Predictive Value of Routine Circulating Soluble Endothelial Cell Adhesion Molecule Measurements during Pregnancy

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Background: The present study was aimed at determining whether routine prenatal measurements of circulating soluble intercellular adhesion molecule (sICAM-1; CD54) and soluble vascular cell adhesion molecule (sVCAM-1; CD106) in midgestation have predictive value for the identification of pregnant women destined to develop preeclampsia or other complications of pregnancy during late gestation.

Methods: Plasma sICAM-1 and sVCAM-1 were analyzed between weeks 22 and 29 of gestation in 1543 pregnant women and related to the outcome of pregnancy in a prospective longitudinal study.

Results: Plasma sICAM-1 and sVCAM-1 in uncomplicated pregnancies were normally distributed and varied over a small range (sICAM-1, SD = 22.5%; sVCAM-1, SD = 25.5%). Of all analyzed uncomplicated pregnancies, 54 (3.95%) were identified with concentrations of sICAM-1 or sVCAM-1 above the mean + 2 SD. In contrast, of 177 pregnancies with complications (prevalence, 11.5%), 97 (55%) had sICAM-1 or sVCAM-1 concentrations above the same cutoffs weeks before the onset of disease. The sensitivities of sICAM-1 and sVCAM-1 measurements were 66% for preeclampsia and hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome), 42% for gestational hypertension, 50% for fetal retardation, 46% for preterm labor, 50% for gestational diabetes mellitus, 67% for gestational proteinuria, and 70% for infections during pregnancy. Taken together, routine prenatal sICAM-1 and sVCAM-1 measurements had an overall predictive value of 64%.

Conclusions: Midgestation measurements of circulating sICAM-1 and sVCAM-1 have a high predictive value (area under the curve of combined sICAM-1 and sVCAM-1 measurements determined by ROC analysis, 0.85) and may identify up to 55% of pregnant women who will later develop a severe pregnancy-related complication.

The objective of prenatal care is to identify those women who are at risk of developing pregnancy-related complications. To this end, various prenatal care schemes have been implemented that range from 3–4 visits in Switzerland to as many as 14 visits in countries such as Finland, Norway, and the US (1). Usually, more visits are scheduled in the third trimester to detect women with the earliest signs of developing pregnancy-associated hypertensive disorders [preeclampsia, hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome), or pregnancy-induce hypertension], which to this day represent the most frequent pregnancy-related disorders with high maternal and perinatal mortality (2, 3).

In 1989, the Expert Panel on the Content of Prenatal Care published recommendations on the timing and content of prenatal care and concluded that fewer visits than previously recommended may be sufficient (4). A randomized control trial subsequently concluded that a reduction of the average number of prenatal visits from 12.9 to 10.3 during pregnancy could be tolerated without affecting perinatal outcome (5). Laboratory tests cannot replace regular prenatal visits. They can, however, complement existing prenatal care programs and are of par-

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ticular use if they can contribute to the identification of women at risk of developing pregnancy-related complications. Correspondingly, they can help to establish more cost-effective prenatal care schemes.

We recently reported in a preliminary study that the concentrations of the circulating endothelial cell adhesion molecules (CAMs), soluble intercellular adhesion molecule (sICAM-1; CD54) and soluble vascular cell adhesion molecule (VCAM-1; CD106), appear to have predictive value for the identification of women at risk of developing preeclampsia (6). In that study of 140 pregnant women, the 7 who developed preeclampsia were found to have significantly increased concentrations of circulating sICAM-1 and/or sVCAM-1 weeks to months before the onset of clinical symptoms of the disease. These findings were surprising at the time, but can now be considered in line with recent work characterizing the vascular origin of the pathogenesis of preeclampsia (7, 8). According to these studies, pregnancies that are complicated by preeclampsia are characterized by disturbed placentation, which is reflected by an inability of cytotrophoblast cells to acquire a vascular phenotype during their invasion into the maternal spiral arteries (8), which in turn is associated with increased apoptosis of cytotrophoblast cells (9). This defect in early placentation can be compensated for most of the pregnancy until the disease suddenly manifests itself during late gestation as a primarily vascular disease (10). Likewise, the pathogenetic changes during preeclampsia have been interpreted to reflect an excessive maternal inflammatory response to pregnancy (11).

