

Effect of Phoenix dactylifera on Changes in Placental Growth Rate Factors in Pregnant Women

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ABSTRACT/ ABSTRAK

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ABSTRACT. The annual maternal mortality rate (MMR) fluctuates and one of the causes is preeclampsia with 33.3% of the incidence of preeclampsia and maternal mortality. Placental growth factor (PIGF) has a major role in the development of preeclampsia. Objective: Analyzing the Effect of Phoenix Dactylifera on Changes in Levels of Placental Growth Factor (PIGF) as a predictor of preeclampsia in pregnant women. Method: This research uses a hybrid method, which combines two research methods (Quasy Experiment and Prospective Kohort) with a pre-post test control design. A total of 40 respondents (30 respondents in the ajwa date group and 10 respondents in the group recommended to eat fruits and vegetables) the sample size was determined using the Yamane formula with simple random sampling technique. Data analysis using the Wilcoxon test. Results: The Wilcoxon test on changes in PLGF levels based on the pre-post test intervention group produced the Asymp value. Sig 0.000 < 0.05 (Mean: 0.591-3.856) and the control group pre-post test resulted in Asymp values. Sig 0.073 > 0.05 (Mean: 1.040-0.701). Conclusion: The changes that occurred in the intervention group were due to a significant decrease in blood pressure which affected PLGF levels in blood plasma after giving phoenix dactylifera fruit for 8 weeks and given 7 eggs / day (100 grams). Phoenix dactylifera can inhibit the development of PIGF in blood plasma thus preventing the occurrence of preeclampsia in pregnant women who are hypertensive.

ABSTRAK. Angka Kematian Ibu (AKI) setiap tahun mengalami fluktuatif dan salah satu penyebabnya adalah preeklamsi dengan 33,3% sumbangsi kejadian preeklamsi terhadap kematian ibu. *Placental growth factor* (PIGF) memiliki peran besar dalam perkembangan preeklamsi. Tujuan: Menganalisis Pengaruh *Phoenix Dactylifera* Terhadap Perubahan Kadar *Placental Growth Factor* (PIGF) sebagai prediktor preeklamsi pada Ibu Hamil. Metode: Penelitian ini menggunakan metode Hibrid yakni menggabungkan dua metode penelitian (Quasy Eksperimen dan Kohort Prospektif) dengan *pre-post test control design*. Sebanyak 40 responden (30 responden pada kelompok kurma ajwa dan 10 responden pada kelompok yang dianjurkan makan buah dan sayur) besaran sampel ditentukan dengan menggunakan rumus Yamane dengan teknik pengambilan sampel simple random sampling. Analisis data menggunakan uji *Wilcoxon*. Hasil: Uji *Wilcoxon* test pada perubahan Kadar PLGF berdasarkan kelompok Intervensi pre-post test memiliki nilai Asymp. Sig 0.000 < 0.05 (Mean : 0.591-3.856) dan kelompok kontrol *pre-post test* menghasilkan nilai Asymp. Sig 0.073 > 0.05 (Mean : 1.040-0.701). Kesimpulan: Perubahan yang terjadi pada kelompok intervensi karena terdapat penurunan tekanan darah yang mempengaruhi kadar PLGF dalam plasma darah yang signifikan setelah dilakukan pemberian buah phoenix dactylifera selama 8 minggu dan diberikan 7 butir/hari (100 gram). Phoenix dactylifera dapat menghambat perkembangan PIGF dalam plasma darah sehingga mencegah terjadinya preeklamsia pada ibu hamil yang hipertensi.

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INTRODUCTION

World data according to *World Health Organization* (WHO) reported that the maternal mortality rate (AKI) in 2018 was 289,000 people. Some countries have quite high AKI such as Sub-Saharan Africa with 179,000 people, South Asia with 69,000 people, and Southeast Asia with 16,000 people. Especially in Southeast Asia such as Vietnam 49 per 100,000 live births, Thailand 26 per 100,000 live births, Brunei 27 per 100,000 live births and Malaysia 29 per 100,000 live births, and Indonesia 190 per 1000,000 live births, Indonesia still occupies the highest maternal mortality rate in Southeast Asian countries (Irwinda et al., 2016; World Health Organization, 2018).

