Pregnancy Hypertension 13 (2018) 58–61

Contents lists available at ScienceDirect

Pregnancy Hypertension

journal homepage: www.elsevier.com/locate/preghy

Maternal Serum B Cell activating factor in hypertensive and normotensive pregnancies

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ARTICLE INFO

Keywords:
Pre-eclampsia
Fetal growth restriction
BAFF
Pulse wave velocity
Arterial function

ABSTRACT

Objectives: The objective of this study was the analysis of B-Cell Activating Factor (BAFF) levels in pregnancies affected by PE, and in pregnancies affected by fetal growth restriction without Hypertensive disorders and its possible correlation with pulse wave velocity and cardiac output.
Study design: Prospective study of 69 women at 24–40 weeks gestation. Haemodynamic function was assessed in those with Pre-eclampsia (PE, n = 19), fetal growth restriction (FGR, n = 10) and healthy pregnancies (n = 40). Maternal venous BAFF levels at recruitment were measured using ELISA. We analysed the relationship between BAFF and cardiac output (CO), and BAFF and PWV (pulse wave velocity); the gold standard for assessing arterial stiffness. PWV was measured with an oscillometric device and CO using inert gas rebreathing technique. PWV and CO were converted to gestation adjusted indices (z scores).
Main outcome measures: The association between BAFF levels in PE and FGR, and the relationship of BAFF with PWV and CO.
Results: BAFF was higher in PE (p = 0.03) but not in FGR (p = 0.83) when compared to healthy pregnancies. There was a positive correlation between BAFF levels and z score PWV (r = 0.25, p = 0.04), but not CO (r = −0.01, p = 0.91). BAFF levels did not change with gestational age. (r = 0.012, p = 0.925).
Conclusions: These findings provide evidence of a possible contribution of BAFF to both maternal inflammation and arterial dysfunction associated with PE. Though no relationship was found with another disorder of placentation: normotensive FGR, this condition is not thought to be associated with maternal inflammation.

1. Introduction

Pre Eclampsia (PE) is a multi-system disorder that affects the pregnant mother and sometimes the fetus. The underlying pathophysiology is not fully understood, though the most widely accepted hypothesis relates to inadequate physiologic transformation of the uterine spiral arteries secondary to poor trophoblastic invasion of maternal tissues. This leads to release of placental factors into the maternal circulation with endothelial damage caused by pro-inflammatory cytokines derived from visceral fat, dysbiosis and placental oxidative stress. Though the link between inflammation and abnormal vascular function is hypothesized, there is limited mechanistic evidence to support this [1,2].

B-cell activating factor (BAFF) is a cytokine that belongs in the Tumour Necrosis Factor (TNF) family, with a role in proliferation and differentiation of B cells. BAFF is an immune-stimulant and in many autoimmune conditions, BAFF levels are elevated. Previous studies in rat models have demonstrated the role of B cell involvement in PE via activation of pro-inflammatory cytokines [3]. More recently, elevated first trimester BAFF levels have been shown to be associated with hypertensive disease in later pregnancy [4]. An increase in BAFF leads to elevated B cells and subsequently autoantibody and immunoglobulin secretion which is associated with vascular and cardiac remodelling in hypertension [5]. Moreover, BAFF could also be involved in the development of human placenta and functions as an autocrine and paracrine hormone towards local placental cells [6]. However, it is unclear as to whether BAFF is implicated in the disease process of hypertensive pregnancies or whether it may have a role as a biomarker. Hypertension

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https://doi.org/10.1016/j.preghy.2018.05.001
Received 30 November 2017; Received in revised form 18 April 2018; Accepted 2 May 2018
Available online 03 May 2018

in pregnancy is associated with arterial dysfunction. Large artery stiffness is evidenced by higher pulse wave velocity when compared to normotensive pregnancies [7]. Pulse wave velocity (PWV) is the non-invasive gold standard measure of arterial stiffness and is predictive of future cardiovascular risk [8]. We sought to analyse BAFF values in pregnancies affected by PE, and those affected by fetal growth restriction; and to investigate the relationship between BAFF and pulse wave velocity and cardiac output in normotensive and hypertensive pregnancies.

2. Methods

In this prospective study from April 2015 through to April 2017, 69 women between 24 and 40 weeks gestation were recruited. They were subdivided to three groups – pre-eclampsia (PE), fetal growth restriction (FGR) and those with healthy pregnancies. Those with multiple pregnancies, chronic medical problems, known underlying cardiovascular conditions and fetal anomalies were excluded. PE was defined as new onset hypertension after 20 weeks with blood pressure of > 140/90 mmHg and urine protein creatinine ratio of > 30. Fetal growth restriction was defined as fetal abdominal circumference < 10th centile and umbilical Doppler pulsatility index (PI) > 95th centile on ultrasound scan [9–11]. None of the women in the PE group satisfied the diagnosis for FGR and none of those with FGR satisfied the criteria for PE, hence the groups were mutually exclusive.

Arterial function was assessed by the Vicorder system (Skidmore Medical, Bristol, UK). Whilst lying in the left lateral supine position, three cuffs were attached to the left upper arm, the left upper thigh and over the left carotid pulse respectively. The linear carotid femoral distance was measured with a standard measuring tape. Pulse wave velocity was recorded. With the patient standing upright, cardiac output was measured with Innocor (Innovision A/S, Denmark) [12,13], a non-invasive inert gas rebreathing technique previously validated against thermodilution [14].

