The Journal of Maternal-Fetal & Neonatal Medicine

ISSN: 1476-7058 (Print) 1476-4954 (Online) Journal homepage: www.tandfonline.com/journals/ijmf20

B-cell-activating factor (BAFF) and platelet-activating factor (PAF) in pregnancies complicated by maternal obesity and diabetes: a preliminary study

Caterina Neri, Alessandra Ciliberti, Davide Archelao Dessì, Chiara Airoldi, Katia Basello, Andrea Costanzi, Alessandra Familiari, Chiara Tersigni, Mattia Cappelletti, Attilio Francesco Speciani & Antonio Lanzone

To cite this article: Caterina Neri, Alessandra Ciliberti, Davide Archelao Dessì, Chiara Airoldi, Katia Basello, Andrea Costanzi, Alessandra Familiari, Chiara Tersigni, Mattia Cappelletti, Attilio Francesco Speciani & Antonio Lanzone (2023) B-cell-activating factor (BAFF) and platelet-activating factor (PAF) in pregnancies complicated by maternal obesity and diabetes: a preliminary study, The Journal of Maternal-Fetal & Neonatal Medicine, 36:2, 2272010, DOI: 10.1080/14767058.2023.2272010

To link to this article: https://doi.org/10.1080/14767058.2023.2272010

© 2023 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group

Published online: 23 Oct 2023.

Submit your article to this journal

Article views: 1415

View related articles

View Crossmark data

Full Terms & Conditions of access and use can be found at
https://www.tandfonline.com/action/journalInformation?journalCode=ijmf20

THE JOURNAL OF MATERNAL-FETAL & NEONATAL MEDICINE
2023, VOL. 36, NO. 2, 2272010
https://doi.org/10.1080/14767058.2023.2272010

Taylor & Francis
Taylor & Francis Group

RESEARCH ARTICLE

OPEN ACCESS Check for updates

B-cell-activating factor (BAFF) and platelet-activating factor (PAF) in pregnancies complicated by maternal obesity and diabetes: a preliminary study

Caterina Neri[a], Alessandra Ciliberti[a], Davide Archelao Dessì[a], Chiara Airoldi[b], Katia Basello[c], Andrea Costanzi[c], Alessandra Familiari[a], Chiara Tersigni[a], Mattia Cappelletti[c], Attilio Francesco Speciani[c] and Antonio Lanzone[a]

[a]Dipartimento di Scienze della Salute della Donna, del Bambino e di Sanità Pubblica, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome, Italy; [b]Department of Translational Medicine, University of Piemonte Orientale, Novara, Italy; [c]GEK Lab, Milan, Italy

ABSTRACT

Objective: In pregnancies complicated by maternal obesity and diabetes, a disruption in inflammatory mediators occurs, resulting in endothelial microvascular dysfunction, oxidative stress, tissue damage, and maternal and feto-neonatal complications. To outline this proinflammatory status, an innovative approach is represented by the measurement of proinflammatory cytokines. Among these biomarkers, B-cell-activating factor (BAFF) and platelet-activating factor (PAF) play a key role in metabolic regulation, immune response to infections, tissue homeostasis, and "food-related inflammation." The aim of the present study is to investigate the blood expression of BAFF and PAF in a cohort of pregnant women affected by obesity and diabetes compared with a control group of healthy pregnant women.

Methods: A prospective longitudinal cohort study has been conducted on pregnant women referred to Fondazione Policlinico Universitario Gemelli IRCCS in Rome. For each pregnant woman, a capillary sample was collected with a swab in three different consecutive evaluations carried out in the three trimesters of pregnancy.

Results: A total of 77 pregnant women have been enrolled. No significant differences in BAFF and PAF levels were longitudinally observed between groups. Focusing on the exposed group, in the third trimester of pregnancy, both PAF and BAFF levels were lower than the basal time. Among the selected group of patients who developed Gestational Diabetes, only PAF values were longitudinally lower when compared to other groups. The multivariate analysis showed that BAFF levels were positively correlated with thyroid-stimulating hormone levels. No macrosomia, no shoulder dystocia, no major perineal lacerations at birth, and no intrauterine growth restriction were observed in the whole population.

Conclusions: This study supports the involvement of metabolic and proinflammatory biomarkers in the mechanisms related to pregnancy complications. Improving a good metabolic environment for obese and diabetic pregnant women could break the vicious cycle connecting inflammation, oxidative stress, and metabolic disorders.

