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Maternal serum resistin at 11 to 13 weeks' gestation in normal and pathological pregnancies

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ABSTRACT

The objective was to examine maternal serum levels of resistin at 11 to 13 weeks' gestation in normal and pathological pregnancies. Serum resistin, pregnancy-associated plasma protein A (PAPP-A), and uterine artery pulsatility index (PI) at 11 to 13 weeks were measured in 480 singleton pregnancies, including 240 with normal outcome, 60 that subsequently developed preeclampsia (PE), 60 that developed gestational diabetes mellitus (GDM), 60 that delivered large for gestational age (LGA) neonates, and 60 that delivered small for gestational age (SGA) neonates. Each value in both the normal and pathological outcome groups was expressed as a multiple of the expected normal median (MoM), and the median MoM values in the outcome groups were compared. In the PE group, compared with the controls, there were an increase in median resistin (1.22 MoM, $P = .003$) and uterine artery PI (1.25 MoM, $P < .0001$) and a decrease in serum PAPP-A (0.72, $P < .0001$). There was no significant association between serum resistin with either uterine artery PI ($P = .415$) or serum PAPP-A ($P = .290$). In the SGA, LGA, and GDM groups, serum resistin MoM was not significantly different from that of the controls ($P = .415$, $P = .702$, and $P = .549$, respectively). In pregnancies that develop PE, maternal serum resistin concentration at 11 to 13 weeks is increased in a manner not related to altered placental perfusion or function. In pregnancies complicated by the development of GDM or delivery of SGA or LGA neonates, serum resistin is not significantly altered.

1. Introduction

Resistin, also known as *adipose tissue-specific secretory factor*, is a hormone that is secreted primarily by human adipocytes and mononuclear cells [1,2]. Serum resistin levels are higher in obese compared with lean individuals [3]. There is evidence that resistin impairs glucose intake by adipocytes, increases plasma glucose concentration, and promotes insulin resistance [4]. Resistin has also been shown to block adipocyte differentiation and increases fat deposits in adipose tissue, liver, and skeletal muscle [5]. It promotes proinflammatory changes in vascular endothelium, induces release of the proinflammatory cytokines

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Contribution to authorship: SN conceived and designed the study. SN, LP, MM, and ICA contributed to the design and conduct of the study and the interpretation of the results. KHN is the main supervisor. All the authors participated and contributed to the writing of the manuscript.

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tumor necrosis factor–α and interleukin-12 by macrophages and adipocytes, and promotes angiogenesis [6-10].

In pregnancy, insulin resistance and inflammatory changes have been implicated in the pathogenesis of preeclampsia (PE), gestational diabetes mellitus (GDM), and fetal growth disorders [11-15]. Studies investigating maternal serum concentration of several adipocytokines, including adiponectin, visfatin, and leptin, have reported altered concentrations in these complications that are apparent from the first trimester of pregnancy [16-21].

Resistin is expressed by the human placenta [22,23], and maternal serum levels increase with gestational age [24,25]. Studies investigating maternal serum or plasma resistin levels in pathological pregnancies, including PE, GDM, and those delivering small for gestational age (SGA) or large for gestational age (LGA) neonates, reported that the levels are higher, lower, or not significantly different from pregnancies with normal outcome [26-38]. Only one study examined serum levels of resistin before the clinical onset of disease and reported that the levels at 7 to 12 weeks' gestation in 30 pregnancies that subsequently developed GDM were not significantly different from those of nondiabetic controls [39].

The aim of our study was to establish a reference range of maternal serum levels of resistin at 11 to 13 weeks' gestation and to examine whether the levels are altered in pregnancies that subsequently develop PE or GDM and those resulting in delivery of SGA and LGA neonates. We also examine the possible association of serum resistin with maternal serum concentration of pregnancy-associated plasma protein A (PAPP-A) and uterine artery pulsatility index (PI), which are markers of placentation.