On the basis of our preliminary study (6) and the recent evidence that preeclampsia is pathogenetically a vascular disease (10–12), the present study was aimed at assessing the prognostic accuracy of routine prenatal sICAM-1 and sVCAM-1 measurements for the early identification of women at risk of developing preeclampsia. Furthermore, we had observed in our previous study that prenatal sICAM-1 and sVCAM-1 measurements may also have predictive value for other pregnancy disorders, such as fetal growth retardation (6). On the basis of these preliminary findings, we hypothesized that routine prenatal measurements of sICAM-1 and sVCAM-1 may have predictive value for various pregnancy disorders with a primary involvement of the vascular system. We consequently quantified circulating sICAM-1 and sVCAM-1 in pregnant women between weeks 22 and 29 of pregnancy and related these findings to the outcome of pregnancy.

**Materials and Methods**

**Participants**

Between January 1997 and March 1999, maternal venous plasma samples were collected in collaborating prenatal care centers in the Göttingen (Germany) area from a convenience sample of pregnant women during routine outpatient prenatal visits between weeks 22 and 29 of gestation. Informed consent was obtained from each patient at recruitment. Samples collection was unbiased, with the only selection criterion being that exclusively women with apparently uncomplicated pregnancy at the time of blood sampling were included into the study. Consequently, women who had already been diagnosed with a pregnancy-related complication, e.g., preexisting diabetes, chronic hypertension, and lupus erythematosus, at the time of blood sampling were excluded from the study (~1–2% of all pregnancies). Samples otherwise were meant to reflect the population of pregnant women in the primarily Caucasian Western European population. Samples were collected between weeks 22 and 29 of gestation in an adaptation to the regular prenatal visits of pregnant women in the collaborating centers and to define a realistic prognostic window predominately for preeclampsia, which rarely occurs before 30 weeks of gestation. Blood was collected in EDTA tubes, which were mailed to the laboratory without cooling. On arrival in the laboratory, blood samples were centrifuged at 800g for 15 min, and the supernatant was stored at −50°C before analysis.

**Analysis of soluble endothelial CAMs**

sICAM-1 (CD54) and sVCAM-1 (CD106) were measured in the plasma by a sandwich ELISA method as single or duplicate measurements according to the manufacturer’s instructions (R&D Systems). Reanalysis of individual samples (including all samples with values above the mean ± 2 SD) as well as duplicate analyses showed no changes >10%. The ELISA for sICAM-1 and sVCAM-1 has been validated and quality controlled in detail. Information on intra- and interassay variability (and corresponding CVs) is summarized at www.rndsystems.com/pdf/BBE1B.pdf (sICAM-1) and www.rndsystems.com/pdf/BBE3.pdf (sVCAM-1). Analyses were performed early in pregnancy, without knowledge of clinical outcome.

**Characterization of experimental groups**

The outcome of pregnancy was monitored in all women included in the study. Patients were assigned to the following experimental groups without knowledge of results for sICAM-1 or sVCAM-1: preeclampsia and HELLP syndrome, gestational hypertension (without proteinuria), fetal retardation, preterm labor, gestational diabetes, gestational proteinuria (without hypertension), infections during pregnancy, and miscellaneous pregnancy-related disorders. All other patients were assigned to the control group. No patients were reclassified based on sICAM-1 or sVCAM-1.

Preeclampsia in previously normotensive patients was diagnosed on the basis of a diastolic arterial blood pressure of >90 mmHg on repeated measurements (>4-h intervals) or a single measurement of >110 mmHg in combination with the presence of significant proteinuria (dipstick ++/++++, corresponding to protein concentrations >0.3 g/L) (13). Criteria for the classification of HELLP syndrome were decreased thrombocyte counts...
(<100 000/μL), decreased haptoglobin (<0.45 g/L), increased lactate dehydrogenase (>300 U/L), and increased alanine aminotransferase and aspartate aminotransferase (>50 U/L) (14). Gestational hypertension was defined as an increased diastolic blood pressure (same criteria as for preeclampsia) without significant proteinuria (13). Fetal retardation was diagnosed if the birth weight was below the 10th percentile. The criteria for the diagnosis preterm labor were contractions before 37 weeks of gestation with indication for tocolytic therapy or preterm delivery (<37 weeks of gestation). Gestational diabetes mellitus was diagnosed on the basis of a positive oral glucose tolerance test in women without preexisting diabetes. Gestational proteinuria (without hypertension) was characterized by a positive dipstick test (++/++++), corresponding to the definition of preeclampsia. The following infections were observed during pregnancy: amnionitis, cervicitis (i.e., Streptococcus spp., Chlamydia spp., or Trichomonadida spp.), and urinary infections during pregnancy. Lastly, miscellaneous pregnancy-related disorders comprised lung emboli, placental abruption, intrauterine death, placenta previa, and the feto-fetal transfusion syndrome.

