Efficacy of AT in pre-eclampsia: a case-control prospective trial

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Summary
Pre-eclampsia is an extremely severe condition. It is associated with vasospasm, activation of the coagulation system and abnormal haemostasis. In pre-eclamptic patients increased plasmatic concentrations of fibronectin, laminin, von Willebrand factor (VWF) and endothelin are observed. Experimental studies on rats have also shown that the doses of antithrombin III (AT) needed to mediate anti-inflammatory processes are much higher than those required to obtain the anti-coagulant effect. The study aimed to evaluate the clinical efficacy of treatment with high AT doses (HD) in comparison with standard doses (SD). The primary endpoint was the prolongation of pregnancy defined as time (in days) from enrollment to delivery and to assess the maternal bleeding at and after delivery. The secondary endpoint was to demonstrate a role for AT in controlling haemostasis at conventional doses, and the inflammatory state at higher doses. The biochemical parameters assessed were: AT activity (%), Fibronectin (Fn), Fibrinogen, D-dimer, Uricemia, Proteinuria 24h, Protein C Reactive (PCR), Granulocyte Elastase and Endothelin. This study included 23 pre-eclamptic women. Patients were randomly subdivided into two groups: 10 patients (“cases”) were treated with high doses of AT (6 vials: 3000 units) once daily for 5 days, or until delivery, while 13 women (“controls”) were treated with doses of AT sufficient to maintain at least 80% of the activity. High-dose therapy was associated with prolongation of pregnancy by 2.5 days more when compared with controls (p = 0.03; Mann-Whitney test). The incidence of clinical significant bleeding was lower in cases than in controls (mean 550 mL vs. 650 mL, respectively). Preventive- and conservative-type treatment of moderate-severe pre-eclampsia, based on the administration high doses of AT, allows a significant prolongation of pregnancy, and thus a better neonatal outcome, as well as less maternal intra- and post-operative bleeding. Fn, PCR and elastase levels (markers of inflammation) decrease in the HD group in comparison with SD group. In the HD group, the AT plasma levels were obviously higher both at the end of the treatment (p < 0.0001) and after delivery (p = 0.03), in comparison with SD group. The fibrinogen and D-dimer levels were above the reference interval in both groups. TPA and PAI 1 were found to be significantly raised in the course of pre-eclampsia. In conclusion, the biochemical findings support a role for AT in controlling the haemostasis at conventional doses, and the inflammatory state at higher doses.

Keywords
AT, pre-eclampsia, pregnancy

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Introduction

Pre-eclampsia, a complication of pregnancy and (as H.E.L.L.P. syndrome: Hemolisis, Elevated Liver enzymes and Low platelets) of the immediate post-partum period, may be an extremely severe condition both for the mother and the fetus/neonate (1). The etiologic mechanisms of pre-eclampsia are still unknown, although many authors favour the hypothesis of endothelial damage as the primary mechanism (2). Pre-eclampsia is associated with vasospasm, activation of the coagulation system and abnormal haemostasis (3). In pre-eclamptic patients, increased plasmatic concentrations of fibronectin, laminin, von Willebrand factor (VWF), and endothelin are observed (4, 5). Many of these effects are mediated by increased activity of thrombin, a key enzyme in the coagulation cascade which also mediates different proinflammatory activities and modulates the vascular tone (6). In pre-eclampsia there is a marked increase in thrombin levels and as a result in thrombin-antithrombin (TAT) complexes, but this is accompanied by an equally marked decrease in circulating antithrombin III (AT) levels. Experimental studies on rats have also shown that the doses of AT needed to mediate anti-inflammatory processes are much higher than those required to obtain the anti-coagulant effect (7-9). Only high concentrations of AT may prevent organ damage by improving the tissue permeability index and platelets count. Conventional therapy of pre-eclampsia is aimed at controlling the symptoms, and is effective only in the moderate-mild and late-onset forms. One study has supported a role for high dose AT infusion in pre-eclamptic pregnant women (10). However, the dose of AT which may improve pre-eclampsia is still unknown.

