A comparison of early pregnancy biomarkers associated with metabolic health between Indian and European women, from the Screening for Pregnancy Endpoints (SCOPE) study: a prospective cohort.

Esti C. DE GRAAFF[1], John Thompson[1], Claire Roberts[2], Lynn Sadler[1], Heena LAKHDHIR[3], Rachel SIMON-KUMAR[4], Roshini PEIRIS-JOHN[5], Lesley McCowan[1], and Ngaire Anderson[1]

[1]The University of Auckland Faculty of Medical and Health Sciences
[2]Flinders Health and Medical Research Institute
[3]Te Whatu Ora Health New Zealand Counties Manukau
[4]The University of Auckland School of Population Health
[5]The University of Auckland Section of Epidemiology and Biostatistics

October 19, 2023

Abstract

Objective: Increased rates of pro-inflammatory and metabolic-related disorders, plus perinatal death and other pregnancy complications such as gestational diabetes (GDM), are consistently reported among women of Indian ethnicity. This study compares lipid profiles and early pregnancy biomarkers associated with metabolic dysfunction between healthy nulliparous pregnant women of Indian and European ethnicity. Design: a prospective cohort study. Setting: Australia, Ireland, New Zealand and the United Kingdom; 2004-2011. Population: 138 and 5,240 women of Indian and European ethnicity were included from the prospective Screening for Pregnancy Endpoints cohort study. Methods: Early pregnancy biomarkers were selected *a priori* on the basis of a potential association with the metabolic syndrome, diabetes/GDM or obesity, and compared between ethnic groups. Biomarkers that differed significantly between ethnic groups were adjusted for maternal age, body mass index, smoking, alcohol use and socioeconomic status. Main outcome measures: Mean values for 21 placental, metabolic, inflammatory and cardiovascular biomarkers, plus blood lipids, measured at 15±1 weeks gestation. Results: Ten biomarkers were significantly different by ethnicity, mostly consistent with a pro-inflammatory and less favourable metabolic profile in Indian women: PlGF (p=0.02), adiponectin (p<0.01), NGAL (p<0.01), TNFR1A (p<0.01), CXCL10 (p=0.01), ICAM-1 (p<0.01), ST2 (p<0.01), angiogenin (p<0.01), and proANP (p<0.01). We additionally found increased triglycerides (1.6±0.6 vs 1.5±0.6, p<0.01) and reduced HDL cholesterol (1.7±0.4 vs 1.9±04, p<0.01) in Indian mothers, compared with European. Conclusions: Low-risk mothers of Indian ethnicity have an overall less favourable metabolic health profile at early gestation compared with European women. Future research should investigate the association with pregnancy outcomes.

A comparison of early pregnancy biomarkers associated with metabolic health between Indian and European women, from the Screening for Pregnancy Endpoints (SCOPE) study: a prospective cohort.

Running title: Metabolic-related biomarkers by ethnicity in early pregnancy

Authors and affiliations:

Dr Esti C. DE GRAAFF[a] *(corresponding author)**

e.degraaff@auckland.ac.nz, ORCID 0000-0003-0656-7123

Associate Professor John THOMPSON[a]

j.thompson@auckland.ac.nz, ORCID 0000-0001-6944-381X

Professor Claire T. ROBERTS[b]

claire.roberts@flinders.edu.au, ORCID 0000-0002-9250-2192

Dr Lynn SADLER[a,c]

l.sadler@auckland.ac.nz, ORCID 0000-0003-0681-6652

Dr Heena LAKHDHIR[d]

heena.lakhdhir@middlemore.co.nz

Associate Professor Rachel SIMON-KUMAR[e]

r.simon-kumar@auckland.ac.nz, ORCID 0000-0002-4866-5226

Associate Professor Roshini PEIRIS-JOHN[f]

r.peiris-john@auckland.ac.nz, ORCID 0000-0001-7812-2268

Emeritus Professor Lesley MCCOWAN[a]

l.mccowan@auckland.ac.nz, ORCID 0000-0001-9915-7873

Dr Ngaire ANDERSON[a]

ngaire.anderson@auckland.ac.nz, ORCID 0000-0002-9303-2524

[a] The University of Auckland Faculty of Medical and Health Sciences, Obstetrics & Gynaecology, Auckland, New Zealand

Postal address : Building 507, 22-30 Park Avenue, Grafton, Auckland 1023, New Zealand

[b] Flinders Health and Medical Research Institute, Flinders University, Adelaide, South Australia, Australia

Postal address : Flinders Medical Centre, 1 Flinders Drive, Bedford Park, South Australia, 5051, Australia

[c] Te Toka Tumai Auckland, Te Whatu Ora Health New Zealand

Postal address : 2 Park Road, Grafton, Auckland 1023, New Zealand

[d] Counties Manukau District, Division of Women's Health, Te Whatu Ora - Health New Zealand

Postal address : 100 Hospital Road, Ōtāhuhu, Auckland 2025, New Zealand

[e] The University of Auckland School of Population Health, Auckland, New Zealand

Postal address : Building 507, 22-30 Park Avenue, Grafton, Auckland 1023, New Zealand

[f] The University of Auckland Section of Epidemiology and Biostatistics, Auckland, New Zealand

Postal address : Building 507, 22-30 Park Avenue, Grafton, Auckland 1023, New Zealand

Abstract:

Objective: Increased rates of pro-inflammatory and metabolic-related disorders, plus perinatal death and other pregnancy complications such as gestational diabetes (GDM), are consistently reported among women of Indian ethnicity. This study compares lipid profiles and early pregnancy biomarkers associated with metabolic dysfunction between healthy nulliparous pregnant women of Indian and European ethnicity.

Design: a prospective cohort study.

Setting: Australia, Ireland, New Zealand and the United Kingdom; 2004-2011.

Population: 138 and 5,240 women of Indian and European ethnicity were included from the prospective Screening for Pregnancy Endpoints cohort study.

Methods: Early pregnancy biomarkers were selected *a priori*on the basis of a potential association with the metabolic syndrome, diabetes/GDM or obesity, and compared between ethnic groups. Biomarkers that differed significantly between ethnic groups were adjusted for maternal age, body mass index, smoking, alcohol use and socioeconomic status.

Main outcome measures: Mean values for 21 placental, metabolic, inflammatory and cardiovascular biomarkers, plus blood lipids, measured at 15±1 weeks gestation.

Results: Ten biomarkers were significantly different by ethnicity, mostly consistent with a pro-inflammatory and less favourable metabolic profile in Indian women: PlGF (p=0.02), adiponectin (p<0.01), NGAL (p<0.01), TNFR1A (p<0.01), CXCL10 (p=0.01), ICAM-1 (p<0.01), ST2 (p<0.01), angiogenin (p<0.01), and proANP (p<0.01). We additionally found increased triglycerides (1.6±0.6 vs 1.5±0.6, p<0.01) and reduced HDL cholesterol (1.7±0.4 vs 1.9±04, p<0.01) in Indian mothers, compared with European.