ANALYSIS OF THE DATA
Plasma concentrations of sICAM-1 and sVCAM-1 are expressed in μg/L. After reference values based on uncomplicated control pregnancies were established, we expressed sICAM-1 and sVCAM-1 concentrations in the experimental groups as multiples of the mean (MOM) of the control population. Plasma concentrations of the analyzed endothelial cells adhesion molecules in the experimental groups were compared by the Mann–Whitney U-test.

The prognostic accuracy of sICAM-1 and sVCAM-1 measurements during pregnancy was analyzed by ROC analysis using Rockit 0.9 Beta Version (http://gim.unmc.edu/dxtests). The sensitivities and specificities of routine sICAM-1 and sVCAM-1 measurements were calculated by applying the mean + 2 SD and the mean + 3 SD as cutoff values. On the basis of each of these cutoff values, the clinical sensitivity was calculated as the ratio of test-positive individuals developing a specific pregnancy complication to the total number of pregnant women who developed the respective pregnancy disorder. Likewise, the specificities of sICAM-1 and sVCAM-1 measurements during pregnancy were calculated as the ratios of test-negative individuals to the total number of women in the control population. The predictive value of combined sICAM-1 and sVCAM-1 determinations during pregnancy for the identification of women at risk of developing a pregnancy disorder was calculated according to the Bayes formula (15).

Results
We enrolled 1543 pregnant women, of whom 1366 (88.5%) had an uncomplicated outcome of pregnancy. The mean (SD) sICAM-1 and sVCAM-1 concentrations in these patients were 240 (54) and 524 (133) μg/L, respectively (Fig. 1). As seen in our previous study (6), the distributions in controls were gaussian (Fig. 1). The SDs were 22.5% of the mean for sICAM-1 and 25.5% of the mean for sVCAM-1. As in our previous study (6), sICAM-1 and sVCAM-1 did not vary during uncomplicated pregnancies (not shown).

This study was conducted under field conditions, i.e., blood samples were sent by regular mail to the laboratory without cooling. To assure that handling of the samples did not interfere with exact sICAM-1 and sVCAM-1 quantification (e.g., degradation during prolonged storage without cooling), we analyzed sICAM-1 and sVCAM-1 results for the control population in relation to the duration between blood sampling and further analysis in the laboratory. Immunoreactive sICAM-1 was stable during storage and shipment at room temperature for at least 6 days (Fig. 2). In contrast, sVCAM-1 measurements showed a characteristic decay curve (Fig. 2). As a consequence, the mean sVCAM-1 measurements of the control population of the present study were 25% lower compared with fresh samples (524 vs 699 μg/L) (6). Consequenc
quently, sVCAM-1 concentrations were normalized for all subsequent analyses to day 0 in relation to their duration of shipment according to the decay curve shown in Fig. 2 (i.e., results for 1-day samples were multiplied by 1.14; 2-day samples were multiplied by 1.28; 3-day samples by 1.41; 4-day samples by 1.48; and 5-day samples by 1.55).

Of the control population with uncomplicated pregnancy outcomes (Fig. 1), 30 (2.2%) had sICAM-1 concentrations that exceeded the mean \(\pm 2\) SD \([11 (0.8%) were above the mean \(\pm 3\) SD\], and 24 (1.8%) had normalized sVCAM-1 that exceeded the mean \(\pm 2\) SD \([9 (0.7%) were above the mean \(\pm 3\) SD\]. In 54 individuals (3.95%), sICAM-1 or sVCAM-1 or both were above the appropriate mean \(\pm 2\) SD cutoff \([20 (1.5%) were above the mean \(\pm 3\) SD\].