Study aims

The aim of this study was to evaluate the clinical efficacy and safety of the treatment with high AT doses in comparison with standard doses, i.e. doses able to maintain at least 80% of the activity of plasma AT, in women with pre-eclampsia. The primary endpoint was the prolongation of pregnancy defined as at least 80% of the normal, the formula to calculate the amount of AT to be infused intravenously being: (100 - basal value in %) x Kg (body weight); 10 patients (defined as high dose group “HDG”) received a single AT infusion as above, and thereafter were treated with 3000 units of AT daily for 5 days, or until delivery. The SDG randomisation was performed using a computer-generated randomisation list (Arcus Quickstat) with a block of 8 patients in a 1:1 ratio.

For the purpose of analysis, patients remained in the treatment group to which they had been originally assigned, unless treatment was not actually given or violations of the study protocol occurred.

Maternal and foetal conditions were monitored with a combination of tests which included maternal blood pressure recordings (continuous and/or every 4 hours), 24 hour proteinuria, standard haematological and biochemical blood values checked daily, foetal biophysical profile and heart rate monitoring daily or more frequently in selected cases. The timing of delivery, which was elective or emergency caesarean section in all women, was decided upon by the individual consultant in charge and was usually performed following deterioration of maternal and/or foetal conditions. Foetus was classified as small for gestational age (SGA) if birth weight was below the 10th percentile. The estimated intra and post-operative bleeding was measured. Each patient signed an informed consent, blood samples. All were observed closely for the development of complications, particularly hyaline membrane disease and ventricular haemorrhage. Concomitant therapy with other anticoagulants, antiplatelet agents, and blood preparations except albumin was not permitted during the study. However, other treatments including antihypertensive agents (α-metildopa and nifedipine) were allowed in both AT groups as necessary until the time of delivery. The drug test was prepared by Aventis Behring, Baxter and Grifols. One vial contains 500 IU of antithrombin and does not contain heparin. The specific activity and purity are 6.25 IU/mg and 100%, respectively. This product is

Materials and methods

This study enrolled 23 patients at 24-33 weeks of gestation referred with a diagnosis of pre-eclampsia to the Department of Gynaecology and Human Reproductive Science of the University of Padua, Italy, between June 1998 and January 2003. Patients with chronic hypertension, renal disease, diabetes mellitus, systemic lupus erythematosus, multiple pregnancies, and other severe medical conditions were excluded. Pregnant women were included for this study on the basis of the following criteria: diastolic arterial pressure >90 mmHg and systolic arterial pressure > 140 mmHg on more than three occasions, proteinuria (in a 24-hour sample) > 0.3 g/L and AT ≤ 75%

Upon admission, all subjects underwent 24-hour Holter blood pressure monitoring and four-hourly blood pressure measurements. Each patient signed an informed consent, approved by the local Health Sciences Human Subjects Committee. The women were randomly allocated into two groups: 13 control women (defined as the standard dose group, “SDG”) received one dose of AT sufficient to reach a plasma AT activity of at least 80% of the normal, the formula to calculate the amount of AT to be infused intravenously being: (100 - basal value in %) x Kg (body weight); 10 patients (defined as high dose group “HDG”) received a single AT infusion as above, and thereafter were treated with 3000 units of AT daily for 5 days, or until delivery. The SDG randomisation was performed using a computer-generated randomisation list (Arcus Quickstat) with a block of 8 patients in a 1:1 ratio.

