THE INFLUENCE OF GESTATIONAL AGE AND SMOKING HABITS ON THE RISK OF SUBSEQUENT PRETERM DELIVERIES

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ABSTRACT

Background Previous preterm delivery and maternal smoking are associated with increased risks of preterm delivery. It is not known whether gestational age at the time of a preterm delivery is correlated with gestational age in successive preterm deliveries and whether changes in smoking habits influence the subsequent risk of preterm delivery.

Methods We studied the associations among smoking habits, previous very preterm or moderately preterm delivery (before 32 weeks and at 32 to 36 weeks, respectively), and the risk of a subsequent very preterm or moderately preterm delivery in a population-based cohort of 243,858 women in Sweden between 1983 and 1993. The results were adjusted for covariates known to be associated with preterm delivery.

Results The odds ratios for very or moderately preterm delivery in a subsequent pregnancy among women with a previous very preterm delivery, as compared with women who had a previous term delivery, were 12.4 (95 percent confidence interval, 9.1 to 17.0) and 7.1 (95 percent confidence interval, 6.0 to 8.4), respectively. Among women with a previous moderately preterm delivery, the corresponding odds ratios were 2.3 (95 percent confidence interval, 1.9 to 3.0) and 5.9 (95 percent confidence interval, 5.5 to 6.3), respectively. The odds ratios for a very preterm second delivery among the women who smoked 1 to 9 cigarettes per day and those who smoked 10 or more cigarettes per day, as compared with nonsmokers, were 1.4 (95 percent confidence interval, 1.1 to 1.7) and 1.6 (95 percent confidence interval, 1.3 to 2.0), respectively. The corresponding odds ratios for moderate preterm delivery were 1.3 (95 percent confidence interval, 1.2 to 1.4) and 1.5 (95 percent confidence interval, 1.4 to 1.6). The women who quit smoking between pregnancies were not at increased risk for very or moderately preterm delivery, whereas the women who started to smoke in the second pregnancy had the same risk as those who continued to smoke.

Conclusions The risk of a very preterm delivery in successive pregnancies is increased primarily among women with a previous very preterm delivery. Changes in smoking habits influence the risk of preterm delivery as well. (N Engl J Med 1999;341: 943-8.)

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THE morbidity and mortality associated with preterm delivery, defined as delivery before 37 weeks of gestation, have decreased dramatically in recent decades, and today very preterm deliveries (those occurring before 32 weeks) account for the majority of deaths among preterm infants.[1,2]

Previous preterm delivery is one of the strongest predictors of a subsequent preterm delivery.[3-5] The suggestion that this effect may be especially pronounced with regard to the risk of another very preterm delivery requires confirmation by analysis of a large data set.[6] Smoking during pregnancy has also been associated with preterm delivery,[1,7-10] but whether a change in smoking habits affects the risk of preterm delivery in a subsequent pregnancy is not known. We had the opportunity to assess the associations among gestational age at the time of preterm delivery, smoking habits in two successive pregnancies, and the risk of subsequent very or moderately preterm delivery.

METHODS

Study Design

The Swedish Birth Registry recorded the births of approximately 1.2 million singleton infants between 1983 and 1993. Our study population was restricted to women who delivered consecutive first and second singleton live infants without congenital malformations (discharge codes 740 through 759 in the eighth and ninth revisions of the *International Classification of Diseases*).[11,12] Among these 257,967 women, there were 256,973 (99.6 percent) with pregnancies of at least 22 weeks for whom information on gestational age at both deliveries was available. Because we wanted to examine the smoking-related risk of a preterm delivery independently of small size for gestational age (defined as a birth weight more than 2 SD below the mean birth weight for gestational age), we excluded 13,115 women who delivered a small-for-gestational-age infant in their first or second pregnancy.[13]

We obtained information about maternal characteristics from the standardized prenatal record.[14] At the time of registration for prenatal care, women were categorized as nonsmokers (those who did not smoke daily), moderate smokers (those who had 1 to 9 cigarettes per day), or heavy smokers (those who had at least 10 cigarettes per day). Women were also classified as either living with or not living with the infant's father. We obtained information on the mother's years of formal education as of January 1, 1995, by using the unique national registration number assigned to each Swedish resident to locate records at the Education Registry.[15] We obtained information on the mother's country of birth

