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ORIGINAL ARTICLE

The prediction of hypertensive disorders by maternal hemodynamic assessment in the first trimester of pregnancy

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ABSTRACT

Background: Hypertensive disorders of pregnancy and fetal growth restriction share common etiopathological origins and could be caused by maternal hemodynamic maladaptation to pregnancy.

Objective: The aim of our study is to evaluate if there is a correlation between maternal hemodynamic detected by UltraSonic Cardiac Output Monitor (USCOM®) during the first trimester and the pregnancy outcome.

Study design: We recruited a nonconsecutive series of women in the first trimester of pregnancy with no previous history of hypertensive disorders. We measured the pulsatility index uterine arteries and performed a hemodynamic evaluation by USCOM® device. After delivery, we reported the development of hypertensive disorders or intrauterine fetal growth restriction later during gestation.

Results: A total of 187 women were enrolled during the first trimester; 17 (9%) developed gestational hypertension or preeclampsia while 11 (6%) delivered a restricted growth fetus. Mean uterine artery pulsatility index above the 95th percentile was significantly more frequent in both women who developed hypertension and those with fetal growth restriction compared to controls. Hemodynamic parameters (reduced cardiac output and increased total vascular resistance) were significantly different in the group that developed hypertensive disorders, compared to uncomplicated pregnancy. ROC curves demonstrated the usefulness of uterine artery pulsatility index in the prediction of fetal growth restriction, while hemodynamic parameters were significantly associated to the development of hypertensive disorders.

Conclusions: Hemodynamic maladaptation to pregnancy may predispose to the development of hypertension, while we demonstrated a significative relationship between growth restriction and mean uterine pulsatility index. Further studies are needed to assess the value of hemodynamics evaluation in screening protocols of preeclampsia.

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Introduction

Hypertensive disorders of pregnancy and fetal growth restriction are two of the major concerns in Obstetrics, often sharing a common etiopathogenesis [1–3]. Much effort has focused on the early identification of women at greater risk of developing these complications, in order to implement effective preventive strategies, such as the administration of acetylsalicylic acid [4,5]. In recent times, the hypothesis that these hypertensive disorders may originate, rather than being the cause, from a maladaptation of the maternal organism to pregnancy has emerged [6–8]. During uncomplicated gestations, we observe a reduction in mean arterial pressure and total peripheral resistance (TVR), accompanied by a specular increase in cardiac output (CO) [9]. In pregnancies complicated by hypertensive disorders and/or fetal growth restriction, it has now been widely demonstrated that these changes in maternal hemodynamics are lacking, with a persisting low cardiac output and high peripheral resistances [10–13]. To carry out these assessments in a noninvasive, simple and reproducible way, even in the hands of operators not dedicated to maternal echocardiography, the USCOM® (Ultrasonic Cardiac Output Monitor) system was introduced [14–16]. In the

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present study, we therefore evaluated if the hemodynamic evaluation, assessed by this technology, could correlate with the development of hypertensive disorders and/or fetal growth restriction later in pregnancy in an unselected group of women referred to our Obstetric Unit for the screening of first trimester aneuploidies.

Materials and methods

This was a prospective study conducted in the unit of Obstetrics and Prenatal Medicine at Sant'Orsola-Malpighi University Hospital in Bologna, Italy. We recruited a nonconsecutive series of women referred for the first trimester screening of chromosomal abnormalities with a gestational age between 11 and 13 + 6 weeks and who subsequently delivered in our Obstetric Unit. We excluded smoking patients, twin pregnancies, women with previous hypertensive disorder of pregnancies or previous growth restricted fetus, with chronic hypertension, kidney disease or pre-gestational diabetes mellitus. We also excluded from the analysis those fetuses with fetal anatomical abnormalities such as cystic hygroma, holoprosencephaly and other malformations visible in the first trimester. Both primigravid and patients with previous uncomplicated pregnancy were included, such as both spontaneous pregnancies and pregnancies achieved with homologous assisted fertilization techniques. Demographic, ultrasound and biochemical data were collected. Patients with high-risk test and a chromosomal abnormality confirmed at the chorionic villous sampling were excluded from the analysis. During the ultrasound, we measured the pulsatility index of right and left uterine artery (UTPI) by transabdominal method, thus calculating the mean pulsatility [17]. The cutoff used to define an increased mean pulsatility in the first trimester was 2.35, as reported by the recent guidelines of ISUOG [18]. We then proceeded with the hemodynamic evaluation, performed by the same expert operator, carried out using USCOM®, after 15 min of rest in the supine position. We evaluated blood pressure, the stroke volume (SV, volume of blood pumped by the heart per cardiac cycle, cm^3), cardiac output (CO, l/min), total peripheral vascular resistances (TVR, dyne s/cm^5) and inotropic index (INO, $Watt/m^2$). CO, SV and TVR were then indexed and their percentile were calculated, by means of the Excel normograms calculator developed by the London group [19]. After delivery, we collected the outcomes of those pregnancies by consulting clinical charts and records. We reported the onset of hypertensive disorders or intrauterine fetal growth restriction (IUGR) during pregnancies, the mode of delivery and its gestational age, neonatal weigh, Apgar score, the admission to Neonatal Intensive Care Unit, pH and base excess at delivery and postpartum hemorrhages defined as a blood loss of more than one liter.

