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THE DETERMINANTS IN THE MANAGEMENT OF PREGNANCIES COMPLICATED WITH IMMUNE THROMBOCYTOPENIA*

İMMÜN TROMBOSİTOPENİYLE KOMPLİKE GEBELİKLERİN YÖNETİMİNDE BELİRLEYİCİLER

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ABSTRACT

Objective: This study aims to determine the hematologic and obstetric factors that would affect the management of immune thrombocytopenia (ITP) during pregnancy.

Material and Method: This is a retrospective review of 54 pregnancies that were complicated by ITP at a single tertiary center. All of the patients were followed-up and delivered at the same center. Subgroup analysis for obstetric outcomes was made according to the platelet counts at the time of delivery (<50x103/mm^3 or ≥50x10^3/mm^3), the time of diagnosis (before or during pregnancy) and neonatal platelet counts (≤100x10^3/mm^3 or >100x10^3/mm^3).

Result: Transfusion of blood products, steroid administration per se, or in combination with intravenous immunoglobulins (IVIG), were significantly more often administered in those with platelet counts <50x10^3/mm^3 at the time of delivery (p=0.020, p=0.020, and p=0.004, respectively). The patients who were first diagnosed with ITP during pregnancy had higher rates of transfusion of blood products (p=0.041), higher rates of vaginal deliveries (p=0.048), and lower rates of preterm delivery (p=0.044) when compared to the patients who had ITP diagnosed before the on-

ÖZET

Amaç: Bu çalışma, gebelikte immün trombositopeni (İTP) yönetimini etkileyecek hematolojik ve obstetrik faktörleri belirlemeyi amaçlamaktadır.

Gereç ve Yöntem: İTP nedeniyle hastanemizde tedavi edilen ve doğumu hastanemizde yaptırılan İTP ile komplike olmuş 54 gebelik retrospektif olarak incelenmiştir. Obstetrik sonuçlar için alt grup analizi, doğum anındaki (<50x10^3/mm^3 veya ≥50x10^3/mm^3) ve tanı anındaki (gebelik öncesi veya gebelik sırasında) trombosit sayısı ve neonatal trombosit sayısına (≤100x10^3/mm^3 veya >100x10^3/mm^3) göre yapılmıştır.

Bulgular: Doğumda trombosit sayısı <50x10^3/mm^3 olan gebeliklerde steroid uygulaması, intravenöz immünoglobulinler (İVİG) ile birlikte steroid kullanımı ve kan ürünleri transfüzyonu anlamlı olarak daha yüksek saptanmıştır (sırasıyla, p=0,020, p=0,020, p=0,004). Gebelik öncesi İTP tanısı alan hastalara göre gebelikte İTP tanısı alan hastalarda, gebelik esnasında transfüzyon ve vajinal doğum oranının anlamlı olarak daha yüksek, erken doğum oranının anlamlı olarak daha düşük olduğu ve doğum anındaki gebelik yaşı, doğum ağırlığı ve neonatal trombosit sayısının an-

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set of pregnancy. Gestational age at birth (p=0.020), birth weight (p=0.002) and neonatal platelet count (p=0.002) were significantly higher in those who were diagnosed during the pregnancy. History of maternal splenectomy, intensive care unit admission, IVIG administration, and blood transfusion were significantly more frequent in neonates with platelet counts ≤100x10^3/mm^3 (p=0.028, p=0.001, p=0.001, and p=0.025, respectively).

Conclusion: The women diagnosed with ITP before the pregnancy and those who were diagnosed during the pregnancy had comparable rates of postpartum bleeding. However, there was a tendency towards overtreatment of the women who developed ITP during pregnancy.

Keywords: Immune thrombocytopenia, pregnancy, bleeding

lamlı olarak daha yüksek olduğu belirlenmiştir (sırasıyla, p=0,041, p=0,048, p=0,044, p=0,020, p=0,002 ve p=0,002). Trombosit sayısı ≤100x10^3/mm^3 olan yenidoğanlarda maternal splenektomi öyküsü, yoğun bakım gereksinimi, IVIG tedavisi ve kan transfüzyon gereksinimi anlamlı olarak daha yüksek bulunmuştur (sırasıyla p=0,028, p=0,001, p=0,001 ve p=0,025).