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derived from the plasma of healthy donors negative for HbsAg, anti-HCV, anti-HIV-1, anti-HIV-2 and high titre screening for parvovirus B19 genome. The serum levels of AST/ALT are also determined and donations rejected if values are above double the upper limit of the specified normal range. Inactivation and/or removal of enveloped viruses (e.g. HIV, herpes simplex) and no enveloped viruses (e.g. poliomyelitis, parvovirus B19) were validated in important production procedures, including heat-treatment in aqueous solution at 60 centigrade for 10 h (pasteurisation). A complete blood count, biochemistry tests, urine analyses, and blood coagulation tests were performed before the start of treatment (on day 0), one day after the infusion completion (on day 5), on the day of delivery (at the time of discontinuation), and on day 13. The AT activity was measured with the Testzym AT commercially available from Chromogenix AB (Mölndal, Sweden), using a chromogenic substrate. The D-dimer level was measured with Lapidia D dimmer, an ELISA commercially available from Fuji Rebio (Japan) developed by an Australian company, MabCO. Plasma fibropectin was assayed by nephelometry using biochemical kits (Boehringer Mannheim, Indianapolis, IN, USA); values between 250 and 400 ng/L were considered normal. To measure endothelin (ET), blood was drawn and placed in a test-tube containing EDTA, and centrifuged at 3000 rpm for 5 minutes. The plasma, placed in special test-tubes, was stored at –80°C until analysis. Since ET has a half-life of less than a minute, its 38-amino acid precursor, BIG-ET, was actually measured, but this parameter has an equivalent significance. An immunoenzymatic test was used, employing the “sandwich” technique. The threshold value in non-pregnant individuals is < 0.7 fmol/ml. To determine PCR (Protein C Reactive) plasma levels we used an immunonephelometric assay. The polystyrene particles sensitised with monoclonal anti-PCR Ig are agglutinated during mixing with samples containing the PCR to be measured. The intensity of the light dispersed by the nephelometer is determined by the PCR content of the sample. We chose as an inflammatory marker (alongside the traditional PCR), granulocyte elastase (GE). Measurement of this marker was performed purely for research purposes, as its clinical use is still in the experimental stage and restricted to the areas of traumatology, sepsis, haemodialysis, genital, obstetric and intestinal infections, and sports-related pathologies. GE is a protease contained in the azurophil granules of neutrophils (PMNs) able to degrade exogenous elements and self-damaged tissue. To measure this marker, blood was drawn, placed in a test-tube with Na citrate and centrifuged at 3000 rpm for 5 minutes and the plasma stored at –80°C in special test-tubes until analysis. An immunoenzymatic test was used, employing the “sandwich” technique. The threshold value calculated on a small sample (no.=57) of non pregnant individuals was 57 nm/ml.

To measure the tPA and PAI 1, drawn blood was placed in test-tubes containing Na citrate; these were agitated to prevent platelet aggregation and the start of coagulation, then centrifuged at 3000 rpm for 10 minutes. The plasma was stored at –80°C until analysis. A 2-step immunoenzymatic test was used. In this test, the plasma to be analysed is placed on a support to which specific anti-human tPA (or PAI 1) monoclonal IgGs are fixed. After washing, a second monoclonal Ig is introduced which binds another tPA (or PAI 1) epitope to which a peroxidase is bound; after washing again the substrate of the peroxidase is introduced, which will change colour in a manner directly proportional to the concentration of tPA (or PAI 1) Ag present.

### Statistical analysis

Statistical analysis was performed using a SPSS (Statistical Package for the Social Sciences) version 11.0 software package (SPSS Inc 2002, USA). The Wilk-Shapiro test was used to check the normality of distribution of the main variables. The Fisher exact test was used to compare categorical variables and the Mann-Whitney test and the Student’s paired t-test were used when appropriated to compare continuous variables. A ROC (Receiver Operating Characteristic) curve analysis was performed comparing the prolongation time to delivery in the case and in control groups. The data were expressed as mean values ± 1 standard deviation. A p value of 0.05 was taken to indicate statistical significance.

### Results

Table 1 shows the baseline characteristics of all patients. There were no differences in age, parity, weight, and blood pressure values and gestational age on admission between HD and SD groups. In the HDG a total of 126,000 AT units were infused (mean dose per patient: 12600 units). In the SDG a total of 43,800 AT units were infused (mean dose per patient: 3370 units). Therefore, patients in the HD group received an AT dose 3.7 times higher than the dose used in patients of the SD group. No adverse effects were observed in either group, with the exception of rare instances of allergic or anaphylactic reactions, or raised body temperature in patients with a known hypersensitivity to the components of the drug.

### Table 1: Clinical characteristics of the patients.

<table>
<thead>
<tr>
<th>CASES (no.=10)</th>
<th>CONTROLS (no.=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>32 ± 4</td>
</tr>
<tr>
<td>Weight</td>
<td>76 ± 5</td>
</tr>
<tr>
<td>Primigravida</td>
<td>0.7</td>
</tr>
<tr>
<td>Syst. art. press.</td>
<td>145 ± 13</td>
</tr>
<tr>
<td>Diast. art. press.</td>
<td>93 ± 9</td>
</tr>
<tr>
<td>Gestational age</td>
<td>28 ± 3.8</td>
</tr>
</tbody>
</table>
Biochemical results