Conclusions: Low-risk mothers of Indian ethnicity have an overall less favourable metabolic health profile at early gestation compared with European women. Future research should investigate the association with pregnancy outcomes.

Funding:

EdG was provided with scholarship support from the University of Auckland and the NHMRC Centre of Research Excellence in Stillbirth. There were no external requirements associated with this funding.

Keywords: pregnancy, biomarkers, ethnicity, South Asia, metabolic syndrome, inflammation, lipids, prospective studies.

Introduction:

Multiple reports demonstrate that women of Indian ethnicity in high-income countries experience more adverse perinatal outcomes than women of other ethnic groups.[1-7] In a recent study we confirmed that South Asian women in New Zealand (NZ), the majority of whom are of Indian ethnicity, have an approximate 50% independently increased risk of perinatal death compared with women of NZ European ethnicity, with most excess perinatal deaths occurring at extremely preterm gestations <24 weeks.[8] It is furthermore well-established that women of Indian ethnicity are more likely to develop gestational diabetes (GDM),[9-12] even at a lower BMI.[13-16] Other metabolic disorders are also more common among Indian peoples, such as type II diabetes,[17,18] cardiovascular disease,[19] the metabolic syndrome (MetS),[20] polycystic ovarian syndrome,[21] thyroid disease,[22,23]and anaemic disorders.[24]

There is a growing body of evidence suggesting that women with features of the metabolic syndrome have an increased risk of pregnancy complications, possibly caused by a pro-inflammatory phenotype.[25] The metabolic syndrome is defined by a combination of risk factors which can lead to chronic health conditions such as diabetes or cardiovascular disease, including abdominal obesity, hypertension, high fasting blood glucose and an abnormal lipid profile.[26] Typically a favourable lipid profile is characterised by lower triglycerides and low-density lipoprotein (LDL) cholesterol, with increased high-density lipoprotein (HDL) cholesterol. A study by Grieger et al. found that the risk of GDM was 3.5 to 4 times higher among women with the metabolic syndrome, utilising data from the same prospective cohort as in the current study.[27] In addition to clinical risk factors, we previously identified that South Asian women with perinatal death <28 weeks gestation were significantly more likely to have features of chorioamnionitis in placental histology compared with NZ European women (aOR 1.87, 95%CI 1.19-2.94).[28] Acute chorioamnionitis is a maternal inflammatory response of the chorionic plate of the placenta and chorioamniotic membranes,[29] and the pro-inflammatory metabolic syndrome may contribute to this by providing a poor*in-utero* environment.[30,31] Smaller studies have shown an association between diabetes or GDM and chorioamnionitis.[32-34]

Considering the consistent findings of pro-inflammatory and metabolic disorders amongst women of Indian (or South Asian) ethnicity, we hypothesise that a less favourable metabolic health profile may contribute to the increased risk of adverse pregnancy outcome among these mothers. The aim of this study was to compare early pregnancy (15±1 weeks) lipid profiles and biomarkers associated with metabolic dysfunction between healthy pregnant women of Indian and European ethnicity.

Methods:

In this study we used demographic, clinical and biobank data from the Screening for Pregnancy Endpoints (SCOPE) study (trial registration ACTRN 12607000551493).[35] Ethical approval was obtained from local ethics committees. SCOPE was a prospective multicentre cohort study of healthy nulliparous women, undertaken between 2004 and 2011 in study centres in Australia (Adelaide), Ireland (Cork), NZ (Auckland) and the United Kingdom (Leeds, London and Manchester). Informed consent was obtained from each individual participant. The primary objective of the SCOPE study was to develop screening tests to predict pre-eclampsia, small for gestational age births and spontaneous preterm birth, based on a detailed set of clinical risk factors and early pregnancy biomarkers measured at 15±1 weeks gestation. Therefore, all women with major clinical risk factors for one of these adverse outcomes were excluded from SCOPE, including women with pre-existing hypertension or diabetes. Other exclusion criteria were based on obstetric and gynaecological history, and complications of the index pregnancy.[35]Women with uncomplicated singleton pregnancies were recruited before 15 weeks gestation and assessed for a wide range of demographic, psychological and lifestyle factors.[36] Physical measures (such as height, weight, waist and hip circumference, and blood pressure) and the collection of peripheral blood samples, was performed at two time points: at 15±1 and 20±1 weeks gestation. All women were followed until delivery.

Maternal body mass index (BMI) was calculated as per the international World Health Organization definitions.[37] In addition, ethnic-specific BMI criteria for Asian populations were reported,[38] to adjust for variations in body composition by ethnicity such as the ratio of body fat and lean tissue mass.[39] In the SCOPE study the maternal socioeconomic index was calculated using the NZ Socioeconomic Index 1996,[40] including for the non-NZ study centres. Socioeconomic status is described by this index on a continuous scale from 10 to 90, with 10 being the lowest socioeconomic score and 90 the highest. This continuous score is subsequently divided into six classes, with women of lowest socioeconomic status in the 6^{th}class (score <24). Maternal anaemia at 15±1 weeks gestation was defined as haemoglobin <110 g/L. Diet was categorised as not vegetarian, demi-vegetarian (i.e. does not eat meat, but may eat fish; as defined by SCOPE), and vegetarian (a diet without meat or fish). GDM was diagnosed based on national guidelines of the respective countries included in SCOPE. At the time of recruitment it was universal practice to screen for GDM in Australia and NZ, but not in the United Kingdom or Ireland, where only risk factor screening was performed. The composite variable for hypertensive disorders diagnosed during pregnancy included chronic hypertension, gestational hypertension, preeclampsia and superimposed preeclampsia. Birthweight was adjusted for maternal height, booking weight, parity, ethnicity and infant sex, to create customised birthweight centiles.[41]

Serum samples were tested by Luminex or ELISA immunoassays (Alere, San Diego) on 57 biomarkers. In 2014, stored samples were additionally tested for serum lipids, insulin, adiponectin and alanine aminotransferase. For this study we were interested in early pregnancy biomarkers in relationship to metabolic health. Placental, metabolic, inflammatory and cardiovascular biomarkers were therefore selected*a priori* on the basis of a possible association with the metabolic syndrome, diabetes or GDM. Five biomarkers were subsequently excluded, as over 50% of women had a value below the lowest limit of detection (insulin, human placental growth hormone, pentraxin-3, plasminogen activator inhibitor-1, and endothelin-1). See supplemental table S1 for a list of biomarkers included in this study, with more detail on immunoassay methods. Finally, 21 original biomarkers were included, plus lipid variables. Not all tests were performed on all women (see table 2 for n per biomarker), but data missingness appeared to be random by study centre. Women of Indian ethnicity were analysed as the population of interest, and mothers of European ethnicity were included as the referent group.

