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A real-life prospective blinded evaluation of placental biometry and macroscopic morphology from 1008 unselected consecutive pregnancies

Chiara Tasca [a], Francesca Parisi [a], Marta Zambon [a], Susanna Bonato [a], Martina Bombelli [a], Roberta Simona Rossi [b], Emilio Caselli [b], Duccio Petrella [c], Manuela Nebuloni [b], Irene Cetin [a,*]

[a] Department of Obstetrics and Gynecology, Vittore Buzzi Children's Hospital, University of Milan, Milan, Italy
[b] Pathology Unit, Department of Biomedical and Clinical Sciences "Luigi Sacco", University of Milan, Milan, Italy
[c] Pathology Unit, Fatebenefratelli Hospital, University of Milan, Milan, Italy

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ABSTRACT

Introduction: The study of the macroscopic appearance of the placenta may represent a useful tool to understand the pathophysiology of adverse pregnancy outcomes. The aim of this study was to evaluate biometry and morphology of placentas in relation to maternal, neonatal and pregnancy course characteristics.
Methods: Clinical and placental data (biometry and macroscopic features of chorionic disk and adnexa) from unselected consecutive singleton pregnancies were recorded at the same Institution. Placental efficiency was approximated as ratio between fetal and placental weight (FPR). The total population was grouped according to the presence of any maternal comorbidity or pregnancy complication (group 1), neonatal complications diagnosed only at birth (2) and absence of any comorbidity (3). Multi-adjusted general linear and logistic regression models were performed to analyze associations between groups and placental biometry and morphology.
Results: The study population counted 1008 pregnancies: 576 (57.2 %) classified as group 1, 76 (7.5 %) as group 2 and 356 (35.3 %) uncomplicated controls (group 3). In multivariate models adjusted for confounding factors, no significant differences in placental biometry and macroscopic features were observed among the three groups. Maternal BMI was significantly associated with higher placental and birth weight and lower FPR; moreover FPR was significantly higher in pregnancies carrying males compared to female neonates.
Discussion: Maternal comorbidity or pregnancy disease was not associated with significant changes in placental macroscopic biometry and morphology. Conversely, maternal pregestational BMI and fetal sex impact on placental biometry and efficiency, suggesting different intrauterine adaptations in obese mothers and in male and female fetuses.

1. Introduction

Mother and fetus are connected by the placenta, a complex interface responsible for respiration, nutrition, hormone production, filtering and protection of the conceptus. Reduced placental efficiency was associated with both short-term pregnancy complications, such as pre-eclampsia, fetal growth restriction (FGR), preterm labor (PTL), and stillbirth, as well as with increased long-term risks of non-communicable diseases in the offspring [1–3].

Several maternal features are known to correlate with placental development and function, including nutritional status, ethnicity, hypertensive disease, anemia, pre-gestational body mass index (BMI), weight gain during pregnancy and gestational diabetes (GDM) [4,5]. The main insults impacting on placental and fetal development are represented by inflammation and hypoxia [6], leading to epigenetic alterations in mitochondrial function finally deranging placental function and efficiency [7]. Obesity may also influence placental metabolic functions, as shown by placental metabolome analyses of obese pregnancies revealing significant differences in metabolites involved in antioxidant defenses, nucleotide production, lipid synthesis, and energy production compared to lean controls, thus supporting a shift towards a higher placental metabolism [7]. Abnormal placental function is likely based on derangements in placental development occurring during early pregnancy, further determining anomalies in placental dimensions, shape and umbilical cord insertion, with consequently lack of efficiency [8].

* Corresponding author.
E-mail address: irene.cetin@unimi.it (I. Cetin).

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According to the Amsterdam Placental Workshop Group Consensus Statement, the macroscopic evaluation of the placenta consists in the measurement of placental weight and dimensions and in the description of umbilical cord and membranes appearance. All these features have been related to placental efficiency and function [2]. Therefore, the macroscopic evaluation of the placenta could be useful to obtain information about pregnancy diseases. In this context, the ratio between fetal and placental weight has been specifically proposed as a proxy of placental efficiency [9]. Weight at birth and up to the age of 7 has been strictly linked with other placental growth features, such as weight, maximum and minimum diameters, thickness, area and cord insertion [10]. Finally, placental efficiency and macroscopic morphology seem to be influenced by fetal sex, as fetal/placental weight ratio (FPR), as the main proxy of placental efficiency, has been reported as higher in males, while females seem more susceptible to surface and shape features [11].