According to data from the Ministry of Health of the Republic of Indonesia in 2015, the maternal mortality rate decreased from 359 per 100,000 KH in 2012 to 305 per 100,000 KH in 2015 and the data in 2018-2019 showed a significant decrease from 4,226 to 4,221 maternal deaths in Indonesia. This has not significantly affected the decline in maternal mortality in Indonesia. Nationally in 2019, the most common causes of maternal death were bleeding (1,280 cases), hypertension in pregnancy (1,066 cases), and infections (207 cases) (Kemenkes RI, 2019).

The data from the Ministry of Health, the most AKI is on the island of Java and South Sulawesi Province also contributes quite high to the increase in AKI in Indonesia. The profile of the South Sulawesi Provincial Health Office in 2020 shows that the maternal mortality rate is still fluctuating from 2016-2018, namely in 2016 at 63 per 100,000 Live Births (KH), increased in 2017 to 153 per 100,000 KH, and in 2018 decreased to 53 per 100,000 KH. The main causes of maternal death in the city of Makassar were 42.4% of bleeding, 33.3% of hypertension and 18% of infections. Based on data from the medical records of the Mother and Child Hospital (RSIA) Sitti Khadijah 1 Makassar, there were 126 cases of PE from 3812 normal pregnant women visiting in 2015, there were 127 cases of PE from 3815 pregnant women who visited in 2016 and 127 cases of preeclampsia and 2 cases of eclampsia from 3813 normal pregnant women who visited in the January period – December 2019 (Dinkes Provinsi Sul-Sel, 2018; Sembiring, 2020).

The high mortality rate due to gestational hypertension and preeclampsia is related to the complications it causes. Lai and Coulter, (2017) Proving the role of gestational hypertension in increasing the risk of heart disease, kidney disease and stroke in mothers. In preeclampsia, maternal complications include *oliguria*, *anuria*, *solusio plasenta* and syndrome *hemolysis*, *elevated liver enzyme*, *low platelets* (HELLP). In infants, gestational hypertension may increase the risk *Intra-uterine Growth Restriction (IUGR)*, *Small for Gestational Age (SGA)* and premature birth, while preeclampsia, increases the risk of intrauterine death, stunted fetal growth, prematurity and perinatal asphyxia (Roberts *et al.*, 2013).

SCOPE conducted cohort research related to the characteristics of pregnant women that can turn into preeclampsia, premature delivery, full-term and preeclampsia. Pregnant women who give birth before 34 weeks of early onset of preeclampsia are more common in mothers with primigravida, namely 50%: 23%. Pregnant women who have obesity with *Body Mass Index* (BMI) ≥ 30 kg/m² is 21% : 15%. The pregnant woman had an average systole blood pressure and diastole at the age of 14 weeks – 16 weeks was an average systole of 116 ± 13 mmHg: 107 ± 10 mmHg, while the average diastole was 73 ± 10 mmHg: 65 ± 8 mmHg. When compared to pregnant women who do not have the onset of preeclampsia at the

beginning, they will have an Asymp.Sig value $p < 0.01$ (Kenny et al., 2014; Mustafa et al., 2012).

Intrinsically the pathogenesis of preeclampsia is still unclear, but there are several theories that mention the involvement of angiogenic factors, namely *Placental Growth Factor (PLGF)* and *Soluble FMS Like Tyrosine Kinase-1*. These two angiogenic factors have a major role in the increase in systolic and diastole blood pressure as well as proteinuria caused by the increase in the angiogenic compound sFLT-1 and the decrease in the angiogenic compound PLGF. The imbalance of the two compounds will cause disruption of vasculogenesis and angiogenesis in the fetomaternal circulation (Burke et al., 2016; Luft, 2014).

Sulistiyowati *et al.*, (2017) conducted research in 2011 related to recombinant vascular endothelial growth factor in the PE model placenta. Sulistiyowati et al. concluded that pregnant women ≥ 37 weeks gestation with preeclampsia had increased serum sFlt-1 levels (high) and decreased serum PIGF levels (low) compared to pregnant women without preeclampsia. Pregnant women who are not preeclampsia/normal pregnant women have a positively correlated ratio of sFlt-1 and PIGF levels. An imbalance in serum sFlt-1 and PIGF ratios can provide a sign of damage or disruption of vasculogenesis and angiogenesis which can be used to detect preeclampsia early in pregnant women starting at ≥ 18 weeks gestational age compared to measuring biomarkers separately/single in pregnant women who have normal blood pressure (Akolekar *et al.*, 2013; Sovio *et al.*, 2017).