Statistical methods

Statistical analyses were performed using SAS Enterprise Guide 8.2. Maternal and infant demographics were analysed using t-tests or Mann-Whitney U tests for continuous variables. Chi-square or Fisher's Exact tests were performed on categorical data. Early pregnancy biomarkers were assessed for normality and log-transformed where the data was skewed. Outliers were not deleted, as the referent values for pregnant women are currently unknown for the chosen biomarkers. This resulted in wide confidence intervals for some biomarkers. In addition, the lowest limit of detection was used for observations that fell below this level. Biomarker univariable analysis was performed using t-tests. Significant biomarkers in univariable analyses were included in a multivariable model, adjusting for maternal characteristics associated with metabolic health (age, BMI, smoking, alcohol use and socioeconomic status). We performed two additional sensitivity analyses excluding all women who (1) developed GDM or hypertensive disease during pregnancy, and (2) those with low haemoglobin (defined as <110 g/L) at 15±1 weeks gestation.

Results:

One hundred and thirty eight women of Indian, and 5,240 women of European ethnicity were included in this study.

Demographic characteristics

Maternal and infant demographics are described in table 1. BMI and hip circumference were higher among European women (p<0.01), although there were no differences in waist circumference or waist-hip ratio between ethnic groups. Only 1.5% and 2.9% of Indian women smoked or drank alcohol at 15±1 weeks gestation, compared with 11.1% and 10.9% among European women, respectively (p <0.01 for each).

Women of Indian ethnicity were more likely to have been treated for anaemia before the index pregnancy (19.6% vs 12.9%, p=0.02) and have anaemia at 15±1 weeks gestation (haemoglobin <110 g/L; 6.5% vs 1.8%, p<0.01). A vegetarian diet was also significantly more likely in Indian (15.2%) compared with European (1.5%, p<0.01). There was a 1 g/L difference in haemoglobin levels between non-vegetarian and vegetarian women of Indian ethnicity (124.2 vs 123.2 g/L, p=0.67). Almost double the number of Indian mothers compared with European reported having polycystic ovarian syndrome (11.6% vs 6.3%, p=0.01). However, there were no differences in history of infertility or fertility treatment to conceive the index pregnancy. Finally, Indian women were more often diagnosed with GDM (8.7% vs 2.3%, p<0.01), while rates of hypertensive disorders diagnosed during pregnancy were not significantly different. For infants, mean birthweight was lower among those born to Indian mothers (3,065g), compared with those born to European (3,412g, p<0.01 adjusted for gestational age alone), but there was no difference in customised birthweight centiles. Although European women had a higher mean gestational age at birth, there was no difference in the prevalence of preterm birth <37 weeks gestation (p=0.38).

Early pregnancy biomarkers

Table 2 shows early pregnancy biomarkers between women of Indian and European ethnicity. Mean haemoglobin was significantly lower among women of Indian ethnicity, compared with European (123.9 vs 129.0 g/L respectively, p<0.01). Random blood glucose at 15±1 and 20±1 weeks gestation was similar between groups. Indian mothers had an overall less favourable lipid profile, including increased triglycerides (1.6±0.6 vs 1.5±0.6, p<0.01), and reduced HDL cholesterol (1.7±0.4 vs 1.9±04, p<0.01). Indian women also had a higher total cholesterol/HDL ratio after adjustment for confounding factors (p<0.01).

We observed statistically significant differences between Indian and European women in univariable analysis, for the following 11 biomarkers: adiponectin (p<0.01), placental growth factor (PlGF; p=0.02), plasma specific neutrophil gelatinase-associated lipocalin (NGAL; p<0.01), periostin (p=0.03), matrix metalloproteinase-9 (MMP-9; p=0.04), intracellular adhesion molecule-1 (ICAM-1; p<0.01), tumour necrosis factor receptor superfamily member 1A (TNFR1A; p=0.01), CXC motif chemokine 10 (CXCL10; p=0.04), interleukin-1 receptor-like 1 (ST2; p=0.01 and p=0.03), angiogenin (p=0.01), and atrial natriuretic peptide propeptide (proANP; p=0.01). After adjustment for maternal characteristics this effect remained for all biomarkers except TNFR1A (p=0.14). Particularly large differences in mean values were observed for adiponectin (4.1

ug/ml [±1.6], Indian vs 4.6 [±2.1], European) and ICAM-1 (1,032 ng/ml [±2,559], Indian vs 704 [±682], European). In addition, neither sensitivity analyses significantly changed the results as presented in table 2. See supplemental table S2 for a correlation matrix of the included biomarkers (lipids excluded). As is expected, correlations between many of the biomarkers were observed, with adiponectin showing the least correlations with other biomarkers.

Discussion:

Main findings

In this novel study we compared the levels of early pregnancy biomarkers associated with metabolic health between healthy nulliparous women of Indian and European ethnicity. We found that even in low-risk pregnancies at early gestations, Indian women have a less favourable metabolic health profile than European. The relationship between these findings and adverse pregnancy outcomes should be further investigated, which might extend to the pre-conception period.

Strengths and limitations

The strengths of this study are the novel approach and the use of high-quality prospective clinical and biobank data incorporating a large number of early pregnancy biomarkers. To our knowledge, this is the first study to investigate a range of metabolic and inflammatory-related biomarkers in a multi-centre cohort of low-risk nulliparous women, by ethnicity. The main limitation of this study was the relatively small number of Indian participants in SCOPE. Stratification by ethnicity did therefore not allow us to investigate the association between early pregnancy biomarkers and adverse pregnancy outcome. We did, however, observe remarkable differences in metabolic profile by ethnicity and further research is therefore needed to investigate this relationship. It should be noted that the reported mean values for some biomarkers may be different than expected, as we did not exclude outliers from this study; however, data was transformed prior to analysis and checked for normality. Secondly, as Indian women are more likely to have various types of anaemia and are more likely to be vegetarian,[42] it would have been helpful to investigate the association between ferritin and biomarker profile. Unfortunately ferritin testing was not routinely performed in the SCOPE study, and only 37% of Indian women were tested. Similarly, over a quarter of women were not routinely screened for GDM. Finally, while biomarkers were significantly different between ethnicities, many were correlated. This is to be expected as an inflammatory response encompasses multiple pathways that lead to an overall adverse milieu, which can consequently result in poor outcomes. Each biomarker, therefore, is unlikely to exert influence on outcomes independently of other biomarkers. The presented biomarker profiles rather show an overall picture of inflammation and/or adverse metabolic health.

Interpretation

Lipid profile

We observed differences in lipid profiles between ethnicities. Pregnancy is a state of physiologic hyperlipidaemia to accommodate the growing fetus,[43] but reference values for serum cholesterol during pregnancy have not been established. Values for both ethnicities fell within a 'normal' range reported in a single cross-sectional pregnancy study.[44] The overall lipid profile was less favourable among Indian women with increased triglycerides and lower HDL levels, which are considered important components of the metabolic syndrome.[26,45] In line with our findings and hypothesis, a systematic review and meta-analysis showed that triglyceride levels were significantly increased in women with GDM, compared with those without insulin resistance (across all three trimesters). In that study, HDL was also reduced among those with GDM (in the 2nd and 3rd trimesters), while there were no differences in LDL and total cholesterol levels.[46] In addition to a less favourable lipid profile, our study showed that adiponectin (i.e. an adipokine protein with insulin-sensitising and ani-inflammatory effects) was lower among mothers of Indian ethnicity. Reduced adiponectin has been associated with obesity, diabetes and components of the metabolic syndrome,[47,48] and the findings in this study may be of clinical importance to Indian mothers.