Maternal venous blood was obtained from peripheral venepuncture and serum stored at −80 Celsius. Upon completion of all sample collection, samples were thawed and pipetted in 50 µl on dried blood spot cards (50 µl per spot), then let air-dry 30 min. Following that, 6 mm punch circles were collected in 1.5 ml tubes and PBS was then added for elution (25 µl per 6 mm circle). Tubes were vortexed and the supernatants were recovered into new tubes for processing. BAFF was measured in triplicate according to the corresponding ELISA kit protocol (R &D Systems, Minneapolis, USA). The manufacturer reports lower limits of detection of 2.68 pg/ml with intra-assay precision of 5.7% and inter-assay precision of 10.5%.

The main outcome measures was the association between BAFF levels in PE and FGR. Descriptive non parametric statistics was applied for basic demographic and Kruskal-Wallis p-value was used to test differences between groups. BAFF concentration in PE, FGR and healthy pregnancies was analysed by a univariate test and reported as box and whiskers plot.

3. Results

Nineteen patients with pre-eclampsia (PE) and ten patients with fetal growth restriction (FGR) were recruited with forty cases of healthy pregnancies. Kruskal-Wallis test showed no statistically significant differences between maternal age and gestational age at recruitment [Table 1].

We found that BAFF levels were higher in women with PE (mean 0.22 ng/ml, SD 0.06) compared to healthy controls (0.18 ng/ml, SD 0.06 – p = 0.03). BAFF levels were no different in women with normotensive FGR (0.18 ng/ml, SD 0.06) (p = 0.83) [Chart 1]. There was no correlation between BAFF levels and gestation of sampling within this third trimester cohort (r = 0.012, p = 0.925).

PWV (Z score corrected for gestation) was higher in PE (1.049, SD 1.49) when compared to healthy controls (0.039, SD 0.879) (p = 0.0018). There was no difference in PWV between FGR cases and healthy controls. (p = 0.15) There was a correlation between PWV (Z score corrected for gestation) and BAFF levels in the cohort (r = 0.25, p = 0.04) [Chart 2].

There was no significant difference in CO (Z score corrected for gestation) between PE (0.41, SD 1.65) and healthy controls (−0.01, SD 1.09) (p = 0.25). Furthermore, CO did not correlate with BAFF levels (r = −0.01, p = 0.91).

Table 1
Baseline demographic characteristics of the study population.

	Healthy pregnancies	FGR	PE	Kruskal-Wallis p value
Number of cases	40	10	19	–
Maternal Age, Median (IQR)	34 (31–36)	35 (31–39)	32 (27.5–36.5)	0.10
Nulliparous, n (%)	23 (56%)	5 (50%)	13 (68%)	
Gestational Age, Median (IQR)	32 (28–36)	31.5 (28–34)	35 (26.5–36.5)	0.50
Birth weight Z score, mean (SD)	0.44 (0.85)	−2.70 (0.94)	1.06 (1.96)	
Caesarean Section, n (%)	12 (30%)	7 (70%)	11 (57.8%)	

4. Discussion

BAFF is a key modulator of B cell function and was higher in PE when compared to healthy pregnancies or FGR. PWV was higher in PE than FGR and healthy controls; in the whole group there is a significant positive association between PWV and BAFF. This suggests a plausible link might exist between inflammation and arterial dysfunction particularly as inflammation is thought to be related specifically to pre-eclampsia but not normotensive FGR. The relationship between PWV and BAFF is of potential importance as PWV is a known marker of cardiovascular risk in hypertension and has been used as a predictor of future cardiovascular mortality [15]. Our findings support those previously reported where arterial stiffness is found to be elevated in pre-eclampsia [7]. There is conflicting data regarding cardiac output changes in pre-eclampsia, some studies suggesting higher CO and others low CO [12,16,17]. This may explain the lack of association between CO and BAFF in our cohort which was not sufficiently large to subdivide for different clinical phenotypes of preeclampsia [18].

BAFF plays a key role in regulating immune system. This cytokine, belonging to the TNF family, has pro-inflammatory action [19] and modulates many functions of the immune system and in particular of B cells. Autoimmune diseases including haemolytic anaemia, systemic lupus erythematosus and rheumatoid arthritis have been associated with an increase in BAFF serum levels [20–22]. In addition, BAFF plays a role in the development of the human placenta [6] and this activity is probably mediated by its action on the endothelium [23]. Other studies hypothesize the role of this inflammatory molecule in the pathogenesis of atherosclerosis [24] and the mechanisms leading to hypertension through a greater production of angiotensin II [25].

Though inflammation has been much discussed as underlying the pathogenesis of PE [26], there is little understanding of the mechanism by which this might be and how inflammation affects endothelial function. PE and FGR are thought to be placental disorders [27,28], however it is becoming clear that they are associated with different cardiovascular phenotypes [29,30]. Through BAFF's key role in B cell activation [31] and a recent report of its possible use as an early biomarker of PE [4], it is a plausible candidate linking inflammation and the arterial dysfunction that characterizes PE but not the placental insufficiency that characterizes FGR.