Statistical analysis

Numerical variables were summarized as mean ± standard deviation and as median [interquartile range]; categorical variables were summarized as frequencies and percentages. To investigate the presence of systematic differences according to hypertension, IUGR or either conditions, we performed the Mann–Whitney test or Fisher's exact test, where appropriate. Accuracy and predictive ability of all numerical independent variables was further evaluated with nonparametric receiver operating characteristic (ROC) analysis. More specifically, the optimal cut-point value was determined using the Youden method, which maximizes the sum of the sensitivity and specificity. All analyses were carried out using Stata software, version 15 (StataCorp, 2017, Stata Statistical Software: Release 15, College Station, Texas, USA: StataCorp LP). The significance level was set at 5%.

Ethics

The study protocol was approved by our local ethics committee (147/2019/Oss/AOUBo) and coheres the ethical guidelines of the "World Medical Association Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects" adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the 59th WMA General Assembly, Seoul, South Korea, October 2008.

Results

For the purpose of the study, 187 women were enrolled during the first trimester of pregnancy. The summary of the demographic, ultrasound and hemodynamic data detected by USCOM® are shown in Table 1. Of these, 26 women (14%) developed subsequently hypertensive disorders of pregnancy and/or fetal growth restriction; in particular, 17 (9%) developed gestational hypertension or preeclampsia while 11 (6%) delivered a restricted growth fetus (two of them had both complications). The data regarding pregnancy outcomes are reported in Table 2.

Table 1. Characteristics of women enrolled.

	Media ± SD or N (%)
Maternal age (years)	34 ± 5
Parity	Primigravid 59% (n. 110)
	others 41% (n. 77)
Gestational age (week)	12 ± 1
Mode of onset of pregnancy	Spontaneous 90% (n. 168)
	Assisted reproductive technology 6% (n. 11)
	Intracytoplasmic sperm injection 4% (n. 8)
BMI (kg/m^2)	23 ± 4
CRL (mm)	62 ± 7
bHCG (MoM)	1.11 ± 0.67
PAPP-A (MoM)	1.35 ± 0.74
Mean UTPI	1.49 ± 0.43
Mean UTPI > 95th percentile	4.3% (8/187)
CO (l/min)	5.6 ± 1.3
CO < 5th percentile	15.5% (29/187)
TVR (dyne s/cm^5)	1304 ± 299
TVR > 95th percentile	17.6% (33/187)
TVR > 1500 dyne s/cm^5	24% (45/187)
SV (cm^3)	70 ± 14
INO (Watt/m^2)	1.58 ± 0.37

Abbreviations: BMI: body mass index; CRL: crown rump length; bHCG: free fraction of human chorionic gonadrotropin; PAPP-A: pregnancy-associated plasma protein-A; UTPI: mean pulsatility index of uterine arteries; Vpk: peak systolic velocity; HR: heart rate; CO: cardiac output; TVR: total peripheral vascular resistances; SV: stroke volume; INO: inotropic index.

Table 2. Pregnancy outcomes of the population enrolled.