Placental biomarkers

As infants of Indian women are generally born with a lower mean birthweight compared with other ethnic groups,[16,49-51]and as birthweight and placental weight are highly correlated,[52] one may expect lower levels of PlGF among Indian mothers. Nonetheless we observed the contrary, in line with an Asian study that found significantly higher PlGF levels among Indian, compared with Chinese and Malay women [?]18 weeks gestation (although not between 11 and 14 weeks).[53] PlGF belongs to the vascular endothelial growth factor family, and is highly expressed in the placenta throughout pregnancy.[54] PlGF promotes vascular placental growth, but is also found in other organs and stimulates angiogenesis during inflammatory response.[55] Limited clinical data shows increased PlGF in obese non-pregnant adults and children with the metabolic syndrome and diabetes.[56-58] While studies are small and data sometimes conflict, a positive association between elevated PlGF and GDM has been established.[59-61] A recent literature review concludes that although large-scale research is missing, most studies agree with this observation.[62] Similarly, increased levels of PlGF have been detected in the placentas of anaemic women, compared with non-anaemic controls.[63] In both diabetic disease and anaemia the increase in PlGF is thought to be caused by an adaptive angiogenic response to a relatively hypoxic placental environment, seen with hyperglycaemia and low haemoglobin.[63,64] While placental hypoxia is considered physiological during first trimester pregnancies,[65] biomarkers were collected at 15+-1 weeks gestation in this study. As women of Indian ethnicity have higher rates of both disorders, these pathways may explain some of the differences seen in PlGF in our study.

Metabolic/obesity biomarkers

Certain adipokines such as NGAL have been positively associated with low-level systemic inflammation in the metabolic syndrome, obesity, hyperglycaemia and insulin resistance in human studies.[66,67] We found significantly lower levels of NGAL among Indian women compared with European. Animal studies, however, show conflicting results, with some reporting diet-induced obesity and insulin resistance in NGAL knockout mice, accompanied by an increase in pro-inflammatory mediators.[68,69] The latter finding is consistent with our hypothesis, that lower NGAL in Indian women is associated with a less favourable metabolic health profile. Further research needs to be done into the relationship between NGAL and metabolic health, to fully understand our findings by ethnicity.

Other significant metabolic biomarkers in multivariable analysis were periostin and MMP-9. Periostin is an extracellular matrix protein involved with tissue remodelling and repair,[70] and has been positively associated with obesity, type II diabetes, insulin resistance, cardiovascular disease, lipids, chronic inflammation, and polycystic ovarian syndrome.[71-74] Periostin levels were significantly increased among Indian women in this study, compared with European. MMP-9 is also responsible for tissue remodelling, and is particularly overexpressed with diabetes and the metabolic syndrome, as a consequence of oxidative stress in endothelial cells.[75,76] In our analysis MMP-9 levels were significantly reduced among Indian, compared with European mothers, which is in contrast to our hypothesis. The reason for this is unknown.

Inflammatory biomarkers

In a recent study we reported that Indian mothers have higher rates of perinatal death at extremely preterm gestations.[8] We hypothesised that a pro-inflammatory environment during these early weeks may lead to preterm birth, as an important antecedent factor for perinatal death.[77] In the current study, several important pro-inflammatory biomarkers were increased among women of Indian ethnicity, compared with European. For example, levels of ICAM-1 were significantly higher, which has been associated with an increased risk of preterm birth when analysed in serum,[78-80]cervicovaginal fluid,[81] and amnion.[82] Of these studies, only Chen et al. included serum samples at early gestation (mean=16 weeks), granted with a standard deviation of +-4.5 weeks.[78] ICAM-1 is a surface glycoprotein expressed on endothelium and immune cells which regulates several inflammatory pathways.[83] It is elevated in activated endothelium,[83] in the metabolic syndrome,[84,85] and seems to be inversely correlated to HDL.[85] Another biomarker with pro-inflammatory properties, CXCL10, was significantly increased among Indian mothers compared with European. CXCL10 has been associated with a range of chronic inflammatory disorders, including type II diabetes and the metabolic syndrome.[86-88] Some studies even suggest that CXCL10 is a potential biomarker for the onset of adipose tissue inflammation in obese people.[89,90]

Cardiovascular biomarkers

ANP is mostly known for its properties in cardiovascular, endocrine and renal functions, and is stored as the biologically inactive variant proANP in atrial myocytes.[91] In addition, ANP indirectly influences glucose metabolism.[92,93] In this study we observed significantly lower levels of proANP among women of Indian ethnicity. This is in line with our hypothesis, as other studies report an inverse relationship between different fragments of proANP (NT-ANP, MR-ANP) and the risk of developing diabetes.[94,95] Furthermore, a Turkish study found progressively lower ANP levels in women with GDM,[96]although non-significant, while another study was able to confirm this.[97]

Furthermore, our findings are consistent with a previous study observing overall higher angiogenin levels among South Asian subjects, compared with European ethnicities in the United States.[98]Angiogenin levels rise during pregnancy with increasing gestation,[99] and seem to promote placental vascular development during the prenatal period.[99,100] Although not widely investigated, a meta-analysis found decreased levels of angiogenin among patients with type II diabetes, but this was not statistically significant.[101] It is unclear whether this also occurs with GDM. We hypothesise that relative placental hypoxia (e.g. due to maternal hyperglycaemia or low haemoglobin) may play a role in the observed increased angiogenin level in pregnant Indian women in our study. Finally, ST2, a cardiovascular biomarker positively associated with diabetes and the metabolic syndrome (including related markers such as triglycerides, liver function and glucose),[102-104] was found in lower levels among Indian women compared with European in the current study. The reason for this is unclear.

Routine testing

Although it is widely recognised that women of Indian ethnicity have higher rates of pre-existing diabetes,[8,17,18] and increased odds of developing GDM,[9-12,16] random blood glucose levels at 15+-1 and 20+-1 weeks did not differ between groups. This is not surprising, as women with pre-existing diabetes were excluded from enrolment in the SCOPE study. Additionally, there was a statistically significant difference in mean haemoglobin between ethnic groups. It is, however, unclear whether this finding is of clinical relevance as both mean values fell within normal range for pregnant women (>110 g/L). It may indicate that women of Indian ethnicity have a lower threshold for developing anaemia and associated disorders, as pregnancy progresses further into a physiologic anaemic state. In this study there was no difference in haemoglobin levels between non-vegetarian and vegetarian women of Indian ethnicity. While we observed a large difference in rates of anaemia between Indian and European (6.5% vs. 1.8% respectively), when anaemic women were excluded in sensitivity analyses biomarker profiles between Indian and European women did not change. This may be due to the low number of women with anaemia in each ethnic group, and further investigation is warranted.

