

Beyond Aneuploidies: Exploring the Glycometabolic Link to Pregnancy-Associated Plasma Protein A in Pregestational Diabetes

Moira Barbieri^a Gabriele Rossi^a Valeria Maggi^a Mariana Rita Catalano^b
Beatrice Coppa^a Agnese Caneschi^a Giulia Zamagni^c Enrico M. Ferrazzi^{a,d}
Nicola Persico^b Irene Cetin^{a,d}

^aUnit of Obstetrics and Maternal Fetal Medicine, Department of Women, Newborns and Children, Fondazione IRCCS Ca Granda, Ospedale Maggiore Policlinico, University of Milan, Milan, Italy; ^bUnit of Prenatal Diagnosis and Fetal Surgery, Department of Women, Newborns and Children, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, University of Milan, Milan, Italy; ^cClinical Epidemiology and Public Health Research Unit, IRCCS Burlo Garofolo, University of Trieste, Trieste, Italy; ^dDepartment of Community and Clinical Sciences, Research Center for Maternal, Fetal and Neonatal Medicine, University of Milan, Milan, Italy

Keywords

HbA1c · Pregnancy-associated plasma protein A · First-trimester screening

Abstract

Introduction: Pregnancy-associated plasma protein A (PAPP-A) is a glycoprotein produced by the syncytiotrophoblast and decidua, as well as vascular smooth muscle cells. While type 2 diabetes is typically associated with chronically low PAPP-A levels – contributing to vascular dysfunction – the relationship between glycometabolic control and PAPP-A in pregestational diabetes (pre-GD) remains under-explored. This study investigated the correlation between PAPP-A levels and glycated hemoglobin (HbA1c) in pregnant women with type 1 and type 2 pre-GD. **Methods:** This retrospective study analyzed 96 pregnant women with pre-GD (type 1 and type 2) who underwent first-trimester combined screening. PAPP-A levels were correlated with both pregestational and first-trimester HbA1c values. In type 2 pre-GD, multivariate analysis was employed to assess the impact of HbA1c on PAPP-A levels while accounting for ethnic differences. **Results:**

In women with type 1 pre-GD, a significant inverse correlation was observed between PAPP-A and both pregestational ($R = -0.69$; $p < 0.01$) and first-trimester HbA1c ($R = -0.49$; $p < 0.01$). In type 2 pre-GD, multivariate analysis showed divergent results based on ethnicity: for each unit increase in HbA1c, PAPP-A decreased by 0.03 units in Caucasian women but increased by 2.7 units in South American women. **Conclusion:** These findings suggest that glycometabolic compensation significantly influences PAPP-A levels. Clinical risk assessments for aneuploidy should consider HbA1c as a continuous parameter rather than treating pre-GD history as a binary variable. Incorporating specific glycometabolic data and ethnicity may improve the accuracy of first-trimester screening for women with pre-GD.

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Introduction

Pregnancy-associated plasma protein A (PAPP-A) is a glycoprotein produced by the syncytiotrophoblast and the decidua during pregnancy; it is also synthesized in

other tissues, including vascular smooth muscle cells and fibroblasts [1]. PAPP-A plays a pivotal role in fetal development by modulating the insulin-like growth factor system, which promotes trophoblast invasion and placental growth [2, 3]. Aberrations in PAPP-A levels may reflect underlying issues with placental function, often observed in chromosomal abnormalities.

Between 11 + 0 and 13+6 weeks of gestation, the measurement of PAPP-A levels, combined with free beta-human chorionic gonadotropin (β -HCG) and nuchal translucency measurements, is one of the biomarkers of first-trimester screening for chromosomal aneuploidies [4]. Reduced PAPP-A levels (often <0.5 median multiple) are a key risk marker for increased of trisomy 21 [5], 18, and 13 [4] and are also associated with other adverse pregnancy outcomes, including pre-eclampsia associated with fetal growth restriction, fetal growth restriction, and stillbirth. PAPP-A levels can be influenced by factors unrelated to aneuploidies, such as maternal smoking, obesity, diabetes, and assisted reproductive technologies [6]. A correction for these variables is considered when calculating the median multiple, before using it in the risk algorithm [7]. Conditions characterized by insulin resistance, such as type 2 diabetes (pre-GD), are associated with chronically low PAPP-A levels. These low values contribute to vascular dysfunction and impaired metabolic health [1, 8], thus requiring correction in the calculation of chromosomal abnormality risk [9, 10].