The biochemical values are shown in Table 2. Fn, PCR and Elastase levels (markers of inflammation) decrease in the HD group in comparison with SD group. In the HD group, the AT plasma levels were obviously higher both at the end of treatment (p < 0.0001) and after delivery (p = 0.03), in comparison with SD group (Fig. 1). It is, however, important to remark that only patients in the HD group showed a direct correlation between the AT increasing percentage and weeks of gestation, reached at the time of delivery (R = 0.35; p = 0.2) (Fig. 2). The fibrinogen and D-dimer levels were above the reference interval in both groups. tPA was found to be significantly raised in the course of pre-eclampsia, recording values of 15.2 ± 6.4 ng/ml in relation to those of pregnant women of equivalent gestational age not affected by pre-eclampsia (indicated in the literature as 7.6 ± 1.6 ng/ml). PAI 1 was found to show an increasing trend in pre-eclampsia, recording values (47.87 ± 25.46 ng/ml) higher than the mean ones for normal pregnancy reported in the literature (38 ng/ml). Uricemia was found to be increased in relation to normal levels in the 2 groups (0.44 ± 0.17 and 0.36 ± 0.07 vs. reference values of 0.15-0.35 mmol/L), and higher in the HDG than in the SDG. Proteinuria, which, after all, is a

Table 2: Change of the hematological-chemical parameters during the treatment with “high” (HDG) and “standard” doses (SDG) of AT.

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>Baseline</th>
<th>Change</th>
<th>Postpartum</th>
<th>P valuea</th>
<th>Baseline</th>
<th>Change</th>
<th>Postpartum</th>
<th>P valuea</th>
<th>for HDG vs SDG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen (g/L)</td>
<td>4.47 ± 0.83</td>
<td>4.63 ± 1.28</td>
<td>5.23 ± 1.54</td>
<td>N.S.</td>
<td>4.17 ± 0.74</td>
<td>4.58 ± 1.77</td>
<td>5.17 ± 0.73</td>
<td>N.S.</td>
<td><strong>0.41</strong></td>
</tr>
<tr>
<td>D-dimer (µg/L)</td>
<td>399.6 ± 317.4</td>
<td>384 ± 299.9</td>
<td>471.87 ± 190*</td>
<td>*0.40</td>
<td>412 ± 340</td>
<td>621.57 ± 434</td>
<td>940.2 ± 937**</td>
<td><strong>0.35</strong></td>
<td></td>
</tr>
<tr>
<td>Fibronectin (mg/L)</td>
<td>830 ± 240</td>
<td>773 ± 234*</td>
<td>1.05 ± 0.07*</td>
<td>*0.63</td>
<td>600 ± 156</td>
<td>700 ± 182**</td>
<td>1.66</td>
<td>N.S.</td>
<td></td>
</tr>
<tr>
<td>Uricemia (mmol/L)</td>
<td>0.44 ± 0.17</td>
<td>0.40 ± 0.06</td>
<td>0.35 ± 0.07*</td>
<td>*0.29</td>
<td>0.36 ± 0.07</td>
<td>0.38 ± 0.07</td>
<td>0.34 ± 0.09**</td>
<td><strong>0.63</strong></td>
<td></td>
</tr>
<tr>
<td>Proteinuria 24h (g)</td>
<td>1.56</td>
<td>5.14</td>
<td>2.95</td>
<td>N.S.</td>
<td>3.07</td>
<td>2.85</td>
<td>1.66</td>
<td>N.S.</td>
<td></td>
</tr>
<tr>
<td>PCR (mg/L)</td>
<td>7.53 ± 5.3</td>
<td>11.5 ± 8.9*</td>
<td>0.42</td>
<td>N.S.</td>
<td>12 ± 9.32</td>
<td>24 ± 17.82**</td>
<td><strong>0.2</strong></td>
<td>N.S.</td>
<td></td>
</tr>
<tr>
<td>Granulocyte Elastase (µg/mL)</td>
<td>139 ± 124</td>
<td>112 ± 46*</td>
<td>*0.59</td>
<td>N.S.</td>
<td>124 ± 101</td>
<td>198 ± 54</td>
<td>N.S.</td>
<td>N.S.</td>
<td></td>
</tr>
<tr>
<td>Endothelin (pg/mL)</td>
<td>1.46 ± 0.99</td>
<td>1.71 ± 1.28</td>
<td>N.S.</td>
<td>1.51 ± 0.54</td>
<td>215 ± 1.04</td>
<td>N.S.</td>
<td>1.51 ± 0.54</td>
<td>215 ± 1.04</td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as mean values and standard deviation. The “baseline” blood samples were drawn before the beginning of the treatment (day 0), and the “Change” ones were drawn on day 5, or on the day of the delivery. The P values compare the initial values with the final values and with those of the postpartum. The P values compare the HDG group with the SDG group. For the data analysis a t Student test for unpaired data was used.