2. Methods

2.1. Study population

This study was drawn from a large prospective observational study for early prediction of pregnancy complications in women attending for their routine first hospital visit in pregnancy at King's College Hospital, London, UK. In this visit, which was held at 11^{+0} to 13^{+6} weeks of gestation, we recorded maternal characteristics and medical history and performed combined screening for aneuploidies by measurement of the fetal crown-rump length (CRL) and nuchal translucency thickness and maternal serum free β-human chorionic gonadotrophin and PAPP-A [40,41]. In addition, transabdominal Doppler studies were carried out; and the mean uterine artery PI was measured [42]. Women attending for this visit were invited to participate in the research; and from those who agreed, serum and plasma samples were stored at –80°C for subsequent biochemical analysis. The study was approved by the King's College Hospital Ethics Committee.

Women were asked to complete a questionnaire on maternal age, racial origin (white, African, South Asian, and East Asian), parity (nulliparous, parous), cigarette smoking during pregnancy (yes or no), mode of conception (spontaneous or after use of assisted reproduction technologies), and medical history, including chronic hypertension and diabetes mellitus. A physician, along with the patient, then reviewed the questionnaire; and the maternal weight and height were measured.

In this study, we measured maternal serum resistin concentration in 240 singleton pregnancies with no medical complications, such as hypertensive disorders or diabetes mellitus, resulting in the birth after 37 weeks' gestation of phenotypically normal neonates with birth weight between the 5th and 95th percentiles for gestational age [43]. The values were compared with those from 60 pregnancies that subsequently developed PE, 60 that developed GDM, 60 that delivered LGA neonates with birth weight greater than the 95th percentile, and 60 that delivered SGA neonates with birth weight less than the 5th percentile. The cases of PE, GDM, SGA, and LGA were selected at random from our database of stored samples for these conditions. Each case was matched to one control that was sampled on the same day.

Preeclampsia was defined according to the criteria by the International Society for the Study of Hypertension in Pregnancy [44]. Screening for GDM in our hospital is based on a 2-step approach. In all women, random plasma glucose is measured at 24 to 28 weeks of gestation; and if the concentration is more than 6.7 mmol/L, a 100-g oral glucose tolerance test is carried out within the subsequent 2 weeks. The diagnosis of GDM is made if the fasting plasma glucose level is at least 6 mmol/L or if the plasma glucose level 2 hours after the oral administration of 75 g glucose is 7.8 mmol/L or more [45].

2.2. Sample analysis

Maternal serum resistin was measured by a quantitative enzyme-linked immunosorbent assay technique using the Quantikine Human Resistin ELISA Kit (Catalogue no. DRSN00l R&D Systems Europe, Abingdon, UK). The lower limit of detection of the assay was 0.026 ng/mL. The intraassay and interassay coefficient of variation varied from 3.8% to 5.0% and 7.8% to 9.2%, respectively. All samples were done in duplicates, and samples with a coefficient of variation exceeding 10% were reanalyzed. None of the samples in this study were previously thawed and refrozen.

2.3. Statistical analysis

Comparisons between outcome groups were by χ^2 test or Fisher exact test for categorical variables and by Mann-Whitney *U* test with post hoc Bonferroni correction for continuous variables.

The distributions of serum resistin, PAPP-A, and uterine artery PI were logarithmically transformed, and Kolmogorov-Smirnov test ($P = .546$, $P = .061$, and $P = .075$, respectively) were used to confirm Gaussian normality. In the normal outcome group, multiple regression analysis was used to determine the factors from maternal characteristics and gestation that provided significant contribution in the prediction of $\log_{10}$ resistin. Each value in both the normal and pathological outcome groups was expressed as a multiple of the expected normal median (MoM). The median MoM values of serum resistin in the outcome groups were compared. Similarly, the measured values of uterine artery PI and serum PAPP-A were converted into MoMs as previously described [46,47]; and these median MoM values were compared between the outcome groups.

The statistical software package SPSS 16.0 (SPSS, Chicago, IL) was used for data analyses.

2.4. Literature search

We searched MEDLINE and EMBASE from 2000, when resistin was first described [4,5,48], to July 2011 to identify English-language articles reporting on circulating maternal serum or plasma levels of resistin in pregnancy. We included all case-control and cohort studies that reported data regarding the outcome measures of PE, GDM, and birth of SGA or LGA neonates.