To date, it is unclear whether there is a correlation between glycometabolic compensation and serum levels of plasma markers used for estimating the risk of aneuploidies; therefore, the main objective of our study was to investigate whether the components of biochemical factors used in first-trimester screening are influenced by glycated hemoglobin (HbA1c) values in pregnant women with pregestational diabetes (pre-GD).

Methods

We conducted a retrospective analysis, on singleton-pregnant women with type 1 and type 2 pre-GD, who had been referred for early prenatal first-trimester screening for aneuploidies at the Unit of Prenatal Diagnosis and Fetal Surgery of our Research Hospital. Detailed demographic and clinical data on maternal age, body mass index (BMI), parity, ethnicity, and medical history, were collected from electronic medical records and an ultrasound database. Glycemic control indices, including HbA1c serum concentration, were retrieved from the pregestational period

and for each trimester of pregnancy to evaluate temporal trends and their association with the biochemical markers of the first-trimester screening. The primary objective was to assess the correlation coefficients between the biochemical markers of the first-trimester combined test (free β -HCG and PAPP-A) and maternal HbA1c levels at different time points during gestation. This analysis aimed to determine whether glycometabolic compensation, as indicated by HbA1c, influenced the levels of these markers. The multivariate analysis also accounted for potential confounders, including maternal demographic characteristics, clinical factors, and glycemic control, ensuring robust and reliable findings.

HbA1c values were treated both as continuous and categorical variables. For descriptive purposes, metabolic control was classified as “good” when HbA1c was below 48 mmol/mol (6.5%), “suboptimal” between 48 and 58 mmol/mol (6.5–7.5%), and “poor” above 58 mmol/mol (>7.5%), in line with current international guidelines (ADA 2023; NICE 2020). To minimize intra-laboratory variation, all HbA1c measurements were performed in the same certified biochemical laboratory using high-performance liquid chromatography, standardized according to the IFCC reference method. Missing or incomplete clinical data were excluded from the analysis to avoid imputation bias.

Statistical Analysis

Categorical variables were summarized as counts and percentages, while continuous variables as mean and standard deviation or median and interquartile ranges, based on the results of the Shapiro-Wilk normality test. Differences between groups were evaluated using the chi-square test (or Fisher’s exact test, when appropriate) for categorical variables and the Student’s *t* test or its non-parametric analog (i.e., the Wilcoxon-Mann Whitney test). Correlation between the variables of interest was assessed using the Pearson or the Spearman’s correlation coefficient. Moreover, the effect of HbA1c on PAPP-A was evaluated in the two groups of diabetic women by adjusting for potential confounders (age, ethnicity, BMI, and parity). Statistical significance was set at $\alpha = 0.05$. All analyses were conducted with Stata/IC 14.2 for Windows (Stata-Corp LLC, College Station, USA).

Results

We recruited 96 women, of whom 43 with type 1 pre-GD and 53 with type 2 pre-GD. Table 1 reports the demographic data of our cohort of pregnant women with

