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Blood volume determination in obese and normal weight gravidas: the Hydroxyethyl Starch Method

Laura K. Vricella, MD,

Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Case Western Reserve University-MetroHealth Medical Center, Cleveland, OH, and Department of Obstetrics and Gynecology, Mercy Hospital, St Louis, MO

Judette M. Louis, MD, MPH,

Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of South Florida, Morsani College of Medicine, Tampa, FL

Edward Chien, MD, and

Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Case Western Reserve University-MetroHealth Medical Center, Cleveland, OH

Brian M. Mercer, MD

Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Case Western Reserve University-MetroHealth Medical Center, Cleveland, OH

Abstract

Objective—The impact of obesity on maternal blood volume in pregnancy has not been reported. We compared the blood volumes of obese and normal weight gravidas using a validated Hydroxyethyl Starch (HES) dilution technique for blood volume estimation.

Study Design—Blood volumes were estimated in 30 normal weight (pregravid body mass index; BMI < 25 kg/m²) and 30 obese (pregravid BMI > 35 kg/m²) gravidas after 34 weeks gestation using a modified HES dilution technique. Blood samples obtained before and 10 minutes after HES injection were analyzed for plasma glucose concentrations after acid hydrolysis of HES. Blood volume was calculated from the difference between glucose concentrations measured in hydrolyzed plasma.

Results—Obese gravidas had higher pregravid and visit BMI (mean [Std Dev]): pregravid (41[4] vs 22[2] kg/m², p=0.001); visit BMI (42[4] vs 27[2] kg/m², p=0.001), but lower weight gain (5[7] vs. 12[4] kg, p=0.001) than normal weight women. Obese gravidas had similar estimated total blood volume to normal weight women (8103 ± 2452 vs. 6944 ± 2830 mL, p = 0.1), but lower blood volume per kilogram weight (73 ± 22 vs. 95 ± 30 mL/kg, p = 0.007).

Corresponding Author: Laura K. Vricella, MD, 621 S. New Ballas Rd. Suite 2007B, St. Louis, MO 63141, P: (314) 991-5000, lpvricella@gmail.com.

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Conclusion—Obese gravidas have similar circulating blood volume, but lower blood volume per kilogram body weight, than normal weight gravidas near term.

Keywords

blood volume; obesity; obstetric anesthesia; hydroxyethyl starch

Introduction

Blood volume expansion in pregnancy is believed to be important for supporting normal obstetric outcomes.¹ Obese individuals, despite having increased total blood volume, are known to have lower unit blood volume than lean individuals because fat mass is underperfused when compared to lean body mass.^{2,3} The prevalence of obesity among pregnant women continues to rise.⁴⁻⁶ The impact of obesity on circulating blood volume in pregnancy has not been well studied. In lean women, unit blood volume is 65 mL/Kg in the nonpregnant state and increases to a mean of 100 mL/Kg (range 90-200 mL/Kg) near term pregnancy.^{2,7,8} Unit blood volume has been shown to decrease asymptotically with increasing body mass, to a nadir of 45 mL/Kg in nonpregnant Class III obese women.^{7,9} A decrease in unit blood volume could contribute to the increased frequency of obstetric complications in obese gravidas including anesthesia-related adverse events.¹⁰⁻¹³

Hypotension is a common complication of obstetric regional anesthesia placement and can result in category 2 and 3 fetal heart rate tracings and emergent delivery.¹⁴⁻¹⁸ Regional anesthesia induces sympathetic blockade, leading to decreased venous return that is mediated by blood volume.¹⁹ The resulting hypotension is commonly treated with additional intravenous volume and vasopressor administration.²⁰⁻²³ Prophylactic intravenous volume and/or vasopressor administration is commonly used prior to regional anesthesia to minimize the occurrence of hypotension.^{16,22,24} In our previously published studies, we have observed that Class III obese women (Body Mass Index, BMI ≥ 40 kg/m²) undergoing regional anesthesia for childbirth have more anesthesia-related hypotension and fetal heart rate abnormalities than lean gravidas.^{25,26} These factors may contribute to the increased cesarean delivery rate and associated perioperative morbidity among Class III obese women, such as hemorrhage, endometritis, wound infection, venous thromboembolism, and respiratory depression.²⁷⁻³¹