Accordingly, the evaluation of placental biometry and macroscopic morphology could represent a useful tool to predict clinically relevant diseases and to understand the physiopathology underlying adverse pregnancy outcomes. Nevertheless, up to now no studies evaluated placental biometry and morphology in a large, unselected population of uncomplicated and complicated pregnancies. Furthermore, in clinical settings placental macroscopic and microscopic characteristics are often not specific of pregnancy diseases or adverse neonatal outcome. Therefore, the main objective of this study is to investigate associations between maternal, neonatal, pregnancy course characteristics and the morphological appearance and biometry of placentas and fetal adnexa in consecutively collected unselected singleton pregnancies.

2. Methods

This was a prospective study including all pregnant women delivering at the Vittore Buzzi Children's Hospital (Milan, Italy) between November 2019 and March 2020. Clinical maternal and pregnancy data, and biometry data of all placentas were collected prospectively and consecutively from all pregnancies at delivery. Multiple pregnancy represented the only exclusion criterion.

Patients were enrolled at the time of admission in the delivery room. Maternal history, clinical data of pregnancy course, maternal hemoglobin concentrations at term, delivery and neonatal outcomes were recorded.

The total study population was firstly divided according to the presence or absence of specific complications. The complications taken into consideration were either maternal, placental, or fetal-neonatal, based on our clinical protocol for indications to perform placental morphological evaluation in the Pathology department. The total study population was consequently grouped as follows: the first group included both maternal chronic comorbidity (i.e. obesity, chronic hypertension, pregestational diabetes) and pregnancy complications (i.e. GDM, hypertensive disorders of pregnancy, FGR, cholestasis, oligo/polyhydramnios) (group 1). The second group was defined according to the presence of neonatal complications diagnosed only at birth in previously uncomplicated pregnancies and included: Apgar score <7 at 5 min after birth; pH < 7 and/or Base Excess < -12 mmol/L in the umbilical artery sampled immediately at delivery, hypoglicemia, admission to neonatal intensive care unit, respiratory distress, neonatal infections (group 2). Finally, the third group (group 3) was represented by uncomplicated controls during pregnancies and at birth. Secondly, single subgroups of diseases were considered as follows: a first subgroup included FGR and hypertensive disorders of pregnancy (chronic hypertension, gestational hypertension and preeclampsia), as a proxy of placental insufficiency; a second subgroup included both pregestational and gestational diabetes mellitus; a third subgroup of preterm births (lower than 37 weeks of gestation); and a fourth subgroup of hypothyroidism (both chronic or diagnosed during pregnancy under replacement therapy).

Placentas and fetal adnexa were macroscopically analyzed by a restricted team of trained gynecologist and measured after trimming of the membranes and of the umbilical cord from the chorionic disc. After dabbing the exceeding blood, placentas were weighted and their maximum and minimum diameters were measured. Placental area and thickness were calculated from these parameters, assuming placenta to have ellipsoidal shape, as previously described [12]. Any possible alteration of shape, discontinuity, hematoma, clots or calcifications was recorded. We then measured the umbilical cord length and thickness, the number of vessels, any alteration in insertion point, knots or entanglements.

Placentas were then stored in a refrigerator at 4 °C for a maximum period of 72 h, packed in proper plastic bags, before being sent to the Pathology Department, where a macroscopic analysis was repeated by trained pathologists.

The reproducibility of the measurements was analyzed in a previous pilot study [13].

2.1. Statistical analysis

Descriptive statistics were obtained for demographic, clinical, and placental features (expressed as mean and standard deviation or median and range for continuous variables, and absolute and relative frequencies for categorical variables). Intraclass correlation coefficients were calculated to evaluate the reproducibility of placental macroscopic evaluation between gynecologist and pathologist.

All variables were firstly compared among the three study groups in order to identify significant differences in demographic, clinical and placental data. χ^2 test was used for categorical variables and Student's T test or Kruskal-Wallis test based on distribution for continuous variables. Bivariate correlations were performed to evaluate univariate associations between maternal, neonatal and placental morphological characteristics.

For the multivariate analysis, general linear models after log-10 transformation of non-normal variables and logistic regression models were performed in order to evaluate associations between group, maternal and neonatal characteristics (independent variables) and placental biometry and morphological characteristics (dependent variables), including adjustment for confounding factors (maternal age, pregestational BMI, ethnicity, conception mode, gestational age at delivery, gestational weight gain, fetal sex, hemoglobin concentrations at delivery, delivery mode). Additionally, the same multivariate analysis was performed to investigate associations between the previously defined single disease subgroups and placental features. In particular, multi-adjusted general linear and logistic regression models were performed to evaluate associations between 1. hypertensive disorders of pregnancy + FGR; 2. pregestational and gestational diabetes mellitus, 3. preterm delivery, and 4. thyroid disease (independent variables) and placental biometry and morphological characteristics (presence of hematomas, malodorous, calcifications) (dependent variables).