Table 1. Maternal characteristics of the study population

Variables	Maternal data			
	total (N = 96)	pre-GD type 1 (N = 43)	pre-GD type 2 (N = 53)	p value
Maternal age in the beginning of pregnancy, years	33.3 (4.7)	32.5 (3.7)	33.9 (5.3)	0.174
Pre-pregnancy BMI	26.6 (23.0–30.7)	25.3 (22.3–27.9)	27.6 (23.8–32.0)	0.036
Pre-pregnancy weight	70.5 (62–80)	68.6 (60.0–77.0)	72.5 (63.0–85.5)	0.144
Ethnicity				<0.001
Caucasian	60 (63.2)	39 (90.7)	21 (40.4)	
Asian	28 (29.5)	4 (9.3)	24 (46.1)	
African	1 (1.1)	0	1 (1.9)	
Hispanic	6 (6.3)	0	6 (11.5)	
Smoker	4 (4.2)	3 (7.0)	1 (1.9)	0.322
Pre-GD duration, years	10 (4–19)	18 (11–23)	4 (1–8)	<0.001
Age at pre-GD diagnosis	21.6 (9.9)	15.8 (7.9)	29.2 (6.6)	<0.001
Pre-GD related diseases	22 (22.9)	12 (27.9)	10 (18.9)	0.295
Multiparous pregnant women	43 (44.8)	13 (30.2)	30 (56.6)	0.013
Previous macrosomic newborns	10 (10.4)	3 (7.0)	7 (13.2)	0.504
Previous intrauterine fetal death	5 (5.2)	3 (7.0)	2 (3.8)	0.654
Mode of conception				0.127
Spontaneous	91 (94.8)	42 (97.7)	49 (92.5)	
ART	4 (4.2)	0	4 (7.6)	
Unknown	1 (1.0)	1 (2.3)	0	
Twin pregnancies	2 (2.1)	1 (2.3)	1 (1.9)	1.000

Data are reported as number and percentage, mean and SD, or median and IQR, where appropriate. pre-GD, pregestational diabetes; BMI, body mass index; ART, assisted reproductive technology; IQR, interquartile range; SD, standard deviation.

type 1 and type 2 pre-GD. We did not observe differences in maternal age and pre-pregnancy weight, but as expected BMI was significantly higher in women with type 2 pre-GD. Women of Caucasian ancestry represented the 91% of cases of type 1 pre-GD (39/43), whereas they represented only 40% of cases of type 2 pre-GD. Table 2 reports the data of the combined test, the HbA1c values, and pregnancy outcome.

Both β -HCG and PAPP-A were higher in women with pre-GD type 1. The distribution of HbA1c levels at pre-pregnancy time and during the three trimesters are shown in Figure 1. In women with type 1 pre-GD a significant linear correlation was found between PAPP-A and HbA1c before gestation ($R = -0.69$; p value <0.001) (Fig. 2a). In addition, in these same patients, a linear correlation was found between PAPP-A and HbA1c in the first trimester ($R = -0.49$; p value = 0.007) (Fig. 2b). No significant correlations were found between PAPP-A and HbA1c in women with type 2 pre-GD, both before pregnancy and in the first trimester ($R =$

0.04 and $R = -0.15$, respectively; $p > 0.05$). However, in a multivariate analysis, in women with type 2 pre-GD, adjusting for possible confounders (ethnicity, BMI, maternal age, parity), PAPP-A decreased, on average, by 0.03 units for each unit increase in HbA1c and increased by 2.7 for Hispanic women compared with Caucasians. No significant correlations were found in both groups between HbA1c and free β -HCG.

Discussion

The present study observed significant relationships between PAPP-A levels and glycometabolic control assessed by HbA1c in pregnancies complicated by pre-GD. The different findings observed in the two different types of pre-GD, might be explained by the systemic role of PAPP-A as a marker of vascular health. This role provides a plausible explanation for these differences.

Table 2. Combined test parameters, HbA1c values, and pregnancy outcome of the study population