	Media ± SD or N (%)
Gestational time at delivery (week)	39 ± 2
Mode of delivery	Vaginal delivery 67.4% (n.126)
	Urgent cesarean section 18.2% (n. 34)
	Elective cesarean section 14.4% (n. 27)
Onset of hypertensive disorders and / or fetal growth restriction	13.9% (n. 26)
Onset of gestational hypertension / preeclampsia	9 % (n. 17)
Onset of fetal growth restriction	6% (n. 11)
Postpartum hemorrhage	7% (n. 13)
Neonatal weight (grams)	3320 ± 674
pH of umbilical artery	7.31 ± 0.09
Excess of bases of umbilical artery	−3.4 ± 4.17
Apgar score after 1 min	9 (3 to 10)
Apgar score after 5 min	10 (6 to 10)
Admission to NICU	3.2% (n. 6)

Note: NICU: neonatal intensive care unit.

We then compared the demographic, biochemical, ultrasound and hemodynamic characteristics of the women who developed hypertensive disorders and/or IUGR, as reported in Table 3. Patients who developed hypertension in pregnancy are significantly older than the others, which is not confirmed for the IUGR, as well as in this group the use of assisted fertilization is more frequent. As for gestational age at delivery and neonatal weight, they are obviously lower than in patients with uncomplicated pregnancy, while we have not reported statistically significant differences regarding the mode of delivery and the onset of postpartum hemorrhage. The onset of hypertension is significantly more frequent in those pregnancy conceived with assisted reproductive technologies.

Mean-UTPI above the 95th percentile was significantly more frequent in both women who developed hypertension and those with fetal growth restriction compared to patients with uncomplicated pregnancy. The hemodynamic parameters (CO, TVR, SV), instead, were significantly different in the group that developed hypertensive disorders, compared to uncomplicated pregnancy, showing a reduced CO and an increase in TVR since the first trimester of gestation. We also aimed to evaluate how these parameters can predict hypertension/preeclampsia (Table 4), IUGR (Table 5) or at least one of the two (Table 6). Age, BMI, and biochemical markers were not significantly related with the development of these pregnancy complications.

The ROC curve of mean UTPI for the prediction of either hypertension/IUGR shows an AUC (area under the curve) of 62.4 (48.9 to 74.8, $p = .04$) and an AUC of 85.6 (71.0 to 94.1, $p = .001$) for IUGR alone. It was not related, instead, in the first trimester with the onset of hypertensive disorders alone (Figure 1), AUC of 50.3 (34.8 to 66.2, $p = .95$). CO instead showed an AUC of 69.6 (56.9 to 82.0, $p = .005$) for the prediction of

Table 3. Association of hypertension and intrauterine growth restriction (IUGR) with demographic, biochemical, ultrasound, and hemodinamics parameter.