3. Results

The maternal characteristics of the study groups are presented in Table 1. Maternal weight and body mass index (BMI) were significantly higher and the percentage of white women was lower in the groups of PE, GDM, and LGA than in the controls. The percentage of nulliparous women and those with chronic hypertension was higher in the PE group than the controls, and the percentage of smokers was higher in the SGA group than the controls. The gestational age at delivery was lower in the PE, GDM, and SGA groups and higher in the LGA group than the controls. The birth weight percentile was lower in the PE and SGA groups and higher in the GDM and LGA groups than the controls.

3.1. Normal controls

In the normal outcome group, multiple regression analysis demonstrated that serum resistin did not change significantly with maternal characteristics, including maternal weight ($P = .630$), maternal height ($P = .686$), maternal age ($P = .181$), racial origin ($P = .909$), cigarette smoking ($P = .554$), mode of conception ($P = .165$), and parity ($P = .904$), or with fetal CRL ($P = .188$).

3.2. Preeclampsia

In the PE group, compared with the unaffected controls, there were a significant increase in median serum resistin (1.22, interquartile range [IQR] 0.91-1.72 MoM vs 1.00, IQR 0.81-1.36 MoM, $P = .003$; Fig. 1; Table 2) and uterine artery PI (1.25, IQR 1.05-1.48 MoM vs 1.00, IQR 0.83-1.15 MoM, $P < .0001$) and a decrease in serum PAPP-A (0.72, IQR 0.46-1.14 MoM vs 1.01, IQR 0.76-11.35 MoM, $P < .0001$).

The median gestation at delivery of the PE group was 35.9 (range, 28-41) weeks. There was a significant negative association between gestation at delivery and serum resistin ($r = –0.255$, $P = .049$; Fig. 2), uterine artery PI ($r = –0.289$, $P = .038$), and serum PAPP-A ($r = 0.274$, $P = .036$). There was no significant association between serum resistin and either uterine artery PI ($P = .415$) or serum PAPP-A ($P = .290$).

3.3. Gestational diabetes mellitus

In the GDM group, compared with the unaffected controls, there was no significant difference in median serum resistin (1.01, IQR 0.66-1.41 MoM vs 1.00, IQR 0.81-1.36 MoM, $P = .549$; Fig. 1; Table 2), uterine artery PI (0.96, IQR 0.86-1.22 MoM vs 1.00, IQR 0.83-1.15 MoM, $P = .535$), or serum PAPP-A (0.99, IQR 0.75-1.41 MoM vs 1.01, IQR 0.76-11.35 MoM, $P = .779$).

3.4. Small for gestational age

In the SGA group, compared with the unaffected controls, there was no significant difference in median serum resistin (1.11, IQR 0.79-1.46 MoM vs 1.00, IQR 0.81-1.36 MoM, $P = .415$; Fig. 1; Table 2); but uterine artery PI was increased (1.24, IQR 0.94-1.49 MoM vs 1.00, IQR 0.83-1.15 MoM, $P < .0001$), and serum PAPP-A was decreased (0.70, IQR 0.44-0.89 MoM vs 1.01, IQR 0.76-11.35 MoM, $P < .0001$).

