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Original Article

Efficacy of allylestrenol combined with ritodrine in treating preterm labour with preeclampsia and associated risk factors for pregnancy outcomes

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Abstract: Objectives: To evaluate the efficacy of diethylstilbestrol combined with ritodrine in treating preterm labor due to preeclampsia and to identify risk factors for different pregnancy outcomes. Methods: A retrospective cohort study was conducted on 112 preterm pregnant women treated at Maanshan Maternal and Child Health Care Hospital from January 2022 to December 2023. Patients were divided into an observation group (n = 60) receiving allylestrenol tablets (10 mg daily, reduced to 5 mg after contractile reaction disappeared) and ritodrine injection (100 mg in 500 mL sedative, infused at 0.05-0.35 mg/min for 12-18 hours), and a control group (n = 52) treated with magnesium sulfate injection. Measured outcomes included symptom score, gestational age at delivery, treatment efficacy, adverse reactions, blood magnesium (MG), serum progesterone-induced blocking factor (PIBF), interleukin-6 (IL-6), cervical length (CL), and fetal fibronectin (fFN) levels. Results: The observation group had a significantly higher effective rate (78%) compared to the control group (54%, $\chi^2 = 9.73$, $P = 0.008$). Adverse events occurred in 8% of the observation group versus 27% in the control group ($\chi^2 = 6.41$, $P = 0.011$). Post-treatment symptom scores were lower in the observation group, with reduced preterm birth rates, higher gestational age, and increased neonatal weight. Premature births were associated with elevated IL-6 and fFN, reduced PIBF and CL, and lower MG levels. Logistic regression revealed higher PIBF reduced preterm birth risk, while increased IL-6 and fFN heightened the risk. ROC analysis identified PIBF as the best predictor of preterm birth. Conclusions: Allylestrenol combined with ritodrine is effective for managing preterm labor due to preeclampsia, improving maternal and fetal outcomes with good safety. This treatment warrants further clinical application.

Keywords: Threatened abortion, allylestrenol, ritodrine, pregnancy outcomes, risk factors

Introduction

Preeclampsia is a common pregnancy-related condition characterized by mild vaginal bleeding, intermittent lower abdominal pain, and lower back pain [1]. It is often associated with dark red or bloody leucorrhea before the 28th week of pregnancy. As pregnancy progresses, vaginal bleeding and abdominal pain typically worsen, and without timely intervention, spontaneous miscarriage may occur.

The etiology of preeclampsia can generally be categorized into maternal and embryonic factors [2]. Maternal factors include endocrine disorders, anatomical abnormalities of the reproductive tract, and inflammation, while the most common embryonic factor is fetal chromosomal abnormality. However, some cases of preeclampsia remain of unknown origin [3].

Clinical data indicate a rising trend in advanced maternal age, coupled with the increasing demands of modern life and work, leading to a higher incidence of preterm miscarriage [4, 5]. Consequently, research has increasingly focused on effective prevention and treatment strategies for preeclampsia to improve pregnancy outcomes [6-8].

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Progesterone is commonly used in clinical practice for treating preeclampsia, but it carries a risk of teratogenicity [9, 10]. Recent studies suggest that allylestrenol promotes placental nutrient secretion and enhances endogenous progesterone and human chorionic gonadotropin secretion [11]. Meanwhile, ritodrine has demonstrated efficacy in prolonging pregnancy by inhibiting uterine contractions and is widely used to support fetal development [12, 13].

This study aimed to evaluate the efficacy and assess the risk factors associated with different pregnancy outcomes in women with preeclampsia treated with a combination of allylestrenol and ritodrine.

Materials and methods

Sample size calculation

The sample size was calculated based on the expected abortion rate and the anticipated treatment effect difference. The formula used was: $n = (Z\alpha/2+Z\beta)2 \times [P1 (1-P1)+P2 (1-P2)]/(P1-P2)^2$. Where n was the required sample size per group, P1 and P2 were the expected abortion rates in the control and observation groups, respectively, $Z\alpha/2$ was the critical value for a type I error ($\alpha = 0.05$), $Z\beta$ was the critical value for a type II error ($\beta = 0.2$).