We hypothesize that the obese gravida requires a larger volume infusion prior to sympathetic blockade and resulting peripheral venodilation than the normal weight gravida.³ Fluid volumes that are sufficient to expand intravascular volumes and avert hypotension in normal weight women may be inadequate to prevent hypotension in obese women who have greater circulatory volume capacity. A better understanding of the blood volume of obese gravidas at term may contribute to alterations in intrapartum hemodynamic management. We sought to compare the total and relative blood volume of obese and lean gravidas near term using a dilution technique based on the colloid volume expander, Hydroxyethyl Starch (HES).³² We also sought to compare these calculations to blood volume estimates based on weight alone.⁷

Materials and Methods

This study was performed in the Clinical Research Unit of the Case Western Reserve University Clinical Translational Research Collaborative (CTSC-CRU, UL1 RR024989) at MetroHealth Medical Center, with institutional review board approval, and with written consent of each participant. All studies were performed on otherwise healthy women who were at least 18 years of age and at least 34 weeks gestation. Women were recruited into two groups: lean (pregravid BMI < 25 kg/m²) and obese (pregravid BMI > 35 kg/m²). Women with preeclampsia, chronic hypertension requiring medication, insulin-dependent diabetes mellitus, renal or autoimmune diseases, bleeding disorders, congestive heart failure, and known allergy to corn or HES were excluded.

Hydroxyethyl Starch (HES) Method

The HES method has been found to be highly accurate and precise and has been validated against the carbon monoxide method in anesthetized neurosurgical patients in the ICU.³² HES is used clinically for plasma volume expansion in obstetric patients, and has been administered in various clinical trials for this purpose in the obstetric and anesthesia literature.^{21, 33-36} The HES method for blood volume estimation is a rapid, safe, and acceptable technique for use in pregnant patients, and does not cross the placenta.^{32,33,37,38}

Proposed by Tschaikowsky et al³² in 1997, the HES method uses hydroxyethyl starch as a dilution marker and calculates blood volume from the difference of glucose concentration obtained by acid hydrolysis of plasma before and after injection of HES.^{39,40} Blood samples are collected before and after intravenous injection of HES. Derived plasma samples then undergo acid hydrolysis to disrupt the alpha glycosidic bonds and produce constant proportions of glucose and hydroxyethyl glucose. Comparison of hydroxyethyl glucose concentrations in the two samples yields a reproducible calculated total blood volume.³²

Baseline Measurements

Height, weight, blood pressure, pulse, and fetal heart tones were obtained on arrival at the CTSC-CRU and used to calculate body mass index and body surface area. Pre-gravid weights were obtained from direct measurements in the 3 months prior to pregnancy or at the first prenatal visit if prior to 10 weeks gestation. Urine specific gravity and serum creatinine were measured to gauge hydration status.

Sample Collection

Patients were placed in the left lateral recumbent position for 30 minutes. An 18-gauge antecubital intravenous catheter was placed. Hespan® (6% hetastarch in 0.9% sodium chloride) (DuPont, Wilmington, DE), 170 mL, was injected intravenously over 4 minutes followed by a 1 mL saline flush. Whole blood was collected in EDTA tubes prior to, and then 10 minutes after HES injection, from opposite arms. The timing of the second blood draw was determined by a preliminary mixing study in which HES concentration was measured at 5-minute intervals from 0 to 60 minutes after HES injection in 10 volunteers (5 lean and 5 obese), with steady state observed at 10 minutes post-injection for both groups.

Body composition measurements were performed using air displacement plethysmography (BOD POD®; COSMED, Rome, Italy) to estimate the subject's percent lean and fat mass.

Hematocrit was determined using a microhematocrit centrifuge. Plasma was separated from whole blood by centrifugation. Plasma (0.6 mL) was transferred into steam-tight tubes containing 0.15 mL concentrated hydrochloric acid (12M) and hydrolyzed in boiling water for 7 minutes. 0.65 mL of 3.33 M Trisbuffer was then added and incubated at room temperature for 6 minutes to bring the pH to 7.0 ± 0.5 . The supernatant was recovered by centrifugation (3600 RPM, 16 min). Glucose in the supernatant was measured using the HemoCue 201 Glucose Photometer (HemoCue™, Biotest, Frankfurt, Germany).^{41,42}

HES Blood Volume Calculation

Blood volume was calculated using the equation: blood volume [mL] = $k \text{ (HESV [mL])} / \text{glucose} / (1 - \text{hematocrit})$. HESV equals the volume of HES injected (mL). glucose (mg%) is the difference of glucose concentration, after hydrolysis in plasma. The constant, k (3082 (mg%)), is the slope of the linear regression line obtained by plotting glucose against the HES volume (HESV)/Plasma volume (PV) ratio for varying in vitro dilutions of HES in whole blood.³²