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TABLE 1. CHARACTERISTICS OF WOMEN WHO DELIVERED TWO SUCCESSIVE LIVE SINGLETON INFANTS BETWEEN 1983 AND 1993 IN SWEDEN AND UNIVARIATE ASSOCIATIONS WITH THE RISK OF PRETERM DELIVERY IN THE SECOND PREGNANCY.*

CHARACTERISTIC	NO. OF SECOND DELIVERIES (N=243,858)	SECOND DELIVERY BEFORE 32 WK (N=1096)		SECOND DELIVERY AT 32 TO 36 WK (N=7954)	
		NO. (%)	ODDS RATIO (95% CI)	NO. (%)	ODDS RATIO (95% CI)
Gestational age at first delivery					
<32 wk	1,424	64 (4.5)	12.0 (9.3–15.5)	240 (16.9)	7.5 (6.5–8.6)
32–36 wk	12,140	132 (1.1)	2.8 (2.3–3.4)	1644 (13.5)	5.8 (5.5–6.1)
≥37 wk†	230,294	900 (0.39)	1.0	6070 (2.6)	1.0
Smoking status					
Nonsmoker in both pregnancies†	155,347	544 (0.35)	1.0	4480 (2.9)	1.0
Nonsmoker in 1st pregnancy and smoker in 2nd pregnancy	6,793	39 (0.57)	1.6 (1.2–2.3)	230 (3.4)	1.2 (1.0–1.4)
Smoker in both pregnancies†	38,769	231 (0.60)	1.0	1667 (4.3)	1.0
Smoker in 1st pregnancy and nonsmoker in 2nd pregnancy	13,608	52 (0.38)	0.6 (0.5–0.9)	412 (3.0)	0.7 (0.6–0.8)
Data missing	29,341	230 (0.78)		1165 (4.0)	
Maternal age at second delivery					
≤24 yr	54,664	296 (0.54)	1.4 (1.2–1.7)	2166 (4.0)	1.4 (1.3–1.5)
25–29 yr†	108,462	414 (0.38)	1.0	3173 (2.9)	1.0
30–34 yr	63,842	269 (0.42)	1.1 (0.95–1.3)	1962 (3.1)	1.1 (1.0–1.1)
≥35 yr	16,791	117 (0.70)	1.8 (1.5–2.3)	648 (3.9)	1.3 (1.2–1.5)
Data missing	99	0		5	
Education					
≤11 yr	141,711	680 (0.48)	1.3 (1.1–1.4)	4919 (3.5)	1.2 (1.2–1.3)
≥12 yr†	96,988	370 (0.38)	1.0	2769 (2.9)	1.0
Data missing	5,159	46 (0.89)		266 (5.2)	
Living with the baby's father					
Yes†	210,669	846 (0.40)	1.0	6623 (3.1)	1.0
No	5,284	45 (0.85)	2.1 (1.6–2.9)	225 (4.3)	1.4 (1.2–1.6)
Data missing	27,905	205 (0.73)		1106 (4.0)	
Mother's country of birth					
Nordic country†	227,815	977 (0.43)	1.0	7271 (3.2)	1.0
Other country	13,532	80 (0.59)	1.4 (1.1–1.7)	538 (4.0)	1.3 (1.1–1.4)
Data missing	2,511	39 (1.6)		145 (5.8)	
Interpregnancy interval					
<4 mo	4,186	21 (0.50)	1.3 (0.8–1.9)	250 (6.0)	2.0 (1.8–2.3)
4–8 mo	17,948	115 (0.64)	1.6 (1.3–2.0)	737 (4.1)	1.4 (1.3–1.5)
>8–36 mo†	180,030	720 (0.40)	1.0	5454 (3.0)	1.0
>36 mo	40,818	233 (0.57)	1.4 (1.2–1.7)	1460 (3.6)	1.2 (1.1–1.3)
Data missing	876	7 (0.80)		53 (6.1)	
Year of second delivery					
1983–1987	51,267	262 (0.51)	1.2 (1.1–1.4)	1846 (3.6)	1.2 (1.1–1.2)
1988–1990	88,959	407 (0.46)	1.1 (1.0–1.3)	2860 (3.2)	1.0 (1.0–1.1)
1991–1993†	103,632	427 (0.41)	1.0	3248 (3.1)	1.0

*CI denotes confidence interval. Deliveries before 32 weeks of gestation were classified as very preterm, and those from 32 to 36 weeks as moderately preterm.