ARTICLE HISTORY
Received 3 July 2023
Revised 28 September 2023
Accepted 12 October 2023

KEYWORDS
Maternal obesity; gestational diabetes; B-cell-activating factor; platelet-activating factor; proinflammatory cytokines

Introduction

In pregnancy, obesity is associated with increased mortality and morbidity for both mother and offspring [1–3]. According to the World Health Organization (WHO), obesity is defined as body mass index (BMI) $\geq$30 kg/m^2 [4].

Obese women are at greater risk for developing pregnancy complications such as hypertensive disorders (gestational hypertension and preeclampsia), glyco-metabolic (insulin resistance and gestational diabetes) and thromboembolic diseases, cardiovascular and metabolic disorders in later life [2], as well as higher incidence of cesarean section and postpartum hemorrhage [5].

Moreover, maternal obesity has been associated with both intrauterine growth restriction (IUGR) and large-for-gestational-age (LGA) fetuses and is contributing to the epidemic of childhood obesity and metabolic disorders [3], such as metabolic syndrome [6],

CONTACT Caterina Neri caterina.neri@policlinicogemelli.it Dipartimento di Scienze della Salute della Donna, del Bambino e di Sanità Pubblica, Fondazione Policlinico Universitario A. Gemelli, IRCCS, L.go A. Gemelli 8, 00168 Rome, Italy

© 2023 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group
This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. The terms on which this article has been published allow the posting of the Accepted Manuscript in a repository by the author(s) or with their consent.

propagating the vicious cycle of metabolic disorders into the next generation [7, 8]. An attractive approach, to decrease the future burden of obesity and to break this vicious cycle, is to improve the metabolic environment of obese and diabetic pregnant women.

The idea that adipose tissue should only be considered an organ where the excess of triglycerides is stored has changed over the past few years. Recent studies have shown that adipose tissue is able to secrete a wide variety of cytokines, proteins, and signal molecules that play both paracrine and endocrine functions and determine a wide-ranging influence on the metabolic and physiological function of other organs [9]. These molecules, collectively called adipocytokines, are involved in the regulation of inflammation, insulin sensitivity, energy balance, and control of appetite. A state of chronic positive energy balance, such as obesity, leads to cellular dysfunction resulting in dysregulated release of adipokines, consequent microvascular endothelial dysfunction, oxidative stress, and tissue damage [10, 11], leading to chronic, low-grade inflammatory state, termed "metainflammation" or metabolically induced inflammation [12].

In recent years, there has been increased interest in the role of inflammation as a mediator of programming of metabolic disorders following exposure to the adverse intrauterine environment in maternal obesity. In particular, placental inflammation has been observed in pregnancies complicated by obesity [13] and gestational diabetes mellitus (GDM) [14] and may play a central role in determining the fetal environment in these pregnancies. These changes in placental function caused by altered inflammatory profiles can lead to the co-morbidities observed in these pregnancies [15–19]. So, obesity in pregnancy and GDM have been linked to the disruption in several inflammatory mediators in the maternal and fetal compartments.

Thus, pregnancy represents a crucial time of intervention to create and maintain an adequate intrauterine environment that guarantees a normal fetal development.

Measuring biomarkers of inflammation represents an innovative approach to outline the inflammatory status in obese and diabetic patients that can be modulated by a customized dietary intervention [20]. A better knowledge of the inflammatory status enables the personalization of this intervention, as described by Piuri et al. [21] in the context of GDM and in irritable bowel syndrome by Cappelletti et al. [22].

B-cell-activating factor (BAFF) and platelet-activating factor (PAF) are both pro-inflammatory cytokines [23], expressed by many types of cells – especially monocytes, macrophages, dendritic cells, and T cells – with an important role as regulators of inflammation, immune response to infections and tissue homeostasis [24, 25].

BAFF is a member of tumor necrosis factor family and is a costimulator of B-cell maturation and function. The increase of BAFF level is strongly correlated to type of diet, insulin resistance, and fat gain, as well as celiac and autoimmune diseases [26–29].

Moreover, BAFF is an adipocytokine; the dysregulation and the increase of its secretion have important roles, linking the adipose tissue, inflammation, and metabolic disorders [30].

PAF is a phospholipid-derived mediator with an established role in multiple inflammatory states [31]. In addition to its role in platelet aggregation and activation, PAF contributes to allergic and nonallergic inflammatory diseases, such as asthma, anaphylaxis, sepsis, cardiovascular disease – in particular stroke – neurological disease, and malignancy [31, 32].

The absence of PAF, as well as the excess of it, can stimulate fatness and obesity; only a specific right amount can properly work, while when unbalanced it can cause alterations in metabolic regulation [33, 34].

