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Influence of Diagnosis Timing and Therapeutic Regimens of Allergic Rhinitis on Pregnancy Outcomes in Pregnant Patients

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Article

Keywords: Pregnancy, Allergic rhinitis, Diagnosis timing, Therapeutic regimen, Pregnancy outcome

Posted Date: November 19th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11410674/v1

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Additional Declarations: No competing interests reported.

Abstract

Background and Objective Allergic rhinitis (AR) is a common allergic comorbidity in pregnant women. However, the correlation between AR onset/intervention timing and pregnancy outcomes remains insufficiently supported by large-sample evidence, and no unified standard has been established for the clinical application of different therapeutic regimens. This study aimed to investigate the influence of AR diagnosis timing and different therapeutic regimens on pregnancy outcomes in pregnant patients with AR, thereby providing evidence-based references for the standardized diagnosis and treatment of gestational AR.

Methods This multicenter retrospective cohort study enrolled 5,083 pregnant patients with AR from two clinical centers: the Harvard University Partners Healthcare System (PARTNERS), and Longgang District Maternity & Child Healthcare Hospital of Shenzhen City in China. All participants completed full pregnancy follow-up between January 2016 and December 2024. The baseline data, AR diagnosis timing, therapeutic regimens and pregnancy outcome-related indicators of the patients were collected. The correlations of AR diagnosis timing (pre-pregnancy vs. intra-pregnancy) and four therapeutic regimens (intranasal corticosteroids, oral antihistamines, combination therapy, and no treatment) with pregnancy outcomes were analyzed.

Results A total of 80.1% of patients were diagnosed with AR before pregnancy. The vaginal delivery rate in the pre-pregnancy diagnosis group was significantly higher than that in the intra-pregnancy diagnosis group (90.6% vs. 71.7%, $P < 0.001$), while the rates of cesarean section (9.4% vs. 28.3%, $P < 0.001$), low birth weight (4.0% vs. 6.9%, $P = 0.002$), neonatal complications (36.3% vs. 44.1%, $P < 0.001$), and abnormal 1-minute (7.7% vs. 16.3%, $P < 0.001$) and 5-minute Apgar scores < 7 (0.8% vs. 4.7%, $P < 0.001$) were significantly lower. No significant difference was observed in the preterm birth rate between the two groups (10.4% vs. 11.6%, $P = 0.18$). Significant differences in pregnancy outcomes were also found among therapeutic regimens ($P < 0.05$). Notably, the combination therapy group showed an unusually high vaginal delivery rate (98.2%) and elevated low birth weight rate (9.3%), which warrant careful data verification.

Conclusion Pre-pregnancy diagnosis and standardized intervention for AR are associated with improved maternal and infant prognosis and reduced risk of adverse pregnancy outcomes. Treatment of gestational AR should follow the principle of individualization, with regimens selected based on patients' high-risk factors. Given the univariable nature of the regression analysis, these findings should be interpreted as observational associations rather than independent effects, and prospective studies with confounder adjustment are needed for confirmation.

Introduction

Allergic rhinitis (AR) is a globally prevalent allergic respiratory disease characterized by non-infectious inflammation of the nasal mucosa as the core pathological change, with typical clinical manifestations including pruritus nasi, paroxysmal sneezing and clear rhinorrhea [1, 2]. Its incidence rate among adults

worldwide has been on the rise, and the upward trend is particularly prominent in childbearing-aged women [3]. Environmental allergen exposure and the imbalance of the body's immune status are recognized as important inducing factors [4]. Pregnancy represents a unique physiological stage for women, during which dramatic fluctuations in the levels of estrogen and progesterone not only trigger nasal mucosal vasodilation, increased vascular permeability and hypersecretion of mucosal glands, but also induce plastic remodeling of the immune system [5, 6]. To maintain pregnancy, the maternal body needs to establish immune tolerance to the fetus, which leads to the imbalance of innate and adaptive immunity. This physiological change significantly elevates the risk of AR onset in pregnant women, and exacerbation or acute attacks are common in those with a pre-existing history of AR, making AR one of the most prevalent comorbidities during pregnancy [7]. AR during pregnancy not only exerts a direct adverse impact on the maternal physical state, causing sleep disorders, chronic nasal obstruction and even intermittent hypoxia, thus impairing the quality of life in pregnancy, but also may indirectly affect the intrauterine growth and development of the fetus through pathways such as decreased maternal blood oxygen saturation and abnormal placental microcirculation perfusion [8]. Several small-sample studies have suggested a potential association between AR and adverse pregnancy outcomes including cesarean section, low birth weight and poor neonatal prognosis [9, 10], yet the specific strength of this association and the underlying mechanisms remain unclear.