Weight-based Blood Volume Calculation

Weight-based estimate of blood volume was determined using the equation developed by Feldschuh and Enson.⁷ It uses gender, height, weight, and deviation from desired weight to calculate blood volume as follows: Blood Volume (mL) = [Blood Volume to Body Weight Ratio (mL/kg)] [body weight (kg)] = $45.2 + 25.3 \exp(-0.0198 \times \text{DDW})$. DDW is Deviation from Desirable Weight (%) = $100 [\text{body weight (kg)} - \text{DW (kg)}] / [\text{DW (kg)}]$. DW is Desirable Weight (kg) for women = $7.090 \exp[0.01309 * (\text{body height (cm)})]$.⁷

Statistics and Sample Size Estimate

We note that the unit blood volume for normal weight gravidas near term is 100 mL/Kg.^{2,7,8} To detect at 30 percent decrease in unit blood volume in obese gravidas, at an alpha of 0.05 and a beta of 0.1, 30 women would be needed in each group, giving a sample size of 60 patients. We compared patient characteristics and blood volume estimation techniques between lean and obese gravidas using T-tests for paired and independent samples and Mann-Whitney U test for non-normally distributed data. We performed simple linear regressions to compare HES blood volume estimates using body mass index and body composition as measured by air displacement plethysmography. Statistical analyses were performed using commercially available software (SPSS, version 18.0; SPSS Inc, Chicago, IL).

Results

A total of 60 gravidas at 34 weeks gestational age or beyond enrolled in the study. 30 women had pregravid BMI of 25 kg/m² or below and 30 women had pregravid BMI of 35 kg/m² or above. The data from one patient was excluded due to sample processing errors, leaving 29 lean and 30 obese patients. The mean pregravid and gravid BMIs were 22 ± 2 and 27 ± 2

kg/m² for the normal weight patients and 41 ± 4 and 42 ± 4 kg/m² for the obese patients ($p < 0.001$ for both) (Table 1). The lean women gained more weight during pregnancy than the obese women (12 ± 4 kg vs. 5 ± 7 kg, $p < 0.001$). Mean body composition, as determined by the Bod Pod was: 72 ± 5 percent lean and 28 ± 5 percent fat mass in the lean group, compared with 57 ± 5 percent lean and 43 ± 5 percent fat mass in the obese group ($p < 0.001$) (Table 1). A patient experienced a hypersensitivity reaction consisting of a rash and urticaria after HES injection, and was treated with oral antihistamines without further complications.

Blood Volume Comparisons

For the total cohort, the HES method produced a higher mean blood volume estimate than the weight-based formula, $7,500 \pm 2,600$ versus $5,000 \pm 500$ mL ($p = 0.001$). For both lean and obese women, the blood volume estimates by the HES method were higher than for Feldschuh and Enson's equation based on gender, height, weight, and deviation from desired weight (Table 2). Although total blood volumes calculated by the HES method were similar between obese and lean women (8103 ± 2452 vs. 6944 ± 2830 mL, $p = 0.1$), obese women had lower blood volume per kilogram when compared with normal weight women (73 ± 22 vs. 95 ± 30 mL/kg, $p = 0.007$).

Comparison of body mass index and blood volume calculated by the HES method revealed that the blood volume per kilogram decreased as Body Mass Index increased ($y = -1.372x + 130$, adjusted r^2 of 0.2) (Figure 1). Evaluation of blood volume calculated relative to percent lean body mass, as measured by air displacement plethysmography, revealed a weakly positive correlation ($y = 0.91x + 25$, adjusted $r^2 = 0.1$) (Figure 2).

Comment

We applied the HES method of blood volume determination that has previously been validated in intensive care unit patients to lean and obese gravidas in order to determine the impact of maternal obesity on obstetric blood volume. Obese gravidas had similar circulating blood volume, but lower blood volume per kilogram body weight, compared with normal weight gravidas. We found wide variation in total blood volumes, and a poor correlation between the HES method and a weight-based method of blood volume estimation. The HES blood volume per kilogram total body weight estimates were negatively correlated with body mass index and positively correlated with lean body mass.