In women with GDM, a significant increase in PAF can be useful for monitoring and potentially help to explain the hidden mechanisms behind metabolic and inflammatory interactions in GDM [21].

Measuring the level of inflammation with an innovative approach, such as blood analyses to evaluate the action of these cytokines, allows to better understand the body's inflammatory status. In this field of research, there is a lack of data on behavior and trend of these proinflammatory cytokines during pregnancy.

The aim of the present study is to evaluate the behavior of these biomarkers, BAFF and PAF, in pregnancies complicated by maternal obesity/diabetes, gestational diabetes, and healthy pregnant women.

Materials and methods

A prospective longitudinal cohort study has been conducted on pregnant women referred to Fondazione Policlinico Universitario A. Gemelli IRCCS of Rome. Maternal anthropometric and anagraphic characteristics, obstetric history, health status information, and maternal and neonatal outcomes have been collected. Inclusion criteria were BMI $\geq$30 kg/m2 and/or type 1–2 diabetes (DM1–DM2) or GDM diagnosed with a routine 75-g oral glucose tolerance test between 24 and

28 weeks of gestation – according to the International Association of Diabetes and Pregnancy Study Groups criteria – age ≤40 years, ability to sign a written informed consent. Healthy women with pre-pregnancy BMI <30 kg/m^2 and age ≤40 years were controls. All patients with age ≥41 years, chronic hypertension, gestational hypertension, autoimmune diseases, smoking during pregnancy, and inability to sign a written informed consent were excluded.

The study protocol has been drawn up in compliance with the European Union's Standards of Good Clinical Practice, with the current revision of the Declaration of Helsinki (1964, and its amendments and subsequent clarification) and it has been approved by the Ethics Committee of the Fondazione Policlinico Universitario A. Gemelli IRCCS of Rome (Protocol number ID 1927).

For each patient, a capillary sample in three different consecutive evaluations – first, second, and third trimesters – has been collected.

Sample collection was performed by finger pricks using a nylon swab for the storage of dried blood (Copan Diagnostics, Inc., Murrieta, CA, USA). Blood samples were reconstituted in 0.15 mL of phosphate buffer saline (pH 7.6), the tubes were vortexed and centrifugated and the supernatants were recovered into new tubes for processing.

All samples were assayed to measure serum inflammatory markers, BAFF and PAF, by an antigen-capture enzyme-linked immunosorbent assay (ELISA) using a specific kit (Human BAFF/BLyS/TNFSF13B Immunoassay Quantikine® ELISA, lower range of detection 0 pg/mL, Cat. No. PDBLYS0B, R&D Systems Inc., Minneapolis, MN, USA; Human Platelet Activating Factor ELISA Kit, lower range of detection 0.313 ng/mL, sensitivity 0.188 ng/mL, Cat. No. E-EL-H2199, Elabscience Houston, TX, USA, respectively) using the Biomek 4000 ELISA microplate liquid reagent dispensing automation tool (Beckman Coulter, Brea, CA, USA) and the EL405LS ELISA microplate automated washing system (Bio Tek Instruments, Winooski, VT, USA). The absorbance of each well was read at a wavelength of 450 nm with a Multiskan FC plate reader (Thermo Scientific, Waltham, MA, USA). The average zero standard optical density was subtracted from all absorbances, and a standard curve was generated using a four-parameter logistic (4-PL) curve fit. The concentration in the test sample was calculated through interpolation along the standard curve by multiplying the result by the dilution factor.

Descriptive analyses were conducted on the whole sample and, separately, for the obese and/or pregestational, gestational diabetic, and healthy women. For the categorical variables, absolute frequency and percentages are reported, while for the numerical ones, the mean and the standard deviation (*SD*) or median and interquartile range (IQR), where appropriate. Differences between groups at baseline were investigated using the chi-square/Fisher's test and ANOVA test, as appropriate.

First, analysis of PAF and BAFF was conducted by performing a graphical representation and evaluating the differences between trimesters and baseline. To take into account time and groups, repeated measures models were conducted and beta with 95% confidence intervals were reported.

Subsequently, analysis evaluating the association/correlation among PAF and BAFF values at baseline with neonatal and maternal outcomes was conducted using ANOVA and correlation tests. Correlation was also calculated for other blood values and rho and *p*-values were reported.

All the analyses were conducted using the software SAS 9.4 and R, significant threshold was set to two-tailed 0.05.

Results

A total of 77 pregnant women have been enrolled in the present study: 42 (54.5%) were healthy pregnant women (control group), 26 (33.8%) patients were obese and/or diabetic at the time of enrollment, and nine (11.7%) developed GDM during the pregnancy.