With $P1 = 0.6$, $P2 = 0.3$, $\alpha = 0.05$, and $\beta = 0.2$, the minimum sample size required was 45 cases per group. This study included 112 patients, with 60 in the observation group and 52 in the control group, meeting statistical requirements.

Patient characteristics

This retrospective cohort study assessed the efficacy of allylestrenol combined with ritodrine for treating preterm labor and its impact on pregnancy outcomes. The study included 112 pregnant women with preterm labor admitted to Maanshan Maternal and Child Health Care Hospital from January 2022 to December 2023. Patients were divided into an observation group (n = 60) and a control group (n = 52) based on the treatment regimen they received. Treatment decisions were guided by clinical practice, with physicians providing options and patients making informed choices. This study was approved by the Ethics Review Committee of Maanshan Maternal and Child Health Care Hospital.

Inclusion criteria: Singleton pregnancy; Gestational age between 28 and 36 weeks (+6 days); Regular or irregular contractions with progressive cervical canal shortening; Age between 22 and 41 years; Complete case data.

Exclusion criteria: Diabetes mellitus; Hypertension; Cardiovascular or cerebrovascular diseases; Psychiatric disorders; Cardiopulmonary dysfunction.

Treatment methods

Observation group: Patients received oral allylestrenol tablets (Changzhou Shiyao Pharmaceutical Co., Ltd., State Pharmaceutical Licence H20113293, 5 mg × 20 tablets). Initial dose: 10 mg daily. Maintenance dose: 5 mg daily after contractions ceased. They also received intravenous ritodrine (Jichuan Pharmaceutical Group Co., Ltd.), with a regimen of: 100 mg of ritodrine diluted in 500 mL of sedative solution (0.2 mg/mL). Initial infusion rate: 0.05 mg/min, increased by 0.05 mg/min every 10 minutes until effective. Optimal infusion rate: 0.15 to 0.35 mg/min. After contractions ceased, the infusion continued for 12 to 18 hours.

Control group: Patients were administered intravenous magnesium sulfate (Sinopharm Group Rongsheng Pharmaceutical Co., Ltd., State Drug Permit H20043974), with dosage adjusted to patient-specific needs. Recommended for preterm delivery before 32 weeks of gestation. Used as a fetal central nervous system protection agent if labor occurred before 32 weeks. Maximum dosage: No more than 48 hours and 25 g/day.

Observation indicators

(1) Data extraction: Data were obtained from patients' electronic health records. Two researchers independently extracted the data, followed by cross-validation to ensure accuracy.

(2) Baseline data: Baseline information included age, education level, smoking history, and the presence of gestational diabetes mellitus (GDM).

(3) Symptom scoring: Symptoms including lower abdominal pain, lumbago, vaginal bleeding, and abdominal distension, were scored on a 1-3 scale: Score 1: Mild symptoms; no medication needed; normal daily activities. Score 2: Moderate symptoms; medication required but no bed rest or hospitalization. Score 3: Severe symptoms; medication and possible bed rest or hospitalization needed. A higher score indicates worse symptoms, while a lower score reflects better clinical status.

(4) Treatment effectiveness: Significant effect: Complete symptom resolution, enabling pregnancy continuation beyond 37 weeks. Effective: Pregnancy continued for at least 2 days, with symptoms subsequently resolved. Ineffective: Preterm birth during treatment. Total Effective Rate = Significant + Effective.

(5) Adverse reactions: Adverse events monitored included nausea, vomiting, and loss of appetite.

(6) Laboratory testing: Before treatment, both groups underwent tests for: blood magnesium (MG), serum progesterone-induced blocking factor (PIBF), and Interleukin-6 (IL-6) levels, as well as the assessment of cervical length (CL) and the presence of fetal fibronectin (fFN) in cervical secretions. These pre-treatment data helped establish baseline conditions and account for potential drug-induced data fluctuations.

