy prior to the procedure. For this approach, the woman is placed in the lithotomy position and the external and internal genitalia are prepped in a sterile fashion. A speculum is inserted into the vagina and ring forceps are used to grasp the cervix and gently pull it towards the operator in order to manipulate the uterus into a more axial position. Under continuous ultrasound guidance, a metal sound is inserted into the endocervical canal to determine its curvature. A transcervical cannula is then bent to resemble the same curvature and, under ultrasound guidance, is inserted through the endocervical canal until the placenta is reached. A syringe containing medium is attached to the catheter. The needle is then moved back and forth within the placenta in order to obtain an adequate sample of tissue. The aspirated tissue in medium is then sent for cell culture and fetal karyotyping.

The choice of whether to perform the procedure transvaginally or transcervically is dependent in part on the location of the placenta and in part on the operator's personal preference and skill (26). If the placenta is in an anterior position, a transabdominal approach may be safer, whereas a transcervical approach may allow easier access to a placenta that is in a posterior position. A learning curve has been described for successful and safe performance of the procedure (27). The operator should be adept with the use of ultrasound in order to visualize the needle tip and the relevant anatomy or have an experienced sonographer assist with the procedure.

The indications for CVS are in essence the same as those for amniocentesis. The most common indication is an increased risk of fetal aneuploidies due to advanced maternal age, family history of genetic disorders, or an abnormal first trimester screening. Contraindications to transcervical CVS include vaginismus, cervical stenosis, cervical or lower uterine segment myomas, active genital tract infection, severe anteflexion or retroflexion of the uterus such that uterine assess impaired, and body habitus that precludes clear ultrasound visualization or uterine assess (2). Contraindications to transabdominal CVS include extreme uterine retroflexion with obstructive intestinal loops or fetal position that obstructs access to a posterior placenta. Relative contraindications to both modes include vaginal bleeding or spotting, maternal isoimmunization, presence of an intrauterine device (IUD), and the presence of risk factors for neural tube defects (2). Unsensitized Rh negative women should be given anti-D immunoglobulin prophylaxis after undergoing the procedure. Chorionic villus tissue samples cannot be used for alpha-fetoprotein (AFP) testing for neural tube defects.

There are several advantages to pursuing chorionic villus sampling over midtrimester amniocentesis. The main advantage is that CVS can be safely performed in the first trimester, as early as 10 weeks gestation, whereas amniocentesis is generally not performed before 14 weeks gestation. This advantage may be especially important for a mother who would consider pregnancy termination in the face of abnormal results. Furthermore, the results of CVS are available more quickly than with midtrimester amniocentesis. CVS allows for a larger amount of DNA to be extracted, which allows for more reliable DNA analysis within days of sampling. There is also some data to suggest that there is a smaller risk of culture failure with CVS compared to midtrimester amniocentesis (1).

Despite these advantages, there are several disadvantages and complications that must be weighed against the benefit of earlier testing and results. First, safe and successful CVS requires a higher level of skill, expertise, and experience than amniocentesis. There is also a higher incidence of mosaic results with CVS compared to amniocentesis (1). Chromosomal mosaicism is the presence of two or more cell lines with different karyotypes in a single sample.

Perhaps the most important complication to consider is the increased risk of fetal loss with CVS compared to midtrimester amniocentesis. A Cochrane review in 2003 compared the safety and efficacy of transcervical CVS, transabdominal CVS, and midtrimester amniocentesis, which was defined as amniocentesis after 15 weeks gestation (1). The review included 14 randomized studies that analyzed pregnant women undergoing invasive prenatal diagnostic testing for fetal genetic abnormalities. Four trials that compared transcervical CVS to midtrimester amniocentesis were analyzed

(28)(29)(30)(31). They found a higher total pregnancy loss rate that was consistently higher in the patients who underwent transcervical CVS (14.5% vs. 11%) and this overall difference was statistically significant except in the Canadian trial by Lippman et al. in 1992 (28). When transabdominal CVS was compared to midtrimester amniocentesis, they found no significant difference in total pregnancy loss (6.3% vs. 7%) (29).