Maternal characteristics, anthropometric data at basal time, and information about delivery and neonatal outcomes are reported in Table 1.

The mean maternal age at recruitment was 32.35 (±4.12) years, ranging from 22 to 39 years. The median BMI of the healthy women was 20.81 kg/m^2 [IQR 19.84–22.89], 30.41 kg/m^2 [26.22–35.88] for obesity and/or pregestational diabetes and 23.51 kg/m^2 [21.23–24.98] for patients with GDM ($p < .0001$).

Median gestational weight gain for obese patients was 2 kg (±9.6 *SD*).

The only statistically significant variable ($p = .0244$) on obstetric history was a higher rate of recurrent abortion in patients with maternal obesity and/or pregestational diabetes compared to healthy and GDM women (34.62% vs. 11.9% and 11.1%, respectively).

The percentage of cesarean section was higher in patients with maternal obesity and/or pregestational diabetes when compared to others ($p = .0487$). In this subset of patients, there was a very high percentage of patients (58%) with a history of previous C-section not willing to undergo a trial of labor. In one case the

Table 1. Maternal characteristics and maternal and neonatal outcomes.

	All patients ($n = 77$) N (%)	Healthy women ($n = 42$) N (%)	Obese and/or pregestational diabetes ($n = 26$) N (%)	Gestational diabetes ($n = 9$) N (%)
Age, y/o Mean (*SD*)	32.3 (4.1)	31.9 (3.9)	32.35 (4.5)	34.44 (3.3)
Height, cm Mean (*SD*)	163.7 (5.7)	163.8 (5.4)	163.2 (6.4)	164.4 (5.7)
Weight, kg Median [q1–q3]	62 [54; 74]	56 [54; 62]	80.5 [70; 94]	68 [53.00–71.00]
BMI Median [q1–q3]	22.9 [20.3; 27]	20.8 [19.8; 22.9]	30.4 [26.2; 35.9]	23.5 [21.2–25]
Smoke	6 (7.79)	2 (4.76)	2 (7.69)	2 (22.22)
History of miscarriage	15 (19.5)	5 (11.9)	9 (34.6)	1 (11.1)
IVF	2 (2.60)	1 (2.38)	1 (3.85)	0
Type of birth				
Vacuum	6 (8.0)	4 (9.7)	2 (8.0)	0
Vaginal delivery	49 (65.3)	29 (70.7)	11 (44.0)	9 (100)
C-section	20 (26.7)	8 (19.5)	12 (48.0)	0
Neonatal sex				
Female	32 (42.7)	15 (36.6)	12 (48.0)	5 (55.6)
Male	43 (57.3)	26 (63.4)	13 (52.0)	4 (44.4)
Neonatal weight, g Mean (*SD*)	3247.3 (394.6)	3250.6 (378.1)	3209.4 (459.1)	3337.8 (282)
Apgar 1 min				
≤7	3 (4.0)	1 (2.4)	1 (4.0)	1 (11.1)
>7	72 (96.0)	40 (97.6)	24 (96.0)	8 (88.9)
Apgar 5 min				
≤7	1 (1.33)	1 (2.44)	0	0
>7	74 (98.67)	40 (97.56)	25 (100)	9 (100)

Table 2. BAFF and PAF values in each trimester of pregnancy.

	All patients ($n = 77$)		Healthy women ($n = 42$)		Obese and/or pregestational diabetes ($n = 26$)		Gestational diabetes ($n = 9$)	
	PAF							
Baseline	70	6.83 (6.06)	39	7.33 (6.72)	22	7.08 (5.65)	9	4.03 (2.85)
T1 vs. T0	60	−0.32 (3.66)	35	−0.54 (3.65)	18	−0.15 (4.39)	7	0.33 (1.16)
T2 vs. t0	43	0.25 (5.78)	23	−0.31 (6.02)	15	1.2 (6.42)	5	−0.04 (1.26)
	BAFF							
Baseline	77	0.35 (0.15)	42	0.38 (0.16)	26	0.3 (0.12)	9	0.33 (0.11)
T1 vs. T0	66	0.01 (0.16)	38	−0.01 (0.16)	21	0.04 (0.15)	7	0.03 (0.16)
T2 vs. t0	49	−0.02 (0.2)	26	−0.08 (0.19)	18	0.05 (0.21)	5	0.06 (0.18)

T0: first trimester; T1: second trimester; T2: third trimester.

indication for C-section was breech presentation. In the remaining cases (four patients, 33%) failure of induction occurred.