In the last 20 years there has been extensive research mainly as a consequence of the shift in screening *aneuploidies* from the second trimester to the first trimester of pregnancy and an early biophysical series and biochemical markers of implantation failure have been identified. Using a novel method *Bayes-Based* which is a combination of several things: preliminary information about the mother's characteristics and medical history, *uterine artery pulsatility index (PI)*, *mean arterial Pressure (MAP)*, *maternal serum pregnancy-associated plasma protein-A (PAPP-A)* dan *placental growth factor (PIGF)* at 11-13 weeks gestation has been shown to identify a high proportion of pregnancies that are at high risk of experiencing early-onset PE (Akolekar *et al.*, 2013; Tsiakkas *et al.*, 2015).

Placental growth factor (PIGF) plays an important role in the clinical management of pre-eclampsia. This review outlines the role of PIGF in human physiology, but focuses specifically on the current understanding of PIGF in normal and pathological placental development. The differences in peripheral concentrations of PIGF between normal and pre-eclampsia pregnancies are highlighted and the utility of PIGF as a predictive or diagnostic test for pre-eclampsia are discussed. Finally, it is possible PIGF and is considered as a treatment for pre-eclampsia (De Falco, 2012; Sovio et al., 2017).

From this description, preeclampsia occurs which has been explained that the process that is responsible is to combine the components *stress okxidative* with the occurrence of imbalances in production *Plasental Growth Factor (PIGF)* which can cause endothelial dysfunction. In this case, efforts are needed to prevent the development of diseases through antioxidant supplements from natural ingredients (Chau et al., 2017).

Phenolic compounds contribute directly as antioxidants due to the presence of hydroxyl around the nucleus which functions as a strong Hydrogen donor. The anti-oxidant effect of phenolic compounds in plants through various mechanisms including the ability to

hunt free radicals, the presence of Kelat ions which function as antioxidant enzymes and inhibit oxidase. It is reported that the increase in *PLGF* in the maternal circulation occurs from the beginning of pregnancy to the end of the first two trimesters of pregnancy starting from the 30th week until delivery, *PLGF* will experience a decrease. The decrease that occurred in pregnant women with preeclampsia was found to be more than in normal pregnant women (March *et al.*, 2015).

Hamad *et al.*, (2015) conducted a metabolic analysis of 12 types of dates originating from Saudi Arabia to determine the nutritional content of each date. The study showed that the highest phenol content was found in Ajwa Al-Madinah dates and the highest flavonoids in dates Saffawy followed by dates Ajwa Al-Madinah. This research proves that what the Prophet Muhammad PBUH mentioned a few centuries ago about the benefits of Ajwa dates to ward off poison is true. Based on the data above, the researcher is interested in conducting research on the effect of *phoenix dactylifera* on changes in *placental growth factor levels* in pregnant women with the aim of analyzing the influence of *phoenix dactylifera* on changes in *placental growth factor levels* in pregnant women, so that pregnant women can walk physiologically and avoid pathological problems.

RESEARCH METHOD

This study uses a *hybrid* method, which combines two research methods (*Experimental Quasy and Prospective Khohort*) with a *pre-post test control design* in pregnant women at risk to determine the effect of *phoenix dactylifera* on changes in PIGF levels of at-risk pregnant women. In the intervention group, ajwa dates (*Phoenix dactylifera L*) were given 7 pieces (100 grams) daily for 8 weeks, starting from 20 weeks to 28 weeks of gestation, while in the control group, counseling on pregnancy nutrition was given 3 times a week for 8 weeks. Blood pressure measurements are carried out every day starting at 20 weeks to 28 weeks of gestation. Blood sampling for PLGF levels was taken 2 times, at 20 weeks and 28 weeks gestation (before being given ajwa dates/nutrition counseling in the UK 20 weeks and after being given ajwa dates/nutrition counseling in the UK 28 weeks). The population of this study is all pregnant women with UK 20 weeks who have an ANC visit at the Sitti Khadijah 1 Muhammadiyah Makassar Maternal and Child Hospital with a total of 150 respondents and a sample size of 40 respondents (30 respondents in the ajwa date group and 10 respondents in the group that is recommended to eat fruits and vegetables) the sample size is determined using the Yamane formula with a sampling technique with *simple random sampling*. Sampling is taken until the number of samples is met based on inclusion and exclusion criteria.