Table 1 – Maternal and pregnancy characteristics in the outcome groups

Maternal characteristics	Control	PE	GDM	LGA	SGA
Sample size (n)	240	60	60	60	60
Maternal age (y), median (IQR)	33.0 (27.3-35.9)	32.9 (27.4-37.0)	32.0 (28.5-35.6)	32.5 (29.0-36.9)	30.4 (24.8-35.8)
Maternal weight (kg), median (IQR)	64.0 (58.9-70.0)	71.5 (63.0-85.7)*	76.5 (64.3-94.0)*	75.5 (69.0-89.2)*	63.0 (54.3-77.3)
Maternal height (cm), median (IQR)	165 (159-169)	162 (158-167)	163 (159-168)	167 (163-172)*	162 (157-165)*
Maternal BMI (kg/m^2), median (IQR)	23.8 (21.7-26.2)	27.4 (23.2-32.7)*	28.6 (24.6-34.2)*	27.3 (24.8-32.6)*	24.4 (21.4-29.1)
CRL (mm), median (IQR)	63.2 (58.5-69.7)	59.8 (55.4-65.4)	63.7 (58.1-71.6)	65.1 (60.1-71.7)	60.7 (56.0-67.4)
Gestation at sampling (d), median (IQR)	88.9 (86.1-91.2)	87.1 (84.8-90.0)	89.1 (86.2-93.1)	89.9 (87.3-93.2)	87.6 (85.1-91.0)
Racial origin					
White, n (%)	172 (71.7)	31 (51.7)*	30 (50)*	32 (53.3)*	33 (55.0)
African, n (%)	51 (21.3)	21 (35.0)	19 (31.7)	28 (46.7)*	22 (36.7)
Asian, n (%)	17 (7.1)	8 (13.3)	11 (28.3)	0	5 (8.3)
Parity					
Nulliparous, n (%)	102 (42.5)	39 (65.0)*	19 (31.7)	24 (40.0)	36 (60.0)
Parous, n (%)	138 (57.5)	21 (35.0)*	41 (68.3)	36 (60.0)	24 (40.0)
Cigarette smoker, n (%)	22 (9.2)	2 (3.3)	2 (3.3)	2 (3.3)	20 (33.3)*
Chronic hypertension, n (%)	1 (0.4)	11 (18.3)*	0 (0)	1 (1.7)	1 (1.7)
Gestation at delivery (wk), median (IQR)	39.7 (38.6-40.5)	35.9 (32.9-38.5)*	38.5 (38.1-39.6)*	40.3 (39.2-41.4)*	36.0 (34.2-37.2)*
Birth weight percentile, median (IQR)	50.6 (30.9-67.0)	15.4 (6.21-46.3)*	67.9 (38.3-89.2)*	97.8 (96.7-98.9)*	0.5 (0.0-2.2)*

Comparison between outcome groups by Mann-Whitney U test with post hoc Bonferroni correction and χ^2 (chi square) test or Fisher exact test for categorical variables. * Adjusted significance level $P = .01$.

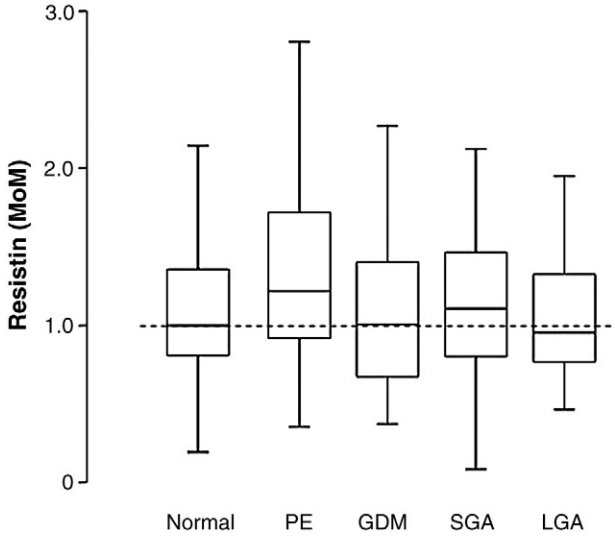

Fig. 1 – Box (median, IQR) and whisker (range) plot of maternal serum resistin MoM in normal and pathological pregnancies.

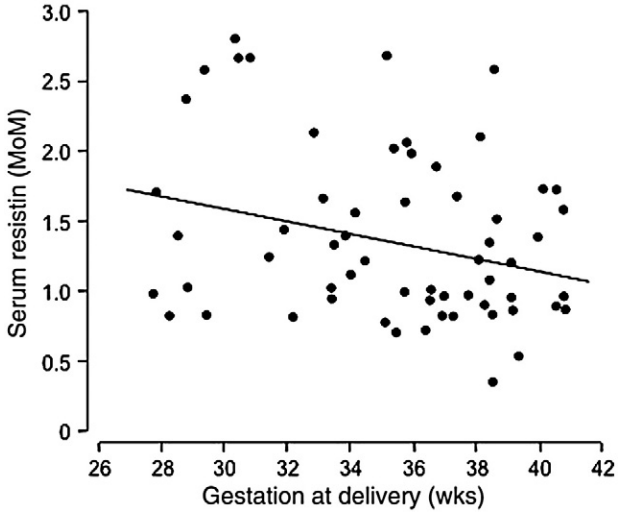

Fig. 2 – Relationship between serum resistin in pregnancies subsequently developing PE and gestational age at delivery.