Moreover, all newborns had a good APGAR value (≥7, both after 1 and 5 min), except for two newborns at 1 min and a newborn with APGAR <7, both after 1 and 5 min, whose mother was enrolled in the control group, with cesarean birth for fetal distress and hospitalization in neonatal intensive care.

Neonatal emogasanalysis values have been collected in 52 cases and no pathological pH values have been reported. Median pH value was 7.31 (±0.07 *SD*) and median base excess was −4.1 (±1.1 *SD*). In the remaining cases, the umbilical cord collapsed after birth and emogasanalysis was not technically feasible.

Table 2 provides BAFF and PAF levels, during the three trimesters of pregnancy, separately for patients' groups. Mean basal PAF in the whole population measures 6.83 ($SD = 6.06$), it slightly decreases at T1 (-0.32 ± 3.66) and slightly increases at T2 (0.25 ± 5.78). An opposite behavior is noted for BAFF. None of these differences were statistically significant ($p > .5$). Instead, when the whole sample was divided into three different groups (healthy women/gestational diabetes/obese and/or pregestational diabetes), PAF values seemed lower in patients with GDM (4.03 ± 2.85) when compared to other groups (7.33 ± 6.72 and 7.08 ± 5.65, respectively, for healthy women and obese/pregestational diabetic patients).

These results were confirmed when repeated models were performed: among pregnant women who developed GDM, PAF values were significantly lower at −4.08 [95% CI −6.32, −1.85] when compared to healthy women. No statistically significant results were observed for BAFF values.

Correlation analysis showed that BAFF and PAF were positively correlated ($\rho = 0.07$, 0.07) with neonatal weight but did not reach statistical significance ($p > .50$). Correlation with serum maternal levels was also performed and the only statistically significant positive correlation was observed among BAFF levels with thyroid-stimulating hormone (TSH) levels ($r = 0.33$, $p = .0071$).

Discussion

Measuring proinflammatory biomarkers represents an innovative approach to outline the inflammatory status in obese and diabetic patients.

This is the first study, to the best of our knowledge, in which the role of two proinflammatory cytokines – BAFF and PAF – has been analyzed in obese and/or diabetic patients compared to healthy pregnant controls, evaluating their behavior longitudinally, in each trimester of pregnancy.

Regarding the behavior of PAF, no significant differences were observed in the trend of its levels, both in healthy, obesity, and/or pregestational diabetes and GDM women. In particular, there was an irregular trend in the healthy women and a slight decrease in its values in the exposed patients.

Focusing on BAFF levels, there was an irregular trend between the three trimesters, but the data in the third trimester were lower than basal time, in both groups.

So, in cases, in the third trimester of pregnancy, both PAF and BAFF levels were lower than in the first trimester.

As already known in the literature, BAFF and PAF levels are strongly correlated to the type of diet [21, 23, 35]. All the subjects enrolled in the present study were referred to a third-level center with a high-risk pregnancy unit department and were meticulously followed during pregnancy for their pathology (obesity and/or diabetes) by a multidisciplinary team composed of experienced obstetricians and diabetologists, in order to reach an optimal glyco-metabolic balance with an adequate and personalized dietary regimen, eventually combined with insulin therapy if needed. It's interesting to note that in this cohort of high-risk patients, no major maternal and feto-neonatal complications – such as macrosomia, intrauterine death, shoulder dystocia, IUGR, or severe perineal lacerations at birth – have been observed. The glyco-metabolic balance was defined as an optimal glycemic control achieved in self-reported four measurements registered during the day (fasting glucose $<$90 mg/dL and $<$130 mg/dL 1 h after breakfast, lunch, and dinner).

In the sub-group of pregnant women who developed GDM, PAF values were lower when compared to healthy obese and pre-pregnancy diabetic patients.

In support of these results, previous works that investigated the connection of proinflammatory cytokines with obesity and diabetes, have highlighted the positive role of PAF in reducing the risk of gaining weight [33]. This concept was confirmed in Brazilian research [34] that emphasized the way in which PAF works: the absence of this cytokine, as well as the excess of it, can stimulate fatness and obesity, so only the right PAF concentration is protective. A typical so-called "U" relationship, in which only a specific amount can properly work and can be defined as protective. The same thing also happens at a metabolic level: PAF acts in an anti-adipose sense only if in the right concentrations, while, when unbalanced, it can cause alterations in metabolic regulation.

It is also known that pregnant women with GDM have an increased plasma PAF acetylhydrolase (PAF-AH) activity – the enzyme that hydrolases PAF in the circulation – compared to normal pregnant women [36, 37]. These findings suggest that pregnant women with GDM may present a chronic inflammatory status, in which the higher PAF-AH activity could result in a consequent decrease of PAF levels compared to controls, and that could be the reason for lower PAF levels in this subset of patients.