Variables	Maternal data			
	total (N = 96)	pre-GD T1 (N = 43)	pre-GD T2 (N = 53)	p value
GA at combined test, weeks	12.6 (0.6)	12.5 (0.5)	12.7 (0.6)	0.079
CRL, mm	62.3 (6.9)	60.8 (5.7)	63.6 (7.6)	0.047
Nuchal translucency, mm	1.80 (0.4)	1.7 (0.4)	1.9 (0.3)	0.096
Risk of preeclampsia				0.856
Low	26 (27.1)	10 (23.3)	16 (30.2)	
High	25 (26.0)	9 (20.9)	16 (30.2)	
Unknown	45 (46.9)	24 (55.8)	21 (39.6)	
f-b-HCG, UI/L	38.0 (26.3–62.8)	49.7 (32.9–72.8)	33.8 (19.3–49.5)	0.004
PAPP-A, UI/L	1.7 (0.9–2.8)	2.4 (1.2–4.3)	1.4 (0.7–2.3)	0.003
PLGF, pg/mL	23.5 (17.4–29.3)	18.4 (16.9–25.4)	26.4 (20.9–38.6)	0.093
Pre-pregnancy HbA1c, mmol/mol	52 (44–60)	53 (48–63)	50.5 (41–60)	0.459
HbA1c 1st trimester	50 (40–57.5)	50 (45–58)	48 (39–57)	0.349
HbA1c 2nd trimester	41 (37–45)	42 (39–46)	38 (35.5–44.5)	0.026
HbA1c 3rd trimester	42 (37–47)	43.5 (40.5–48.5)	39 (36–44)	0.032
Previous pregnancies	1 (0–2)	0 (0–2)	1 (0–2)	0,028
Gestational hypertension	10/96	3/43	7/53	0.504
Preeclampsia	8/96	4/43	4/53	1.000
GA at birth	38.1 (37.9–39.0)	38.2 (37.0–39.0)	38.1 (38.0–38.7)	0.918
Induced labor	33 (34.7)	15 (34.9)	18 (34.6)	0.167
Mode of delivery				0.142
Spontaneous	18 (19.0)	9 (20.9)	9 (17.3)	
Cesarean section	62 (65.3)	28 (65.1)	34 (65.4)	
Kiwi cup vacuum-assisted delivery	7 (7.4)	5 (11.6)	2 (3.8)	
Unknown	8 (8.4)	1 (2.3)	7 (13.5)	
Birthweight, g	3,365 (2,977–3,797)	3,380 (3,000–3,660)	3,337 (2,940–3,875)	0.963
Birthweight >4,000 g	14 (15.9)	5 (11.9)	9 (19.6)	0.391
Apgar score <7 at 5'	10 (9–10)	10 (9–10)	10 (10–10)	0.161

Data are reported as number and percentage, mean and SD, or median and IQR, where appropriate. pre-GD t1, pregestational diabetes type 1; pre-GD t2, pregestational diabetes type 2; GA, gestational age; CRL, crown-rump length; f-β-HCG, free beta-human chorionic gonadotropin; PAPP-A, pregnancy-associated plasma protein A; PLGF, placental growth factor; HbA1c, glycosylated hemoglobin; IQR, interquartile range; SD, standard deviation.

In pre-GD type 2, chronically low PAPP-A levels are consistent with systemic vascular dysfunction typical of insulin resistance. This basal reduction occurs independently of acute glycemic control and possibly reflects long-term underlying vascular disease. In pre-GD type 1 in contrast, PAPP-A levels correlate strongly with HbA1c, highlighting that the better was the metabolic control the significantly higher were PAPP-A levels. This dynamic response observed from pre-pregnancy values to the first trimester when a stricter glycemic control is

rapidly implemented, emphasizes that PAPP-A levels in type 1 pre-GD are modulated by glycemic compensation rather than the intrinsic genetic nature of the disease.

Lower PAPP-A levels observed in women with poorly controlled pre-GD could be attributed to the effects of hyperglycemia on trophoblast function and vascular remodeling. This relationship underscores the dual impact of hyperglycemia on maternal vascular health and placental function, revealing potential pathways through which diabetes affects early pregnancy