†The women with this characteristic served as the reference group.

through record linkage with the Immigration Registry. We divided countries of birth into Nordic countries (Sweden, Denmark, Norway, Finland, and Iceland) and other countries. Information about maternal age was collected by the Birth Registry when the women were discharged from the hospital.

For each woman in the study, the interpregnancy interval was defined as the time that elapsed between the birth of the first child and the estimated conception date of the following child.[16] We obtained information about the infant's date of delivery, birth weight, and sex from the standardized pediatric record, which is routinely filled out immediately after delivery. Gestational age was determined on the basis of information regarding the expected date of delivery, which was collected no later than the second trimester. When available, the results of second-trimester ultrasonography were used for dating the pregnancy. Otherwise, we dated the pregnancy on the basis of the beginning of the last menstrual period. The use of ultrasound screening to date pregnancies became increasingly common during the study period, and after 1990, all pregnant women were offered routine ultrasound screening.[17]

Statistical Analysis

We stratified preterm delivery into two categories: very preterm (before 32 weeks) and moderately preterm (32 to 36 weeks). We calculated the confidence intervals for rates using normal approximations, but if the number of outcomes was 20 or fewer, we calculated exact limits on the basis of either the Poisson or the binomial distribution. We used multiple logistic-regression analysis to evaluate the associations between smoking habits in the second pregnancy, gestational age in the first pregnancy, and the risk of very or moderately preterm delivery in the second pregnancy. In all analyses, we adjusted the estimates for maternal age, maternal educational level, whether the mother was living with the infant's father, mother's country of birth, interpregnancy interval, and

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TABLE 2. RATES OF VERY PRETERM AND MODERATELY PRETERM DELIVERY IN SECOND PREGNANCY ASSOCIATED WITH SMOKING HABITS IN TWO SUCCESSIVE PREGNANCIES.*

SMOKING HABITS	1ST DELIVERY BEFORE 32 WK (N=1130)		1ST DELIVERY AT 32 TO 36 WK (N=10,412)		1ST DELIVERY AT 37 WK OR MORE (N=202,975)	
	2ND DELIVERY BEFORE 32 WK (N=51)	2ND DELIVERY AT 32 TO 36 WK (N=183)	2ND DELIVERY BEFORE 32 WK (N=90)	2ND DELIVERY AT 32 TO 36 WK (N=1397)	2ND DELIVERY BEFORE 32 WK (N=725)	2ND DELIVERY AT 32 TO 36 WK (N=5209)
	percent of women (95 percent confidence interval)					
Nonsmoker in both pregnancies	3.8 (2.5–5.4)	16.8 (14.1–19.5)	0.77 (0.58–0.97)	12.8 (12.0–13.5)	0.31 (0.28–0.34)	2.3 (2.2–2.4)
Nonsmoker in 1st pregnancy and smoker in 2nd pregnancy	9.8 (2.7–25.0)	17.1 (6.9–35.2)	0.90 (0.18–2.6)	9.3 (6.3–13.1)	0.50 (0.34–0.70)	3.0 (2.6–3.4)
Smoker in both pregnancies	6.6 (3.9–10.6)	15.6 (11.1–20.0)	1.1 (0.71–1.7)	16.3 (14.7–18.0)	0.53 (0.45–0.60)	3.6 (3.4–3.8)
Smoker in 1st pregnancy and nonsmoker in 2nd pregnancy	2.3 (0.3–8.2)	12.5 (6.2–22.4)	1.1 (0.45–2.3)	14.2 (11.5–17.0)	0.33 (0.23–0.43)	2.4 (2.1–2.7)

*Only women for whom data on smoking habits during both pregnancies were available were included in the analyses. Deliveries before 32 weeks of gestation were classified as very preterm, and those from 32 to 36 weeks as moderately preterm.

year of delivery. In the analyses of smoking habits, we also adjusted for gestational age at delivery in the first pregnancy, and in the analyses of gestational age in the first pregnancy, we adjusted the estimates for smoking habits during both pregnancies. We excluded from our analyses 49,792 women for whom information on covariates was missing. Odds ratios were calculated to approximate relative risks and are presented with 95 percent confidence intervals. We estimated the fraction of the incidence of preterm delivery that might be reduced when certain risk factors, such as prior preterm delivery and cigarette smoking, are eliminated.