Conclusion:

In conclusion, within a cohort of low-risk nulliparous pregnant women we observed significant differences in a wide range of metabolic and inflammatory-related early pregnancy biomarkers between women of Indian and European ethnicity. Overall, women of Indian ethnicity had a less favourable metabolic health profile based on both serum lipids and biomarkers at 15+-1 weeks gestation. Future investigation should be performed to confirm our findings in a larger cohort, and to assess the relationship between these biomarkers and pregnancy outcome.

Acknowledgements:

The authors would like to acknowledge the University of Auckland and the NHMRC Centre of Research Excellence in Stillbirth for scholarship support.

Disclosure of Interest:

The authors have no competing interests to disclose.

Contribution to Authorship:

EdG set up the study, performed the analyses and prepared the manuscript as part of her PhD thesis. JT was involved in the design of statistical analyses, interpretation of data and review of manuscript. CTR, NA, LS and LM participated in the intellectual planning of the project, including review of the data and manuscript. HL, RSK and RPJ participated in the review of the data and manuscript, including cultural safeguarding from a South Asian perspective.

Details of Ethics Approval:

In this study we used data from the Screening for Pregnancy Endpoints (SCOPE) study, with trial registration ACTRN 12607000551493 (approved 26 October 2007). Ethical approval was also obtained from local ethics committees of participating countries (New Zealand: Northern X Regional Ethics Committee [ref AKX/02/00/364, approved 23 April 203]; Australia: Central Northern Adelaide Health Service, Ethics of Human Research Committee [ref 2005082, approved 2 September 2005]; United Kingdom: South East Multicentre Research Ethics Committee & Central Manchester Research Ethics Committee [ref 06/MRE01/98, approved 19 January 2007]; Ireland: Clinical Research Ethics Committee of the Cork Teaching Hospitals [ref 06/MRE01/98, approved 19 January 2007]).

Data availability statement:

The data that support the findings of this study are available from the Screening for Pregnancy Endpoints study. Restrictions apply to the availability of these data, which were used under license for this study. Data will be shared on request to the corresponding author with permission of the data custodians. Please contact the corresponding author (EdG) for any data requests.

Reference list:

1. Perinatal and Maternal Mortality Review Committee. Fifteenth Annual Report of the Perinatal and Maternal Mortality Review Committee | Te Pūrongo ā-Tau Tekau mā Rima o te Komiti Arotake Mate Pēpi, Mate Whaea Hoki: Reporting Mortality and Morbidity 2020 | Te Tuku Pūrongo mō te Mate me te Whakamate 2020. Wellington: Health Quality & Safety Commission; 2022.

2. Mozooni M, Preen DB, Pennell CE. Stillbirth in Western Australia, 2005–2013: The influence of maternal migration and ethnic origin. Med J Aust. 2018; 209(9):394-400.

3. Davies-Tuck ML, Davey M-A, Wallace EM. Maternal region of birth and stillbirth in Victoria, Australia 2000–2011: A retrospective cohort study of Victorian perinatal data. PLoS One. 2017; 12(6):e0178727.

4. Li Y, Quigley MA, Macfarlane A, Jayaweera H, Kurinczuk JJ, Hollowell J. Ethnic differences in singleton preterm birth in England and Wales, 2006-12: Analysis of national routinely collected data. Paediatr Perinat Epidemiol. 2019; 33(6):449-58.

5. Ministry of Health. Report on Maternity web tool: Wellington: Ministry of Health; 2020 [Available from: https://www.health.govt.nz/publication/report-maternity-web-tool].

6. Draper ES, Gallimore ID, Smith LK, Fenton AC, Kurinczuk JJ, Smith PW, et al, on behalf of the MBRRACE-UK Collaboration. MBRRACE-UK perinatal mortality surveillance report, UK perinatal deaths for births from January to December 2018. Leicester: The Infant Mortality and Morbidity Studies, Department of Health Sciences, University of Leicester; 2020.

7. Bartsch E, Park AL, Pulver AJ, Urquia ML, Ray JG. Maternal and paternal birthplace and risk of stillbirth. J Obstet Gynaecol Can. 2015; 37(4):314-23.

8. De Graaff E, Sadler L, Lakhdhir H, Simon-Kumar R, Peiris-John R, Burgess W, et al. An in-depth analysis of perinatal related mortality among women of South Asian ethnicity in Aotearoa New Zealand. BMC Pregnancy Childbirth. 2023; 23(1):535.

9. Hedderson MM, Darbinian JA, Ferrara A. Disparities in the risk of gestational diabetes by race-ethnicity and country of birth. Paediatr Perinat Epidemiol. 2010; 24(5):441-8.

10. Mukerji G, Chiu M, Shah BR. Gestational diabetes mellitus and pregnancy outcomes among Chinese and South Asian women in Canada. J Matern Fetal Neonatal Med. 2013; 26(3):279-84.

11. Audette MC, Levytska K, Lye SJ, Melamed N, Kingdom JC. Parental ethnicity and placental maternal vascular malperfusion pathology in healthy nulliparous women. Placenta. 2018; 66:40-6.

12. Urquia M, Glazier RH, Berger H, Ying I, De Souza L, Ray JG. Gestational diabetes among immigrant women. Epidemiol. 2011; 22(6):879-80.

13. Chiu M, Austin PC, Manuel DG, Shah BR, Tu JV. Deriving ethnic-specific BMI cutoff points for assessing diabetes risk. Diabetes Care. 2011; 34(8):1741-8.

14. Hedderson M, Ehrlich S, Sridhar S, Darbinian J, Moore S, Ferrara A. Racial/ethnic disparities in the prevalence of gestational diabetes mellitus by BMI. Diabetes Care. 2012; 35(7):1492-8.

15. Bryant M, Santorelli G, Lawlor DA, Farrar D, Tuffnell D, Bhopal R, et al. A comparison of South Asian specific and established BMI thresholds for determining obesity prevalence in pregnancy and predicting pregnancy complications: findings from the Born in Bradford cohort. Int J Obes. 2014; 38(3):444-50.

16. De Graaff E, Sadler L, Lakhdhir H, Simon-Kumar R, Peiris-John R, Burgess W, et al. Grouping women of South Asian ethnicity for pregnancy research in New Zealand. Aust N Z J Obstet Gynaecol. 2022; 63(4):499-508.

17. Gujral UP, Pradeepa R, Weber MB, Narayan KM, Mohan V. Type 2 diabetes in South Asians: Similarities and differences with white Caucasian and other populations. Ann N Y Acad Sci. 2013; 1281(1):51-63.

18. Parackal S, Coppell K, Yang CL, Sullivan T, Subramaniam RM. Hidden figures and misnomers: a case for disaggregated Asian health statistics in Aotearoa New Zealand to improve health outcomes. N Z Med J. 2021; 134(1546):109-16.