Two trials in the Cochrane review presented data comparing CVS by any route and midtrimester amniocentesis (29)(32). This data showed that the overall pregnancy loss rate was higher after CVS than midtrimester amniocentesis (11% vs. 8.2%) and that this difference was statistically significant (RR 1.43, 95% CI 1.22-1.67). They also found that more repeat tests were necessary after transcervical CVS than midtrimester amniocentesis (6.3% vs. 0.2%), there were more problems analyzing placental tissue from CVS than analyzing amniotic fluid from amniocentesis. When transcervical CVS was compared to midtrimester amniocentesis, the transcervical CVS group had a higher rate of laboratory failure (1.7% of cases vs. 0.07%), more cytogenetic abnormalities confined only to placenta (2.3% vs. 0.4%), and more false positive and false negative results (2.2% vs. 0.2% and 0.3% vs. 0%, respectively) than the midtrimester amniocentesis group (1). It was noted that complications after either procedure were uncommon and none were life-threatening. Vaginal bleeding was more common after transcervical CVS and there was no significant difference in amniotic fluid leakage post-procedure (1)(32).

When transcervical and transabdominal CVS were compared head-to-head, the Cochrane review reported that transabdominal CVS is associated with a significant reduction in both total pregnancy loss (RR 1.23, 95% 1.06-1.42) and spontaneous

miscarriage (RR 1.75, 95% CI 1.33-2.29). The success of cytogenetic analysis was comparable for both procedures, but transcervical CVS appeared to be more technically demanding, required multiple insertions more frequently (11.2% vs. 4.1%), and caused more vaginal bleeding (10% vs. 1.6%).

The overall conclusions drawn by the Cochrane review were that midtrimester amniocentesis is safer than transcervical CVS or early amniocentesis performed before 15 weeks gestation. The authors reiterated that the benefits of early prenatal genetic diagnosis must be weighed carefully against the increased risks of performing more technically demanding and invasive procedures. If early diagnosis is required or desired, transabdominal CVS is the preferred method to early amniocentesis or transcervical CVS. If transabdominal CVS is technically difficult or not possible, transcervical CVS in the first trimester or midtrimester amniocentesis should be considered (1).

A more recent review compiled data from over 45 articles on the procedure-related complications of amniocentesis and chorionic villus sampling (33). This review reported that the pooled pregnancy loss within 14 days of midtrimester amniocentesis was 0.6 percent (95% CI 0.5-0.7), pregnancy loss before 24 weeks was 0.9 percent (95% CI 0.6-1.3), and total pregnancy loss was 1.9 percent (95% CI 1.4-2.5). This was compared to CVS which had corresponding figures of 0.75 percent, 1.3 percent, and 2.0 percent (95% CI 1.4-2.6). This study highlighted some of the major limitations hindering many of the studies looking at risk related to prenatal diagnostic testing. The background risk of women who undergo CVS is generally higher than those who undergo amniocentesis because amniocentesis is performed later in the pregnancy at a gestational age when the risk of spontaneous miscarriage is lower. Many of the studies used in these

reviews were nonrandomized and lacked adequate control groups, which makes it difficult to estimate the true risk of the procedures.

Chorionic villus sampling provides an alternative to early amniocentesis for women who desire prenatal genetic information in the first trimester. CVS has been proven safe and effective in the hands of an experienced and skilled operator, however there are several risks that should be discussed with the patient and weighed against the benefit of earlier genetic diagnosis. Given the risks associated with chorionic villus sampling, many women often opt for less invasive ways of obtaining information about the genetic composition and general well-being of their baby, such as first trimester aneuploidy screening with nuchal translucency.