3.5. *Large for gestational age*

In the LGA group, compared with the unaffected controls, there was no significant difference in median serum resistin (0.95, IQR 0.76-1.33 MoM vs 1.00, IQR 0.81-1.36 MoM, $P = .702$; Fig. 1; Table 2) or uterine artery PI (0.95, IQR 0.68-1.19 MoM vs 1.00, IQR 0.83-1.15 MoM, $P = .280$); but the median serum PAPP-A was increased (1.26, IQR 0.92-1.77 MoM vs 1.01, IQR 0.76-11.35 MoM, $P = .003$).

3.6. *Literature search*

The data from previous studies comparing serum or plasma resistin levels in pathological pregnancies and normal controls are summarized in Table 3.

4. Discussion

This study has demonstrated that maternal serum resistin concentration at 11 to 13 weeks' gestation in pregnancies that subsequently develop PE is increased. In pregnancies that develop GDM and those that result in delivery of SGA and LGA neonates, serum resistin is not significantly different from pregnancies with normal outcome.

In normal pregnancies, serum resistin concentration was not affected by maternal characteristics or gestational age within the narrow range of 11 to 13 weeks. Previous longitudinal studies in pregnancy have also shown that the serum or plasma concentrations of resistin are independent of maternal BMI or parity [24,49]. Maternal serum or plasma resistin levels are higher in pregnant than nonpregnant women [24,26,27], but there is conflicting evidence about the variation in levels with gestational age. Chen et al [26] reported that the levels in the first and second trimester are similar but, in the third trimester, they are increased. Nien et al [24] reported similar findings and showed that the levels peak at term. In contrast, Cortelazzi et al [27] reported that serum resistin levels are higher in pregnant than in nonpregnant women; the levels decrease with gestational age between 10 and 41 weeks.

Studies in pregnancies with established PE have reported that maternal serum or plasma resistin concentrations may be increased [28,29], decreased [26,27], or not significantly different from those of normal controls [30]. Our findings indicate that increased maternal serum resistin precedes the clinical onset of PE and is apparent from the first trimester of pregnancy. It is therefore possible that resistin, through its effects on inflammation and insulin resistance, could be implicated in the pathogenesis of PE. There is extensive evidence that the underlying mechanism for severe PE requiring early delivery is impaired trophoblastic invasion of the maternal spiral arteries and reduced placental perfusion [50,51]. In late PE, placental perfusion and fetal growth are often normal; and the main pathophysiological processes resemble those of the metabolic syndrome, with an increase in adipose tissue and impaired glucose and lipid metabolism [52,53]. The increase in serum resistin concentration was inversely related to the gestational age at delivery; and consequently, the role of resistin in the pathogenesis of PE is more likely to be related to the process of impaired placentation rather than its effects on

Table 2 – Median and IQRs of maternal serum resistin in the outcome groups

Outcome group	Serum resistin		*P* value
	ng/mL	MoM	
Control	8.28 (6.68-11.24)	1.00 (0.81-1.36)	
PE	10.08 (7.52-14.23)	1.22 (0.91-1.72)	.003
SGA	9.15 (6.55-12.12)	1.11 (0.79-1.46)	.415
LGA	7.89 (6.25-10.97)	0.95 (0.76-1.33)	.702
GDM	8.32 (5.50-11.68)	1.01 (0.66-1.41)	.549

Comparison between outcome groups by Mann-Whitney *U* test with post hoc Bonferroni correction; adjusted significance level $P = .01$.

Table 3 – Studies comparing maternal mean or median serum or plasma resistin levels in pregnancies affected by GDM, PE, and delivery of SGA or LGA neonates with unaffected controls