Sonuç: Gebelik öncesi İTP tanısı alan kadınlar ve gebelik sırasında İTP tanısı konulan kadınlar, postpartum kanama bakımından benzerdir. Buna karşılık, gebelik sırasında İTP gelişen kadınların gereğinden fazla tedavi edilmesine yönelik bir eğilim söz konusudur.

Anahtar Kelimeler: İmmun trombositopeni, gebelik, kanama

INTRODUCTION

Thrombocytopenia is the second most common hematological disorder in pregnancy after iron deficiency anemia (1). Thrombocytopenia refers to a platelet count less than 150x10^3/mm^3 and its prevalence ranges between 6.6% and 11.6% in pregnancy (2).

Immune thrombocytopenia (ITP) has an incidence of 1.6 to 3.9 per 100,000 patient-years. It has been reported that this incidence increases with age and has a slight female predominance (3). ITP affects 1 or 2 of every 1000 pregnancies and accounts for 5% of pregnancies with thrombocytopenia (4). This autoimmune disease can be diagnosed for the first time during pregnancy as its onset may be triggered by gestation (5). ITP during pregnancy might also present as an exacerbation of a previously diagnosed disease, particularly in the last trimester (5, 6).

The prevalence of chronic active ITP corresponds to 245 cases per million in adults and 10%-15% of this adult population comprises women of childbearing age (7). Considering that each woman at reproductive age has an average of two children in most European countries, it can be estimated that about 2 out of 10,000 women with chronic active ITP will become pregnant (6, 7). Similarly, the incidence of severe chronic ITP has been designated as 0.83 in 10,000 pregnant women by a nationwide survey conducted in the United Kingdom (8).

The most important maternal concern related to ITP is the risk of intractable bleeding especially at the time of delivery (9). Similarly, the major ITP-related fetal problem is the risk of intracranial hemorrhage due to neonatal thrombocytopenia induced by the transplacental passage of maternal antiplatelet antibodies (10). Therefore, prompt diagnosis and treatment of ITP should be made to prevent complications (11).

This study aims to determine the hematologic and obstetric factors that would affect the management of ITP during pregnancy.

MATERIAL and METHODS

The present study was approved by the Institutional Review Board and Ethical Committee of Istanbul University Istanbul Faculty of Medicine where the study was conducted (Date: 05.28.2021, No:11). This is a retrospective review of 54 pregnancies of 49 women complicated with ITP and, treated and delivered at the obstetrics department of the study center between January 2013 and May 2020. The study includes the pregnancies that were complicated with ITP and got the first diagnosis during that index pregnancy (n=17) and all pregnancies of the women who had a known diagnosis of ITP before pregnancy (n=37).

The diagnosis of ITP was made by a senior hematologist. The patients with platelet count <150x10^3/mm^3 with normal white and red blood cell counts, whose bone marrow biopsy showed a normal or increased number of megakaryocytes, and who had other obstetric and hereditary causes of thrombocytopenia were excluded. Other causes of thrombocytopenia that were excluded consisted of incidental gestational thrombocytopenia, preeclampsia, HELLP syndrome (Hemolysis, Elevated Liver enzyme levels, Low Platelets), viral infections such as hepatitis C, cytomegalovirus, human immunodeficiency virus, sepsis, disseminated intravascular coagulation, drug-induced thrombocytopenia, liver disease and autoimmune conditions such as systemic lupus erythematosus, hemolytic uremic syndrome, thrombotic thrombocytopenic purpura and other hereditary thrombocytopenias. The pregnant women who received anticoagulant drugs and the pregnant women who were diagnosed with gestational thrombocytopenia were also excluded from the study. The diagnosis of gestational thrombocytopenia was made in patients with platelet counts >70x10^3/mm^3 and

in those with platelet counts within a normal range preceding or succeeding the pregnancy.

Data related to maternal age, time of ITP diagnosis (before or during pregnancy), minimum platelet count during pregnancy, medical treatment during pregnancy (steroids or steroids combined with IVIG), history of maternal splenectomy, transfusion of blood products during pregnancy, mode of delivery (vaginal or cesarean section), platelet counts at the time of delivery, postpartum bleeding, gestational age (GA) at delivery, preterm delivery and birth weight were acquired from medical records. Data related to the neonates including platelet counts, need for intensive care, length of stay at the intensive care unit, medical treatment (IVIG, phototherapy, or transfusion of blood products) and intracranial bleeding were also recorded.