19. Volgman AS, Palaniappan LS, Aggarwal NT, Gupta M, Khandelwal A, Krishnan AV, et al. Atherosclerotic cardiovascular disease in South Asians in the United States: Epidemiology, risk factors, and treatments: A scientific statement from the American Heart Association. Circ. 2018; 138(1):e1-e34.

20. Wali M, Ram CVS. Metabolic Syndrome in South Asians. In: Ahima RS, editor. Metabolic Syndrome: A Comprehensive Textbook. Cham: Springer International Publishing; 2016. p. 73-85.

21. Williamson K, Gunn AJ, Johnson N, Milsom SR. The impact of ethnicity on the presentation of polycystic ovarian syndrome. Aust N Z J Obstet Gynaecol. 2001; 41(2):202-6.

22. Sletner L, Jenum AK, Qvigstad E, Hammerstad SS. Thyroid function during pregnancy in a multiethnic population in Norway. J Endocr Soc. 2021; 5(7): bvab078.

23. Vaidya B, Anthony S, Bilous M, Shields B, Drury J, Hutchison S, et al. Detection of thyroid dysfunction in early pregnancy: Universal screening or targeted high-risk case finding? J Clin Endocrinol Metab. 2007; 92(1):203-7.

24. Fischbacher C, Bhopal R, Patel S, White M, Unwin N, Alberti KG. Anaemia in Chinese, South Asian, and European populations in Newcastle upon Tyne: Cross sectional study. BMJ (Clinical research ed). 2001; 322(7292):958-9.

25. Sattar N, Greer IA. Pregnancy complications and maternal cardiovascular risk: Opportunities for intervention and screening? BMJ (Clinical research ed). 2002; 325(7356):157-60.

26. International Diabetes Federation. The IDF worldwide defi nition of the metabolic syndrome. 2006.

27. Grieger JA, Bianco-Miotto T, Grzeskowiak LE, Leemaqz SY, Poston L, McCowan LM, et al. Metabolic syndrome in pregnancy and risk for adverse pregnancy outcomes: A prospective cohort of nulliparous women. PLoS Med. 2018; 15(12):e1002710.

28. de Graaff E, Bartlett K, Sadler L, Lakhdhir H, Simon-Kumar R, Peiris-John R, et al. Placental pathology findings amongst extremely preterm perinatal deaths in Aotearoa New Zealand. Placenta. 2023; 137:78-87.

29. Cox P, Cohen MC, Scheimberg IB. Acute Chorioamnionitis. In: Khong TY, Mooney EE, Nikkels PGJ, Morgan TK, Gordijn SJ, editors. Pathology of the Placenta: A Practical Guide. Cham: Springer International Publishing; 2019. p. 103-7.

30. Pantham P, Aye ILMH, Powell TL. Inflammation in maternal obesity and gestational diabetes mellitus. Placenta. 2015; 36(7):709-15.

31. Kalagiri RR, Carder T, Choudhury S, Vora N, Ballard AR, Govande V, et al. Inflammation in complicated pregnancy and its outcome. Am J Perinatol. 2016; 33(14):1337-56.

32. Zhang X, Liao Q, Wang F, Li D. Association of gestational diabetes mellitus and abnormal vaginal flora with adverse pregnancy outcomes. Medicine. 2018; 97(34):e11891.

33. Scholl TO, Sowers M, Chen X, Lenders C. Maternal glucose concentration influences fetal growth, gestation, and pregnancy complications. Am J Epidemiol. 2001; 154(6):514-20.

34. McCoy J, Downes KL, Levine LD. 840: Risk factors associated with development of chorioamnionitis during labor induction with a standardized labor protocol. Am J Obstet Gynecol. 2018; 218(1):S501-S2.

35. McCowan L, North R, Taylor R. ACTRN12607000551493. Australian New Zealand Clinical Trials Registry. www.anzctr.org.au/trialSearch.aspx; 2007.

36. Kenny LC, Black MA, Poston L, Taylor R, Myers JE, Baker PN, et al. Early pregnancy prediction of preeclampsia in nulliparous women, combining clinical risk and biomarkers: The Screening for Pregnancy Endpoints (SCOPE) international cohort study. Hypertens. 2014; 64(3):644-52.

37. WHO. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. 1995.

38. WHO expert consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet. 2004; 363(9403):157-63.

39. World Health Organization Regional Office for the Western Pacific. The Asia-Pacific perspective: Redefining obesity and its treatment. 2000.

40. Galbraith C, Jenkin G, Davis P, Coope P. New Zealand Social Economic Index 1996 Users Guide. Statistics New Zealand, Wellington; 2003.

41. Gardosi J, Francis A. Customised Weight Centile Calculator. GROW v6.7.8. Gestation Network, www.gestation.net, 2016.

42. Lim K, Beck KL, Von Hurst PR, Rutherfurd-Markwick KJ, Badenhorst CE. Iron deficiency and risk factors in pre-menopausal females living in Auckland, New Zealand. Asia Pac J Clin Nutr. 2020; 29(3):638-47.

43. Rodie VA, Freeman DJ, Sattar N, Greer IA. Pre-eclampsia and cardiovascular disease: Metabolic syndrome of pregnancy? Atheroscler. 2004; 175(2):189-202.

44. Bartels Ä, Egan N, Broadhurst DI, Khashan AS, Joyce C, Stapleton M, et al. Maternal serum cholesterol levels are elevated from the 1st trimester of pregnancy: A cross-sectional study. J Obstet Gynaecol. 2012; 32(8):747-52.

45. Grundy SM. Metabolic syndrome update. Trends Cardiovasc Med. 2016; 26(4):364-73.

46. Ryckman K, Spracklen C, Smith C, Robinson J, Saftlas A. Maternal lipid levels during pregnancy and gestational diabetes: a systematic review and meta-analysis. BJOG. 2015; 122(5):643-51.

47. Choi HM, Doss HM, Kim KS. Multifaceted physiological roles of adiponectin in inflammation and diseases. Int J Mol Sci. 2020; 21(4):1219.

48. Vecchiola A, García K, González-Gómez LM, Tapia-Castillo A, Artigas R, Baudrand R, et al. Plasminogen activator inhibitor-1 and adiponectin are associated with metabolic syndrome components. Am J Hypertens. 2021; 35(4):311-8.

49. Moore S, Daniel M, Auger N. Socioeconomic disparities in low birth weight outcomes according to maternal birthplace in Québec, Canada. Ethn Health. 2009; 14(1):61-74..

50. Kelly Y, Panico L, Bartley M, Marmot M, Nazroo J, Sacker A. Why does birthweight vary among ethnic groups in the UK? Findings from the Millennium Cohort Study. J Public Health. 2008; 31(1):131-7.

51. Villar J, Cheikh Ismail L, Victora CG, Ohuma EO, Bertino E, Altman DG, et al. International standards for newborn weight, length, and head circumference by gestational age and sex: The Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. Lancet. 2014; 384(9946):857-68.

52. Williams LA, Evans SF, Newnham JP. Prospective cohort study of factors influencing the relative weights of the placenta and the newborn infant. BMJ. 1997; 314(7098):1864-8.