Current clinical research on AR during pregnancy has mostly focused on the safety of a single therapeutic regimen, while studies investigating the impact of AR diagnosis timing (pre-pregnancy vs. intra-pregnancy) on pregnancy outcomes lack support from large-sample clinical data. Meanwhile, there remains considerable controversy regarding the effects of different therapeutic strategies (e.g., intranasal corticosteroids, oral antihistamines and their combined use) on pregnancy outcomes in patients with AR during pregnancy [11, 12]. Due to excessive concerns about the potential adverse effects of medications on the fetus, clinicians tend to adopt a conservative approach to the treatment of AR in pregnant women, in some cases, standardized pharmacological intervention is even abandoned for patients with moderate to severe symptoms, with only basic nursing measures applied [13–15]. This conservative practice often results in poor control of AR symptoms, which may conversely increase the risk of adverse pregnancy outcomes. In addition, patients with AR during pregnancy are often complicated with a personal history of allergy, depressive disorder and abnormal pre-pregnancy body mass index (BMI), all of which are independent risk factors for adverse pregnancy outcomes in their own right [16, 17]. Existing studies have rarely integrated these confounding factors with AR diagnosis timing and therapeutic regimens in a single comprehensive analysis [18, 19], which further adds to the uncertainty of clinical diagnosis and treatment decisions for AR during pregnancy.

Therefore, based on large-sample clinical data of pregnant patients with AR, this study comprehensively analyzed the correlations between AR diagnosis timing, different therapeutic regimens and pregnancy outcomes, and clarified the effects of these factors on key pregnancy outcome indicators including vaginal delivery, cesarean section, preterm birth and low birth weight. The present study aimed to provide clinical references for the pre-pregnancy screening, early diagnosis and individualized treatment of AR

during pregnancy, so as to achieve effective control of AR symptoms, reduce the incidence of adverse pregnancy outcomes and ultimately improve maternal and infant prognosis.

Materials and Methods

Study Subjects

This multicenter retrospective cohort study included 5,083 pregnant women with a confirmed diagnosis of allergic rhinitis (AR). Data were derived from two clinical centers:

(1) United States center: Pregnant women with AR were identified from the Harvard University Partners Healthcare Systems. The data were extracted from the EPIC electronic health record (EHR) system, covering seven affiliated hospitals: Brigham and Women's Hospital, Massachusetts General Hospital, Newton-Wellesley Hospital, North Shore Medical Center, Martha's Vineyard Hospital, Cooley Dickinson Hospital, and Nantucket Cottage Hospital. The study period at this center was June 2015 to June 2019.

(2) China center: Pregnant women with AR were enrolled from Longgang District Maternity & Child Healthcare Hospitalof Shenzhen City, Shenzhen, China. Data were extracted from the hospital's electronic medical record system. The study period at this center was January 2023 to December 2024.

All participants from both centers completed full pregnancy follow-up. To ensure data consistency across centers, AR diagnosis was uniformly established based on clinical symptoms (pruritus nasi, paroxysmal sneezing, clear rhinorrhea, and nasal obstruction), nasal endoscopy findings, and allergen test results (skin prick test or serum specific IgE), in accordance with a standardized diagnostic protocol. Data from both centers were independently extracted, de-identified, and then merged into a unified dataset for analysis.

This study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Partners Human Research Committee (Partners HealthCare) (Approval No.: 2018P002646) and the Longgang District Maternity & Child Healthcare Hospital of Shenzhen City in China Medical Ethics Committee (Approval No.: LGFYKYXMLL-2024-20). All methods were performed in accordance with the relevant guidelines and regulations. Given the retrospective design and the use of de-identified electronic health record data at both centers, the requirement for written informed consent was waived by both Institutional Review Boards / Ethics Committees. All clinical data were used in accordance with the Health Insurance Portability and Accountability Act (HIPAA) guidelines in the United States and relevant ethical regulations in China.

Inclusion criteria: □ Single intrauterine pregnancy with complete gestational cycle and available delivery data; □ Conforming to the diagnostic criteria for AR with complete clinical diagnosis, treatment and follow-up data of AR during pregnancy; □ No concealment or missing of study-related data.

Exclusion criteria: □ Complicated with other organic respiratory diseases such as bronchial asthma and chronic obstructive pulmonary disease; □ Complicated with severe gestational complications including gestational diabetes mellitus, preeclampsia and placental abruption; □ Complicated with systemic diseases such as autoimmune diseases, malignant tumors and severe cardiovascular diseases; □ Complicated with severe mental disorders such as schizophrenia and bipolar disorder (excluding patients with a history of depression); □ Use of non-AR therapeutic drugs that may affect pregnancy outcomes (e.g., immunosuppressants and hormonal drugs) before or during pregnancy; □ Interrupted follow-up, incomplete clinical data or distorted data during pregnancy [20]. □ Patients whose data could not be standardized or merged into the unified dataset due to inconsistent variable definitions across data sources. □ Patients whose delivery records could not be linked within the respective EHR system or whose data could not be standardized across centers. The detailed enrollment, stepwise exclusion and dual-dimensional grouping process of all study participants are systematically presented in Fig. 1.