Data analysis used *the Wilcoxon test*. In this study, respondents were subjected to ultrasound examinations, filled out *informed consent*, filled out instrument A, namely a questionnaire to measure obstetric characteristics and history with a structured questionnaire containing general data on age, parity, pregnancy interval, history of hypertension, education status, occupation, income, and immunization status. Instrument B is a food recall questionnaire to measure the nutritional intake of respondents which can be used as an analysis material that can interfere with the results of the research and instrument C is an observation sheet on blood pressure and PIGF levels in pregnant women, blood pressure is measured using *Spignomanometer* tension (mmHg) while PIGF levels are measured using *the Reybio kit* by taking blood plasma samples at the laboratory of Hasanuddin University Hospital Makassar. This research has also received ethical approval from the Health Research

RESULTS

Respondent Characteristics

Table 1. Frequency Distribution of Respondent Characteristics

Sample characteristics	Intervention		Control		p
	n	(%)	n	(%)	
Age					
Low risk	25	83.3	7	70.0	0.312
High risk	5	16.7	3	30.0	
Pregnant					
First	13	43.3	5	50.0	0.497
Multi	17	56.7	5	50.0	
Pregnancy Interval					
Good	27	90.0	8	80.0	0.367
Bad	3	10.0	2	20.0	
History. Hypertension					
Normal	3	10.0	1	20.0	0.700
Abnormal	27	90.0	9	80.0	
Education					
< 9 Years	11	36.7	4	40.0	0.568
≥ 9 Years	19	63.3	6	60.0	
Work					
IRT	21	70.0	6	50.0	0.751
Self employed	2	6.7	1	20.0	
Merchant	2	6.7	1	10.0	
Kary. Private	2	6.7	2	20.0	
Honor	2	6.7	0	0	
PNS	1	3.3	0	0	
Income					
≥ 2.7 Million	20	66.7	5	50.0	0.283
< 2.7 Million	10	33.3	5	50.0	
Energy					
Enough	4	13.3	2	20.0	0.474
Not enough	26	86.7	8	80.0	
Fat					
Enough	5	16.7	2	20.0	0.572
Not enough	25	83.3	8	80.0	
Potassium					
Enough	1	3.3	1	10.0	0.442
Not enough	29	96.7	9	90.0	
Calcium					
Enough	2	6.7	1	10.0	0.509
Not enough	28	93.3	9	90.0	
Magnesium					
Enough	4	13.3	2	20.0	0.474
Not enough	26	86.7	8	80.0	
PLGF Maternal					
Normal	0	0	0	0	0.115
High Risk	30	100.0	10	100.0	

Primary Data, Frequency Distribution, Chi Square

Table 1. showing the distribution results on all characteristics showed no significant differences between age, parity, pregnancy interval, history of hypertension, education, occupation, income and nutritional status of pregnant women. All the characteristics used as a study sample did not differ significantly between the group given ajwa dates and the group not given ajwa dates. So this shows that the sample in the study is homogeneous.

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Table 2. Results of the Wilcoxon Test Analysis on Changes in PLGF Levels according to the Intervention Group and the Control Group in Pregnant Women at RSIA Sitti Khadijah 1 Makassar.

Variabel	Group					
	Intervention			Control		
	Mean Pre test	Mean Post test	<i>p</i>	Mean Pre test	Mean Post test	<i>p</i>
PLGF	0.591	+3.856	0.000	1.040	-0.701	0.073

Primary Data, Wilcoxon Test test, (+) Up, (-) Down

Table 2. Showing data from the PIGF *pre-test – post test* level variables in the intervention group has a *significance* value of $0.000 < 0.05$, meaning that there is a change in PIGF levels before being given ajwa dates and after giving ajwa dates to pregnant women at risk of preeclampsia. Meanwhile, the control group showed data from the PIGF *pre-test – post test* level variables resulting in *Asymp values*. The *significance* was $0.073 > 0.05$ which means that there was no change in PIGF levels in pregnant women at risk of preeclampsia.