3. Results

3.1. Characteristics of the study population

The study population consisted of 1008 consecutively enrolled singleton pregnancies. Mean age and pre-gestational BMI were 33 years (range 17–49 years) and 22.6 kg/m^2 (range 15–43.8 kg/m^2), respectively. 423 women (42 %) were nulliparas and 33 (3.3 %) pregnancies were conceived through *in vitro* fertilization (IVF).

According to the study design, the population was firstly divided into three groups, based on the presence or absence of specific complications. Fig. 1 shows the disease distribution in the complicated groups 1 and 2. Interestingly, 57.2 % of the total study population (576/1008) showed a pregnancy-related disease or chronic comorbidity, being categorized as group 1 (Fig. 1a). In this group, the diabetic population (n = 96, 9.5 % of the total study population) included 94 % GDM and 6 % pregestational

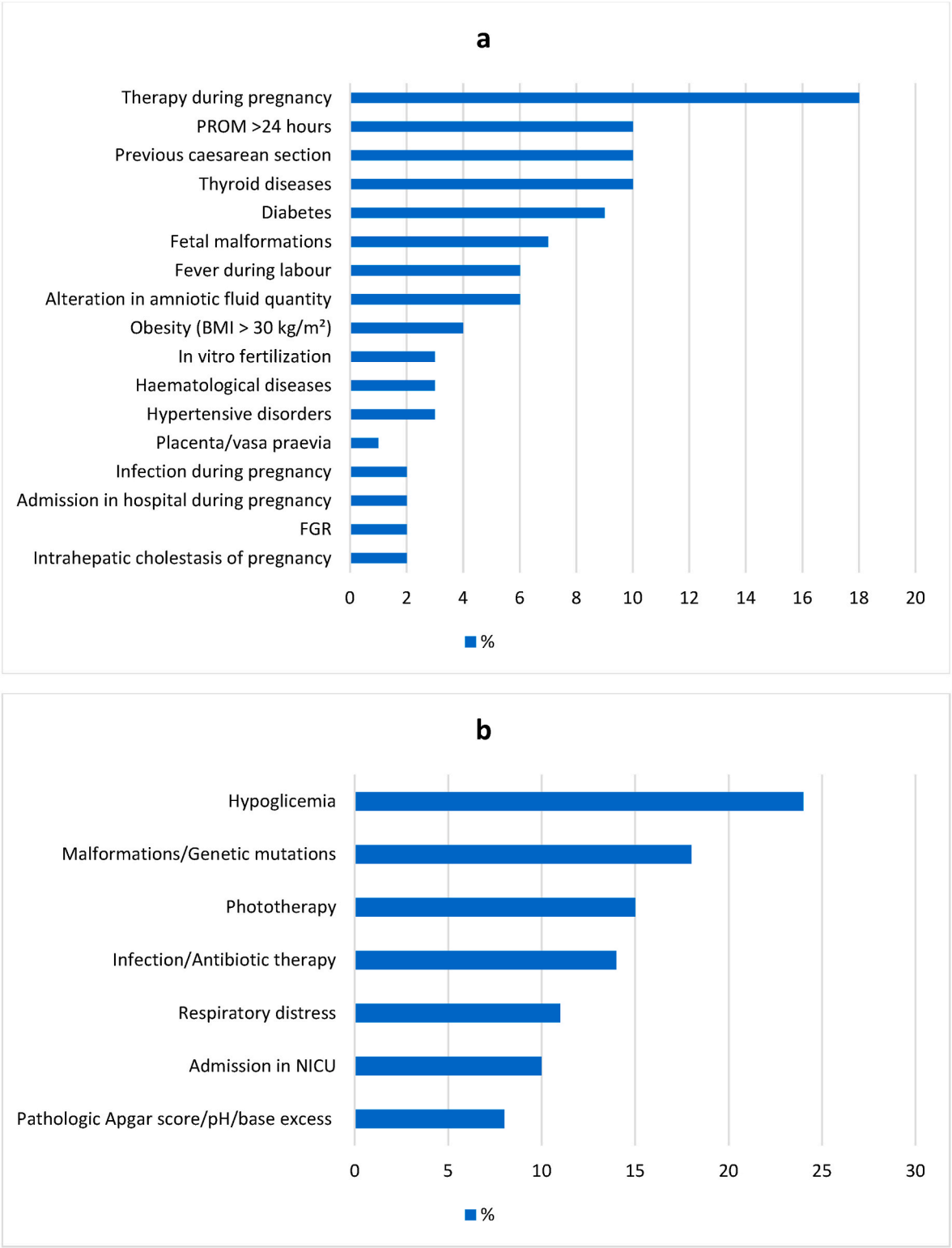

Fig. 1. Frequency (%) of maternal and neonatal complications in the total study population
1a: maternal chronic comorbidity and pregnancy adverse outcome
1b: neonatal complications
PROM - Premature Rupture Of Membranes; BMI – Body Mass Index; FGR – Fetal Growth Restriction; NICU – Neonatal Intensive Care Unit.

