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Prevalence of low antithrombin levels in preeclamptic women and perinatal outcome

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ABSTRACT

Objective. The aim of this study is to evaluate the prevalence of low antithrombin levels in our population in order to assess an intervention trial feasibility.
Methods. This is a retrospective study. A database was created by using queries to find out medical records of patients requiring hospitalization for preeclampsia or gestational hypertension or superimposed preeclampsia to chronic hypertension at Modena University Hospital between June 2015 and July 2019.
Results. We screened 11845 deliveries. Overall, 221 (1.9%) cases of preeclampsia were identified. Antithrombin level was available for 201 women, thus included in the analysis. Median antithrombin value was 87% (IQ range: 77-98). The prevalence of low antithrombin levels was 9%. Antithrombin < 80% was found in 21% of the subjects. The remnant showed normal values. Median antithrombin was significantly lower in severe respect with mild preeclampsia (83% ± 14 *vs* 89% ± 14, p = 0.003). The rate of small for gestational age was significantly higher in low antithrombin levels group (44.4% *vs* 22.4%, p = 0.042). Considering mean values, antithrombin levels were also significantly lower in case of small for gestational age (84% ± 14 *vs* 89% ± 14; p = 0.040).
Conclusions. In our population, low antithrombin levels (1 in 10 patients) were associated with severity of preeclampsia, namely with small for gestational age babies. Data suggest this subpopulation as a better target for trials assessing the efficacy of antithrombin supplementation.

SOMMARIO

Obiettivo. Lo scopo di questo studio è valutare la prevalenza di bassi livelli di antitrombina nella popolazione da noi studiata con lo scopo di valutare un trial di intervento.
Metodi. Si tratta di uno studio retrospettivo. È stato creato un database attingendo i dati dalle cartelle cliniche delle pazienti che sono state ricoverate per preeclampsia semplice o sovraimposta, ipertensione gestazionale presso l'Azienda Ospedaliero Universitaria di Modena dal giugno 2015 al luglio 2019.
Risultati. Sono state analizzate 11845 cartelle cliniche. Sono stati identificati 221 casi di preeclampsia (1.9%), i livelli di antitrombina erano stati dosati in 201 casi con un valore mediano di 87% (intervallo QI:77-98). La prevalenza di bassi livelli di antitrombina era del 9%. Livelli di antitrombina inferiori a 80% sono stati riscontrati nel 21% dei casi, mentre i restanti presentavano valori normali. I valori di antitrombina mediana erano significativamente più bassi in caso di preeclampsia grave (83% 14 *vs* 89% 14; p < 0.003).
La percentuale di neonati piccoli per l'età gestazionale era significativamente più alta nel gruppo con bassi livelli di antitrombina (44.4% *vs* 22.4%, p < 0,042) e i valori medi di antitrombina erano più bassi in queste pazienti (84% ± 14 *vs* 89 ± 14; p < 0,003)
Conclusioni. Nella nostra popolazione bassi livelli di antitrombina (1 su 10 pazienti) erano associati alla gravità della preeclampsia, in particolare se complicata dalla nascita di neonati piccoli per età gestazionale. I dati suggeriscono che questa popolazione rappresenta il miglior target per studi che vadano a valutare l'utilizzo di antitrombina.

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Key words
Antithrombin; gestational hypertension; preeclampsia; small for gestational age; chronic hypertension.