The normal control values are: Fibrinogen (1.60-5.50 g/L), D-dimer (<200 µg/L), Fibronectin (250-400 mg/L), Uricemia (0.15-0.35 mmol/L), Proteinuria 24h (0-0.15 g), PCR (20 mg/L), Granulocyte Elastase (52 ± 9 µg/mL), Endothelin (0.56 pg/mL).

Figure 1: AT plasma levels in High Dose Group (HDG) and Standard Dose Group (SDG).
diagnostic criterion of pre-eclampsia, was found to be clearly
outside the normal range (1.56 ± 1.54 and 3.07 ± 4.15 g/24h vs.
reference values of 0-0.15 g/24h). We also measured plasma
endothelin, and found, on average, decreased levels in the
HDG in comparison with SDG (1.46 ± 0.99 pg/ml vs. 215 ±
104 pg/ml, with a reference range in normal pregnancy of
0.56 pg/ml).

Clinical results
High-dose AT therapy was found to be able to prolong pregnan-
cy by 2.5 days more than purely maintenance doses, despite
operating in conditions that tended to be more critical. This
result shows a good level of statistical significance (p = 0.03),
even taking into account the small size of the sample analysed
(Fig.2). The mean values obtained were 6 days in the HDG,
with a median value of 5.5, and 3.5 days in the SDG, with a
median of 3. This prolongation was more significant in the 2
cases affected by HELLP syndrome (7 and 11 days) and in one
case presenting major placental involvement but little kidney
involvement (11 days) (Table 3). Two patients in the HDG were
recruited at very early stages of pregnancy (23 and 22 weeks’
gestation) and ended in an induced abortion and a therapeutic
interruption of pregnancy. The therapeutic intervention was per-
formed in order to alleviate at least the maternal pathology and
to allow abortion to occur vaginally, avoiding the need for sur-
gical intervention. This was proved to be possible only in the
first of the 2 cases; in the second, complicated by the presence
of type 1 diabetes with marked uncompensation a caesarian sec-
tion was deemed preferable and the operation was carried out
without complications during surgery (normal bleeding) or
post-operative problems in terms of difficulty in achieving hae-
mostasis or controlling inflammation (there was no need of sub-
fascial drainage, and the patient did not develop a temperature).
The incidence of complications, in terms of bleeding that is
heavy and difficult to control, associated with the surgical inter-
vention (caesarean section) was lower in the HDG than in the
SDG (mean 550 ml vs. 650 ml respectively). The post-operative
course was normal in 70% of the patients in the HDG (as
opposed to 46% of the patients in the SDG), a second surgical
intervention (for subfascial haematoma drainage) being
required in only 2 cases (20%), in just 1 of whom the blood loss
necessitated a transfusion of 3 bags of concentrated red cells.
Only 46% of the patients in the SDG had a normal intra- and
post-operative course. In six (46%) of the operations, serious
difficulty in achieving haemostasis was encountered, and in 2
(16%) uterine atony. In the post-operative period, 3 of the SDG
patients (31%) required transfusional therapy and 2 (13.5%) a
further laparotomy for the removal of a subfascial haematoma
(5 haemorrhagic events in all). A number of other complica-
tions were also encountered, including a worsening of the pre-
eclampsia (inability to control the hypertension and proteinuria)
in 2 subjects, and sepsis, pulmonary oedema, and paralytic
ileum each occurring in 1 patient. Finally, 1 subject required
psychological support of medium duration in order to overcome
the event. There were no differences in mean length of stay in
intensive care or on the ward between the 2 groups. The results
regarding neonatal outcome (Table 4) were very encouraging:
the significant prolongation of pregnancy obtained in the HDG
correlated with a higher birth weight (the mean values of the
two groups being 1185 and 1005 gr) (p = 0.3). The neonates
recorded different intrauterine growth percentiles with the bet-
ter parameters emerging among the HDG (19.5 vs. 12.81) (p =

![Figure 2: "Surviving" curve defined as gained time to the delivery.](image-url)
We believe that this demonstrates the efficacy of the utero-placental flow, obtained through the administration of high doses of AT, which limit the fibrin deposition and diffuse microthrombosis and improve foetal oxygenation and nutrition. As regards to the immediate complications, the incidence of prematurity-related hyaline membrane disease was practically the same in the two groups, affecting severely premature infants in both of them. The incidence of ventricular haemorrhage, more related to the coagulatory status, was significantly higher in the SDG in comparison with HDG (60 vs. 25%). Furthermore, given that this is a neurological-type complication, we can reasonably suppose that the long-term outcomes of these neonates will differ. Two subjects from the SDG group died (20% mortality), both as a result of ventricular haemorrhage. No deaths were recorded among the HDG, even though these subjects were, as an effect of the casual patient recruitment, on average a week more premature.