53. Ng QJ, Han JY, Saffari SE, Yeo GS-H, Chern BSM, Tan KH. Longitudinal circulating placental growth factor (PlGF) and soluble FMS-like tyrosine kinase-1 (sFlt-1) concentrations during pregnancy in Asian women: a prospective cohort study. BMJ Open. 2019; 9(5):e028321.

54. De Falco S. The discovery of placenta growth factor and its biological activity. Exp Mol Med 2012; 44(1):1-9.

55. Kang M, Jeong J, Lee J, Park S, Sung Y, Choi M, et al. Placental growth factor (PlGF) is linked to inflammation and metabolic disorders in mice with diet-induced obesity. Endocr J. 2018; 65(4):437-47.

56. Pervanidou P, Chouliaras G, Akalestos A, Bastaki D, Apostolakou F, Papassotiriou I, et al. Increased placental growth factor (PlGF) concentrations in children and adolescents with obesity and the metabolic syndrome. Hormones. 2014; 13(3):369-74.

57. Siervo M, Ruggiero D, Sorice R, Nutile T, Aversano M, Stephan BCM, et al. Angiogenesis and biomarkers of cardiovascular risk in adults with metabolic syndrome. J Intern Med. 2010; 268(4):338-47.

58. Duran EK, Cook NR, Bobadilla M, Kim E, Manson JE, Buring JE, et al. Plasma placental growth factor concentrations are elevated well in advance of type 2 diabetes mellitus onset: Prospective data from the WHS. J Am Heart Assoc. 2019; 8(15):e012790.

59. Eleftheriades M, Papastefanou I, Lambrinoudaki I, Kappou D, Lavranos D, Akalestos A, et al. Elevated placental growth factor concentrations at 11–14weeks of gestation to predict gestational diabetes mellitus. Metabol. 2014; 63(11):1419-25.

60. Nuzzo AM, Giuffrida D, Moretti L, Re P, Grassi G, Menato G, et al. Placental and maternal sFlt1/PlGF expression in gestational diabetes mellitus. Sci Rep. 2021; 11(1):2312.

61. Gorkem U, Togrul C, Arslan E. Relationship between elevated serum level of placental growth factor and status of gestational diabetes mellitus. J Matern Fetal Neonatal Med. 2020; 33(24):4159-63.

62. Yanachkova V, Staynova R, Stankova T, Kamenov Z. Placental growth factor and pregnancy-associated plasma protein-A as potential early predictors of gestational diabetes mellitus. Medicina. 2023; 59(2):398.

63. Venkata Surekha M, Singh S, Sarada K, Sailaja G, Balakrishna N, Srinivas M, et al. Study on the effect of severity of maternal iron deficiency anemia on regulators of angiogenesis in placenta. Fetal Pediatr Pathol. 2019; 38(5):361-75.

64. Cvitic S, Desoye G, Hiden U. Glucose, insulin, and oxygen interplay in placental hypervascularisation in diabetes mellitus. Biomed Res Int. 2014; 2014:145846.

65. Burton GJ, Cindrova-Davies T, Yung Hw, Jauniaux E. Hypoxia and reproductive health: Oxygen and development of the human placenta. Reprod. 2021; 161(1):F53-F65.

66. Recinella L, Orlando G, Ferrante C, Chiavaroli A, Brunetti L, Leone S. Adipokines: New potential therapeutic target for obesity and metabolic, rheumatic, and cardiovascular diseases. Front Physiol. 2020; 11: 578966.

67. Wang Y, Lam KS, Kraegen EW, Sweeney G, Zhang J, Tso AW, et al. Lipocalin-2 is an inflammatory marker closely associated with obesity, insulin resistance, and hyperglycemia in humans. Clin Chem. 2007; 53(1):34-41.

68. Guo H, Jin D, Zhang Y, Wright W, Bazuine M, Brockman DA, et al. Lipocalin-2 deficiency impairs thermogenesis and potentiates diet-induced insulin resistance in mice. Diabetes. 2010; 59(6):1376-85.

69. Meyers K, López M, Ho J, Wills S, Rayalam S, Taval S. Lipocalin-2 deficiency may predispose to the progression of spontaneous age-related adiposity in mice. Sci Rep. 2020; 10(1):14589.

70. Conway SJ, Izuhara K, Kudo Y, Litvin J, Markwald R, Ouyang G, et al. The role of periostin in tissue remodeling across health and disease. Cell Mol Life Sci. 2014; 71(7):1279-88.

71. Landry NM, Cohen S, Dixon IMC. Periostin in cardiovascular disease and development: A tale of two distinct roles. Basic Res Cardiol. 2017; 113(1):1.

72. Azharuddin M, Kapur P, Sharma M. Circulating periostin level as a potential biomarker for early cardiovascular risk in subjects with type-2 diabetes mellitus: Evidence from a cross-sectional study. Metab. 2021; 116:154499.

73. Luo Y, Qu H, Wang H, Wei H, Wu J, Duan Y, et al. Plasma periostin levels are increased in Chinese subjects with obesity and type 2 diabetes and are positively correlated with glucose and lipid parameters. Mediators Inflamm. 2016; 2016:6423637.

74. Chen X, Huo L, Ren L, Li Y, Sun Y, Li Y, et al. Polycystic ovary syndrome is associated with elevated periostin levels. Exp Clin Endocrinol Diabetes. 2019; 127(09):571-7.

75. Uemura S, Matsushita H, Li W, Glassford AJ, Asagami T, Lee KH, et al. Diabetes mellitus enhances vascular matrix metalloproteinase activity: Role of oxidative stress. Circ Res. 2001; 88(12):1291-8.

76. Gonçalves FM, Jacob-Ferreira ALB, Gomes VA, Casella-Filho A, Chagas ACP, Marcaccini AM, et al. Increased circulating levels of matrix metalloproteinase (MMP)-8, MMP-9, and pro-inflammatory markers in patients with metabolic syndrome. Clin Chim Acta. 2009; 403(1):173-7.

77. Anderson JG, Baer RJ, Partridge JC, Kuppermann M, Franck LS, Rand L, et al. Survival and major morbidity of extremely preterm infants: A population-based study. Pediatr. 2016; 138(1):e20154434.

78. Chen X, Scholl TO. Maternal biomarkers of endothelial dysfunction and preterm delivery. PLoS One. 2014; 9(1):e85716.

79. Raba G, Tabarkiewicz J. Cytokines in preterm delivery: Proposal of a new diagnostic algorithm. J Immunol Res. 2018; 2018:8073476.

80. Davutoglu EA, Fırat AA, Ozel A, Madazli R. Assessment of the circulating soluble endothelial cell adhesion molecules and pentraxin 3 levels in predicting preterm delivery within 72 hours. Int J Med Biochem. 2023; 6(1):1-7.

81. Marvin KW, Keelan JA, Zhou RLI, Mitchell MD, McCowan LME, Coleman MAG. Intercellular adhesion molecule-1 (ICAM-1) in cervicovaginal fluid of women presenting with preterm labor: Predictive value for preterm delivery. Am J Reprod Immunol. 2000; 43(5):264-71.