*Hypertensive Disorders of Pregnancy:*

There are several major hypertensive disorders that can complicate pregnancy and collectively they form a major cause of maternal morbidity and mortality. Preeclampsia (PEC) is defined as new onset hypertension after 20 weeks gestation in a previously normotensive woman and the presence of new onset proteinuria. Based on the degree of hypertension, the degree of proteinuria, and on presence of symptoms, preeclampsia can be classified as mild or severe. Table 1 shows the definitions of hypertensive disorders that occur in pregnancy, including the distinction between mild and severe preeclampsia. Eclampsia (EC) is defined as the presence of seizures not attributable to any other cause in a woman with preeclampsia. Chronic hypertension (or preexisting hypertension) is defined as a systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or both that is present before 20 weeks gestation or persists beyond 12 weeks postpartum. Chronic hypertension (CHTN) can be a primary disorder or it can be secondary to other medical disorders. Gestational hypertension (previously called pregnancy-induced hypertension or PIH) refers to hypertension without proteinuria or other signs of preeclampsia that develops after 20 weeks gestation in a previously normotensive woman. Gestational hypertension (GHTN) should resolve by 12 weeks postpartum. If the hypertension persists after 12 weeks postpartum, then the diagnosis is likely chronic hypertension that was masked in the early stages of pregnancy. About 25 percent of women diagnosed with gestational hypertension will go on develop preeclampsia later in the pregnancy (34).

The exact incidence of preeclampsia is unknown and reports vary depending on the study population (2)(35). It has been reported that hypertensive disease complicates

between 12 to 22 percent of pregnancies and is responsible for 17.6 percent of maternal deaths in the United States (35)(36). Chronic hypertension occurs in about 3 percent of pregnancies and gestational hypertension develops in about 6 percent of pregnancies (37). It has been reported that preeclampsia occurs in 3 to 14 percent of all pregnancies worldwide and in about 5 to 8 percent of pregnancies in the United States (2). One study reported that in the United States, 75 percent of preeclampsia cases are classified as mild and 25 percent of cases are severe (38). Preeclampsia is considered one of the leading causes of maternal death, along with hemorrhage, embolism, and infection, and the condition also contributes to the rate of stillbirths and neonatal morbidity and mortality (2)(39).

Several risk factors for the development of preeclampsia have been identified (40). Women with a previous history of preeclampsia are at a serious increased risk of developing preeclampsia (RR 7.19, 95% CI 5.85-8.83) compared to women with no history of preeclampsia. Advanced maternal age or maternal age greater than or equal to 40 is an independent risk factor for preeclampsia with a relative risk of 1.96 for multiparous women (95% CI 1.34-2.87). Nulliparity increases the risk for developing preeclampsia (RR 2.91, 95% CI 1.28-6.61), although the reason for this association is unclear. Patients with pre-existing diabetes are also at increased risk (RR 3.56, 95% CI 2.54-4.99) compared to women with no history of diabetes. Multiple gestation is another risk factor with the relative risk for twin pregnancies being 2.93 (95% CI 2.04-4.21) and this risk increases as the number of fetuses increases. Obesity as determined by body mass index (BMI) has been shown to increase the risk of developing preeclampsia. In one study, the relative risk of preeclampsia in a woman with an increased pre-pregnancy

BMI is 2.47 (95% CI 1.66-3.67) and the relative risk in a woman with an increased BMI on admission (pregnancy BMI) is 1.55 (95% CI 1.28-1.88). There is also an increased prevalence of hypertensive disorders in African-American patients compared to Caucasian patients. Other risk factors include preexisting hypertension, antiphospholipid syndrome, prolonged interval between pregnancies, vascular and connective tissue disease, and a family history of preeclampsia (2)(35)(40).