diabetes mellitus. In the "hypertensive disorders" category (n = 31, 3.1 % of the total study population), preeclampsia was diagnosed in 39 % of cases, gestational hypertension in 23 %, chronic hypertension in 6 % and increased arterial pressure at term in 13 %. 19 % of cases showed borderline blood pressure values. Oligohydramnios and polyhydramnios occurred in 53 % and 47 % of cases of "alterations in amniotic fluid quantity", respectively. Fetal growth restriction occurred in 26 cases (2.6 % of the total study population) and fetal malformation coexisted in 38 % of cases. A thyroid disease, including both pregestational or diagnosed during pregnancy requiring replacement therapy, was

detected in 107 women (10.6 % of the total study population). Therapies during pregnancy were either specific for chronic disease (78 %), prophylactic for thrombophilia (5 %), or antibiotics (13 %), and therapies related to obstetric conditions such as threatened preterm birth (4 %). The main reasons for hospital admission during pregnancy were threatened preterm labor (58 %), preterm premature rupture of membranes (16 %) and polyhydramnios (10 %). Main hematological diseases were thrombophilia (47 %), alterations in coagulation factors (24 %) and in blood cell count (i.e. thrombocytopenia) (29 %). "Infections during pregnancy" included hepatitis B (22 %) and C (33 %) and infections from the TORCH group (45 %).

Overall, fetal and neonatal complications were observed in 200 cases, as presented in Fig. 1b. Of these, 76/1008 were neonatal complications diagnosed only at birth from previously uncomplicated pregnancies, representing therefore the group 2 (7.5 % of the total study population). The main reasons for admission in neonatal intensive care unit (NICU) were malformations (41 %), respiratory distress (28 %), prematurity (21 %), infections (7 %) and hypoglycemia (3 %).

The remaining 35.3 % (356/1008) of the total study population included uncomplicated pregnancies and newborn (group 3).

Table 1 shows the main demographic and clinical characteristics of the study population with comparisons among the three study groups. Significant differences were detected between the groups in pregestational BMI, rates of IVF, gestational age at delivery, number of cesarean sections ($p < 0.001$) and birthweight ($p < 0.05$).

3.2. Placental biometry and morphology in relation to group

High intraclass correlation coefficient were reported for all biometrical and morphological characteristics between the gynecologist and pathologist, with the only exclusion for the presence of hematomas, suspected placenta accreta and circumvallata. Table 2 shows placental characteristics and biometry, with univariate comparisons among the study groups. In line with lower gestational age and birth weight, group 1 showed smaller placentas with lower placental weight, diameters and area. However, no significant differences were found in FPR, as the main measure of placental efficiency. Moreover, no significant differences were found in macroscopic morphology of placenta and adnexa among the three groups (Table 3).

Table 1
Maternal baseline characteristics and delivery outcomes with comparisons among the study subgroups.

Characteristic	Group 1 (n = 576)	Group 2 (n = 76)	Group 3 (n = 356)	p value
Age (years)	33.3 ± 5.7	32.2 ± 5.7	33.0 ± 4.8	0.30
BMI (Kg/m^2)	23.3 ± 4.4*	22.3 ± 2.8	21.4 ± 2.9	<0.001
IVF n(%)	33 (5.7)	0	0	<0.001
Nulliparous (%)	66.7	65.8	61.5	0.82
Hb at term (g/dL)	11.9 ± 1.1	11.6 ± 1.1*	12.0 ± 1.0	0.02
Gestational weight gain (Kg)	11.7 ± 4.7	12.0 ± 4.5	11.8 ± 3.7	0.82
Gestational age at delivery (weeks)	39.1 ± 1.6*	39.4 ± 1.9	39.6 ± 1.1	<0.001
Delivery mode, n (%)				
Vaginal delivery	393 (68 %)	55 (72 %)	305 (86 %)	
Cesarean section	144 (25 %)	14 (18 %)	29 (8 %)	<0.001
Vacuum delivery	39 (7 %)	7 (9 %)	22 (6 %)	
Male newborn (%)	54.2	57.9	53.6	0.79
Birth weight (g)	3280.6 ± 535.4*	3387.9 ± 537.8	3375.6 ± 346.9	<0.05

Group 1: maternal chronic comorbidity/pregnancy complications.
Group 2: neonatal complications diagnosed at birth.
Group 3: uncomplicated pregnancies; reference.
BMI: body mass index; IVF: *in vitro* fertilization; Hb: hemoglobin.
χ^2 test was used for categorical variables and ANOVA test for continuous variables with Bonferroni post-hoc test. *indicates significant inter-groups differences considering group 3 as reference.