	Hypertension			IUGR			Either one		
	Yes ($n = 17$)	*No* ($n = 170$)	*p* Value	Yes ($n = 11$)	No ($n = 176$)	*p* Value	Yes ($n = 26$)	No ($n = 161$)	*p* Value
Age, years	37.4 ± 5.2	33.3 ± 4.3	.003*	30.5 ± 3.8	33.9 ± 4.5	.02*	34.8 ± 5.9	33.5 ± 4.2	.32
	37 [34–42]	34 [30–36]		31 [27–34]	34 [31–37]		34.5 [30–40]	34 [31–36]	
BMI, kg/m^2	25.7 ± 6.1	23.2 ± 3.7	.11	23.5 ± 4.1	23.4 ± 4.1	.94	24.7 ± 5.3	23.2 ± 3.8	.29
	24.2 [21.5–27.1]	22.8 [20.5–24.7]		21.6 [20.5–26.3]	22.8 [20.7–25]		23 [21.2–26.7]	22.8 [20.6–24.6]	
ART	7 (41.2%)	12 (7.1%)	<.001*	0 (0.0%)	19 (10.8%)	.61	7 (26.9%)	12 (7.5%)	.007*
Beta-hCG, MoM	1.09 ± 0.73	1.11 ± 0.67	.65	0.72 ± 0.41	1.13 ± 0.68	.01*	0.97 ± 0.67	1.1 ± 0.7	.08
	0.88 [0.67–1.29]	0.93 [0.70–1.45]		0.65 [0.46–0.90]	0.96 [0.70–1.46]		0.79 [0.46–1.20]	1 [0.7–1.5]	
PAPP-A, MoM	1.32 ± 0.69	1.36 ± 0.75	.87	1.01 ± 0.39	1.38 ± 0.75	.11	1.23 ± 0.61	1.37 ± 0.76	.42
	1.20 [0.76–1.68]	1.20 [0.80–1.76]		0.97 [0.62–1.29]	1.22 [0.80–1.78]		1.05 [0.76–1.65]	1.22 [0.84–1.78]	
Mean BP, mmHG	90.9 ± 12.5	87.3 ± 8.9	.29	88.6 ± 9.9	87.5 ± 9.3	.95	90.5 ± 11.5	87.1 ± 8.9	.26
	90 [80–93.3]	87 [83–93]		86.7 [80–97]	88 [82.5–93]		90 [80–97]	87 [83–93]	
Mean UTPI	1.56 ± 0.53	1.49 ± 0.42	.95	2.05 ± 0.39	1.46 ± 0.41	<.001*	1.69 ± 0.5	1.46 ± 0.41	.04*
	1.44 [1.16–1.71]	1.43 [1.18–1.76]		2.06 [1.80–2.39]	1.41 [1.16–1.71]		1.68 [1.28–2.06]	1.42 [1.16–1.71]	
Mean UTPI >95th perc.	3 (17.6%)	5 (2.9%)	.03*	3 (27.3%)	5 (2.8%)	.007*	4 (15.4%)	4 (2.5%)	.01*
Cardiac output, L/min	4.8 ± 1.1	5.7 ± 1.3	.005*	5.3 ± 1.5	5.7 ± 1.3	.21	5.1 ± 1.3	5.7 ± 1.3	.01*
	4.7 [4.0–5.6]	5.7 [4.9–6.6]		5.2 [4.0–5.8]	5.6 [4.8–6.4]		5.3 [4.0–5.7]	5.7 [4.9–6.6]	
Cardiac output, perc.	23.1 ± 25.6	43.3 ± 31.1	.006*	33.5 ± 34.5	42.0 ± 30.9	.27	29.1 ± 29.5	43.4 ± 31.0	.02*
	10.2 [2.4–40.7]	39.2 [14.0–73.0]		30.0 [2.0–59.0]	37.9 [13.9–70.4]		23.9 [3.0–42.0]	39 [14.3–73.0]	
Cardiac output <5th perc.	6 (35.3%)	23 (13.5%)	.03*	4 (36.4%)	25 (14.2%)	.07	8 (30.8%)	21 (13.0%)	.04*
TVR, dyn·s/cm^5	1636.5 ± 435.2	1271.1 ± 261.3	<.001*	1421.7 ± 272.5	1296.9 ± 299.8	.13	1535.3 ± 398.9	1267 ± 262.8	<.001*
	1683 [1363–1788]	1232 [1096–1397]		1336 [1200–1651]	1244 [1099–1480]		1533 [1292–1753]	1232 [1090–1396]	
TVR, percentile	86.7 ± 20.0	66.1 ± 27.0	<.001*	77.4 ± 22.0	67.3 ± 27.2	.25	82.0 ± 21.4	65.7 ± 27.2	.001*
	95.9 [85.0–98.3]	71.0 [48.0–88.1]		84.1 [58.7–96.1]	74.0 [48.5–91.6]		92.5 [72.0–97.0]	71.0 [46.8–88.0]	
TVR >95th percentile	9 (52.9%)	25 (14.7%)	.001*	4 (36.4%)	30 (17.0%)	.12	12 (46.2%)	22 (13.7%)	<.001*
Stroke volume, mL	58.6 ± 11.6	71.4 ± 13.6	<.001*	65.5 ± 16.5	70.5 ± 13.7	.20	62.1 ± 13.9	71.5 ± 13.5	.001*
	60 [54–62]	70 [62–79]		65 [53–76]	69 [61–79]		61 [54–66]	70 [63–79]	
Inotrope index	1.4 ± 0.3	1.6 ± 0.4	.15	1.6 ± 0.5	1.6 ± 0.4	.62	1.5 ± 0.4	1.6 ± 0.4	.25
	1.5 [1.3–1.5]	1.5 [1.4–1.8]		1.4 [1.2–1.9]	1.5 [1.4–1.7]		1.5 [1.3–1.7]	1.5 [1.4–1.8]	
Gestational age at birth, weeks	37.9 ± 1.6	39.1 ± 1.6	.003*	38.0 ± 1.5	39.0 ± 1.6	.01*	38.0 ± 1.6	39.1 ± 1.6	<.001*
	38 [37–39]	39 [38–40]		38 [38–39]	39 [38–40]		38 [37–39]	39 [39–40]	
Birth weight, g	3096 ± 386	3342 ± 693	.05*	2686 ± 310	3359 ± 671	<.001*	2952 ± 417	3379 ± 690	<.001*
	3055 [2860–3335]	3325 [3000–3630]		2765 [2620–2810]	3338 [3020–3630]		2865 [2745–3140]	3350 [3035–3650]	
Type of delivery			.02*			.80			.41
Vaginal	7 (41.2)	119 (70.0)		9 (81.8)	117 (66.5)		15 (57.7)	111 (68.9)	
Emergency CS	7 (41.2)	27 (15.9)		1 (9.1)	33 (18.8)		7 (26.9)	27 (16.8)	
Elective CS	3 (17.6)	24 (14.1)		1 (9.1)	26 (14.8)		4 (15.4)	23 (14.3)	
Postpartum hemorrhage	2 (11.8)	11 (6.5)	.34	0 (0.0)	13 (7.4)	>.99	2 (7.8)	11 (6.8)	>.99