In addition to this, an analysis performed in this work demonstrated a statistically significant correlation between BAFF and TSH levels. The thyroid gland also plays a key role in metabolism regulation. Previous studies demonstrated that proinflammatory cytokines – such as BAFF – could be the concause of thyroid autoimmune dysfunction [29, 38–43]. It is also known that the production of BAFF is strongly linked to food-induced inflammation; so a wrong diet can stimulate the increase in BAFF, which can induce and maintain the various forms of autoimmune thyroiditis over time. Thus, the authors conclude that a customized diet can help rebalance and control the thyroid gland function, rather than using hormone replacement therapy alone [44, 45].

The reported results cannot be considered conclusive due to the limited number of patients, but open an interesting window for future research in the area of "metainflammation," especially in the setting of gestational diabetes.

Conclusions

This study supports the involvement of metabolic biomarkers, like BAFF and PAF, in the mechanisms related

to pregnancy complications. A customized dietary intervention could normalize the changes in proinflammatory biomarkers, leading to the creation and maintenance of an adequate intrauterine environment that can guarantee normal fetal development. Improving a good metabolic environment for obese and diabetic pregnant women could break the vicious cycle connecting inflammation, oxidative stress, and metabolic disorders.

In conclusion, the identification of proinflammatory cytokines linked to metabolic distress in maternal obesity, pre-pregnancy diabetes, and GDM can lead to better counseling and management during pregnancy, in order to improve maternal and neonatal outcomes.

Ethics statement

This study was performed in line with the principles of the Declaration of Helsinki. Ethics approval for this study was obtained from the Ethics Committee of Catholic University of the Sacred Heart University in May 2018 (ID 1927).

Author contributions

NC: conception, data collection, analysis, interpretation, and drafting. CA1 and DAD: data collection, analysis, interpretation, and drafting. AC: data analysis, interpretation, and drafting. BK and CA2: data collection, analysis, and interpretation. FA and TC: data collection and analysis. CM: data analysis and interpretation. SAF: data analysis, interpretation, and critical revision. LA: critical revision.

Disclosure statement

The authors declare no conflict of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability statement

The authors agree to make data and materials supporting the results or analyses available upon reasonable request.

References

[1] American College of Obstetricians and Gynecologists. ACOG Committee opinion no. 549: obesity in pregnancy. Obstet Gynecol. 2013;121(1):213–217.

[2] Pantham P, Aye ILMH, Powell TL. Inflammation in maternal obesity and gestational diabetes mellitus. Placenta. 2015;36(7):709–715. doi: 10.1016/j.placenta.2015.04.006.

[3] Renault KM, Norgaard K, Nilas L, et al. The treatment of obese pregnant women (TOP) study: a randomized controlled trial of the effect of physical activity intervention assessed by pedometer with or without dietary intervention in obese pregnant women. Am J Obstet Gynecol. 2014;210(2):134.e1–134.e9. doi: 10.1016/j.ajog.2013.09.029.

[4] World Health Organization. WHO report. 2022. Available from: http://www.who.int/mediacentre/factsheets/fs311/en/

[5] Poston L, Caleyachetty R, Cnattingius R, et al. Preconceptional and maternal obesity: epidemiology and health consequences. Lancet Diabetes Endocrinol. 2016;4(12):1025–1036. doi: 10.1016/S2213-8587(16)30217-0.

[6] Neri C, Di Cesare C, Labianca A, et al. Obesity in pregnancy as a model to identify women at risk for later metabolic syndrome. Gynecol Endocrinol. 2018;34(1):28–31. doi: 10.1080/09513590.2017.1342792.

[7] Jones CW. Gestational diabetes and its impact on the neonate. Neonatal Netw. 2001;20(6):17–23. doi: 10.1891/0730-0832.20.6.17.

[8] Hales CN, Barker DJ. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. 1992. Int J Epidemiol. 2013;42(5):1215–1222. doi: 10.1093/ije/dyt133.

[9] Krakowiak P, Walker CK, Bremer AA, et al. Maternal metabolic conditions and risk for autism and other neurodevelopmental disorders. Pediatrics. 2012;129(5):e1121–e1128. doi: 10.1542/peds.2011-2583.

[10] Huda SS, Brodie LE, Sattar N. Obesity in pregnancy: prevalence and metabolic consequences. Semin Fetal Neonatal Med. 2010;15(2):70–76. doi: 10.1016/j.siny.2009.09.006.