82. Marvin KW, Keelan JA, Sato TA, Coleman MA, McCowan LM, Miller HC, et al. Enhanced expression of intercellular adhesion molecule-1 (ICAM-1) in amnion with term and preterm labour. Placenta. 2000; 21(1):115-21.

83. Bui TM, Wiesolek HL, Sumagin R. ICAM-1: A master regulator of cellular responses in inflammation, injury resolution, and tumorigenesis. J Leukoc Biol. 2020; 108(3):787-99.

84. Tziomalos K, Athyros VG, Karagiannis A, Mikhailidis DP. Endothelial dysfunction in metabolic syndrome: Prevalence, pathogenesis and management. Nutr Metab Cardiovasc Dis. 2010; 20(2):140-6.

85. Lee HA, Choi EJ, Park B, Lee H, Hong YS, Kim HS, et al. The association between metabolic components and markers of inflammatory and endothelial dysfunction in adolescents, based on the Ewha Birth and Growth Cohort Study. PLoS One. 2020; 15(5):e0233469.

86. Sajadi S, Khoramdelazad H, Hassanshahi G, Rafatpanah H, Hosseini J, Mahmoodi M, et al. Plasma levels of CXCL1 (GRO-alpha) and CXCL10 (IP-10) are elevated in type 2 diabetic patients: Evidence for the involvement of inflammation and angiogenesis/angiostasis in this disease state. Clin Lab. 2013; 59(1-2):133-7.

87. Maier R, Weger M, Haller-Schober EM, El-Shabrawi Y, Wedrich A, Theisl A, et al. Multiplex bead analysis of vitreous and serum concentrations of inflammatory and proangiogenic factors in diabetic patients. Mol Vis. 2008; 14:637-43.

88. Tisato V, Toffoli B, Monasta L, Bernardi S, Candido R, Zauli G, et al. Patients affected by metabolic syndrome show decreased levels of circulating platelet derived growth factor (PDGF)-BB. Clin Nutr. 2013; 32(2):259-64.

89. Kochumon S, Madhoun AA, Al-Rashed F, Azim R, Al-Ozairi E, Al-Mulla F, et al. Adipose tissue gene expression of CXCL10 and CXCL11 modulates inflammatory markers in obesity: Implications for metabolic inflammation and insulin resistance. Ther Adv Endocrinol Metab. 2020; 11:2042018820930902.

90. Azar Sharabiani MT, Vermeulen R, Scoccianti C, Hosnijeh FS, Minelli L, Sacerdote C, et al. Immunologic profile of excessive body weight. Biomark. 2011; 16(3):243-51.

91. Weidmann P, Saxenhofer H, Shaw SG, Ferrier C. Atrial natriuretic peptide in man. J Steroid Biochem. 1989; 32(1, Part 2):229-41.

92. Cannone V, Cabassi A, Volpi R, Burnett JC. Atrial natriuretic peptide: A molecular target of novel therapeutic approaches to cardio-metabolic disease. Int J Mol Sci. 2019; 20(13):3265.

93. Schlueter N, de Sterke A, Willmes DM, Spranger J, Jordan J, Birkenfeld AL. Metabolic actions of natriuretic peptides and therapeutic potential in the metabolic syndrome. Pharmacol Ther. 2014; 144(1):12-27.

94. Marjara J, Scott C, Adel F, Chen HH. Predicting the development of metabolic syndrome and diabetes in healthy patients using serum insulin, atrial natriuretic peptide, and aldosterone levels. J Am Coll Cardiol. 2023; 81(8_Supplement):1813.

95. Magnusson M, Jujic A, Hedblad B, Engström G, Persson M, Struck J, et al. Low plasma level of atrial natriuretic peptide predicts development of diabetes: the prospective Malmo Diet and Cancer study. J Clin Endocrinol Metab. 2012; 97(2):638-45.

96. Kansu-Celik H, Ozgu-Erdinc AS, Kisa B, Findik RB, Yilmaz C, Tasci Y. Prediction of gestational diabetes mellitus in the first trimester: comparison of maternal fetuin-A, N-terminal proatrial natriuretic peptide, high-sensitivity C-reactive protein, and fasting glucose levels. Arch Endocrinol Metab. 2019; 63:121-7.

97. Yuksel MA, Davutoglu AE, Temel Yuksel I, Kucur M, Ekmekci H, Balci Ekmekci O, et al. Maternal serum atrial natriuretic peptide (ANP) and brain-type natriuretic peptide (BNP) levels in gestational diabetes

mellitus. J Matern Fetal Neonatal Med. 2016; 29(15):2527-30.

98. Bennett PC, Gill PS, Silverman S, Blann AD, Balakrishnan B, Lip GYH. Ethnic/racial differences in circulating markers of angiogenesis and their association with cardiovascular risk factors and cardiovascular disease. Int J Cardiol. 2013; 167(4):1247-50.

99. Kolben M, Bläser J, Ulm K, Schmitt M, Schneider KTM, Tschesche H, et al. Angiogenin plasma levels during pregnancy. Am J Obstet Gynecol. 1997; 176(1, Part 1):37-41.

100. Pavlov N, Frendo JL, Guibourdenche J, Degrelle SA, Evain-Brion D, Badet J. Angiogenin expression during early human placental development; association with blood vessel formation. Biomed Res Int. 2014; 2014:781632.

101. Yu D, Cai Y, Zhou W, Sheng J, Xu Z. The potential of angiogenin as a serum biomarker for diseases: Systematic review and meta-analysis. Dis Markers. 2018; 2018:1984718.

102. Miller AM, Purves D, McConnachie A, Asquith DL, Batty GD, Burns H, et al. Soluble ST2 associates with diabetes but not established cardiovascular risk factors: A new inflammatory pathway of relevance to diabetes? PLoS One. 2012; 7(10):e47830.

103. Sabbatinelli J, Giuliani A, Bonfigli AR, Ramini D, Matacchione G, Campolucci C, et al. Prognostic value of soluble ST2, high-sensitivity cardiac troponin, and NT-proBNP in type 2 diabetes: A 15-year retrospective study. Cardiovasc Diabetol. 2022; 21(1):180.

104. Zong X, Fan Q, Zhang H, Yang Q, Xie H, Chen Q, et al. Soluble ST2 levels for predicting the presence and severity of metabolic syndrome. Endocr Connect. 2021; 10(3):336-44.

Hosted file

`Table 1.docx` available at https://authorea.com/users/675233/articles/673310-a-comparison-of-early-pregnancy-biomarkers-associated-with-metabolic-health-between-indian-and-european-women-from-the-screening-for-pregnancy-endpoints-scope-study-a-prospective-cohort

Hosted file

`Table 2.docx` available at https://authorea.com/users/675233/articles/673310-a-comparison-of-early-pregnancy-biomarkers-associated-with-metabolic-health-between-indian-and-european-women-from-the-screening-for-pregnancy-endpoints-scope-study-a-prospective-cohort