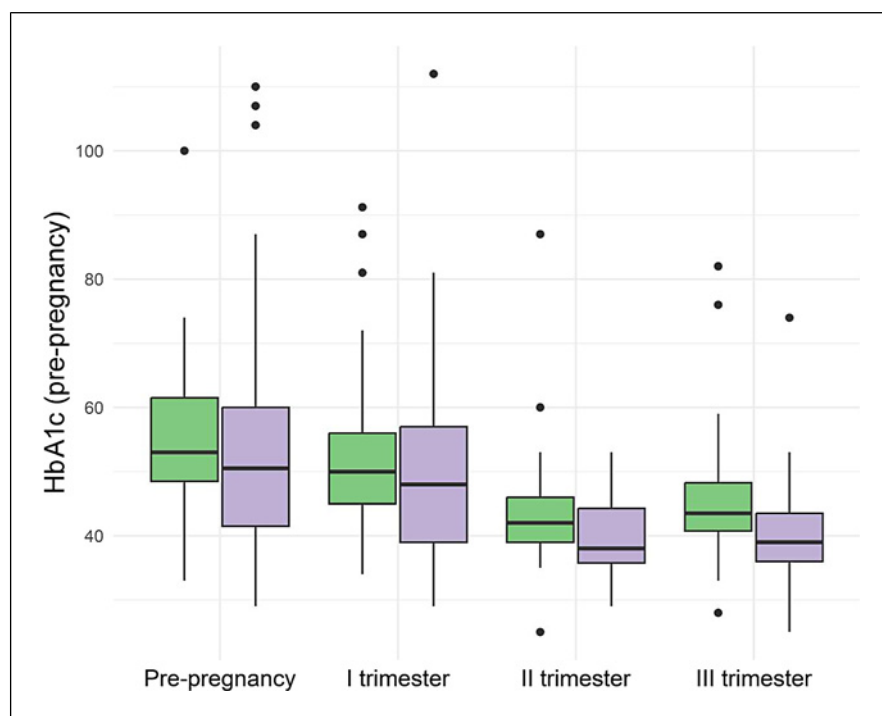


Fig. 1. The distribution of HbA1c levels at pre-pregnancy and during the three trimesters (green box, type 1 pre-GD; purple box, type 2 pre-GD).

biomarkers. In pregnancies complicated by pre-GD, elevated HbA1c levels – indicating poor glycemic control – are often associated with increased placental dysfunction. This dysfunction may further reduce PAPP-A levels, as such, adding its already diminished reliability as a biomarker in pregnancies complicated by pre-GD. Chronic hyperglycemia may exacerbate oxidative stress and inflammation within the placenta, impairing the secretion of PAPP-A.

There are limited research and contradictory results on the relationship between biochemical screening markers and gestational diabetes (GD). One study reported significant reductions in both PAPP-A and free β -hCG levels in pregnancies complicated by GD [11], while other studies found either no significant impact or a reduction, but only in PAPP-A levels. [9, 12, 13]. Regarding pre-conception diabetes, a study conducted by Madsen and co-workers showed lower PAPP-A levels in women with type 1 pre-GD compared to a control group of normal pregnancies [14].

Our results highlight interesting patterns of the relationship between glycometabolic control in pre-GD and serum PAPP-A level. Women with type 2 pre-GD had lower serum levels of PAPP-A than women with type 1 pre-GD for HbA1c values below 50 mmol/mol. We could hypothesize that obesity, a comorbidity significantly associated in our study in women with type 2 pre-GD, might explain these differences. In fact, the visceral adipose tissue

is a highly active metabolic tissue capable of autocrine, paracrine and endocrine signaling functions and especially of contributing to chronic low-grade systemic inflammation [15] as such contributing to endothelial dysfunction [16]. This production of pro-inflammatory cytokines and oxidative stress caused by obesity contributes to placental inflammation and impaired vascular function [17, 18]. The low values of serum PAPP-A might be the net result of these dysfunctions.

Low maternal serum levels of both PAPP-A and free β -hCG are associated with adverse outcomes such as hypertensive disorders of pregnancy and intrauterine growth retardation [19–21]. PAPP-A, in fact, is produced by the syncytiotrophoblast and secreted into the maternal circulation, where its concentration increases until term, thus playing a role in regulating the bio-availability of insulin-like growth factor, which in turn plays a critical role in fetal growth and placental function [11, 22, 23]. The role of ethnicity adds another layer to this complexity. In fact, the null relationship between PAPP-A and HbA1c, in type 2 pre-GD, when adjusted during multivariate analysis for ethnicity, BMI, and other confounders the relationship resulted in a significant decrease in PAPP-A for each unit increase of HbA1c in women of Caucasian ancestry and in an opposite greater increase in women of South American ancestry. These findings suggest potential genetic or