Note: Values are mean ± standard deviation and median [interquartile range], or *n* (%).

Abbreviations: BMI: body mass index; ART: assisted reproductive technology; hCG: human chorionic gonadotropin; PAPP-A: pregnancy-associated plasma protein A; UA-BP: blood pressure; UTPI: uterine artery pulsatility index; TVR: total vascular resistance; CS: cesarean section.

*p Value ≤.05.

Table 4. Accuracy and predictive ability of potential risk factors for hypertension; point estimates are presented along with 95% confidence intervals.

Variable	Area under the ROC curve (%)	Youden's optimal Cut-point	Accuracy and predictive ability at optimal cut-point			
			Sensibility (%)	Specificity (%)	PPV (%)	NPV (%)
Age, years	69.6 (53.4–84.1)	38.5 (34.5–41.5)	47.1 (26.2–69.0)	88.2 (82.5–92.3)	28.6 (15.3–47.1)	94.3 (89.6–97.0)
BMI, kg/m^2	61.9 (46.7–78.0)	25.6 (23.2–39.7)	47.1 (26.2–69.0)	80.6 (74.0–85.8)	19.5 (10.2–34.0)	93.8 (88.7–96.7)
Beta-hCG, MoM	53.4 (37.6–68.7)	0.46 (0.37–1.2)	23.5 (9.6–47.3)	91.2 (86.0–94.6)	21.1 (8.5–43.3)	92.3 (87.2–95.4)
PAPP-A, MoM	51.2 (36.3–65.4)	0.83 (0.52–0.94)	41.2 (21.6–64.0)	74.7 (67.7–80.6)	14.0 (7.0–26.2)	92.7 (87.1–96.0)
Mean BP, mmHG	55.7 (39.7–72.2)	87.5 (71.7–105.8)	70.6 (46.9–86.7)	51.2 (43.7–58.6)	12.6 (7.4–20.8)	94.6 (87.9–97.7)
Mean UTPI	50.3 (34.8–66.2)	2.37 (0.97–2.55)	17.6 (6.2–41.0)	98.2 (94.9–99.4)	50.0 (18.8–81.2)	92.3 (87.4–95.3)
Cardiac output, L/min	69.6 (56.9–82.0)	5.8 (5.9–5.9)	94.1 (73.0–99.0)	41.2 (34.1–48.7)	13.8 (8.7–21.2)	98.6 (92.4–99.8)
TVR, dyn·s/cm^5	78.2 (61.9–89.8)	1609 (1356–1811)	58.8 (36.0–78.4)	88.8 (83.2–92.7)	34.5 (19.9–52.7)	95.6 (91.1–97.8)
Stroke volume, mL	76.4 (63.6–85.8)	62.5 (54.5–62.5)	82.4 (59.0–93.8)	74.7 (67.7–80.6)	24.6 (15.2–37.1)	97.7 (93.4–99.2)
Inotrope index	55.6 (42.3–69.0)	1.6 (1.5–2.2)	76.5 (52.7–90.4)	47.6 (40.3–55.1)	12.7 (7.6–20.6)	95.3 (88.5–98.2)

Abbreviations: ROC: receiver operating characteristic; PPV: positive predictive value; NPV: negative predictive value; BMI: body mass index; hCG: human chorionic gonadotropin; PAPP-A: pregnancy-associated plasma protein A; BP: blood pressure; UTPI: uterine artery pulsatility index; TVR: total vascular resistance.