(7) Efficacy criteria: Effective: Contractions ceased, cervical shortening reversed, pregnancy extended >48 hours or 7 days. Ineffective: Persistent contractions and cervical shortening, leading to delivery within 48 hours or 7 days. Preterm labor was defined per the 2014 preterm labor guidelines, with regular contractions (approximately 1 per 5 minutes, 30 seconds duration) and cervical canal shortening between 28 and 37 weeks of gestation. Preeclampsia with preterm labor was diagnosed under the same gestational age range, with or without cervical changes and vaginal bleeding.

(8) Follow-up: Patients were monitored from admission through delivery or treatment completion. Follow-up included clinical record reviews and telephone interviews, focusing on pregnancy progress and adverse events.

(9) Data management and missing values: Missing data primarily resulted from missed follow-up visits or incomplete clinical records. The Last Observation Carried Forward method was used to maintain comprehensive follow-up data.

Statistical methods

Statistical analysis was performed using SPSS 22.0. Normally distributed data were expressed as mean ± standard deviation, count/grade data as percentages. Intergroup comparisons were conducted using the Pearson chi-square or continuity-corrected chi-square test. Influencing factors was performed using binary logistic regression analysis. A *P*-value of less than 0.05 was considered statistically significant.

Results

Comparison of general information

No significant differences were observed between the two groups in terms of age, educational background, smoking history, miscarriage history, and GDM (all P>0.05, **Table 1**).

Comparison of treatment effects

The overall treatment efficacy in the observation group was 78%, significantly higher than the 54% in the control group (χ^2 = 9.73, P = 0.008) (**Table 2**).

Comparison of adverse event rates

The incidence of adverse events was significantly lower in the observation group (8%) compared to the control group (27%) (P<0.05, **Table 3**).

Comparison of symptom scores, preterm birth rates, gestational age at delivery, and neonatal weight

Prior to treatment, symptom scores were similar between the two groups (P>0.05). However, post-treatment, the control group exhibited significantly higher symptom scores than the observation group. Additionally, the control group showed a higher preterm birth rate, lower gestational age at delivery, and reduced neonatal weight compared to the observation group (both P<0.05, **Table 4**).

Table 1. Comparison of general information of the two data groups

Indicators		Observation (n = 60)	Control (n = 52)	t/χ^2	p
Age (years)		29.87±3.29	29.85±2.53	0.03	0.98
Education level	Primary and below	8 (0.13)	6 (0.12)	0.19	0.91
	Secondary or post-secondary	14 (0.23)	11 (0.21)		
	College and above	38 (0.64)	35 (0.67)		
Smoking history	No	52 (0.87)	47 (0.90)	0.37	0.54
	Yes	8 (0.13)	5 (0.10)		
Abortion history	0	40 (0.67)	38 (0.73)	0.62	0.73
	1	18 (0.30)	13 (0.25)		
	≥2	2 (0.03)	1 (0.02)		
Gestational diabetes	Yes	14 (0.23)	11 (0.21)	0.07	0.78
	No	46 (0.76)	41 (0.78)		
MG (mmol/L)		0.68±0.17	0.64±0.15	1.77	0.08
PIBF (nmol/L)		93.45±8.17	92.14±7.41	0.45	0.72
IL-6 (pg/mL)		26.22±6.24	25.78±5.87	0.77	0.44
CL (mm)		33.58±4.57	32.67±4.37	-1.54	0.13
fFN (ug/L)		109.48±16.18	110.12±16.14	-0.068	0.95

MG: blood magnesium; PIBF: progesterone-induced blocking factor; IL-6: Interleukin-6; CL: cervical length; Ffn: fetal fibronectin.

Table 2. Comparison of treatment effects

	Markedly effective	Efficiently	Ineffective	Overall efficiency rate
Observation (n = 60)	27 (0.45)	20 (0.33)	13 (0.22)	47 (0.78)
Control (n = 52)	11 (0.21)	17 (0.33)	24 (0.46)	28 (0.54)
χ^2		9.73		
p		0.008		

Table 3. Comparison of adverse event rates

	Vomiting	Nauseating	Loss of appetite	Total
Observation (n = 60)	1 (0.02)	2 (0.03)	2 (0.03)	5 (0.08)
Control (n = 52)	5 (0.10)	4 (0.08)	5 (0.10)	14 (0.27)
χ^2		6.41		
p		0.011		

Comparison of pregnancy outcomes in term vs. preterm groups

Participants were classified into a term group (n = 75) and a preterm group (n = 37) based on pregnancy outcomes. The incidence of gestational diabetes was significantly higher in the preterm group compared to the term group (P<0.05, **Table 5**).