INTRODUCTION

Preeclampsia (PE) is a multifactorial disease, characterized by abnormal vascular response to placentation that is associated with increased systemic vascular resistance, enhanced platelet aggregation, activation of the coagulation system and endothelial dysfunction (1). The main pathological feature is the incomplete transformation of the spiral arteries, leading to hypoperfusion of the placenta and insufficient nutrient supplies to the fetus, and resulting in impaired vascular function and fetal growth restriction. Endothelial disfunction is involved in the pathogenesis of preeclampsia. Endothelial damage triggers a thrombotic microangiopathy with platelets and coagulation factors consumption (2).
From a clinical point of view, PE is classified in two distinct subtypes based on the timing of onset: early-onset (< 34 weeks) and late-onset preeclampsia (≥ 34 weeks). In a population-based study the overall preeclampsia rate was 3.1% with an incidence of early-onset and late-onset preeclampsia respectively of 0.38% and 2.72%. Early-onset preeclampsia confers a higher risk of maternal complications and perinatal mortality (3). Antithrombin (AT) is a glycoprotein involved in both coagulation system and inflammatory processes. AT is the principal inhibitor of thrombin and factor Xa, involved in both extrinsic and intrinsic coagulation pathways. When AT binds thrombin formed the irreversible thrombin-antithrombin (TAT) complex. Moreover, AT binds heparin-like glycosaminoglycans on the surface of endothelial cells, and promotes endothelial cell release of prostacyclin, which impacts inflammatory processes (4).
AT normally decreases during the third trimester of pregnancy and falls during postpartum period. In early-onset preeclampsia there are significantly reduced antithrombin levels, probably reflecting increased consumption, impaired liver function and urinary loss (5, 6).
In a previous observational prospective study, we reported that in patients with PE, a progressive reduction of AT values is associated with deteriorating clinical conditions leading to indication to delivery (7). Since AT reduction is a result of increased consumption due to the hypercoagulable state, and decreased hepatic synthesis (8), it has been speculated that AT administration could restore the AT levels. Therefore, clinical trials have been designed to assess if the AT administration in women with severe PE was associated with prolongation of pregnancy, improvement in fetal growth and maternal hypertension (9-12).
Our aim is thus to evaluate the prevalence of low AT levels in our population in order to assess an intervention trial feasibility.

METHODS

This is a retrospective study and database was created by using queries to find out medical records of patients requiring hospitalization for PE or gestational hypertension or superimposed PE to chronic hypertension at Modena University Hospital which served as Hub for the Modena area. Each patient's file has been sorted and checked for consistency by two of us. Patients with diagnoses that falls within the ISSHP criteria (13) have been included. PE occurring at less than 34 weeks of gestation was identified as early-onset disease, whereas PE that occurred at 34 weeks or later was labeled late-onset disease. Severe PE was defined by blood pressure higher than 160/110 mmHg or signs and symptoms of organ involvement. Low AT levels were considered for AT < 70%.
Blood samples were collected immediately before birth in cases of expedite delivery till 2 days before for women already admitted to the Hospital. Patients received routine treatment with antenatal corticosteroids.

For every subject we collected information on age, ethnicity, body mass index, obstetric history, need of assisted reproductive technology (ART), small for gestational age (SGA) defined as birthweight ≤ 10th centile (corrected for gender and gestational age) diagnosis, gestational age at admission, gestational age at delivery, mode of delivery, AT levels before delivery, blood chemistry and coagulation profile. Outcomes of pregnancy were also collected. Statistical analysis was performed by using SPSS® Statistics software, version 19. Continuous variables were evaluated with Student t-test while categorical variables with chi-square test. AT levels distribution was analyzed as median and interquartile range, and comparison between groups was evaluated with U Mann-Whitney Test. A logistic regression analysis was performed to evaluate possible factors associated with low AT levels. Statistical significance was considered for p value less than 0.05.

RESULTS

We screened 11845 deliveries occurring between June 2015 and July 2019. Overall, 221 (1.9%) cases of preeclampsia were identified. AT level in blood samples was available for 201 women which were included in the analysis.

Sociodemographic characteristics are described in **table I**. According to AT, there were no differences except for the higher rate of chronic hypertension among patients with normal AT levels.

We found no differences between normal AT group and low AT group in gestational age (GA) at admission as well as for other clinical features such as systolic and diastolic blood pressure at admission, rate of early onset PE or severe PE (**table II**).

Median AT value was 87% (IQ range: 77-98). Overall, the prevalence of low AT levels, considering AT < 70% as a threshold, was 9%. AT < 80% was found in 21% of the subjects. Seventy percent of women had normal AT levels (AT ≥ 80%). Other laboratory tests did not differ between normal AT and low AT group, except for higher LDH levels in low AT group (**table III**).