*CVS and Hypertensive Outcomes: Background Literature*

A thorough understanding of the pathophysiology of preeclampsia remains elusive and several theories for the development of preeclampsia have been proposed. One theory in the literature suggests that preeclampsia may be related to abnormal placentation in the early stages of pregnancy. Given this theory, Silver et al. asked whether the placental disruption caused by invasive prenatal diagnostic procedures early in the pregnancy is correlated with the development of hypertensive disorders later in pregnancy (41). This study obtained subjects from a randomized trial by the National Institute of Child Health and Human Development, which compared early amniocentesis and transabdominal chorionic villus sampling in weeks 13 and 14. They compared the rate of hypertensive outcomes in patients with different degrees of placental disruption. A total of 3,698 randomized patients with genetically normal pregnancies were studied and 3 cohorts were compared: late CVS in which the placenta was directly sampled, early amniocentesis in which the placenta was traversed, and early amniocentesis in which the placenta was not traversed. They proposed that placental disruption is greatest for the CVS group because a sample of the chorionic villus is removed and least for the early amniocentesis group in which the placenta was not traversed.

A diagnosis of gestational hypertension or preeclampsia was made in 166 patients (4.5%). Their results showed a significantly higher rate of gestational hypertension or preeclampsia in women undergoing CVS compared to women undergoing early amniocentesis (5.4% vs. 3.5%, $p = 0.005$). A stepwise difference in risk of hypertensive outcome was found with the highest risk being the CVS group (5.4%), the next highest risk being the early amniocentesis group in which the placenta was traversed (3.9%), and

the lowest risk being the early amniocentesis group in which the placenta was not traversed (3.4%, $p = 0.02$). According to this data, the likelihood of gestational hypertension or preeclampsia is greater as the degree of placental disruption increases. The authors concluded by saying that this data supports the theory that disturbances in early placentation lead to maternal hypertension later in pregnancy. Several limitations of the study were discussed by the authors including the possibility that misclassification could have occurred given that the subjects of the study were obtained through another trial that was not designed to study hypertensive outcomes as a primary endpoint.

In a more recent study, Adusumalli et al. conducted a retrospective review to analyze the possible relationship between chorionic villus sampling between 10 and 13 weeks and hypertensive disorders of pregnancy (42). This study enrolled 1540 women who underwent CVS between 10 and 13 weeks gestation and 840 control subjects who underwent first-trimester screening with nuchal translucency assessment and biochemical testing between 11 and 13 weeks gestation. A total of 76 (4.9%) of patients in the chorionic villus sampling group were diagnosed with hypertensive disorders of pregnancy compared to 37 (4.4%) patients in the control group ($p = 0.31$). They concluded that there was no association between CVS at 10 to 13 weeks and hypertensive disorders of pregnancy. However, they did find an association between CVS and severe hypertensive disorders which included severe preeclampsia, eclampsia, and HELLP (Hemolysis, Elevated Liver enzymes, and Low Platelet count) syndrome.

## Purpose

The purpose of this study was to compare patients who underwent chorionic villus sampling with patients who underwent first trimester aneuploidy screening with nuchal translucency assessment to determine whether there is an association between chorionic villus sampling and the development of hypertensive disorders later in the pregnancy. This study was initiated in the context of recent studies that presented conflicting data regarding the association between chorionic villus sampling and hypertensive outcomes in pregnancy. We hypothesized that there is no association between chorionic villus sampling and the development of hypertensive disorders in pregnancy.

**Methods**

This study is a single-site retrospective case control study using medical records of patients seen at Yale-New Haven Hospital. Approval was obtained by our institution's Human Investigations Committee on August 1, 2007. Study subjects were identified through records maintained by the Department of Obstetrics, Gynecology, and Reproductive Sciences at Yale-New Haven Hospital of patients who had undergone chorionic villus sampling, genetic amniocentesis, and first trimester aneuploidy screening with nuchal translucency assessment at our institution. Patient data was collected from both inpatient and outpatient medical records.

Only singleton gestations were investigated because multiple gestational pregnancies are already at higher risk of hypertensive complications of pregnancy. We evaluated patients who underwent genetic amniocentesis or CVS between January 1, 2000 and December 31, 2006. Our control group was composed of patients who underwent first trimester aneuploidy screening during the same time period without any invasive testing. Patients who underwent first trimester aneuploidy screening with nuchal translucency measurement as well as invasive prenatal diagnosis (genetic amniocentesis or CVS) were excluded from the control group. This study included only patients who delivered at Yale-New Haven Hospital during this time period.