Comparison of clinical information

The term group demonstrated significantly higher mean values for PIBF and CL, whereas the preterm group had significantly higher mean values for MG, fFN, and IL-6 (all P<0.05, **Table 6**).

Regression analysis results

A binary logistic regression model was used to assess the association between preterm labor (1 = yes, 0 = no) and independent variables, including GDM (1 = yes, 0 = no), MG, PIBF, IL-6, and CL.

As shown in **Table 6**, higher PIBF concentrations were associated with a lower likelihood of preterm labor. Conversely, elevated ketone-induced blocking factor levels increased the probability of preterm labor by 50%. Longer CL reduced the risk of preterm labor, with a 0.29 times lower likelihood compared to shorter CL. Higher MG levels were linked to a 52% higher risk of preterm labor. Elevated IL-6 concentrations increased the risk by 1.65 times. Higher fFN levels also raised the probability of preterm

Table 4. Comparison of symptom score, preterm birth rate, gestational week of delivery, and neonatal weight

Indicators	Symptom score		Prematurity	Average week of delivery	Newborn weight (kg)
	Pre-treatment	Post-treatment			
Observation (n = 60)	8.31±2.54	3.06±0.89	13 (0.22)	38.06±4.63	3.08±0.42
Control (n = 52)	7.82±2.37	5.92±1.62	24 (0.46)	35.35±3.57	2.76±0.55
t/χ^2	1.06	11.26	6.48	2.54	3.41
p	0.29	<0.001	0.011	0.012	0.001

Table 5. Comparison of general information between the two groups

Indicators		Term (n = 75)	Preterm (n = 37)	t/χ^2	p
Age (years)		29.34±3.95	30.72±4.32	-1.69	0.094
Education level	Primary and below	8 (0.1)	5 (0.06)	0.77	0.67
	Secondary or post-secondary	12 (0.16)	13 (0.18)		
	College and above	55 (0.74)	19 (0.76)		
Smoking history	No	65 (0.87)	34 (0.92)	0.39	0.53
	Yes	10 (0.13)	3 (0.08)		
Abortion history	0	51 (0.68)	27 (0.73)	0.29	0.59
	1 or more	24 (0.32)	10 (0.27)		
Gestational diabetes	Yes	11 (0.15)	14 (0.38)	6.39	0.011
	No	64 (0.85)	23 (0.62)		

Table 6. Comparison of clinical treatments

Indicators	MG (mmol/L)	PIBF (nmol/L)	IL-6 (pg/mL)	CL (mm)	fFN (ug/L)
Term (n = 75)	0.95±0.34	111.71±10.3	22.62±2.81	36.98±3.71	92.67±10.6
Preterm (n = 37)	0.30±0.15	78.69±8.62	29.13±3.81	30.87±3.51	106.78±17.76
t	13.91	16.75	-10.21	8.33	-5.23
p	<0.001	<0.001	<0.001	<0.001	<0.001

MG: blood magnesium; PIBF: progesterone-induced blocking factor; IL-6: Interleukin-6; CL: cervical length; Ffn: fetal fibronectin.

Table 7. Regression analysis results

Indicators	B	SE	Wald χ^2	p	OR (95% cl)
PIBF	-0.68	0.013	9.32	0.024	0.50 (0.24-0.78)
CL	-1.21	0.054	10.54	0.013	0.29 (0.11-0.49)
MG	-0.65	0.021	8.71	0.036	0.52 (0.22-0.82)
IL-6	1.18	0.044	8.65	0.038	3.25 (2.13-4.37)
fFN	0.59	0.058	9.14	0.027	1.80 (1.27-2.33)

MG: blood magnesium; PIBF: progesterone-induced blocking factor; IL-6: Interleukin-6; CL: cervical length; Ffn: fetal fibronectin.

labor by 1.8 times compared to lower levels (**Table 7**).