Median AT values were not different in early onset PE (86% ± 13) *vs* late onset PE (88% ± 14) and no significant differences were found in AT < 70% levels between early onset (7.4%) and late onset PE (9.5%). Considering the severity of clinical PE, median AT values were significantly lower in severe PE respect with mild PE (83% ± 14 *vs* 89% ± 14, p = 0.003), but the rate of AT < 70% levels did not differ (13.7% *vs* 7.3%). HELLP syndrome occurred in 6/201 cases (3.0%), 2 of them (33.3%) had AT < 70%. AT levels were slightly, although not significantly, lower in patients with HELLP syndrome (78% ± 20 *vs* 88% ± 14).

Table I. *Sociodemographic characteristics.*

	Whole sample	AT ≥ 70%	AT < 70%	p
	n = 201	n = 183 (91.0)	n = 18 (9.0)	
Age ≥ 35	102 (50.7)	93 (50.8)	9 (50.0)	NS
Ethnicity				
Caucasian	138 (67.7)	126 (68.9)	10 (55.6)	NS
Sub-saharian	38 (18.9)	35 (19.1)	3 (16.7)	
Maghreb	12 (6.0)	9 (4.9)	3 (16.7)	
Others	15 (7.5)	13 (7.1)	2 (11.1)	
Low education (< 8 yrs)	69 (34.3)	66 (36.1)	3 (16.7)	NS
Smoking during pregnancy	8 (4.0)	8 (4.4)	0	NS
Assisted reproductive technology	20 (10.0)	17 (9.3)	3 (16.7)	NS
Nulliparity	102 (50.7)	92 (50.3)	10 (55.6)	NS
Pregestational diabetes mellitus	6 (3.0)	5 (2.7)	1 (5.6)	NS
Gestational diabetes mellitus	57 (28.4)	51 (27.9)	6 (33.3)	NS
Preeclampsia in previous pregnancies	17 (8.5)	17 (9.3)	0	NS
Chronic hypertension	79 (39.3)	77 (42.1)	2 (11.1)	0.007
Pregestational BMI ≥ 30	71 (35.3)	67 (36.8)	4 (22.2)	NS
Excessive weight gain	61 (30.3)	58 (31.7)	3 (16.7)	NS

Table II. *Clinical characteristics.*

	Whole sample	AT ≥ 70%	AT < 70%	p
	n = 201	n = 183 (91.0)	n = 18 (9.0)	
Gestational age at admission (days)	252 ± 29	251 ± 30	256 ± 18	NS
Systolic blood pressure at admission	148 ± 18	148 ± 19	152 ± 16	NS
Diastolic blood pressure at admission	91 ± 12	91 ± 12	94 ± 13	NS
Early onset preeclampsia	54 (26.9)	50 (27.3)	4 (22.2)	NS
Severe preeclampsia	51 (25.4)	44 (24.0)	7 (38.9)	NS

Table III. *Laboratory tests.*

	Whole sample	AT ≥ 70%	AT < 70%	p
	n = 201	n = 183 (91.0)	n = 18 (9.0)	
Antithrombin (mean ± SD)	87 ± 14	90 ± 12	63 ± 7	< 0.001
Antithrombin (median and IQ range)	87 (77-98)	89 (81-98)	66 (63.5-68)	< 0.001
Fibrinogen (mg/dl)	510 ± 95	513 ± 92	485 ± 120	NS
Hemoglobin (g/dl)	11.7 ± 1.3	11.7 ± 1.2	11.7 ± 1.5	NS
Hematocrit (%)	35 ± 4	35 ± 4	35 ± 4	NS
Platelets (103/mm3)	222 ± 67	224 ± 67	198 ± 64	NS
Serum Glutamic Pyruvic Transaminase (U/L)	32 ± 51	33 ± 53	24 ± 9	NS
Lactate dehydrogenase (U/L)	349 ± 96	342 ± 94	421 ± 82	0.001
Urine protein single sample (mg/dl)	91 ± 139	81 ± 130	184 ± 188	NS
Proteinuria (mg/24h)	2553 ± 3375	2603 ± 3456	1997 ± 2485	NS