Table 2
Placental biometry and efficiency with comparisons among the study subgroups.

Characteristic	Group 1 (n = 576)	Group 2 (n = 76)	Group 3 (n = 356)	p value
Placental weight (g)	438.3 ± 101.1 *	456.6 ± 102.8 *	442.5 ± 77.4	<0.05
Maximum diameter (cm)	18.3 ± 2.4 *	18.9 ± 2.4 *	18.6 ± 2.2	<0.05
Minimum diameter (cm)	15.9 ± 2.0 *	16.5 ± 1.9 *	16.3 ± 1.8	<0.05
Area (cm^2)	261.7 ± 66.1 *	276.6 ± 62.4 *	270.9 ± 61.8	<0.05
Thickness/weight ratio (cm/g)	0.0045 ± 0.0018 *	0.0041 ± 0.0011 *	0.0042 ± 0.0010	<0.05
Fetal/placental weight ratio	7.68 ± 1.88	7.63 ± 1.49 *	7.73 ± 1.34	<0.05

Group 1: maternal chronic comorbidity/pregnancy complications.
Group 2: neonatal complications diagnosed at birth.
Group 3: uncomplicated pregnancies; reference.
Only significative p values are shown. Kruskal-Wallis test was used for continuous variables. *indicates significant inter-groups differences considering group 3 as reference.

Table 3
Descriptive and univariate analysis of placental morphology in the main study groups.

Characteristic	Group 1 (n = 576)	Group 2 (n = 76)	Group 3 (n = 356)	p value
Placenta bilobata (%)	3	2.6	3.1	0.97
Placenta circumvallata (%)	0.7	0	0.9	0.72
Succenturized cotyledon (%)	3.3	1.3	3.7	0.57
Loss of entirety (%)	3.3	1.3	1.4	0.65
Hematoma (%)	4.8	6.6	4.2	0.39
Clots (%)	0.4	0	0.6	0.33
Calcifications (%)	9.6	13.1	8.5	0.45
Cord absolute brevity[a] (%)	4.2	2.6	1.7	0.11
Subtle umbilical cord[b] (%)	4	3.9	2	0.15
Thick umbilical cord[c](%)	4	7.9	2.5	0.09
Hypercoiled cord (%)	0.9	2.6	0.6	0.45
Hypocoiled cord (%)	3	2.6	2.8	0.32
Peripheral cord insertion (%)	0.4	1.3	0.6	0.10
Single umbilical artery (%)	0.4	0	0	0.47
Cord knots (%)	0.7	2.6	1.1	0.73
Cord entanglements (%)	24.5	31.6	28	0.15

Group 1: maternal chronic comorbidity/pregnancy complications.
Group 2: neonatal complications diagnosed at birth.
Group 3: uncomplicated pregnancies.
All characteristics are expressed as percentages. χ^2 test was used for comparisons.
[a] Umbilical cord length <30 cm [25].
[b] Umbilical cord thickness <0.8 cm [26].
[c] Umbilical cord thickness >1.5 cm [25].

After including the previously defined confounding factors in a multivariate model, no significant associations were detected between group and placental biometry or morphology.

3.3. Placental biometry and macroscopic morphology in relation to maternal characteristics

Maternal pre-gestational BMI was positively correlated to placental ($r = 0.187$, $p < 0.001$) and birth weights ($r = 0.133$, $p < 0.01$), while it was inversely correlated to FPR, meaning a reduced FPR in mothers with

higher BMI (r = −0.129, p < 0.01) (Fig. 2).