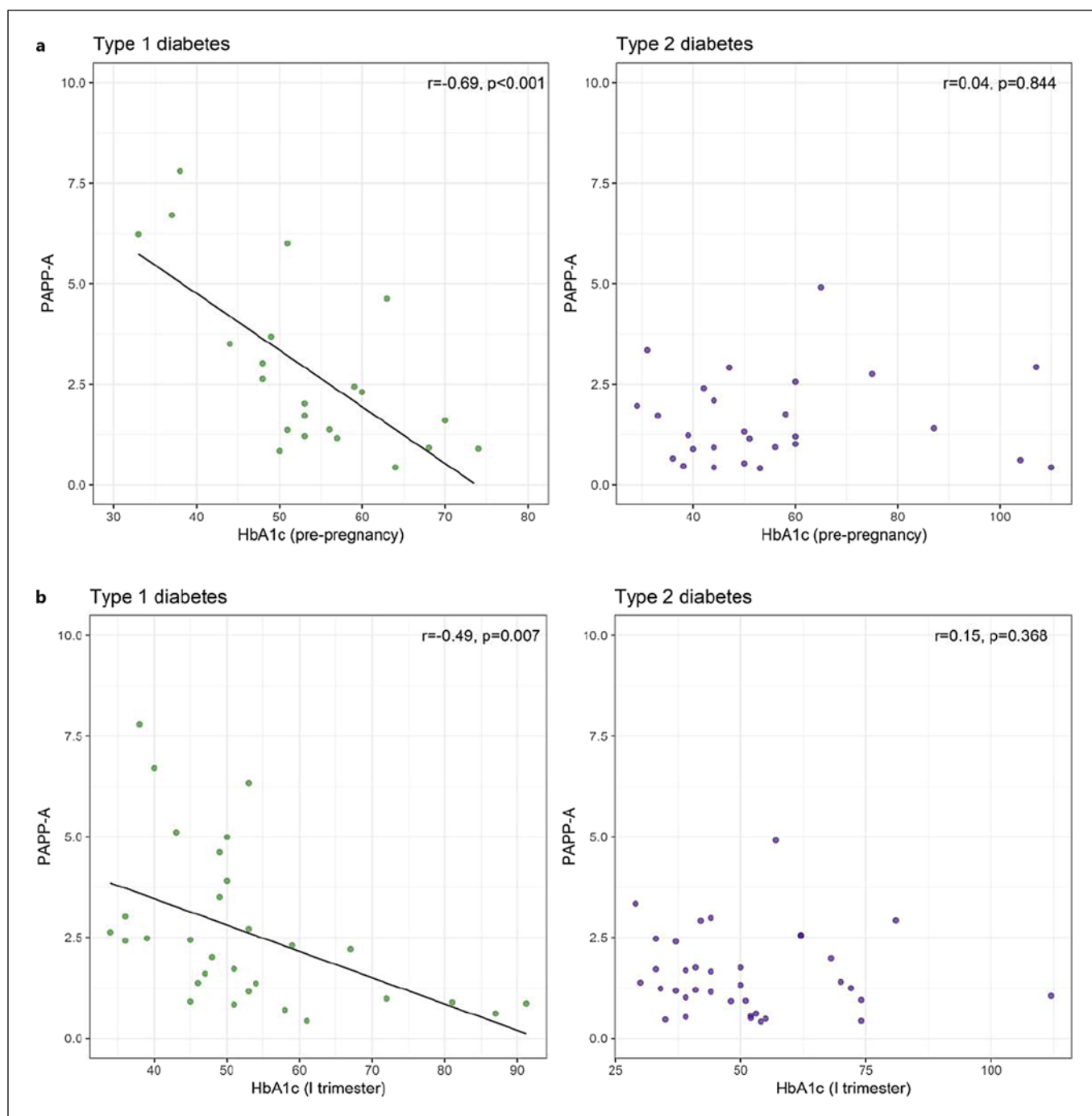


Fig. 2. The correlation between PAPP-A and HbA1c in the study population. Green dots pre-GD type 1, purple dots pre-GD type 2. **a** Correlations at pre-pregnancy between PAPP-A and HbA1c in women with pre-GD type 1 ($R = -0.67$; p value = 0.001) and in women with pre-GD type 2 ($R = 0.04$; $p = 0.844$). **b** Correlations in the first trimester between PAPP-A and HbA1c in women with pre-GD type 1 ($R = -0.54$; p value = 0.001) and in women with pre-GD type 2 ($R = -0.15$; $p = 0.368$).

environmental influences on placental protein expression that could interact with metabolic factors.