Data regarding the mode of CVS, evidence of fetal anomalies, gestational age at the time of procedure, and gestational age and birth weight at the time of delivery was recorded. We also documented the presence of known risk factors for hypertensive outcomes, including maternal age, BMI, race, gravidity and parity, order, presence and extent of maternal diabetes, smoking history, and previous history of preeclampsia or

other hypertensive disorders. The presence of maternal diabetes was documented according to the White classification of diabetes and pregnancy (43).

We utilized definitions for hypertensive disorders of pregnancy outlined by the American College of Obstetrics and Gynecology guidelines and the report of the National High Blood Pressure Education Program Working Group (35)(44). Chronic hypertension was defined as hypertension that was present before 20 weeks gestation. Gestational hypertension was defined as hypertension detected for the first time after 20 weeks gestation without proteinuria. Mild preeclampsia was defined using the following criteria: (1) blood pressure greater than 140/90 that occurs after 20 weeks gestation in a previously normotensive woman and (2) proteinuria of at least 300 milligrams in a 24-hour specimen or 1+ on urine dipstick (44). Severe preeclampsia was defined using the following criteria: (1) blood pressure greater than 160/110 measured on 2 occasions at least 6 hours apart, (2) proteinuria of at least 5 grams in a 24-hour collection or 3+ or greater on urine dipstick, (3) oliguria of less than 500 milliliters in 24 hours, (4) thrombocytopenia, (5) elevated hepatic enzymes or impaired liver function, (6) persistent headache, visual disturbances, or other cerebral disturbances, (7) persistent epigastric pain or right upper-quadrant pain, and (8) fetal growth restriction (29). Eclampsia was defined as the presence of preeclampsia and seizures that are not attributable to any other cause (29).

The prevalence of hypertensive disorders was compared among the three groups. Unadjusted odds ratios were calculated and compared. Odds ratios were then adjusted for maternal age and race. Unadjusted odds ratios were also calculated to assess any association between race and the development of gestational hypertension and

preeclampsia as well as the association between smoking history and the development of hypertensive disorders. Statistical analyses were performed using SPSS 14.0 (SPSS, Inc. Chicago, IL).

**Results**

Data from 124 women who underwent first trimester aneuploidy screening with nuchal translucency assessment (NT group), 119 women who underwent genetic amniocentesis (GA group), and 205 women who underwent chorionic villus sampling (CVS group) at Yale-New Haven Hospital between January 2000 to December 2006 was gathered and analyzed. The number of patients was limited by the fact that only patients who delivered at Yale-New Haven Hospital were included in the study. The NT group was used as the control group for this study. Table 2 summarizes information obtained from medical records at our institution on maternal characteristic, risk factors, and delivery outcomes. The mean maternal age for the NT group, GA group, and CVS group were 32.9, 36.9, and 36.2, respectively. The majority of patients in all three groups were Caucasian. There were more African-American patients in the NT group than in either the GA group or CVS group and there were more Asian women and fewer Hispanic women in the GA group compared to the other two groups. The presence of maternal diabetes of any class among the three groups was 8.9 percent, 7.6 percent, and 6.3 percent, respectively. The majority of all women in the study were nonsmokers, however there were slightly more smokers and ex-smokers in the NT group than the in GA or CVS group.

The prevalence of hypertensive disorders by group is shown in Table 3. Chronic hypertension was present in 3.2 percent, 4.2 percent, and 3.4 percent of the NT, GA, and CVS groups, respectively. There were slightly more patients with gestational hypertension in the NT group compared to the GA and CVS groups. Three patients (1.5%) in the CVS group had mild preeclampsia compared to one patient in the NT group

and no patients in the GA group. The prevalence of severe preeclampsia was similar in all three groups. The total prevalence of preeclampsia, both mild and severe, across all three groups was 2.7 percent.