Authors	Gestation (wk)	Affected		Unaffected		P value
		n	Resistin ng/mL	n	Resistin ng/mL	
PE						
Chen et al, 2005 [26]	29-41	25	5.2	26	8.7	<.001
Cortelazzi et al, 2007 [27]	20-37	9	8.1	14	17.9	<.005
Haugen et al, 2006 [28]	33-39	15	5.7	23	4.7	.028
Seol et al, 2010 [29]	35-39	20	9.7	20	5.9	<.0001
Hendler et al, 2005 [30]	31-42	77	-	22	–	NS
GDM						
Vitoratos et al, 2011 [31]	26-28	30	0.21	30	0.19	.60
	38	30	0.28	30	0.21	.02
Kuzmicki et al, 2009 [32]	24-31	81	21.9	80	19.0	.047
Megia et al, 2008 [33]	26-30	23	4.3	35	9.3	<.001
Chen et al, 2007 [34]	36-40	20	62.4	20	22.2	<.001
Cortelazzi et al, 2007 [27]	37-41	18	8.5	13	6.9	NS
Palik et al, 2007 [35]	21-34	30	15.9	45	13.0	<.01
Lappas et al, 2005 [36]	37-39	11	2.3	9	3.4	NS
SGA						
Brianna et al, 2008 [37]	35-39	20	4.8	20	4.7	NS
Wang et al, 2010 [38]	39-41	30	13.1	40	10.4	<.0001
LGA						
Wang et al, 2010 [38]	39-41	30	8.2	40	10.4	<.0001

NS indicates not significant.

insulin resistance. However, there was no significant association between serum resistin level and the biophysical and biochemical markers of impaired placentation, reflected in increased uterine artery PI and decreased serum PAPP-A. There is some evidence that the main source of resistin may be macrophages and monocytes, rather than adipose tissue [2]. This is supported by our finding of a lack of significant association between serum resistin level and maternal weight. There is also evidence that resistin may not actually have a role in insulin resistance [54]. In this respect, the role of resistin in the pathogenesis of PE may be mediated through an inflammatory process involving macrophages and monocytes.

Our finding that, in pregnancies that developed GDM, the serum concentration of resistin at 11 to 13 weeks was not significantly different from that of normal controls provides further support to the suggestion that resistin may not have a role in insulin resistance [54]. In contrast, the first-trimester maternal serum levels of other adipocytokines that affect insulin resistance, such as adiponectin and visfatin, are altered in pregnancies that develop GDM [16,19]. Previous studies in women with established GDM reported contradictory results in relation to resistin, with levels that were increased, decreased, or not significantly altered [31-36]. Our findings are consistent with the results of the only other first-trimester study, which reported no significant difference in maternal plasma resistin concentration at 9 to 13 weeks between 30 women who subsequently developed GDM compared with 29 nondiabetic controls [39].

In pregnancies that delivered SGA or LGA neonates, serum resistin concentrations at 11 to 13 weeks' gestation were not significantly different from those in pregnancies delivering appropriate for gestational age neonates. These findings are consistent with those of a recent large multicentric study on 1473 women from the subset of the Hyperglycemia and Adverse Pregnancy Outcome Study group, which reported that maternal serum resistin at 28 weeks was not significantly associated with birth weight [14]. Similarly, a study that measured serum resistin levels at 35 to 39 weeks reported no significant differences between pregnancies with SGA and appropriate for gestational age neonates [37]. In contrast, another study that measured serum resistin at 39 to 41 weeks reported increased levels in pregnancies delivering SGA neonates and decreased levels in those delivering LGA neonates [38]. The findings that, in the SGA group, uterine artery PI was increased and serum PAPP-A was decreased are compatible with the results of previous studies and demonstrate that, at least in some of these cases, the underlying cause of reduced fetal growth is impaired placentation [55]. A possible mechanism for the finding of increased serum PAPP-A in the LGA group is related to the proteolytic properties of PAPP-A, which cleaves insulin-like growth factor binding proteins, thereby increasing the bioavailability of insulin-like growth factor that is thought to play a key role in the control of placental growth and transfer of nutrients to the fetus [56,57].

In conclusion, the findings of our study indicate that the reported altered maternal levels of resistin in pregnancies with established GDM and those delivering SGA and LGA neonates are not apparent at 11 to 13 weeks' gestation; and therefore, measurement of this adipocytokine is unlikely to be useful in early screening for these pregnancy complications. In the case of PE, we found that increased levels of resistin are apparent from early pregnancy and that the levels are inversely related to the severity of PE. Further prospective longitudinal studies are needed to assess the contribution of this adipocytokine, alone or in combination with other adipocytokines, in the prediction of PE and other pregnancy complications.

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Conflict of Interest

No conflict of interest.

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