RESULTS

As compared with women whose first pregnancy resulted in a term delivery, women whose first pregnancy resulted in a delivery before 32 weeks of gestation had a greatly increased risk of subsequent very preterm or moderately preterm delivery. Women whose first delivery was moderately preterm also had a higher risk (Table 1). As compared with women who did not smoke during either pregnancy, those who began smoking during their second pregnancy were more likely to have a very or moderately preterm second delivery. Likewise, among women who smoked during their first pregnancy, those who did not smoke during their second pregnancy were less likely to have a very or moderately preterm second delivery.

The rates of very and moderately preterm delivery in the second pregnancy are shown in Table 2 according to gestational age at the first delivery and according to smoking habits in both pregnancies. In the cohort of women with a previous term delivery, beginning smoking during the second pregnancy was associated with increased rates of very and moderately preterm delivery in the second pregnancy, whereas having stopped smoking between pregnancies resulted in reduced rates. In the cohorts of women with a previous very or moderately preterm delivery, there were no clear associations between changes in smoking habits and rates of very or moderately preterm delivery in the second pregnancy.

The gestational age of the first child at delivery did not seem to affect whether the woman ceased smoking during the subsequent pregnancy. Of women who smoked and had a preterm first delivery, 24 percent did not smoke during their second pregnancy, whereas the corresponding rate among smokers who had a term first delivery was 26 percent. A change in smoking from first to second pregnancy was, however, associated with other independent variables, such as maternal age, maternal education, and the living arrangements of the baby's father (data not shown).

The risk of a subsequent very or moderately preterm delivery increased with the amount of smoking during the second pregnancy, and the adjusted smoking-related risks were higher for very preterm deliveries than for moderately preterm deliveries (Table 3). The smoking-related risks of a very or moderately preterm second delivery were unaffected by smoking during the first pregnancy.

In the analysis of smoking habits during both pregnancies, some estimates of the risk related to smoking were nonsignificant (Table 3). This finding may have been due to the small numbers of women in some groups; we therefore analyzed risks related to smoking during the second pregnancy, after adjusting for the covariates listed in Table 3. In a comparison with women who did not smoke during the second pregnancy, the odds ratios for a very preterm delivery were 1.4 (95 percent confidence interval, 1.1 to 1.7) among moderate smokers (1 to 9 cigarettes a day) and 1.6 (95 percent confidence interval, 1.3 to 2.0) among heavy smokers (10 or more cigarettes a day). There was also a dose-dependent effect of smok-

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TABLE 3. ADJUSTED ODDS RATIOS FOR PRETERM DELIVERY IN THE SECOND PREGNANCY ASSOCIATED WITH THE WOMAN'S SMOKING HABITS DURING THE FIRST AND SECOND PREGNANCIES.*

SMOKING IN 1ST PREGNANCY/ SMOKING IN 2ND PREGNANCY	SECOND DELIVERY BEFORE 32 WK (N=772)		SECOND DELIVERY AT 32 TO 36 WK (N=6083)	
	PERCENT	ODDS RATIO (95% CI)	PERCENT	ODDS RATIO (95% CI)
None/None†	0.35	1.0	2.9	1.0
None/1–9 cigarettes per day	0.53	1.3 (0.8–1.9)	3.3	1.1 (0.9–1.3)
None/≥10 cigarettes per day	0.75	1.7 (0.9–3.5)	3.8	1.2 (0.9–1.6)
1–9 cigarettes per day/None	0.38	1.0 (0.7–1.5)	3.1	1.1 (0.9–1.2)
1–9 cigarettes per day/1–9 cigarettes per day	0.54	1.4 (1.1–1.7)	4.1	1.4 (1.3–1.5)
1–9 cigarettes per day/≥10 cigarettes per day	0.66	1.6 (1.1–2.2)	4.3	1.4 (1.2–1.7)
≥10 cigarettes per day/None	0.38	0.9 (0.5–1.8)	2.8	0.9 (0.7–1.2)
≥10 cigarettes per day/1–9 cigarettes per day	0.61	1.5 (1.1–2.2)	3.9	1.2 (1.1–1.4)
≥10 cigarettes per day/≥10 cigarettes per day	0.65	1.6 (1.2–2.2)	4.9	1.6 (1.4–1.8)