Odds ratios were calculated to compare the probability of gestational hypertension and preeclampsia between the groups using the NT group as the control. Table 4 shows the unadjusted odds ratios for gestational hypertension and preeclampsia in the GA and CVS groups compared to the NT group. In the genetic amniocentesis group, the unadjusted odds ratio for gestational hypertension was 3.5 (95% CI 0.6-19.3). When the odds ratio was adjusted for maternal age and race, the odds ratio decreased to 1.9 (95% CI 0.2-170.1). The same trend was seen in the CVS group. The unadjusted odds ratio for gestational hypertension in the CVS group was 0.9 (95% CI 0.1-9.6) and when adjusted for maternal age and race, the odds ratio becomes 0.4 (95% CI 0.03-4.7). However, none of these findings are significant. When unadjusted odds ratios for preeclampsia in the GA and CVS groups were examined, they were identical (0.8). When adjusted for maternal age and race, the odds ratio in the GA group became 1.04 (95% CI 0.19-5.80) and the odds ratio in the CVS group became 0.93 (95% CI 0.8-1.07). These values were also not significant.

Table 5 shows the unadjusted odds ratio for both gestational hypertension and preeclampsia based on race. For gestational hypertension, all races except African-American had an odds ratio of 1.0. The unadjusted odds ratio for African-American ethnicity and gestational hypertension was 18.8 (95% CI 3.5-102.6) and this value was significant ($p < 0.05$). For preeclampsia, the only significant unadjusted odds ratio was for Hispanic race (odds ratio = 7.8, 95% CI 1.4-42.8, $p < 0.05$).

Smoking status was also evaluated for a possible association with gestational hypertension and preeclampsia (Table 6). The unadjusted odds ratio for patients who smoked during the pregnancy and gestational hypertension was 8.2 (95% CI 0.9-76.4) and that of ex-smokers who did not smoke during the pregnancy was 7.4 (95% CI 0.8-68.9). These values were also not statistically significant.

## Discussion

*Summary of Results:*

A total of 448 patients were evaluated in this study to assess the relationship between chorionic villus sampling and the development of hypertensive outcomes in pregnancy. Three groups were compared: patients who underwent first trimester aneuploidy screening with nuchal translucency measurement (control group), patients who underwent genetic amniocentesis, and patients who underwent chorionic villus sampling. Odds ratios, both unadjusted and adjusted for maternal age and race, and 95% confidence intervals were calculated.

This study found no association between chorionic villus sampling and gestational hypertension or preeclampsia. Unadjusted and adjusted odds ratios for genetic amniocentesis and chorionic villus sampling and the development of gestational hypertension or preeclampsia were not significant, which was consistent with our expectations. The data also highlights an association between African-American race and gestational hypertension (unadjusted odds ratio = 18.8, 95% CI 3.5-102.6, $p < 0.05$), which was significant and also expected. An association between Hispanic race and the development of preeclampsia (unadjusted odds ratio = 7.8, 95% CI 1.4-42.8, $p < 0.05$) was both noted and significant. Data on the association between smoking status and gestational hypertension or preeclampsia was also evaluated. Patients who smoked during the pregnancy or who were ex-smokers had higher unadjusted odds ratios for gestational hypertension (unadjusted odds ratio = 8.2 and 7.4, respectively) when compared to nonsmokers. This data approached statistical significance though it did ultimately reach significance (smoker 95% CI 0.9-76.4, ex-smoker 95% CI 0.8-68.9).

*Limitations and Future Directions:*

There were several limitations in this study. The number of patients in the nuchal translucency group and genetic amniocentesis group was substantially less than the chorionic villus sampling group and the overall sample size of the study was relatively small. This was due, in part, to the difficulty in obtaining complete demographic and obstetrical outcome data for women who were eligible for inclusion into the study. In addition, the number of patients included in the study at the outset was limited to only those who delivered at Yale-New Haven Hospital. Given the relatively small sample size, the power of this study was significantly low making it difficult to draw definitive conclusions based on the data.