[11] Taddei S, Ghiadoni L, Salvetti G, et al. Obesity and endothelial dysfunction. G Ital Cardiol (Rome). 2006;7(11):715–723.

[12] Gregor MF, Hotamisligil GS. Inflammatory mechanisms in obesity. Annu Rev Immunol. 2011;29(1):415–445. doi: 10.1146/annurev-immunol-031210-101322.

[13] Aye IL, Lager S, Ramirez VI, et al. Increasing maternal body mass index is associated with systemic inflammation in the mother and the activation of distinct placental inflammatory pathways. Biol Reprod. 2014;90(6):129.

[14] Kleiblova P, Dostalova I, Bartlova M, et al. Expression of adipokines and estrogen receptors in adipose tissue and placenta of patients with gestational diabetes mellitus. Mol Cell Endocrinol. 2010;314(1):150–156. doi: 10.1016/j.mce.2009.08.002.

[15] Hauguel-de Mouzon S, Guerre-Millo M. The placenta cytokine network and inflammatory signals. Placenta. 2006;27(8):794–798.

[16] Jansson N, Rosario FJ, Gaccioli F, et al. Activation of placental mTOR signaling and amino acid transporters in obese women giving birth to large babies. J Clin Endocrinol Metab. 2013;98(1):105–113. doi: 10.1210/jc.2012-2667.

[17] Jansson T, Ekstrand Y, Bjorn C, et al. Alterations in the activity of placental amino acid transporters in pregnancies complicated by diabetes. Diabetes. 2002;51(7):2214–2219. doi: 10.2337/diabetes.51.7.2214.

[18] Jones HN, Jansson T, Powell TL. IL-6 stimulates system A amino acid transporter activity in trophoblast cells through STAT3 and increased expression of SNAT2. Am J Physiol Cell Physiol. 2009;297(5):C1228–C1235. doi: 10.1152/ajpcell.00195.2009.

[19] Jones HN, Woollett LA, Barbour N, et al. High-fat diet before and during pregnancy causes marked up-regulation of placental nutrient transport and fetal overgrowth in C57/BL6 mice. FASEB J. 2009;23(1):271–278. doi: 10.1096/fj.08-116889.

[20] Jarvie E, Hauguel-de-Mouzon S, Nelson SM, et al. Lipotoxicity in obese pregnancy and its potential role in adverse pregnancy outcome and obesity in the offspring. Clin Sci. 2010;119(3):123–129. doi: 10.1042/CS20090640.

[21] Piuri G, Basello K, Rossi G, et al. Methylglyoxal, glycated albumin, PAF, and TNF-α: possible inflammatory and metabolic biomarkers for management of gestational diabetes. Nutrient. 2020;12(2):479. doi: 10.3390/nu12020479.

[22] Cappelletti M, Tognon E, Vona L, et al. Specific serum IgG and symptom reduction with a personalized, unrestricted-calorie diet of six weeks in irritable bowel syndrome (IBS). Nutr Metab. 2020;17(1):101. doi: 10.1186/s12986-020-00528-x.

[23] Speciani AF, Piuri G. Measuring biomarkers for an innovative personal food profile. J Am Coll Nutr. 2015;34(Suppl 1):34–38. doi: 10.1080/07315724.2015.1080109.

[24] Schneider P, MacKay F, Steiner V, et al. BAFF, a novel ligand of the tumor necrosis factor family, stimulates B cell growth. J Exp Med. 1999;189(11):1747–1756. doi: 10.1084/jem.189.11.1747.

[25] Sutherland APR, Mackay F, Mackay CR, et al. Targeting BAFF: immunomodulation for autoimmune diseases and lymphomas. Pharmacol Ther. 2006;112(3):774–786. doi: 10.1016/j.pharmthera.2006.06.002.

[26] Cheema GS, Roschke V, Hilbert DM, et al. Elevated serum B-lymphocyte stimulator levels in patients with systemic immune based rheumatic diseases. Arthritis Rheum. 2001;44(6):1313–1319. doi: 10.1002/1529-0131(200106)44:6<1313::AID-ART223>3.0.CO;2-S.

[27] Ritterhouse LL, Crowe SR, Niewold TB, et al. B lymphocyte stimulator levels in systemic lupus erythematosus: higher circulating levels in African American patients and increased production after influenza vaccination in patients with low baseline levels. Arthritis Rheum. 2011;63(12):3931–3941. doi: 10.1002/art.30598.

[28] Fabris M, Visentini D, De Re V, et al. Elevated b cell-activating factor of the tumour necrosis factor family in coeliac disease. Scand J Gastroenterol. 2007;42(12):1434–1439. doi: 10.1080/00365520701452225.