Moreover, placental weight and FPR were evaluated in relation to maternal hemoglobin concentrations at term. A negative correlation was found between placental weight and hemoglobin concentrations (r = −0.067, p < 0.05), while FPR showed a positive correlation with hemoglobin concentrations (r = 0.089, p < 0.01) and was significantly lower in anemic (Hb < 11 g/dL) than in non-anemic patients (10.23 ± 0.62 versus 12.22 ± 0.78 g/dL, p < 0.05) (data not shown). After including confounding factors in general linear models, no significant associations were detected between maternal hemoglobin concentrations and placental biometry and FPR, whereas pregestational BMI showed positive associations with placental weight (obese versus normal weight women: β = 65.3 (95%IC: 30.6; 100.1)) and birth weight (obese versus normal weight women: β = 219.2 (95%IC: 68.3; 370.1)), and a negative association with FPR (obese versus normal weight women: β = −0.62; (95%IC: −1.24; −0.01)).

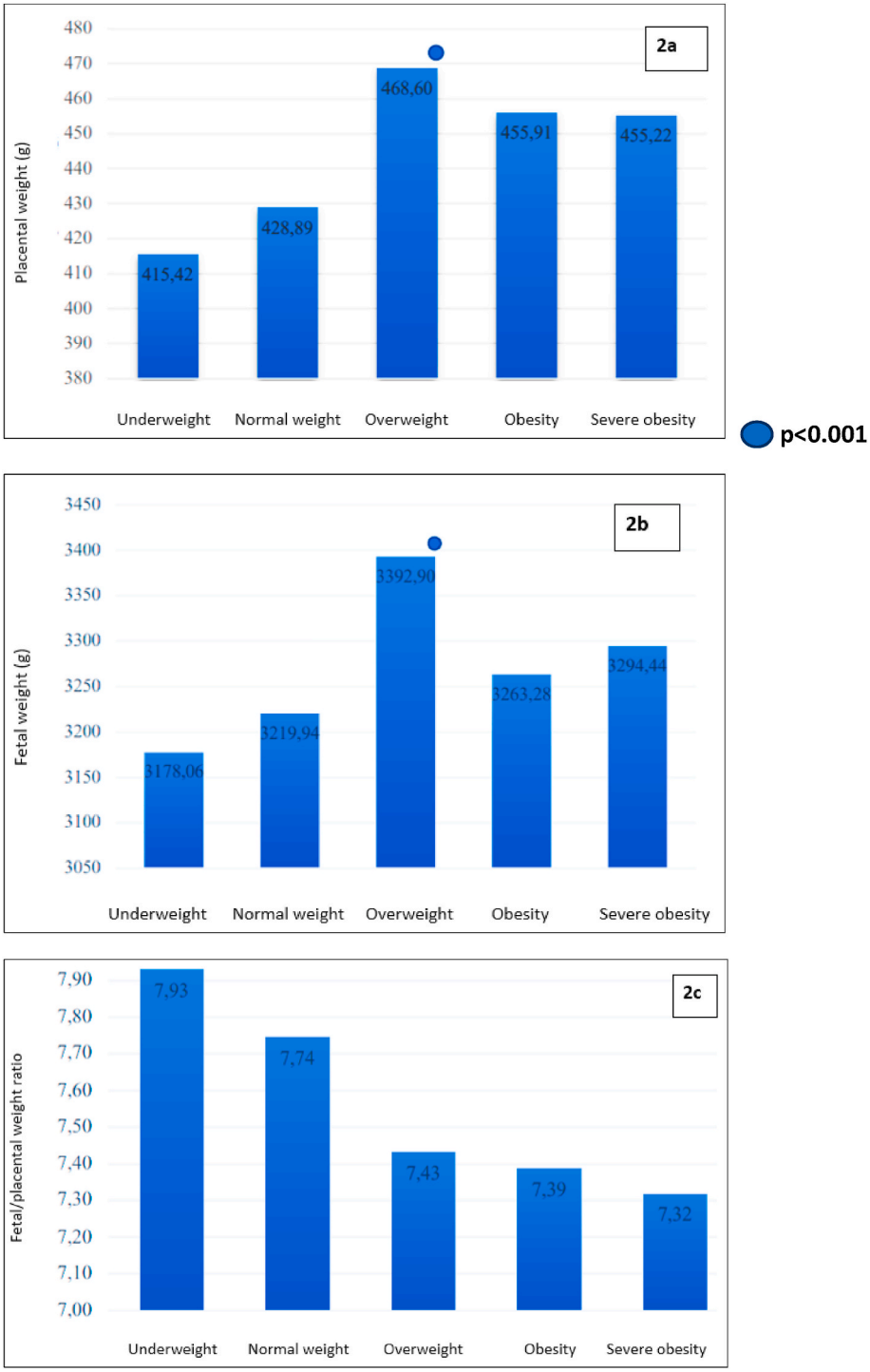

Fig. 2. Variance analysis between BMI classes: underweight: BMI <18.5 kg/m^2; normal weight: 18.5 ≤ BMI <24.9 kg/m^2 (reference); overweight: 25 ≤ BMI <29.9 kg/m^2; obesity: 30 ≤ BMI <34.9 kg/m^2; severe obesity: BMI ≥35 kg/m^2 **2a:** Placental weight (R = 0.187, p < 0.001). **2b:** Fetal weight (R = 0.133, p = 0.002). **2c:** Fetal/placental weight ratio (R = −0.129, p = 0.002). BMI – Body Mass Index.