Additionally, the number of patients diagnosed with preeclampsia in all three groups was lower than the estimated incidence of preeclampsia in the United States, which is about 5 to 8 percent of all pregnancies (2). It is unclear why there was a lower incidence of preeclampsia in our study population. It could have been due to selection or sampling bias during the data collection phase of this study. We limited our study population to only those patients that delivered at Yale-New Haven Hospital. It is also possible that some patients may have been misclassified or they may have had incomplete data points. This bias makes our data difficult to apply because it suggests that perhaps our study population may not be entirely representative of the population at large.

This study would have been made stronger with a larger sample size and relatively equal numbers in each of the three patient groups. The success of a study of this nature is largely dependent on the presence of adequate controls and complete

demographic and risk factor data to control for possible confounders. Having more complete data would have allowed for more patients to be included in the study and would have provided more variables to adjust in our final calculations. We initially obtained data on body mass index (BMI) both pre-pregnancy and during the pregnancy, however, we did not have enough data on enough patients to adequately analyze the relationship between BMI and hypertensive outcomes. Other parameters that may be of study interest in the future include villus sample size, number of device insertions, and the use of assisted reproductive technology.

*Conclusion:*

In conclusion, the results of this study support previous data that has shown no association between chorionic villus sampling and the development of hypertensive disorders later in pregnancy. Though our study is limited by a small sample size and low statistical power, we did not find any statistically significant increase in the odds ratio between patients undergoing genetic amniocentesis or chorionic villus sampling and the development of either gestational hypertension or preeclampsia. Even when the odds ratios were adjusted for maternal age and race, there was still no statistical difference among the three patient groups. An association was noted between African-American race and gestational hypertension, which has been supported by previous studies. Given the low power of our study, we suggest that a larger retrospective case control study be conducted in order to more accurately determine the relationship between chorionic villus sampling and hypertensive outcomes in pregnancy.

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**Figures and Tables**

Table 1. Definitions of Hypertensive Disorders of Pregnancy

| |
|---|
| Chronic Hypertension<br>• BP ≥ 140/90 mmHg on two occasions that presents before 20 weeks gestation |
| Gestational Hypertension<br>• BP ≥ 140/90 mmHg on two occasions in a previously normotensive woman<br>• No proteinuria<br>• BP returns to normal < 12 weeks postpartum |
| Preelampsia<br>*Mild:*<br>• BP ≥ 140/90 mmHg on two occasions after 20 weeks gestation<br>• Proteinuria ≥ 300mg/24 hours or ≥ 1+ dipstick<br>*Severe:*<br>• BP ≥ 160/110 mmHg on two occasions at least 6 hours apart<br>• Proteinuria 5.0g/24 hours or ≥ 3+ dipstick<br>• Oliguria < 500mL/24 hours<br>• Thrombocytopenia<br>• Elevated hepatic enzymes or impaired liver function<br>• Persistent headache, visual disturbances, other cerebral disturbances<br>• Persistent epigastric pain or right upper-quadrant pain<br>• Fetal growth restriction |
| Eclampsia<br>• Presence of preeclampsia<br>• Seizures that cannot be attributed to any other causes |

Adapted from the National High Blood Pressure Program Working Group Report on High Blood Pressure in Pregnancy (44).