Of all analyzed pregnancies, 177 were identified with a pregnancy disorder in the third trimester. This reflected a prevalence of pregnancy disorders of 11.5%. Among these, hypertensive disorders \(\text{[preeclampsia, HELLP syndrome, and gestational hypertension (without proteinuria)] were counted for the largest group (42.4%). Mean sICAM-1 and sVCAM-1 concentrations were, respectively, 28% and 16% higher than in controls (Table 1; \(P < 0.001\)).\] The data in the experimental group were not normally distributed, and the SDs of the distribution of sICAM-1 and sVCAM-1 concentrations were higher in the experimental group than in the controls: the SD for sICAM-1 was 1.73 times the SD for the controls; the SD for sVCAM-1 was 1.57 times the SD for controls; Table 1.

The percentage of women in the experimental group with sICAM-1 and sVCAM-1 concentrations above the mean \(\pm 2\) SD and mean \(\pm 3\) SD cutoffs are shown in Table 2. Of 44 women who developed preeclampsia or HELLP syndrome, 29 (66%) had sICAM-1 or sVCAM-1 above the mean \(\pm 2\) SD cutoff \([10 above mean \(\pm 3\) SD (23%); Fig. 3\]. These measurements were made 1–17 weeks before the onset of clinical symptoms of the disease (median, 9 weeks). Similar results were obtained for the other disease groups, which similarly had increased sICAM-1 or sVCAM-1 concentrations above the mean \(\pm 2\) SD cutoff: gestational hypertension, 42%; fetal retardation, 50%; preterm labor, 46%; pregnancy diabetes, 50%; pregnancy proteinuria, 67%; infections during pregnancy, 70%; and women with various pregnancy disorders \(\text{[lung emboli, placental abruption, intrauterine death, placenta previa, and the fetofetal transfusion syndrome]}, 71%.

The overall positive predictive value of increased sICAM-1 or sVCAM-1 concentrations in combined measurements (either result above the mean \(\pm 2\) SD during 22–29 weeks of gestation) for the development of a severe pregnancy disorders in late gestation was 64%. At this cutoff, 55% of all pregnancy disorders of late gestation were identified weeks before the clinical onset of disease.

![Fig. 2. Concentrations of circulating sICAM-1 (gray columns) and sVCAM-1 (stippled columns) in the plasma of pregnant women with uncomplicated pregnancies between 22 and 29 weeks of gestation in relation to the duration between blood sampling and additional processing in the laboratory. The boxes at the bottom denote the respective percentages of samples that were received in the laboratory after the indicated number of days. The majority of samples (89.5%) were received in the laboratory after 2 or 3 days of transport. The corresponding fresh samples reflect control plasma samples from pregnant women that were processed at 4 °C immediately after blood sampling (6).](https://academic.oup.com/clinchem/article-abstract/48/9/1418/5642403/1418)

![Table 1. Summary of sICAM-1 and sVCAM-1 measurements during 22 and 29 weeks of gestation in women who developed a pregnancy disorder in late gestation.](https://academic.oup.com/clinchem/article-abstract/48/9/1418/5642403/1418)
Discussion

Several pregnancy-related disorders are associated with distinct vascular changes. Among these, hypertensive disorders, including preeclampsia, HELLP syndrome, and gestational hypertension, account for the most important and most frequent complications of pregnancy. Thus, intense research efforts have been directed at developing techniques with predictive value for the early identification of women at risk to develop a hypertensive disorder during pregnancy. Numerous approaches have been proposed toward this end, including second-trimester measurements of total fibronectin and ED1 fibronectin, the determination of urinary kallikrein:creatinine ratios and urinary calcium:creatinine ratios, analysis of platelet activation, midgestational maternal triple screening tests (α-fetoprotein, β-human chorionic gonadotropin, and estriol), and ultrasonographic screening techniques (16–18). All of the proposed methods have a poor sensitivity and/or specificity, and thus a low predictive value, which has largely prevented widespread implementation of any