Table 5. Accuracy and predictive ability of potential risk factors for intrauterine growth restriction (IUGR).

Variable	Area under the ROC curve (%)	Youden's optimal Cut-point	Accuracy and predictive ability at optimal cut-point			
			Sensibility (%)	Specificity (%)	PPV (%)	NPV (%)
Age, years	68.2 (52.9–82.6)	31.5 (27.5–31.5)	63.6 (35.4–84.8)	70.5 (63.3–76.7)	11.9 (5.9–22.5)	96.9 (92.2–98.8)
BMI, kg/m^2	49.3 (28.1–66.6)	25.4 (20.0–32.6)	36.4 (15.2–64.6)	76.7 (69.9–82.3)	8.9 (3.5–20.7)	95.1 (90.2–97.6)
Beta-hCG, MoM	72.1 (53.8–85.6)	0.91 (0.46–0.92)	90.9 (62.3–98.4)	53.4 (46.0–60.6)	10.9 (6.0–18.9)	98.9 (94.3–99.8)
PAPP-A, MoM	64.5 (49.9–78.0)	1.14 (0.58–1.76)	72.7 (43.4–90.3)	55.7 (48.3–62.8)	9.3 (4.8–17.3)	97.0 (91.6–99.0)
Mean BP, mmHG	48.1 (30.6–66.6)	96.8 (75.0–108.5)	27.3 (9.7–56.6)	85.8 (79.9–90.2)	10.7 (3.7–27.2)	95.0 (90.4–97.4)
Mean UTPI	85.6 (71.0–94.1)	1.76 (1.74–1.79)	90.9 (62.3–98.4)	79.5 (73.0–84.8)	21.7 (12.3–35.6)	99.3 (96.1–99.9)
Cardiac output, L/min	60.0 (36.2–78.0)	4.5 (4–5.3.0)	45.5 (21.3–72.0)	80.1 (73.6–85.3)	12.5 (5.5–26.1)	95.9 (91.4–98.1)
TVR, dyn·s/cm^5	63.7 (46.7–80.8)	1612 (1323–1786)	45.5 (21.3–72.0)	86.9 (81.2–91.1)	17.9 (7.9–35.6)	96.2 (92.0–98.3)
Stroke volume, mL	60.6 (37.3–80.1)	54.5 (42.5–55.0)	36.4 (15.2–64.6)	92.6 (87.8–95.6)	23.5 (9.6–47.3)	95.9 (91.7–98.0)
Inotrope index	51.1 (29.6–73.0)	1.4 (1.1–1.4)	45.5 (21.3–72.0)	76.7 (69.9–82.3)	10.9 (4.7–23.0)	95.7 (91.0–98.0)

Note: Point estimates are presented along with 95% confidence intervals.
Abbreviations: ROC: receiver operating characteristic; PPV: positive predictive value; NPV: negative predictive value; BMI: body mass index; hCG: human chorionic gonadotropin; PAPP-A: pregnancy-associated plasma protein A; BP: blood pressure; UTPI: uterine artery pulsatility index; TVR: total vascular resistance.

Table 6. Accuracy and predictive ability of potential risk factors for hypertension or intrauterine growth restriction (IUGR).