Table IV. *Maternal and fetal outcome.*

	Whole sample	AT ≥ 70%	AT < 70%	p
	n = 201	n = 183 (91.0)	n = 18 (9.0)	
Maternal				
GA at delivery (days)	255 ± 26	255 ± 27	258 ± 17	NS
Birth < 37 weeks	77 (38.3)	69 (37.7)	8 (44.4)	NS
Latency (days)	2 (0-4)	2 (0-4)	1.5 (0-4)	NS
IOL	93 (46.3)	84 (45.9)	9 (50.0)	NS
Emergency CS	74 (36.8)	67 (36.6)	7 (38.9)	NS
Neonatal				
IUGR	69 (34.3)	59 (32.3)	10 (55.6)	0.045
SGA	49 (24.4)	41 (22.4)	8 (44.4)	0.042
IUFD	4 (2.0)	4 (2.2)	0	NS
NICU admission	55 (27.4)	47 (25.7)	8 (44.4)	NS

Maternal and neonatal outcomes are reported in **table IV**. GA at delivery was similar between groups. The mean latency from admission to delivery was 2 days (IQ range: 0-4 days), and it was similar in the two groups. Overall, 46.3% of women underwent an induction of labor. The rate of emergency cesarean section was 36.8% in the whole sample.

The number of small for gestational age (SGA) babies was higher in low AT levels group (44.4% *vs* 22.4%, p = 0.042) and also considering mean values, AT levels were significantly lower in case of SGA (84% ± 14 *vs* 89% ± 14; p = 0.040) respect with babies with appropriate birthweight.

In a logistic regression model including elevated maternal age (> 35 years), obesity (BMI > 30 kg/m^2), pre-pregnancy hypertension (chronic hypertension), onset and severity of PE, only gestational hypertension seems to be associated with lower

AT levels (p = 0.029, R2-Nagelkerke 0.117, likelihood ratio 110.112).

DISCUSSION

Low AT levels have been observed in PE in different studies, but there is no consensus on which threshold utilize. This make difficult to define the prevalence of reduced AT levels in such specific population. In our study the majority of subjects had normal value while low AT levels were found in about 9.0% of the women. Another study used the same threshold, although not focused on the detection of AT levels as primary outcome. They reported a prevalence of low AT levels in PE women which was nearly double (14) than here reported. Their sample size however was small and the number of primiparous women was higher than in our population.

Other studies have reported lower AT values (as a mean) in PE women respect than in our population. In such cases, however, only women with gestational hypertension were included (7, 15). A further study including only patients with gestational hypertension reported mean AT levels more similar to the one here reported (16).

As already reported, we found that low AT levels are more prevalent in women with severe PE (17). The same trend, however, was not confirmed in women with early onset PE. There were no other clinical features associated with low AT levels except in the cases of superimposed PE which seem protected again this deficit.

On these grounds, some Authors evaluated the effects of AT administration in preeclamptic women. In severe PE the administration of intravenous AT once a day, for seven days improved maternal symptoms, defined as gestosis index as well as fetal well being evaluated through the biophysical profile (10). In a small study involving women with early onset PE and IUGR fetuses the administration of both AT and heparin compared with heparin alone showed a decrease in systolic blood pressure and improved fetal growth in the treatment group (11). Another trial carried out in early onset severe PE demonstrated a preservation of fetal biophysical status and a prolongation of pregnancy in women treated with AT (12). Therefore, it seems AT supplementation could provide benefit for mothers and fetus, at least in japanese population. In an Italian randomized trial, an increase of AT levels was observed in treatment group, although no differences were found in term of clinical outcomes due to small sample size. It has to be pointed out that the study was stopped by the sponsor because of the slow rate of enrolment (18). It is known that a hypercoagulability state is associated with the occurrence of small babies and this is counteracted by an increased formation of thrombin-antithrombin (TAT) complex (16, 19). These findings agree with the significantly decreased AT activity we found in cases of SGA.

CONCLUSIONS

In conclusion, we reported that low AT levels occur in a significant proportion of women with PE, namely in those with severe features. Of paramount importance, SGA is strongly associated with reduced AT therefore supporting the implementation of large clinical trials evaluating the effects of AT supplementation.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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