DISCUSSION

Age plays a very important role in the incidence of hypertension during pregnancy where the risk of pregnancy and childbirth in women who are less than 20 years old and over 35 years old have a high risk of hypertension. At the age of between 20-35 years the mother is more ready to get pregnant physically and psychologically. At the age of 35 years or more, the mother's health has declined, as a result pregnant women at that age have the potential to have a disabled child, long labor and bleeding that is likely to occur Saraswati and Mardiana, (2016). However, in this study, the age-based risk factors for preeclampsia, both low risk and high risk in the intervention group and the control group were not different. This is in line with research research Ahmed *et al.*, (2018) which involved 200 pregnant women in Sudan and found that there was no difference in the age of pregnant women who were preeclampsia (average 28 years) and those who were normal (average 27 years). In addition to age, Preeclampsia is more common in primigravida compared to multigravida. Of all primigravida, 7.6% were diagnosed with preeclampsia. Primigravida has a greater risk of developing preeclampsia because in primigravida the immunological mechanism in the formation of *blocking antibody* against placental antigens by HLA-G (*human leukocyte antigen G*) is imperfect compared to multigravida (Arihiro, 2018).

However, in this study, the proportion of pregnant women at risk of preeclampsia It is more common in multigravida than primigravida, especially multigravida that has a history of hypertension or preeclampsia. multigravida approximately 85% of preeclampsia occurs in

pregnancy The same results were obtained by Abdulsalam *et al.*, (2017) There was no association with the incidence of preeclampsia with a $p >$ value of 0.05 ($0.213 > 0.05$).

In the same case, a gestational distance of >2 years is the right recommendation for women to get pregnant again. Short intervals between pregnancies (<24 years) were associated with adverse pregnancy outcomes due to maternal nutrient depletion and failure to treat morbidity. While the interval between pregnancies is too long, it allows for a perfect recovery of the mother's reproductive organs, but this is associated with reduced fertility, old age, maternal disorders and partner changes which are also associated with a higher risk of pre-eclampsia. A recent analysis of 894,476 women with consecutive pregnancies in 18 countries in Latin America showed that longer and overly cephalic birth intervals increase the likelihood of preeclampsia (POGI, 2016).

The results of this study also prove Norwitz's theory *et al* in the *Unnes Journal of Public Health* (2016) which states that preeclampsia is an inherited disease, this disease is more often found in female children of mothers with preeclampsia or have a family history of preeclampsia. Genetic/hereditary factors are risk factors for preeclampsia. Likewise, the level of education also did not show a difference between the intervention group and the control group. In line with research Subki *et al.*, (2018) which divided education into two groups, namely < 9 years and ≥ 9 years, obtained the result that there was no difference in the level of education between the normal groups of tension and hypertension in pregnancy. Likewise in research Zhang *et al.*, (2017) who divided the level of education into 3 categories, namely < 13 years, 13-16 years and ≥ 16 years said that there was no significant difference in education level between normal pregnant women with hypertension and pregnant women with hypertension ($p = 0.216$) (Times *et al.*, 2017). Ghajazadeh, (2013) which involved 739 pregnant women obtained results that the employment status of housewives and those who work outside the home in normal tension pregnant women did not have a difference in proportion to pregnant women who experienced hypertension. Nugteren *et al.*, (2012) In its study involving 4465 pregnant women, it was also stated that there was no significant association between work-related risks, such as standing too long, walking, heavy lifting, night shifts and working hours with hypertension disorders in pregnancy.

Based on the results of the *Wilcoxon test* in table 2. It showed that in the *pre-post test* intervention group, PIGF levels increased with a mean of 0.591 – 3.856, compared to the control group PIGF levels decreased with a mean of 1.040 – 0.701. Data from the variable PIGF levels *pre test – post test* in the intervention group had a *significance p value* of $0.000 < 0.05$, meaning that there was a change in the value of PIGF levels before being given ajwa dates and after being given ajwa dates in pregnant women at risk of preeclampsia. Meanwhile, in the variables of pre-test PIGF levels and post-test PIGF levels, a *significance p value* of $0.073 > 0.05$ was obtained, meaning that there was no change in the value of PIGF levels before and after being given nutritional counseling for pregnant women at risk of preeclampsia.