Corticosteroid treatment was carried out by administering prednisone at a daily dose of 40 - 60 mg for a period of one week to nine months until delivery. IVIG treatment was initiated at daily doses of 400 mg/kg for five days. Preterm delivery was defined as delivery before 37 weeks of gestation. Postpartum bleeding has been identified as blood loss of more than 500 ml within 24 hours following a vaginal delivery or more than 1000 ml within 24 hours following cesarean delivery.

Subgroup analysis for perinatal outcomes was made according to the platelet counts at the time of delivery ($<50x10^3/mm^3$ or $\geq50x10^3/mm^3$), the time of ITP diagnosis (before or during pregnancy) and neonatal platelet counts ($\leq100x10^3/mm^3$ or $>100x10/mm^3$).

Statistical analysis

Collected data were analyzed using Statistical Package for Social Sciences version 17.0 (IBM Corporation, Armonk, NY, USA). The distribution of continuous variables was tested by a Shapiro-Wilk test and the assumption of homogeneity of variances was examined using a Levene test. Continuous variables were expressed as mean ± standard deviation or median (minimum-maximum) while categorical variables were denoted as numbers and percentages where appropriate. A Student's t-test and Mann-Whitney U test were used to compare the continuous variables whereas a Pearson's chi-square test, continuity-adjusted chi-square test, Fisher's exact test and, Fisher-Freeman-Halton test were used to compare the categorical variables. Two-tailed p-values less than 0.05 were statistically significant.

RESULTS

The perinatal outcomes of pregnancies with ITP based on platelet counts at the time of delivery are demonstrated in Table 1. When compared to the pregnancies with platelet counts $\geq50x10^3/mm^3$ at delivery, steroid administration, use of steroids in combination with IVIG, and transfusion of blood products were significantly more frequently observed in pregnancies with platelet counts $<50x10^3/mm^3$ at delivery (p=0.020, p=0.020 and p=0.004 respectively).

Table 1: Perinatal outcomes of pregnancies with ITP based on the platelet counts at delivery

	Platelet counts $<50x10^3/mm^3$ (n=15)	Platelet counts $\geq50x10^3/mm^3$ (n=39)	p value
Maternal age (years)	26.7±5.5	29.0±5.3	0.150
ITP diagnosed before pregnancy (n, %)	12 (80.0)	25 (64.1)	0.338
ITP diagnosed during pregnancy (n, %)	3 (20.0)	14 (35.9)	0.338
Steroid use during pregnancy (n, %)	8 (53.3)	15 (38.5)	0.020*
Steroid+IVIG use during pregnancy (n, %)	5 (33.3)	4 (10.3)	0.020*
History of splenectomy (n, %)	0 (0.0)	5 (12.8)	0.306
Transfusion during pregnancy (n, %)	14 (93.3)	18 (46.2)	0.004*
Vaginal delivery (n, %)	7 (46.7)	18 (46.2)	0.999
Cesarean delivery (n, %)	8 (53.3)	21 (53.8)	0.999
Postpartum bleeding (n, %)	2 (13.3)	1 (2.6)	0.183
Gestational age at delivery (weeks)	39 (31-40)	39 (31-41)	0.625
Preterm delivery (<37 weeks) (n, %)	3 (20.0)	6 (15.4)	0.696
Birth weight (gr)	3285.0±383.2	3195.4±621.2	0.605
Neonatal platelet count ($x10^3/mm^3$)	174.4±57.4	166.9±95.8	0.727
Neonatal platelet counts $\leq100x10^3/mm^3$ (n, %)	1 (6.7)	8 (20.5)	0.417
Need for neonatal intensive care (n, %)	3 (20.0)	9 (23.1)	0.999
Stay at neonatal intensive care unit (days)	10 (5-16)	6 (3-16)	0.482
Neonatal IVIG treatment (n, %)	1 (6.7)	7 (17.9)	0.419
Neonatal phototherapy (n, %)	1 (6.7)	2 (5.1)	0.999
Neonatal platelet transfusion (n, %)	0 (0.0)	2 (5.1)	0.999

*p<0.05 was accepted statistically significant, ITP: Immune thrombocytopenia, IVIG: Intravenous immunoglobulins.