ROC analysis of predictive factors for preterm labor

PIBF demonstrated the strongest predictive performance among the five indicators, with the highest AUC (0.990) and sensitivity (0.966) and specificity (0.973), respectively. Additionally, MG demonstrated notable efficacy as a predictor, with an AUC of 0.972, sensitivity of 0.946, and specificity of 0.898. IL-6 and CL exhibited favorable predictive values, with AUCs of 0.916 and 0.880, respectively, though their sensitivity and specificity were slightly lower than those of PIBF and MG. The fFN was found to be the least predictive indicator, with an AUC of 0.728, sensitivity of 0.714 and specificity of 0.949. Overall, PIBF was the most effective predictor of preterm labor, followed by MG. While IL-6, CL, and fFN also showed predictive value, their effectiveness varied (**Figure 1**).

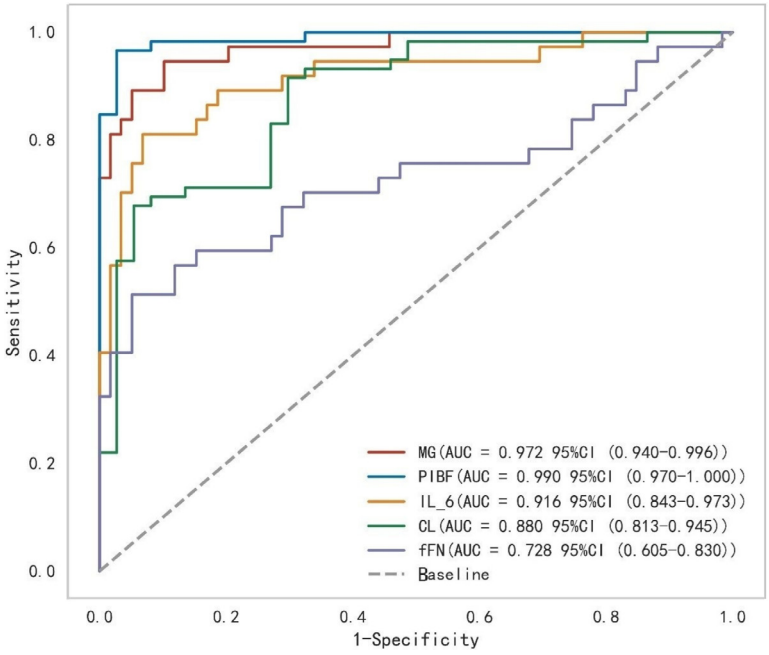

Figure 1. Roc curve. MG: blood magnesium; PIBF: progesterone-induced blocking factor; IL-6: Interleukin-6; CL: cervical length; Ffn: fetal fibronectin.

Discussion

Preeclampsia, a common maternal disorder, involves a complex interplay of intrinsic and extrinsic factors, including age, lifestyle, and environmental influences [14]. A substantial number of preeclamptic miscarriages occur before 16 weeks of gestation, with luteal insufficiency being the primary cause. Without timely intervention, the disease progression may lead to miscarriage, negatively affecting both maternal and fetal health [15].

Pharmacological treatment is the primary approach for managing preeclampsia, demonstrating considerable therapeutic efficacy. In cases of non-embryonic preeclampsia, various medications are used, including progesterone, prostaglandins, nifedipine, ritodrine, atosiban, and magnesium sulfate. However, treatment effectiveness varies depending on the clinical protocol and individual patient variability. Furthermore, declining fertility in advanced maternal age is associated with reduced ovarian function and progesterone secretion, posing challenges to treatment efficacy [16].

Allylestrenol is a potent fetal-preserving agent that inhibits prostaglandin synthesis, reduces contraction frequency, supports pregnancy maintenance, and enhances placental trophoblast endocrine function, boosting the secretion of human chorionic gonadotropin and progesterone [11]. At our medical center, the combination of allylestrenol tablets and ritodrine in treating preeclampsia showed significantly higher efficacy and lower adverse event rates than the control group, suggesting this regimen substantially improves treatment outcomes.