[29] Steri M, Orrù V, Idda ML, et al. Overexpression of the cytokine BAFF and autoimmunity risk. N Engl J Med. 2017;376(17):1615–1626. doi: 10.1056/NEJMoa1610528.

[30] Kim YH, Choi BH, Cheon HG, et al. B cell activation factor (BAFF) is a novel adipokine that links obesity and inflammation. Exp Mol Med. 2009;41(3):208–216. PMID: 19293640. PMC2679246. doi: 10.3858/emm.2009.41.3.024.

[31] Upton JEM, Grunebaum E, Sussman G, et al. Platelet activating factor PAF: a mediator of inflammation. Biofactors. 2022;48(6):1189–1202. PMID 36029481 doi: 10.1002/biof.1883.

[32] Ashraf MA, Nookala V. Biochemistry of platelet activating factor. Treasure Island (FL): StatPearls Publishing; 2022.

[33] Yamaguchi M, Matsui M, Higa R, et al. A platelet-activating factor (PAF) receptor deficiency exacerbates diet-induced obesity but PAF/PAF receptor signaling does not contribute to the development of obesity-induced chronic inflammation. Biochem Pharmacol. 2015;93(4):482–495. doi: 10.1016/j.bcp.2014.12.022.

[34] Filgueiras LR, Koga MM, Quaresma PG, et al. PAFR in adipose tissue macrophages is associated with anti-inflammatory phenotype and metabolic homeostasis. Clin Sci. 2016;130(8):601–612. doi: 10.1042/CS20150538.

[35] Kang SA, Keener AB, Jones SZ, et al. IgG-immune complexes promote B cell memory by inducing BAFF. J Immunol. 2016;196(1):196–206. doi: 10.4049/jimmunol.1402527.

[36] Gao Q, He G-L, Zhang L, et al. Activity and distribution of plasma platelet-activating factor acetylhydrolase in women with gestational diabetes mellitus and their neonates. Diabetes Metab Res Rev. 2016;32(6):634–642. doi: 10.1002/dmrr.2782.

[37] Derbent A, Kargili A, Koca C, et al. Serum platelet-activating factor acetylhydrolase activity: relationship with metabolic syndrome in women with history of gestational diabetes mellitus. Gynecol Endocrinol. 2011;27(2):128–133. doi: 10.3109/09513590.2010.487612.

[38] Mackay F, Schneider P. Cracking the BAFF code. Nat Rev Immunol. 2009;9(7):491–502. PMID: 19521398 doi: 10.1038/nri2572.

[39] Liu S, Miao J-J, Zhou X, et al. High levels of thyroid hormones promote recurrence of Graves' disease via overexpression of B-cell-activating factor. J Clin Lab Anal. 2022;36(10):e24701. PMID: 36097969 PMCID: PMC9550970 doi: 10.1002/jcla.24701.

[40] Lin JD, Wang YH, Fang WF, et al. Serum BAFF and thyroid autoantibodies in autoimmune thyroid disease. Clin Chim Acta. 2016;462:96–102. PMID: 27616625 doi: 10.1016/j.cca.2016.09.004.

[41] Lane LC, Allinson KR, Campbell K, et al. Analysis of BAFF gene polymorphisms in UK graves' disease patients. Clin Endocrinol. 2019;90(1):170–174. PMID: 30281845 doi: 10.1111/cen.13872.

[42] Vannucchi G, Covelli D, Currò N, et al. Serum BAFF concentrations in patients with Graves' disease and orbitopathy before and after immunosuppressive therapy. J Clin Endocrinol Metab. 2012;97(5):E755–E759. PMID: 22399512. doi: 10.1210/jc.2011-2614.

[43] Campi I, Tosi D, Rossi S, et al. B cell activating factor (BAFF) and BAFF receptor expression in autoimmune and nonautoimmune thyroid diseases. Thyroid. 2015;25(9):1043–1049. PMID: 26214745 doi: 10.1089/thy.2015.0029.

[44] Arslan Lied G, Lillestøl K, Valeur J, et al. Intestinal B cell-activating factor: an indicator of non-IgE-mediated hypersensitivity reactions to food? Aliment Pharmacol Ther. 2010;32(1):66–73. PMID20353497 doi: 10.1111/j.1365-2036.2010.04314.x.

[45] Gu L, Yang J, Gong Y, et al. Lower free thyroid hormone levels are associated with high blood glucose and insulin resistance; these normalize with metabolic improvement of type 2 diabetes. J Diabetes. 2021;13(4):318–329. PMID: 32981234 doi: 10.1111/1753-0407.13118.