*The odds ratios have been adjusted for gestational age at first delivery, maternal age, maternal education, living arrangements of the baby's father, mother's country of birth, interpregnancy interval, and year of delivery. The risk of delivery before 32 weeks was calculated through a comparison with all other deliveries (at 32 weeks and later), and the risk of delivering at 32 to 36 weeks was calculated through a comparison with deliveries at 37 weeks and later. Only women for whom data were available were included in the analyses. CI denotes confidence interval.

†The women in this category served as the reference group.

TABLE 4. ADJUSTED ODDS RATIOS FOR PRETERM DELIVERY IN A SECOND PREGNANCY ACCORDING TO GESTATIONAL AGE AT THE FIRST DELIVERY.*

GESTATIONAL AGE AT FIRST DELIVERY	DELIVERY BEFORE 32 WK (N=7772)	DELIVERY AT 32 TO 36 WK (N=6083)
	odds ratio (95% CI)	
≥37 wk†	1.0	1.0
32–36 wk	2.3 (1.9–3.0)	5.9 (5.5–6.3)
<32 wk	12.4 (9.1–17.0)	7.1 (6.0–8.4)

*The odds ratios have been adjusted for smoking habits during the first and second pregnancies, maternal age, education, living arrangements of the baby's father, mother's country of birth, interpregnancy interval, and year of delivery. The risk of delivery before 32 weeks was calculated through a comparison with all other deliveries (at 32 weeks or later), and the risk of delivery at 32 to 36 weeks was calculated through a comparison with deliveries at 37 weeks or later. Only women for whom data were available were included in the analyses. CI denotes confidence interval.

†The women in this category served as the reference group.

ing on moderately preterm delivery. For moderate smokers, the odds ratio for a moderately preterm delivery was 1.3 (95 percent confidence interval, 1.2 to 1.4); and for heavy smokers, it was 1.5 (95 percent confidence interval, 1.4 to 1.6).

The results presented in Table 2 suggest that the smoking-related risk of a very or moderately preterm delivery in the second pregnancy was affected by gestational age at the first delivery. Terms for interaction between smoking habits in the second pregnancy and gestational age at the first delivery also suggested a lower smoking-related risk of preterm delivery among women with a previous preterm delivery than among those with a previous term delivery ($P=0.002$ with smoking on a nominal scale). When we confined our analysis to women whose first pregnancy resulted in a preterm delivery, smoking was not significantly associated with the risk of a subsequent preterm delivery (data not shown).

As compared with women whose first child was delivered at term, women whose first delivery was very preterm were more than 12 times as likely to have a very preterm delivery and 7 times as likely to have a moderately preterm delivery during their second pregnancy (Table 4). The corresponding risks among women with a moderately preterm first delivery were lower.

In total, 12.6 percent of very preterm deliveries and 8.5 percent of moderately preterm deliveries were attributable to smoking. The 0.6 percent of the women who had a previous very preterm delivery accounted for 5.3 percent and 2.5 percent of all very and moderately preterm deliveries, respectively, and the corresponding estimates among women with a previous moderately preterm delivery (5.0 percent of the women) were 7.4 percent and 16.5 percent, respectively.

DISCUSSION

The risk of a very preterm second delivery was especially high among women who had had a previous very preterm delivery. Very preterm delivery has pre-

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viously been associated with second-trimester fetal losses[18] and spontaneous abortions.[19] These associations may be due to intrauterine infections before the pregnancy rather than to ascending infections during pregnancy.[6] Studies have shown that among women with bacterial vaginosis who are at high risk for preterm delivery, antibiotic treatment during pregnancy reduces the risk of a preterm delivery, but there was no decrease in the risk of preterm delivery among the women in these studies who had had a previous preterm delivery and did not have bacterial vaginosis.[20,21] It remains to be determined whether prophylactic antibiotic treatment of women who have had a previous very preterm delivery or a second-trimester loss will reduce the risk of subsequent preterm deliveries.