<table>
<thead>
<tr>
<th>Pregnancy disorder</th>
<th>sICAM-1, % (n)</th>
<th>sVCAM-1, % (n)</th>
<th>sICAM-1 or sVCAM-1, % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;Mean + 2 SD</td>
<td>&gt;Mean + 3 SD</td>
<td>&gt;Mean + 2 SD</td>
</tr>
<tr>
<td>Preeclampsia + HELLP</td>
<td>43 (19/44)</td>
<td>14 (6/44)</td>
<td>28 (12/44)</td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td>23 (7/31)</td>
<td>7 (2/31)</td>
<td>26 (8/31)</td>
</tr>
<tr>
<td>Fetal retardation</td>
<td>42 (16/38)</td>
<td>18 (7/38)</td>
<td>16 (6/38)</td>
</tr>
<tr>
<td>Preterm labor</td>
<td>29 (7/24)</td>
<td>13 (3/24)</td>
<td>29 (5/24)</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>43 (6/14)</td>
<td>0 (0/14)</td>
<td>21 (3/14)</td>
</tr>
<tr>
<td>Gestational proteinuria</td>
<td>40 (4/9)</td>
<td>0 (0/9)</td>
<td>22 (2/9)</td>
</tr>
<tr>
<td>Infections during pregnancy</td>
<td>60 (6/10)</td>
<td>20 (2/10)</td>
<td>20 (2/10)</td>
</tr>
<tr>
<td>Miscellaneous complications</td>
<td>43 (3/7)</td>
<td>29 (2/7)</td>
<td>43 (3/7)</td>
</tr>
<tr>
<td>None</td>
<td>2.2 (30/1366)</td>
<td>0.8 (11/1366)</td>
<td>1.8 (24/1366)</td>
</tr>
</tbody>
</table>
of the proposed methods as a screening assay in routine antenatal care programs. Poor sensitivity and/or specificity is primarily a consequence of the substantial overlap of the quantitative data of the experimental and control populations in all of the proposed approaches.

In line with the identified vascular pathogenesis of preeclampsia as a consequence of a disturbed cytotrophoblast invasion during placentation, the large body of evidence demonstrating changes in endothelial cell function in women with preeclampsia, we concentrated on the analysis of markers of endothelial cell activation to screen for vascular changes that may have predictive value for preeclampsia and possibly other pregnancy disorders with a primary vascular involvement.

Inducible endothelial CAMs have been studied widely as markers of endothelial cell activation. Soluble forms of endothelial CAMs are shed from the endothelial cell surface or synthesized as specific soluble variants and can be detected in the peripheral circulation. Commercially available ELISA test systems facilitate the convenient measurement of soluble CAMs. Reflecting the activation status of endothelial cells, increased concentrations of soluble endothelial CAMs in the circulation have been reported in numerous disease processes, including neoplastic diseases and inflammatory processes, as well as metabolic diseases such as diabetes.

We and others have reported that the concentrations of several soluble endothelial CAMs are increased in the circulation of women with preeclampsia. These observations led us to quantify sICAM-1 and sVCAM-1 concentrations in pregnant women in the second trimester who developed preeclampsia during the third trimester. This preliminary study provided the first evidence that second-trimester sICAM-1 and sVCAM-1 measurements may have predictive value for preeclampsia. On the basis of these preliminary findings, we designed a prospective longitudinal study to assess the predictive value of routine antenatal sICAM-1 and sVCAM-1 measurements. These experiments, which were based on the analysis of >1500 pregnancies, showed that routine sICAM-1 and sVCAM-1 measurements have a high predictive value for the identification of women destined to develop preeclampsia. On the basis of a mean + 2 SD cutoff, two-thirds of all women who develop preeclampsia or HELLP syndrome have significantly increased concentrations of sICAM-1 and sVCAM-1 weeks before the onset of disease. Furthermore, sICAM-1 and sVCAM-1 not only have predictive value for preeclampsia, but also for several other pregnancy-related complications, including gestational hypertension, fetal retardation, preterm labor, gestational diabetes, gestational proteinuria, infections during pregnancy, and other miscellaneous complications. Together, the combined prevalence of disorders for which sICAM-1 and sVCAM-1 measurements were found to have predictive value was 11.5%, indicating that sICAM-1 and sVCAM-1 have predictive value for most clinically relevant pregnancy disorders. Thus, when we collectively analyzed all disorders and applied a mean + 2 SD cutoff, second-trimester sICAM-1 and sVCAM-1 identified 55% of women who developed a pregnancy disorder in the third trimester and had an overall predictive value of 64%. We have performed the assay as a screening test based on a single determination. It is likely that the diagnostic power of the test can be further increased by lowering the mean + 2 SD cutoff and performing a second measurement after 2–3 weeks in women who are sICAM-1 or sVCAM-1 positive in the first measurement. Lowering the cutoff for positivity would further increase sensitivity. The decreased specificity could be compensated by the suggested analysis of a second blood sample after 2–3 weeks.