The results of the study showed a comparison of values between before treatment and after treatment in each group. In the intervention group of *placental growth factor* variables, the results of the analysis of PIGF levels increased by 3,265 pg/ml from the normality value of >3.50 . while in the control group, the results of the analysis of PIGF levels decreased by 0.339 pg/ml from the normality level value >3.50 . The results of blood pressure measurement in the intervention group that experienced a change in value could be caused by the administration of ajwa dates to pregnant women at risk of preeclampsia. Ajwa dates were given weighing 100 grams/day and consumed every morning for 8 weeks by showing different measurement results. There are several micronutrients that have a relationship with

blood pressure, systole, and diastole, some of which are Calcium, potassium, magnesium (Nafiah, 2018).

In ajwa dates weighing 100 mg, they contain Potassium (180.7–796.7 mg/100 grams), magnesium (21.1–97.3 mg/100 g) and calcium (1,644–1,648 mg/100 g). These three substances play a role in lowering blood pressure (Hamad et al., 2015). The antioxidant content in ajwa dates can increase the level of *Placental growth factor* (PIGF) which has effects such as exogenous PIGF, rhPLGF and Pravastatin performed in mice induced by Sflt-1 levels. And it has been proven to increase PIGF levels in mouse plasma (Bashandy et al., 2016; Sulistyowati et al., 2017).

In the control group that did not consume ajwa dates, there were several influencing factors so that the measurement results showed insignificant results. The control group was given counseling on the importance of pregnancy nutrition, out of 10 respondents only 1 respondent experienced a decrease in blood pressure and a decrease in PIGF Levels the main cause was lack of nutrients consumed by the mothers of the control group, judging from the 24-hour recall carried out during the study, environmental factors of pregnant women who are often exposed to free radicals, and stress factors, Pregnant women also lack awareness in maintaining health during pregnancy. The counseling carried out did not give the expected results. Pregnant women know good food however, the majority of pregnant women do not like vegetables and fruits. Eat according to taste without looking at the nutrients contained. PIGF levels decrease as Sflt-1 levels increase. In studies of antioxidant-induced mice, it was proven to increase PIGF levels in pregnant mice induced Sflt-1 levels. In addition, plasma is used to estimate lipid peroxide levels. In PE plasma, the concentration of PIGF was 4.5 higher than in normal pregnancy plasma. In the analysis of plasma PIGF level data using the Tukey double comparison test, it showed that there was a significant difference between the level of PIGF in normal pregnancy plasma and PEB plasma and eclampsia ($p=0.000<0.05$). (Ghnimi et al., 2017).

Several studies explain the effects of antioxidants related to angiogenic balance, mainly proangiogenic roles. Research Maynard et al., (2003) explained that the administration of antioxidant therapy can reduce Sflt-1 levels and increase PIGF in the plasma of preeclampsia pregnant women. Research conducted Sinuraya et al., (2017) explains that antioxidants are proven to be a therapy for preeclampsia, to correct angiogenic imbalances. The antioxidant balance will activate VEGF derived from eNOS, with the production of nitric oxide thus causing vasodilation. The same is proven by Mohamed et al., (2014) Animal experiment of mice by studying the effects of antioxidant therapy on preeclampsia using a mouse model induced with adenoviruses containing sFlt-1. The results proved that the rats given antioxidant therapy returned to normal levels after day 2, while the untreated rats experienced an increase in blood pressure and protein (Levine et al., 2004).

CONCLUSION

Based on the results of the study, it can be concluded that at-risk pregnant women who were given ajwa dates showed increased PIGF levels while at-risk pregnant women who were not given ajwa dates showed a decrease in PIGF levels and there was a comparison of PIGF levels in the group who were given ajwa dates compared to those who were not given ajwa dates in pregnant women at risk of preeclampsia.

Maternal and Child Health Service Facilities need to be counseled to the community, especially pregnant women, about the importance of consuming at least 3 ajwa dates every

day to prevent the incidence of hypertension that refers to preeclampsia, in addition to this study, additional variables are needed to reduce bias due to other factors.

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