Table 2. Maternal Characteristics by Group

| | Nuchal Translucency | Genetic Amniocentesis | Chorionic Villus Sampling |
|---|---|---|---|
| Mean Maternal Age (years) | 32.9 (± 5.1) | 36.9 (± 3.8) | 36.2 (± 4.8) |
| Gravidity | 2 (range 1-9) | 2 (range 1-8) | 3 ( range 1-8) |
| Race | | | |
| Caucasian | 77/100 (77%) | 87/105 (82.8 %) | 88/107 (82.2%) |
| African-American | 10/100 (10%) | 3/105 (2.8%) | 3/107 (2.8%) |
| Asian | 4/100 (4%) | 9/105 (8.6%) | 5/107 (4.7%) |
| Hispanic | 4/100 (4%) | 2/105 (1.9%) | 5/107 (4.7%) |
| Other | 5/100 (5%) | 4/105 (3.8%) | 6/107 (5.6%) |
| Presence of Diabetes | 11/124 (8.9%) | 9/119 (7.6%) | 13/207 (6.3%) |
| Smoking Status | | | |
| Nonsmoker | 112/124 (90.3%) | 112/117 (95.7%) | 200/207 (96.6%) |
| Current smoker | 6/124 (4.8%) | 3/117 (2.6%) | 3/207 (1.4%) |
| Ex-smoker | 6/124 (4.8%) | 2/117 (1.7%) | 4/207 (1.9%) |
| Gestational Age at Delivery (weeks) | 37.7 (± 5.0) | 37.8 (± 4.8) | 35.0 (± 8.9) |
| Birthweight (grams) | 3285.7 (± 747.6) | 3264.3 (± 666.5) | 3275.2 (± 698.9) |

Table 3. Prevalence of Hypertensive Disorders by Group

| | Nuchal Translucency (n = 124) | Genetic Amniocentesis (n = 119) | Chorionic Villus Sampling (n = 205) | Total (all groups) (n = 448) |
|---|---|---|---|---|
| Chronic Hypertension | 4 (3.2%) | 5 (4.2%) | 7 (3.4%) | 16 (3.6%) |
| Gestational Hypertension | | | | |
| Current GHTN | 4 (3.2%) | 1 (0.8%) | 2 (1.0%) | 7 (1.6%) |
| History of GHTN | 5 (4.0%) | 2 (1.7%) | 3 (1.5%) | 10 (2.2%) |
| Preeclampsia | | | | |
| Mild | 1 (0.8%) | 0 (0.0%) | 3 (1.5%) | 4 (0.9%) |
| Severe | 3 (2.4%) | 3 (2.5%) | 2 (1.0%) | 8 (1.8%) |

Table 4. Association Between Hypertensive Disorders and CVS

| | Unadjusted Odds Ratio (95% Confidence Interval) | Adjusted Odds Ratio[A] (95% Confidence Interval) |
|---|---|---|
| Gestational Hypertension | | |
| Nuchal Translucency | 1.0 | 1.0 |
| Genetic Amniocentesis | 3.5 (0.6 – 19.3) | 1.9 (0.2 – 170.1) |
| Chorionic Villus Sampling | 0.9 (0.1 – 9.6) | 0.4 (0.03 – 4.7) |
| | | |
| Preeclampsia | | |
| Nuchal Translucency | 1.0 | 1.0 |
| Genetic Amniocentesis | 0.8 (0.2 – 3.5) | 1.04 (0.19 – 5.80) |
| Chorionic Villus Sampling | 0.8 (0.2 – 2.8) | 0.93 (0.8 – 1.07) |

[A] Adjusted for age and race

Table 5. Unadjusted Odds Ratio of Hypertensive Disorders and Race

| Race | Gestational Hypertension | Preeclampsia |
|---|---|---|
| Caucasian | 1.0 | 1.0 |
| African-American | 18.8 (95% CI 3.5 – 102.6)[A] | 1.0 |
| Asian | 1.0 | 1.0 |
| Hispanic | 1.0 | 7.8 (95% CI 1.4 – 42.8)[A] |
| Other | 1.0 | 1.0 |

[A] $p < 0.05$

Table 6. Unadjusted Odds Ratio of Hypertensive Disorders and Smoking

| Smoking Status | Gestational Hypertension | Preeclampsia |
|---|---|---|
| Nonsmoker | 1.0 | 1.0 |
| Current smoker | 8.2 (95% CI 0.9 – 76.4) | 1.0 |
| Ex-smoker | 7.4 (95% CI 0.8 – 68.9) | 1.0 |