The perinatal outcomes of pregnancies with ITP depending on the time of diagnosis are summarized in Table 2. The patients who were first diagnosed during the pregnancy had higher rates of blood transfusions, vaginal deliveries, GA at birth, birth weight, and neonatal platelet counts when compared to the patients who had the diagnosis of ITP before the pregnancy (p=0.041, p=0.048, p=0.020, p=0.002 and p=0.002 respectively). Preterm deliveries were significantly lower in those with a first diagnosis of ITP during the pregnancy (p=0.044).

The perinatal outcomes based on neonatal platelet counts are displayed in Table 3. When compared to the

Table 2: Perinatal outcomes of pregnancies with ITP based on the time of diagnosis

	ITP diagnosed before pregnancy (n=37)	ITP diagnosed during pregnancy (n=17)	p value
Maternal age (years)	28.4±5.7	28.3±5.0	0.932
History of splenectomy (n, %)	5 (13.5)	0 (0.0)	0.168
Transfusion during pregnancy (n, %)	18 (48.6)	14 (82.4)	0.041*
Platelet count at delivery (x10^3/mm^3)	65.7 (2.8-322.0)	63.0 (34.0-101.0)	0.948
Platelet count <50x10^3/mm^3 at delivery (n, %)	12 (32.4)	3 (17.6)	0.338
Vaginal delivery (n, %)	16 (43.2)	13 (76.5)	0.048*
Cesarean delivery (n, %)	21 (56.8)	4 (23.5)	0.048*
Postpartum bleeding (n, %)	3 (8.1)	0 (0.0)	0.544
Gestational age at delivery (weeks)	38 (31-41)	39 (38-41	0.020*
Preterm delivery (<37 weeks) (n, %)	9 (24.3)	0 (0.0)	0.044*
Birth weight (gr)	3066.3±568.8	3555.3±385.2	0.002*
Neonatal platelet count (x10^3/mm^3)	145.5±77.6	220.0±84.6	0.002*
Neonatal platelet count ≤100x10^3/mm^3 (n, %)	8 (21.6)	1 (5.9)	0.244
Need for neonatal intensive care (n, %)	11 (29.7)	1 (5.9)	0.078
Stay at neonatal intensive care unit (days)	7 (3-16)	5 (5-5)	0.568
Neonatal IVIG treatment (n, %)	7 (18.9)	1 (5.9)	0.411
Neonatal phototherapy (n, %)	2 (5.4)	1 (5.9)	0.999

*p<0.05 was accepted statistically significant, IVIG: Intravenous immunoglobulins.

Table 3: Perinatal outcomes of pregnancies with ITP based on neonatal platelet counts

	Neonatal platelet counts ≤100x10^3/mm^3 (n=9)	Neonatal platelet counts >100x10^3/mm^3 (n=45)	p value
Maternal age (years)	28.3±5.8	28.4±5.4	0.974
Maternal platelet nadir during pregnancy	55.0 (3.0-287.0)	56.2 (3.3-362.0)	0.972
ITP diagnosed before pregnancy (n, %)	8 (88.9)	29 (64.4)	0.244
ITP diagnosed during pregnancy (n, %)	1 (11.1)	16 (35.6)	0.244
Steroid use during pregnancy (n, %)	3 (33.3)	20 (44.4)	0.446
Steroid+IVIG use during pregnancy (n, %)	3 (33.3)	6 (13.3)	0.446
History of splenectomy (n, %)	3 (33.3)	2 (4.4)	0.028*
Transfusion during pregnancy (n, %)	5 (55.6)	27 (60.0)	0.999
Platelet count <50x10^3/mm^3 at delivery (n, %)	1 (11.1)	14 (31.1)	0.417
Vaginal delivery (n, %)	5 (55.6)	24 (53.3)	0.999
Cesarean delivery (n, %)	4 (44.4)	21 (46.7)	0.999
Gestational age at delivery	38 (31-40)	39 (31-41)	0.281
Preterm delivery (<37 weeks) (n, %)	2 (22.2)	7 (15.6)	0.635
Birth weight (grams)	2902.2±774.8	3283.9±498.0	0.063
Need for neonatal intensive care (n, %)	7 (77.8)	5 (11.1)	0.001*
Stay at neonatal intensive care unit (days)	7 (5-16)	6 (3-16)	0.530
Neonatal IVIG treatment (n, %)	8 (88.9)	0 (0.0)	0.001*
Neonatal phototherapy (n, %)	2 (22.2)	1 (2.2)	0.069
Neonatal platelet transfusion (n, %)	2 (22.2)	0 (0.0)	0.025*