The study revealed a significantly higher incidence of GDM in the preterm birth group compared to the full-term group (38% vs. 15%, P = 0.011). This finding indicates that GDM may be a potential risk factor for preterm birth. Possible mechanisms include intrauterine growth retardation, excessive uterine expansion from polyhydramnios, and premature rupture of membranes triggered by inflammatory reactions. Early screening and effective management of GDM could potentially reduce the risk of preterm birth.

Cervical changes during pregnancy are critical indicators of labor onset. Maintaining an adequate CL is essential for promoting full-term fetal development. A shortened CL, particularly when accompanied by uterine contractions, is a strong predictor of preterm labor and can help estimate delivery timing [17]. Studies have found that many high-risk pregnancies show shortened cervixes by 20 weeks of gestation. Notably: Over 20% of these women delivered before 34 weeks of gestation. More than 95% of these preterm births occurred before 24 weeks of gestation [18, 19]. The study by Dudley et al. involving 600 primiparas demonstrated a negative correlation between CL and the risk of preterm birth. The risk increased significantly with progressive cervical shortening [20, 21].

fFN is an extracellular matrix protein primarily secreted by chorionic trophoblast cells, contributing to the adhesion of placental chorionic villi to the decidua [22]. Before 20 weeks of gesta-

tion, fFN can be detected in vaginal and cervical secretions because the fetal membranes are not yet fully adhered to the decidua. Between 22 and 35 weeks, the fusion of the chorionic villi and fetal membranes, limits fFN release, resulting in normal fFN levels of <50 ng/mL in secretions.

A positive fFN test suggests separation of the fetal membranes from the decidua in the lower uterus and hydrolytic degradation of proteins at the uterine decidua-chorionic villi interface [23]. Bastek et al. demonstrated that fFN presence in vaginal secretions correlated with favorable pregnancy outcomes and served as a predictive marker for preterm labor between 22 and 35 weeks [24]. The Kuhrt study further validated fFN as a predictive tool for spontaneous preterm labor before 30 weeks, emphasizing the benefit of combining fFN testing with CL assessment and maternal medical history [25, 26].

In the study by Dawes, fFN, PAMG-1, and other vaginal biomarkers were assessed. A threshold of 200 ng/mL fFN was associated with a higher preterm birth rate, showing a positive correlation between 7-day preterm birth rates and elevated fFN levels (≥200 ng/mL) [27, 28]. In this study, fFN showed the lowest predictive value for preterm labor, with an AUC of 0.728, sensitivity of 0.714, and specificity of 0.949, aligning with previous research findings.

This study identified negative correlation between MG and PIBF levels and preterm birth incidence, as well as positive correlation between IL-6 levels and preterm birth risk. IL-6 plays a dual role by stimulating antibody production against immune cells, and reducing the maternal immune response against the fetal immune system. Increasing the risk of impaired embryo implantation, may lead to early pregnancy loss [29].

This study had several limitations. First, the sample size was relatively small and derived from a single center, which may limit the generalizability of the findings. Second, the study's short follow-up period prevented the assessment of long-term maternal and fetal outcomes. Additionally, as a retrospective cohort study, potential selection and information biases could not be entirely excluded.

Future research should involve larger, multicenter, randomized controlled trials to validate these findings and explore the long-term safety and efficacy of allylestrenol and ritodrine combination therapy. Extending follow-up periods and integrating personalized treatment approaches based on biomarkers such as PIBF, IL-6, and fFN could further enhance clinical outcomes and provide more tailored management strategies for preeclampsia-induced preterm labor.

In conclusion, the combination therapy of allylestrenol and ritodrine for preterm labor caused by preeclampsia significantly reduces the symptom score and preterm labor rate. It also improves key indicators such as PIBF, CL, and fetal outcomes, while decreasing the levels of MG, fFN, and IL-6. The therapy maintains treatment safety and efficacy with minimal adverse reactions. This study offers new perspectives on the clinical management of preeclampsia-induced preterm labor. It supports the early identification of high-risk pregnancies and presents a promising approach to enhance pregnancy outcomes.

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Disclosure of conflict of interest

None.

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