Variable	Area under the ROC curve (%)	Youden's optimal Cut-point	Accuracy and predictive ability at optimal cut-point			
			Sensibility (%)	Specificity (%)	PPV (%)	NPV (%)
Age, years	53.3 (37.8–67.1)	39.5 (35.5–42.5)	26.9 (13.7–46.1)	93.2 (88.2–96.1)	38.9 (20.3–61.4)	88.8 (83.1–92.7)
BMI, kg/m^2	56.4 (44.7–68.5)	25.4 (19.0–26.3)	42.3 (25.5–61.1)	78.9 (71.9–84.5)	24.4 (14.2–38.7)	89.4 (83.3–93.5)
Beta-hCG, MoM	60.7 (47.4–73.5)	0.91 (0.46–1.83)	69.2 (50.0–83.5)	54.0 (46.3–61.6)	19.6 (12.7–28.8)	91.6 (84.3–95.7)
PAPP-A, MoM	54.9 (43.7–66.7)	0.99 (0.62–2.12)	50.0 (32.1–67.9)	64.6 (56.9–71.6)	18.6 (11.2–29.2)	88.9 (81.9–93.4)
Mean BP, mmHG	54.8 (41.5–67.7)	97.5 (89.9–114.5)	23.1 (11.0–42.1)	91.3 (85.9–94.7)	30.0 (14.5–51.9)	88.0 (82.2–92.1)
Mean UTPI	62.4 (48.9–74.8)	1.76 (1.25–2.28)	46.2 (28.8–64.5)	78.9 (71.9–84.5)	26.1 (15.6–40.3)	90.1 (84.0–94.0)
Cardiac output, L/min	64.4 (52.0–75.4)	5.8 (7.2–7.2)	88.5 (71.0–96.0)	42.2 (34.9–50.0)	19.8 (13.6–28.0)	95.8 (88.3–98.6)
TVR, dyn·s/cm^5	72.0 (59.9–82.3)	1609 (1605–1784)	50.0 (32.1–67.9)	90.1 (84.5–93.8)	44.8 (28.4–62.5)	91.8 (86.4–95.1)
Stroke volume, mL	70.0 (55.5–80.9)	62.5 (54.5–62.5)	65.4 (46.2–80.6)	75.2 (67.9–81.2)	29.8 (19.5–42.7)	93.1 (87.4–96.3)
Inotrope index	52.6 (39.5–64.6)	1.6 (1.5–2.8)	69.2 (50.0–83.5)	47.8 (40.3–55.5)	17.6 (11.5–26.2)	90.6 (82.5–95.2)

Note: Point estimates are presented along with 95% confidence intervals.
Abbreviations: ROC: receiver operating characteristic; PPV: positive predictive value; NPV: negative predictive value; BMI: body mass index; hCG: human chorionic gonadotropin; PAPP-A: pregnancy-associated plasma protein A; BP: blood pressure; UTPI: uterine artery pulsatility index; TVR: total vascular resistance.

hypertension, while it was not significantly predictive for IUGR (AUC of 60.0; 36.2 to 78.0, $p = .21$, Figure 2). Finally, the TVR were significantly predictive of hypertension (AUC of 78.2; 61.9–89.8, $p < .001$), while similarly to CO they were not significantly related to the development of IUGR (AUC of 63.7; 46.7 to 80.8, $p = .126$, Figure 3).

Discussion

Our study demonstrates that since the first trimester there is a clear correlation between maternal hemodynamics, uterine artery Doppler and the development of hypertensive disorders or fetal growth restriction [13,20].

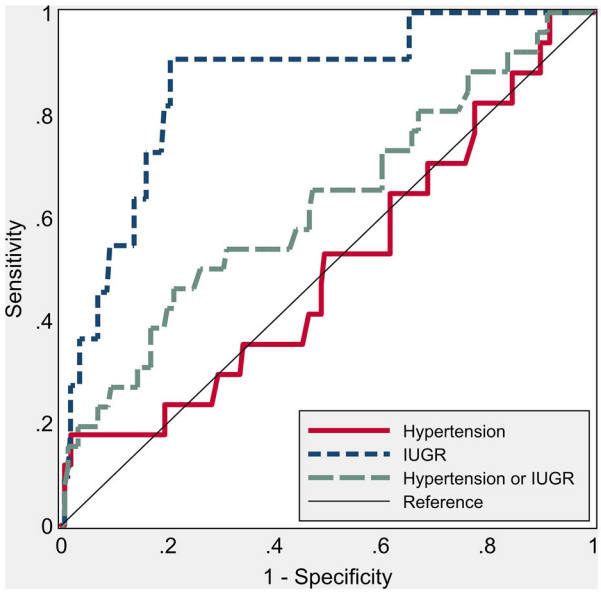

Figure 1. Nonparametric receiver operating characteristic (ROC) curves for umbilical artery pulsatility index (UTPI) to predict hypertension and intrauterine growth restriction. The areas under the ROC curve are shown in Tables 3, 4, and 5.