*p<0.05 was accepted statistically significant, ITP: Immune thrombocytopenia, IVIG: Intravenous immunoglobulins.

neonates born with platelet counts >100x10^3/mm^3, rates of maternal splenectomy, need for neonatal intensive care, neonatal administration of IVIG, and blood transfusions were significantly more frequently observed in the neonates born with platelet counts ≤100x10^3/mm^3 (p=0.028, p=0.001, p=0.001 and p=0.025 respectively).

The clinical characteristics of nine neonates (16.7%) that were born with platelet counts ≤100x10^3/mm^3 are shown in Table 4. Five of these neonates were delivered vaginally while the remaining four (44.4%) were by cesarean section. Eight neonates (88.9%) received IVIG while two neonates (22.2%) underwent phototherapy in combination with IVIG therapy. Intracranial bleeding occurred in only one neonate who was born by cesarean section with a neonatal platelet count of 38,000/mm^3.

with IVIG and transfusion of blood products were significantly more frequently administered to ITP patients with platelet counts <50x10^3/mm^3 compared to those with platelet counts ≥50x10^3/mm^3 at the time of delivery. This finding suggests that pregnant women with platelet counts <50x10^3/mm^3 are more likely to undergo medical treatment and transfusion even though the management of ITP in pregnancy should aim to reduce the risk of postpartum bleeding instead of increasing maternal platelet counts. Such a contradictory finding can be due to our retrospective study design and the relatively small cohort size. Another reason can be the fact that the study center is a tertiary university center that receives many referrals of high- risk pregnancies. The possible overtreatment of asymptomatic patients with ITP might be also considered

Table 4: Clinical characteristics of newborns with platelet count ≤100x10^3/mm^3

Case Number	Maternal splenectomy	Gestational age at delivery (weeks)	Delivery mode	Birth weight (grams)	Neonatal platelet count	Neonatal treatment	Neonatal intracranial bleeding
1	No	37	Cesarean	2510	38000	IVIG	Yes
2	No	39	Vaginal	3460	40900	IVIG+ phototherapy	No
3	No	36	Vaginal	2340	18800	IVIG+ phototherapy	No
4	Yes	38	Cesarean	2500	17000	IVIG	No
5	Yes	40	Cesarean	3730	93300	None	No
6	No	39	Vaginal	3920	15000	IVIG	No
7	No	31	Cesarean	1480	8400	IVIG	No
8	No	37	Vaginal	2940	16500	IVIG	No
9	No	39	Vaginal	3880	19000	IVIG	No

IVIG: Intravenous immunoglobulins.

DISCUSSION

The management of pregnancies complicated with ITP is a challenging issue (12). The American Society of Hematology recommends the treatment of pregnancies with ITP only if platelet counts are <30x10^3/mm^3 and/or there are symptoms of thrombocytopenia (13). Treatment is not required until 36 weeks of gestation or the expected time of delivery if platelet counts are ≥30x10^3/mm^3 without any symptoms of thrombocytopenia (13). A platelet count of ≥50x10^3/mm^3 is accepted as a safe lower limit for vaginal delivery and cesarean section (4).

In this study, rates of postpartum bleeding and neonatal complications did not differ between pregnancies associated with platelet counts <50x10^3/mm^3 or ≥50x10^3/mm^3. However, steroid therapy, steroid therapy in combination as an underlying factor, as suggested by Care et al. (8). Her nationwide survey and a Canadian study have defined the usually benign course of ITP in pregnant women (8, 14). These studies have specified that pregnancies complicated with ITP and healthy pregnancies were comparable with respect to postpartum bleeding and the risk of postpartum bleeding was unrelated to maternal platelet counts (8, 14).