Our blood volume calculations using the HES method are consistent with previously published studies (Table 3). Our finding that obese gravidas had lower blood volume per kilogram compared with lean gravidas is consistent with studies of nonpregnant patients demonstrating that obese patients have lower blood volume per unit body weight because fat mass is relatively under-perfused when compared to lean mass. The HES method of blood volume calculations for lean and obese women were approximately 50% higher than the nonpregnant reference standards, which is consistent with previously validated studies of pregnancy-related increases in blood volume. The wide variation in blood volume estimates among individuals is consistent with previous findings of wide variation in pregnancy-related increases in blood volume from 50 to 200 percent. The poor correlation with the

weight-based blood volume estimate suggests that factors other than body weight may contribute to variation in blood volume during pregnancy.

Estimation of blood volume in pregnancy is challenging. The main limitation of our study is the lack of a “gold standard” comparative blood volume estimation method. The HES method was validated against a “gold standard” carbon monoxide method in anesthetized neurosurgical patients.³² However, carbon monoxide is unacceptable in pregnant women due to its hypoxemic effects. The Evans blue dye technique has previously been used for blood volume estimation in pregnancy; however it is a suspected carcinogen.⁴³ Use of chromium labeled RBCs has been considered the gold standard for red blood cell volume estimation but chromium is actively transported across the placenta and is concentrated in the fetus,^{44,45} and has been found to disrupt placental function in animal studies.⁴⁶ We had one minor reaction to Hesperan that was readily treated with antihistamines. The HES technique was well tolerated and acceptable to the participants.

Our findings have potential implications for fluid management of obese gravidas during obstetric anesthesia placement. Blood volume increases with obesity, although to a lesser extent than body weight and volume. This is because the increase in body size is mostly adipose tissue, which is relatively under-perfused when compared to lean mass. Thus the circulating blood volume theoretically provides a smaller reserve volume available to accommodate changes in venous capacitance that is induced with neuraxial blockade. Weight-adjusted volume expansion may provide a physiologically based intervention targeted at preventing maternal hypotension and fetal heart rate abnormalities after regional anesthesia. This study provides support for a testable hypothesis that weight adjusted volume expansion reduces FHR abnormalities and hypotension.

In conclusion, HES-based blood volume estimation suggests that obese gravidas near term have unit blood volumes that are 50 percent higher than obese nonpregnant patients, but remain significantly lower than lean gravidas. Our findings suggest that clinical blood volume calculation by the HES method is feasible and well tolerated, and is easily performed in healthy gravidas near term. The relative ease, safety, and accessibility of the technique holds promise for future blood volume estimation studies in pregnancy. Further investigations should focus on validation of the laboratory protocol in the obstetric population before clinical application is attempted.

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Figure 1. HES blood volume estimate (ml/kg) according to Body Mass Index (kg/m²) in lean and obese gravidas

Points are labeled according to maternal obesity status. Unit blood volume decreased as body mass index increased.

Figure 2. HES blood volume estimate (mL/kg) according to percent lean body mass
Unit blood volume estimates correlated to percent lean body mass as determined by air displacement plethysmography in obese and lean gravidas.

Table 1
Baseline Characteristics, Lean vs. Obese Gravidas^a

	Lean	Obese	P value
N	29	30	
<u>Weight</u>			
Pregravid BMI (kg/m ²)	22 ± 2	41 ± 4	0.001
Study Visit BMI (kg/m ²)	27 ± 2	42 ± 4	0.001
Weight gain (kg)	12 ± 4	5 ± 7	0.001
<u>Body composition</u>			
Percent lean (%)	72 ± 5	57 ± 5	0.001
Percent fat (%)	28 ± 5	43 ± 5	

^aPresented as Mean ± standard deviation

Table 2
Blood volume estimation in lean and obese gravidas^a

	Lean	Obese	P value
N	29	30	
<u>Blood volume (mL)</u>			
BV-HES ^b	6944 ± 2830	8103 ± 2452	0.1
BV-FE ^c	4417 ± 436	5568 ± 602	<0.001
<u>Blood Volume (mL/kg)</u>			
BV-HES	95 ± 30	73 ± 22	0.007
BV-FE	63 ± 4	50 ± 2	<0.001

^a Presented as Mean ± standard deviation

^b BV-HES is blood volume by hydroxyethyl starch method

^c BV-FE is blood volume by Feldschuh and Enson's equation based on gender, height, weight, and deviation from desired weight

Table 3

Blood Volume Estimates by the HES method and previously published estimates.

Females	Prior studies	HES method
Lean Nonpregnant ^{7,9}	65 ml/kg	--
Obese Nonpregnant ^{7,9}	45 ml/kg	--
Lean Pregnant ³¹	100 ml/kg (range 90-200)	95 ml/kg (95% CI 35-155)
Obese Pregnant	--	73 ml/kg (95% CI 29-117)