### Discussion

Pre-eclampsia continues to be a severe complication of pregnancy (11, 12). Underlying this pathology there is a state of dysfunction/activation of the endothelium (13), the most extensive organ in the human body. A considerable body of scientific evidence supports the view that pre-eclampsia is characterised by a state of vasoconstriction and hypovolemia, hyperaggregability/hypercoagulation with the development of chronic intravascular coagulation, and endothelial inflammation. Thrombin, by participating in the modulation of the vascular tone, and capil-
lary permeability, is also at the root of this vascular damage (14). The administration of AT, the main physiological inhibitor of thrombin and thus of microcirculation damage, represents a possible therapeutic option in the early-onset forms (15). AT, administered promptly upon diagnosis and in high doses, can, in fact, correct the state of hyperaggregability/hypercoagulability, and modulate the vasoconstriction and endothelial inflammation.

We also assayed several coagulation markers to monitor the disease course and the modifications brought about by the treatment. The changes we have observed in several biochemical indices confirm the hypothesis that endothelial damage is the primary mechanism of the pre-eclamptic process and reiterate the typical characteristics of the disorder, i.e., the state of vasoconstriction, disseminated intravascular coagulation and vascular inflammation. The concentrations of all markers were found to be significantly raised when compared to normal pregnancies. High doses of AT were associated with less raised indices of inflammation (Fn, PCR, Elastase) when compared to the standard regimen. High-dose therapy was found to have a positive effect on the Fn, PCR and elastase levels, decreased in the HD group, as opposed to a worsening trend in the SD group. In the literature, too, it has been affirmed that AT exerts a protective effect against endothelial damage only at high doses. As expected, plasma AT levels were higher in women who received high doses of AT, and these levels correlated with the prolongation of pregnancy. Plasma fibrinogen and D-dimer remained unchanged only with the high-dose treatment. This demonstrates the capacity of the AT at high doses to control activation of the fibrinolytic system. tPA was found to be significantly raised in the course of pre-eclampsia; tPA is produced by endothelial cells and typically shows raised values in pathologies in which there is evidence of endothelial damage. High concentrations of this marker reflect a state of fibrinolysis activation as a compensatory response to excessive and continued formation of thrombin. This supports our aetiological hypothesis, according to which endothelial damage and disseminated intravascular coagulation state are fundamental elements underlying the development of pre-eclampsia (11-15). Increased plasma concentrations of PAI 1, produced by the endothelial cells and activated platelets, correlate with the deposition of fibrin in the microcirculation, a prelude to the multi-organ involvement to which this will give rise. This result too supports our hypothesis that pre-eclampsia is characterised by a diffuse microcirculation damage. The treatment completely failed to control this clinical sign. At renal level, the glomerular endothelium is not only in a state of dysfunction/activation, it also presents an anatomical-pathological lesion (glomerular endotheliosis) that is responsible for the loss of function. A number of proteins enter the renal filtrate, and these include, among others, AT (58.2 kD).

Women in the high dose group remained undelivered significantly longer and had less maternal intra- and post-operative complications and less neonatal pathologies. These findings support a role for AT in controlling haemostasis at conventional doses, and the inflammatory state at higher doses. We have also demonstrated in the clinical setting that preventive and conservative-type treatment of moderate-severe pre-eclampsia, based on the administration of AT at high doses, allows a significant prolongation of pregnancy, and thus a better neonatal outcome, as well as fewer intra- and post-operatively maternal complications. The value of the therapy probably lies in the fact that it acts right at the site of the primary damage, the vascular endothelium, exerting a synergy of anti-coagulant and anti-inflammatory effects peculiar to this molecule when it is used in large doses. Obviously, AT cannot correct any anatomical-pathological damage (such as that which occurs in the kidney).

References