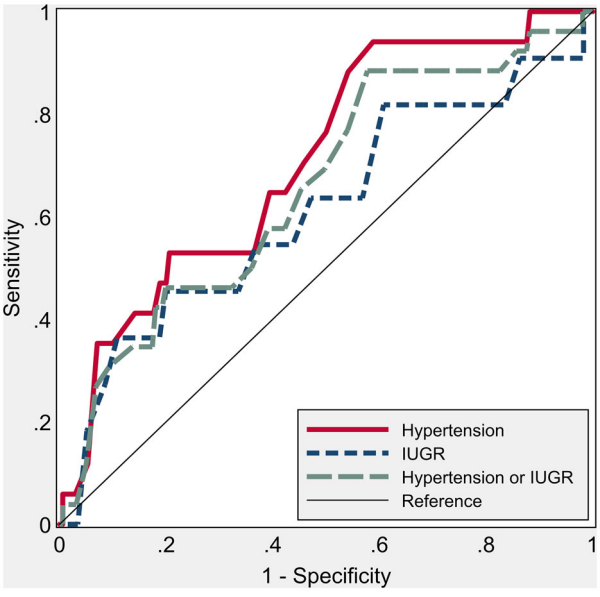

Figure 2. Nonparametric receiver operating characteristic (ROC) curves for cardiac output to predict hypertension and intrauterine growth restriction. The areas under the ROC curve are shown in Tables 3, 4, and 5.

In many studies these complications have often been considered together, as they have a common etiology [2,3,21]. We demonstrated a significative relationship between those combined outcomes with UTPI, hemodynamic parameters (such as CO, TVR, and SV) and the use of techniques of assisted reproduction.

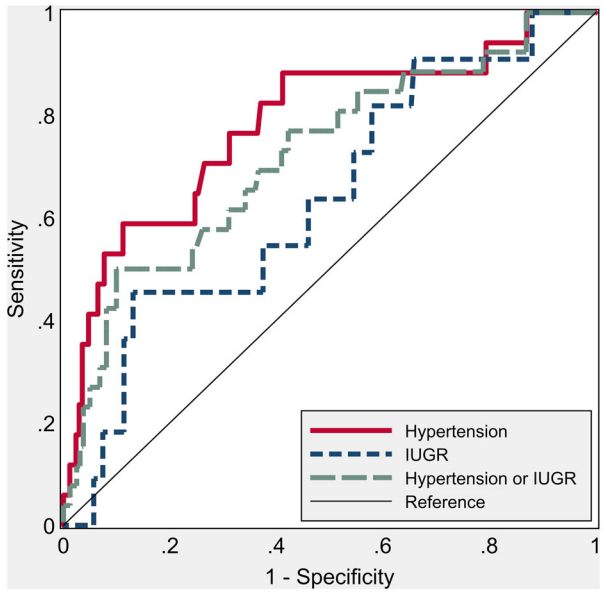

Figure 3. Nonparametric receiver operating characteristic (ROC) curves for total vascular resistance (TVR) to predict hypertension and intrauterine growth restriction. The areas under the ROC curve are shown in Tables 3, 4 ,and 5.

In this paper, we also analyzed IUGR and hypertensive disorders separately. As regards the prediction of IUGR, we reported that the only significantly predictive factor is the mean UTPI, as shown by the ROC curve, while maternal hemodynamics plays a significant role in the prediction of hypertensive disorders alone, with higher peripheral resistance and lower cardiac output. Obviously the sample is small and needs further investigation, but we can speculate that the alteration of the mean UTPI plays a more "localized" role, leading to the development of fetal IUGR. On the contrary, an hemodynamic maladaptation to pregnancy may predispose to the development of hypertension, supporting the hypothesis of a "systemic" and cardiovascular origin of preeclampsia [22,23].

The strength of this study is the prospective enrollment of an unselected population of pregnant women in the first trimester of pregnancy. However, the incidence of mean UTPI and TVR above the 95th percentile or of CO below the 5th percentile is higher than what can be expected from a low-risk population. This is partly explained by the fact that the women referred to our center are older and with a higher prevalence of ART, thus causing a selection bias. These can be also the reasons for the quite high prevalence of hypertensive disorders of pregnancy in our population. A limitation is the small sample and worthy of enlargement.

Considering those data, we could hypothesize the inclusion of maternal hemodynamic assessment by

USCOM® device in the screening protocols of preeclampsia [15]. In particular, it would be interesting to evaluate whether the introduction of prophylaxis with acetylsalicylic acid to those women with low CO and high TVR can reduce the onset of hypertensive disorders later in pregnancy.

The hemodynamic changes that occur since the first trimester of pregnancy can predict the onset of some obstetrics complications, providing important information for the future management of those pregnancies.

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