Smoking was associated with dose-dependent increases in the risk of very or moderately preterm delivery. If smoking is in the causal pathway, a change from being unexposed to being exposed should, in a cohort of women with a first delivery at term, lead to a higher risk of a preterm delivery in the second pregnancy.[22,23] Among nonsmoking women who previously had a term delivery, starting smoking during a subsequent pregnancy increased the risk of very or moderately preterm delivery. A change from smoking to not smoking, on the other hand, should reduce the risk of a subsequent preterm delivery. However, we did not find that a reduction in smoking among women with a previous preterm delivery reduced that risk. Two factors closely associated with recurrent preterm birth are infections and cervical incompetence.[2,24] When such factors are present, smoking may not influence the risk of preterm delivery further.

We were unable to distinguish between spontaneous and induced preterm deliveries. Earlier studies have suggested that smoking may be more strongly associated with spontaneous rather than induced preterm delivery.[6,25] Smoking may increase the risk of intrauterine infections[2,26] and may also stimulate production of prostaglandin E_2, which causes contraction in myometrial tissue.[27,28] Smoking also reduces the level of type III collagen, which may increase the risk of preterm rupture of the membranes.[29,30]

The present study has probably underestimated the smoking-related risk of preterm delivery. First, by purposely excluding deliveries of small-for-gestational-age infants, which constitute a large proportion of preterm deliveries,[31] we underestimated the prevalence of smoking in our study population. Cigarette smoking is causally associated with the risk of delivering a small-for-gestational-age infant,[32,33] whereas the association between smoking and preterm delivery is less certain.[1] We therefore thought it important to study the effects of smoking on the risk of preterm delivery independently of its effect on the delivery of small-for-gestational-age infants. Second, information about maternal smoking was collected by means of interviews in early pregnancy. The pregnancy-related risks of cigarette smoking have been well publicized, and peer pressure may have influenced women to underreport the number of cigarettes that they smoked.[34] Other women may have quit smoking later during pregnancy.[35] Third, a relatively large proportion of women (approximately 20 percent) were excluded from the analyses primarily because information on their smoking habits was missing. The rates of preterm delivery were higher among women who smoked and among women for whom information on smoking habits was missing. If women for whom data on smoking were missing were more likely to be smokers than nonsmokers, the smoking-related risk of preterm delivery that we found may be an underestimation of the true risk.

The availability of each woman's unique Swedish national registration number[15] allowed us to study successive births. The prospective method of data collection precludes recall bias. We controlled for several covariates, and because the prenatal and obstetrical care provided to Swedish women is standardized, possible unmeasured confounders have limited effect. Nevertheless, we lacked information on prepregnancy weight, weight gain, and infections.[1] Partial adjustment for these factors was probably achieved as a result of their association with educational level.

Previous very preterm delivery is associated with a marked increase in the risk of very preterm delivery in subsequent pregnancies. This risk is probably substantially mediated through a wide spectrum of microorganisms,[36] and different strategies of intervention with antibiotics should therefore be evaluated in women with a history of very preterm delivery. The increase in the risk of very preterm delivery associated with smoking is smaller, but smoking is a prevalent risk factor among women of reproductive age. In the present study, smokers with preterm first deliveries did not quit smoking in greater numbers than did women with term deliveries. Although the smoking-related risk of preterm delivery may not be well known to the public, the smoking-related risk of delivering a small-for-gestational-age infant is, and the rates of quitting smoking were similar among smokers who did and who did not deliver a small-for-gestational-age infant in the first pregnancy (data not shown). Strategies to reduce the prevalence of smoking during pregnancy may include intense intervention for women who have had smoking-related adverse outcomes in a previous pregnancy, but primary prevention is probably more important. In Sweden, the rate of daily smoking in early pregnancy decreased from 31 percent in 1983 to 16 percent in 1997, and much of this decrease occurred in young women (Otterblad-Olausson P, National Board of Health and Welfare, Stockholm, Sweden: personal communication).

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