3.4. Placental biometry and macroscopic morphology in relation to neonatal sex

Table 4 shows data according to neonatal sex, by comparing male (n = 549) and female (n = 459) newborns. Female newborns showed significantly smaller placental area and maximum diameter, higher thickness/weight ratio and lower FPR compared to males. After including confounding factors in a multivariate model, the associations between fetal sex and placental area (β = −9.66, 95%IC -18.1; −1.24 cm^2, $p < 0.05$) and FPR were confirmed (β = −0.19; 95%IC -0.40; −0.01, $p < 0.05$), thus indicating a smaller and less efficient placenta in female fetuses independently of group classification and confounding factors.

3.5. Placental features in relation to single disease subgroups

Multi-adjusted general linear and logistic regression models were built to evaluate associations between 1. hypertensive disorders of pregnancy + FGR (n = 53, 5.2 % of the total study population), 2. pregestational and gestational diabetes mellitus (n = 96, 9.5 % of the total study population), 3. preterm birth (gestational age at birth lower than 37 weeks, n = 43, 4.3 % of the total study population), and 4. hypothyroidism requiring replacement therapy (n = 107, 10.6 % of the total study population), with placental biometry and morphological features. The hypertension + FGR subgroup showed significant negative associations with birth (beta = −320.3 (95%IC: −444.0; −196.5), $p < 0.001$) and placental (beta = −28.5 (95%IC: −58.2; −1.22), $p = 0.05$) weights in multi-adjusted models including gestational age, whereas no associations were detected with FPR. The diabetic subgroup only showed positive association with FPR (beta = 0.38 (95%IC: 0.04; 0.72), $p < 0.05$). The preterm subgroup showed significant negative associations with birth weight (beta = −181.8, (95%IC: −356.3; −7.2), $p < 0.05$) in models considering adjustment for gestational age, thus meaning lower birth weight at the same gestational age in case of preterm birth. The hypothyroidism subgroup showed significant association with placental weight (beta = −29.3 (95%IC -49.4; −9.2), $p < 0.01$) and FPR (beta = 0.84 (95%IC: 0.49; 1.18), $p < 0.001$), meaning smaller, but possibly more efficient placentas in hypothyroid women. No associations were detected between any subgroup and other measurements of placental biometry and morphological characteristic.

4. Discussion

4.1. Main findings of the study

The present study shows no significant differences in placental biometry and morphology between complicated (groups 1 and 2) and uncomplicated pregnancies (group 3) in multi-adjusted models including confounding factors. Maternal hemoglobin concentrations at term were positively correlated with FPR, as a proxy of placental efficiency, but the association was not confirmed in multivariate models. Conversely, maternal pregestational BMI was associated with increased placental and birth weight, and lower FPR in both univariate and multivariate models. When fetal characteristics were considered, fetal sex was significantly associated with placental biometry and FPR, meaning smaller and possibly less efficient placentas in female compared to male newborns, independently of group and confounding factors. Finally, when single disease subgroups were considered, multi-adjusted models showed lower birth and placental weight in the hypertensive disorders and FGR subgroup, lower FPR in the diabetic subgroup, lower birth weight in the preterm subgroup and lower placental weight and increased FPR in the hypothyroidism subgroup. No associations were detected between any group or subgroup and placental morphological appereance.

Table 4
Comparisons of placental biometry between male and female newborns.

Features	Males (n = 564)	Females (n = 444)	p value
Gestational age at delivery (wks)	39.5 ± 1.44	39.6 ± 1.45	0.22
Newborn weight (g)	3373.65 ± 492.48	3256.38 ± 460.00	<0.001
Placental weight (g)	443.66 ± 96.21	437.72 ± 89.18	<0.05
Placental maximum diameter (cm)	18.60 ± 2.42	18.36 ± 2.23	0.03
Placental minimum diameter (cm)	16.26 ± 1.96	15.96 ± 1.93	0.42
Placental area (cm^2)	269.76 ± 66.13	260.93 ± 62.15	<0.05
Placental thickness/weight ratio (cm/g)	0.0039 ± 0.0010	0.0041 ± 0.0014	<0.05
Fetal/placental weight ratio	7.83 ± 1.46	7.62 ± 1.35	<0.05

Kuskal -Wallis test was used for comparisons.