The correlation between PAPP-A and HbA1c, in women with type 1 pre-GD, is consistent with the notion that chronic hyperglycemia may exert a more pronounced effect on the placenta in type 1 pre-GD due to its typically longer duration or different metabolic profile compared to type 2 pre-GD. This observation aligns with the findings of Madsen et al. [14] and other recent reports demonstrating that tighter glycemic control during early gestation mitigates adverse placental biochemical changes [14, 24, 25]. Conversely, earlier studies that failed to identify significant associations may have been limited by heterogeneous populations, inclusion of GD cases, or lack of stratification by diabetes type [9, 12, 13]. Our results, therefore, provide a more granular understanding of the specific effects of pre-GD on first-trimester biochemical markers.

In agreement with other studies conducted in the past on this subject [10, 24], free β -HCG levels were comparable in the 2 groups of patients under investigation. The lack of a significant relationship between free β -HCG and HbA1c, despite differences in free β -HCG levels between diabetes types, points to the possibility that free β -HCG may be regulated through mechanisms less directly tied to glycometabolic status. This could imply that PAPP-A and free β -HCG serve distinct roles or reflect different aspects of placental function in diabetic pregnancies. Particularly, PAPP-A and free β -HCG may reflect distinct dimensions of placental function – PAPP-A is more sensitive to metabolic and vascular perturbations, while β -HCG reflects trophoblastic differentiation and hormone synthesis.

Finally, the number of women of this cohort who developed hypertensive disorders during pregnancy despite the good glycemic control achieved since the second trimester of pregnancy, as proved by the observed newborn weight, underline the pre-pregnancy risks for cardiovascular diseases in these women.

Overall, these findings suggest the opportunity to refine first-trimester screening approaches by integrating maternal metabolic markers, such as HbA1c, into risk models for aneuploidies and other complications. Introducing HbA1c as a continuous variable – rather than categorizing pre-GD as a binary condition – could allow for more nuanced, individualized risk assessment. In fact, to date, reduced PAPP-A levels are weighted by aneuploidy risk calculation algorithms for women with type 2 pre-GD [9, 10], ensuring accurate individual risk stratification [7]. The inclusion of HbA1c could introduce a continuous personalized variable instead of a categorical variable for both type 1 and 2 pre-G.

In addition to this, since glycometabolic compensation is a modifiable factor, optimizing maternal glycemic control before and during very early pregnancy could have a positive impact on placental function and screening results, benefiting both maternal and fetal health. These insights reinforce the need to consider glycemic control during the first-trimester risk assessment. Future prospective studies with larger and ethnically diverse cohorts are warranted to validate these associations and to explore whether early intervention in glycemic management could normalize PAPP-A levels and improve screening accuracy.

Conclusions

PAPP-A, a glycoprotein produced by the syncytiotrophoblast and the decidua and maternal vascular, is a key biomarker in the first-trimester screening for aneuploidies. The correlations between PAPP-A and HbA1c highlight the complex interplay between glycemic control and placental function in women with pregestational type 1 and type 2 diabetes. The inclusion of individual HbA1c concentration could add a continuous personalized variable in women with both type 1 and 2 pre-GD, in addition to other continuous variables, such as BMI, instead of a categorical variable, presence or absent pre-GD, so far adopted into the complex risk assessment algorithms. Further studies are warranted to validate the observed correlation across larger cohorts to better understand the mechanistic pathways linking glycometabolic compensation and placental health.

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Statement of Ethics

The study was conducted in accordance with the Declaration of Helsinki. This study protocol was reviewed and approved by the Ethics Committee of Milan Area 2 (07.10.2022/931_2022bis). Patient consent was waived under the general consensus released by any patient undergoing both outpatient and inpatient procedures, granted the anonymity of reported data as no identifying images or other personal or clinical details that compromise anonymity are present in this manuscript. The need for written

and informed consent was waived by the Ethics Committee of Milan Area 2 (Approval No. 07.10.2022/931_2022bis), data of decision 07/10/2022.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

M.B. and G.R. developed the study; M.B., A.C., and B.C. collected the data; G.Z. performed the statistical analysis; M.B. and E.F. wrote the manuscript; and G.R. I.C., N.P., V.M., and M.R.C. contributed to the scientific contents. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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