Corticosteroids and IVIG have been considered as the first-line treatment for pregnancies complicated with ITP (12-14). It has been reported that about 30% to 35% of women receive medical treatment for ITP during pregnancy (15). In this study, corticosteroids were used in 42.6% of the pregnancies and IVIG in combination with steroids was administered in 16.7% of the pregnancies. The relatively high incidence of medical treatment in this study may be

interpreted as the evidence supporting the possibility of overtreatment of asymptomatic patients with ITP diagnosed during pregnancy. The findings of large-scale studies concerning the treatment with corticosteroids, IVIG, or both failed to yield any significant difference in terms of either maternal or fetal outcomes (8, 14, 16).

In this study, neonatal platelet counts were significantly higher in the patients who had ITP diagnosed during the pregnancy than in the patients who had ITP diagnosed before the pregnancy. Samuels et al. were the first to show that neonates born to mothers who had ITP diagnosed before pregnancy were more likely to have severe thrombocytopenia (17). A Japanese study also confirmed the significantly dramatic fall in platelet counts of newborns that were delivered by women with a known history of ITP (18). However, three other studies were unable to detect the relationship between the pre-pregnancy history of ITP and neonatal thrombocytopenia (19-21). Such discrepancy can be attributed to the heterogeneity in the demographic and clinical characteristics of the reviewed patients. It may be speculated that the relatively longer duration of the disease and/or the relatively higher number of exacerbations in pregnant women with a prior history of ITP enhance the production of anti-platelet auto-antibodies. This excessive load of autoantibodies may be conveyed to the fetus in utero, thus, inducing the destruction of fetal platelets and leading to the development of neonatal thrombocytopenia.

This study has indicated that vaginal delivery is significantly more frequently observed and the preterm delivery rate is significantly lower in patients who had an ITP diagnosis during the pregnancy than those diagnosed with ITP before the onset of pregnancy. In fact, the decision for the mode of delivery in pregnancies with ITP should be solely based on obstetric indications. Uncomplicated vaginal delivery appears as safe as cesarean section for the newborn and even safer for the mother (22, 23). However, cesarean section is usually preferred for the pregnancies complicated with ITP. The rationale behind this preference is the theoretically assumed decrease in the risk of intracranial bleeding for the neonates of affected mothers. Similar to our study, the rate of cesarean delivery was 51.7% in a Korean study (24). Obstetric indications might be the underlying reason for the significantly higher rate of cesarean delivery in the pregnancies of women who had a known history of ITP. The evidence favoring this suggestion is the significantly higher rates of preterm delivery in pregnant women with a known history of ITP. That is, indications for emergency preterm cesarean delivery might have been made based on the underlying etiologic factors such as fetal distress, premature rupture of membranes and malpresentation. In this study, the rate of preterm delivery has been estimated as 24.3% for the pregnant women who had ITP diagnosed before pregnancy. This number is higher than the incidence of preterm delivery which has been reported as 15.2% in previously published studies (9, 22).

In this study, the neonates with platelet counts ≤100x10^3/mm^3 or >100x10^3/mm^3 were statistically comparable with respect to minimum maternal platelet count during pregnancy and severe maternal thrombocytopenia (<50x10^3/mm^3) at the time of delivery. This finding supports the existence of a poor correlation between maternal and fetal platelet counts in pregnancies complicated with ITP (20-24). It has been declared that thrombocytopenia is relatively rare in newborns delivered by women with ITP. Previously published studies have yielded an incidence of 10% for thrombocytopenia in infants born to affected mothers (20). On the other hand, the risk of intracranial hemorrhage has been estimated as <1.5% with mortality rates of <1% in newborns with thrombocytopenia (21). In the present study, nine (17.6%) newborns had platelet counts ≤100x10^3/mm^3 and six newborns (11.1%) had platelet counts <30x10^3/mm^3 but only one newborn was diagnosed with intracranial hemorrhage and no deaths occurred. This finding can be the result of vigorous treatment received by the thrombocytopenic neonates.

It has been well established that the management of pregnancies complicated with ITP requires the collaboration of obstetricians, hematologists, and pediatricians at a tertiary center. Our findings imply that and the diagnosis of ITP before pregnancy appears as a risk factor for preterm delivery and cesarean section. Further research has been warranted to standardize the approach for the management of pregnancies complicated with ITP.

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