Despite the present study shows the results on a large unselected population of singleton pregnancies, the setting in a tertiary care center mainly explains a complicated group 1 larger than controls, meaning a high frequency of maternal comorbidity and pregnancy complications. Unexpectedly, no significant differences in placental biometry and morphology were detected when considering group as independent variable in multi-adjusted models. This result may be explained by the inclusion of miscellaneous complications with potential opposite placental effects. As an example, GDM and FGR are commonly related to placental over- and under-growth respectively, thus leading to null results when considered together in group 1. When individually considered, the hypertensive disorders and FGR subgroup showed lower placentas and birth weights, according to the pathogenetic knowledges about these diseases [14]. Moreover, also the preterm subgroup was associated to lower birthweights, confirming the involvement of a pro-inflammatory uterine environment in fetal growth [15]. Additionally, the results of this study confirmed that placentas derived by pregnancies complicated by glucose dysmetabolism show lower efficiency due to oxidative and energetic impairment [16].

Conversely, placentas derived from pregnancies complicated by thyroid diseases showed lower weight and higher FPR in multivariate models. To our knowledge, this is the first report suggesting that hypothyroidism may influence placental development and biometry. This may be part of metabolic placental adaptations to maternal hormonal depletion and should be matter of future research in order to offer an adequate counselling to affected pregnant women.

Another potential risk factor in pregnancy is notoriously represented by high pregestational BMI. Various studies suggested that systemic chronic low-grade inflammation, dysmetabolic environment and altered angiogenesis may negatively impact placentation in obese women [17,18]. The present study is in line with these findings. In fact, maternal pregestational BMI was positively correlated with placental and birth weight, whereas inversely correlated with fetal/placental weight ratio. When including confounding factors, maternal obesity was significantly associated with larger, but less efficient placentas, independently of group. This result suggests that pregestational BMI may represent a more significant risk factor impacting on placental development and function than the onset of pregnancy pathologies or the presence of chronic comorbidity (group 1).

Finally, sex specific placental adaptations were confirmed for both placental biometry and efficiency. This is in line with previous results showing differences in placental adaptation in response to the same maternal adverse environment according to fetal sex [18,19]. Since the pre-implantation embryo, gene expression was shown to be different in males and females [20] and may lead to different placental development and intrauterine adaptations. This may explain the sexually dimorphic responses of the fetus in response to maternal chronic inflammation, with reported higher rates of growth restriction in female compared to male fetuses of mothers with preeclampsia and asthma [21,22]. In line with these results, increased first trimester morphological development according to the Carnegie stages was shown to be associated with

increased mid-pregnancy fetal weight and birth weight in male, but not female fetuses [23]. Previous studies additionally showed differences between females and males in how birthweight and fetal/placental weight ratio are affected by changes in placental proportions and it has been hypothesized that female pregnancies are more responsive to changes in placental growth than males. Greater female resilience (and greater male vulnerability) to gestational stressors is an intriguing interpretation of these findings [24].

All these results suggest differences between males and females starting as early as the intrauterine life, further conditioning different placental development, growth and efficiency with possible impacts on pregnancy outcome and long-term health status. A sex-specific approach in obstetric care should be a crucial focus of future research.

4.2. Strengths and limitations of the study

The major strength of the study is the prospective design with a large sample of singleton pregnancies consecutively recruited. Macroscopic placental evaluation was performed by both gynecologist and pathologist, showing high reproducibility in agreement with previous results [13]. The statistical models including adjustment for confounding factors notoriously related to placenta biometry and efficiency reduce bias of interpretation.

The most relevant limitation of the study is related to the setting in a tertiary care center with high rates of pregnancy disease and comorbidity, thus limiting the external validity of the results. Moreover, it is necessary to specify that the FPR was used as a proxy of placental efficiency, however many pregnancy events and disease processes could distort and sometimes reverse this correlation. To date, there are no studies demonstrating the strength of FPR as a unique and reliable marker of placental efficiency. However, many study groups have included it as assessment of pregnancy outcome [27–30]. Further studies could improve the statistical strength by analyzing each disease with a larger sample size.

5. Conclusions

This study supports and expands previous evidence about placental biometry and macroscopical analysis. Our data suggest that both maternal (BMI) and fetal (sex) variables have an impact on placental biometry and efficiency, whereas less relevant seem the macroscopic evaluation in association with any maternal or neonatal complication.

These macroscopic data are easy to collect, reproducible and could become part of a routine evaluation at delivery to improve maternal counselling and neonatal follow-up.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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