We assessed the predictive power of routine prenatal sICAM-1 and sVCAM-1 measurements, applying the mean + 2 SD and the mean + 3 SD as cutoffs. To unambiguously determine the predictive power of sICAM-1 and sVCAM-1 measurements, we also performed a ROC analysis (Fig. 4). The analysis revealed areas under the curves (AUC) of 0.75 for sICAM-1 and 0.64 for sVCAM-1. The AUC of a combined sICAM-1 and sVCAM-1 measurement was 0.85, showing that routine prenatal sICAM-1 and sVCAM-1 measurements can serve as a screening assay with a very good predictive value. However, we have good reason to assume that the overall positive predictive value of routine prenatal sICAM-1 and sVCAM-1 measurements was underestimated in our analysis of a second blood sample after 2–3 weeks.
study. The “apparent” false-positive rates (3.95% with sICAM-1 or sVCAM-1 above mean + 2 SD and 1.5% with sICAM-1 or sVCAM-1 above mean + 3 SD) were significantly higher than would be expected by the otherwise perfect gaussian distribution curves for sICAM-1 and sVCAM-1 concentrations in the control population. This would strongly suggest that the apparent false-positive group in fact contains a few individuals with other possibly clinically relevant but pregnancy-unrelated complications.

Measurements of sICAM-1 and sVCAM-1 can be performed with several different commercially available ELISA test systems. However, all of the commercially available test systems are currently sold for research purposes only, and none has been approved for diagnostic applications. Our experimental study was based on the ELISA system developed by R&D Systems. Assays from other suppliers are similarly able to reliably measure sICAM-1 and sVCAM-1. We have, however, observed that different assay systems yield different absolute concentrations, which prompted us to analyze sICAM-1 and sVCAM-1 concentrations as MOM of the control population to allow assay-independent interpretation of our data.

Our study was performed under field conditions, i.e., samples were shipped to the laboratory by regular mail. Under these experimental conditions, immunoreactive sICAM-1 could be measured reliably even when the sample had been transported for 5–6 days. sVCAM-1, however, is subject to some degradation, as reflected by a characteristic degradation curve (Fig. 2). We have consequently normalized sVCAM-1 concentrations to correct for the different shipping times of the individual samples. Because 90% of all analyzed samples arrived in the laboratory after 2 or 3 days of shipment, this normalization had a negligible effect on the calculated overall sensitivity and specificity of sVCAM-1 measurements. The correction is, however, necessary when applying the assay to individual patients because the false-positive rate will be higher in samples shipped for 1 day, whereas the false-negative rate will be higher in samples that have been shipped for >3 days.

In conclusion, the present study has established routine prenatal sICAM-1 and sVCAM-1 measurements during weeks 22 to 29 of gestation as a useful laboratory test with positive predictive power to identify at-risk patients who will likely develop a severe pregnancy-related complication in late gestation. The test system has a high overall predictive value for several pregnancy disorders. It cannot discriminate between the different pregnancy disorders and thus is not capable of specifically predicting any of the pregnancy complications for which it has predictive value. Nevertheless, the early identification of >50% of pregnant women who will develop a severe complication of pregnancy in late gestation, which includes two-thirds of all women who develop preeclampsia and HELLP syndrome, weeks before the onset of disease can be considered a major advance of established prenatal care programs. The laboratory screening test-based early definition of a major risk group will markedly improve and complement currently established prenatal care protocols and aid research aimed at rationally studying the underlying vascular disorders of the large majority of pregnancy-related complications.

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