Diagnostic and Evaluation Criteria

Diagnostic criteria for AR: The diagnosis was made comprehensively in accordance with the diagnostic criteria for AR specified in the Diagnostic and Treatment Guidelines for Allergic Rhinitis (2022 Revised Edition) [21], combined with patients' clinical symptoms, nasal endoscopy findings and allergen test results. Patients presented with typical symptoms including pruritus nasi, paroxysmal sneezing, clear rhinorrhea and nasal obstruction; nasal endoscopy revealed pale and edematous nasal mucosa; and positive results were obtained from skin prick test for allergens or serum specific IgE test. Meanwhile, other nasal diseases such as gestational non-allergic rhinitis, upper respiratory tract infection and nasal polyps were excluded.

Evaluation criteria for relevant indicators: Pre-pregnancy body mass index (BMI) was classified according to international universal standards: underweight (BMI < 18.5), normal weight (18.5 ≤ BMI ≤ 24.9), overweight (25.0 ≤ BMI ≤ 29.9) and obese (BMI ≥ 30.0) [22]. Preterm birth was defined as delivery at 28 to less than 37 weeks of gestation. Low birth weight referred to a neonatal birth weight of less than 2,500 g. The neonatal Apgar score was assessed using the standard scoring system, with scores recorded at 1 and 5 minutes after birth; a score of less than 7 was regarded as abnormal.

Clinical Data Collection Methods

Clinical data were independently extracted from the electronic medical record systems of the two participating centers: the EPIC EHR system at the Partners HealthCare centers in the USA, and the hospital electronic medical record system at the China center. At each center, trained research personnel performed data extraction according to a standardized data dictionary. Two senior obstetricians independently performed double-blind data verification; any discrepancy was resolved by a third attending physician. All variables were harmonized across centers according to the standardized data dictionary prior to pooled analysis.

The collected information was grouped into three categories: Baseline data, including patients' age, ethnicity/race, pre-pregnancy BMI, personal history of allergy and history of depression; AR-related data, including the timing of AR diagnosis, therapeutic regimen and duration of medication; Pregnancy outcome data, including mode of delivery (vaginal delivery/cesarean section), preterm birth status, neonatal birth weight, incidence of neonatal complications, and 1-minute and 5-minute Apgar scores.

Study Grouping Method

In accordance with the research objectives, the study subjects were subjected to dual grouping based on two core research factors, and the grouping process strictly followed the objectivity of clinical data without any manual intervention.

Subjects were divided into the pre-pregnancy diagnosis group and the intra-pregnancy diagnosis group according to the timing of AR diagnosis: the pre-pregnancy diagnosis group included patients with a confirmed diagnosis of AR before pregnancy, and the intra-pregnancy diagnosis group included patients who were first diagnosed with AR during pregnancy.

According to the therapeutic regimens for AR during pregnancy, subjects were further divided into four subgroups: the intranasal corticosteroids group (monotherapy with intranasal corticosteroids), the oral antihistamines group (monotherapy with second-generation non-sedating oral antihistamines), the combination therapy group (intranasal corticosteroids combined with oral antihistamines), and the no treatment group (only basic nursing measures such as nasal cavity cleaning were adopted without any AR-related therapeutic drugs).

Statistical Methods

All analyses were conducted with SPSS version 26.0. Continuous variables were expressed as means with 95% confidence intervals (CIs); categorical variables were reported as frequencies (n) with percentages (%) and corresponding 95% CIs.

The Shapiro–Wilk test was used to assess the normality of continuous data; all continuous variables deviated significantly from a normal distribution (all $P < 0.05$; detailed test statistics available upon request). Accordingly, intergroup comparisons were carried out using the Mann–Whitney U test (two groups) or the Kruskal–Wallis H test (multiple groups). For categorical variables, group differences were evaluated using the Pearson χ^2 test, or Fisher's exact test when expected cell frequencies were below 5. All tests were two-tailed, and a P value < 0.05 indicated statistical significance.

To examine associations between AR-related factors and pregnancy outcomes, odds ratios (ORs) with 95% CIs were calculated using univariable binary logistic regression (crude ORs, without covariate adjustment). Dependent variables were selected from among the following pregnancy outcomes: cesarean section (as a binary outcome; vaginal delivery was treated as its complement and not modeled

separately), preterm birth, low birth weight, neonatal complications, and abnormal Apgar scores. Independent variables were timing of AR diagnosis and treatment regimen. Given the univariable design, the reported ORs should be interpreted as crude associations and not as independent effects after controlling for confounders. Missing data accounted for less than 1% of all variables; only complete cases were analyzed.

Results

Baseline Characteristics of the Study Subjects

A total of 5,083 pregnant patients with AR were enrolled in this study, with a mean age of 33.92 years (95% CI: 33.85–34.00 years). In terms of ethnic distribution, White patients were the predominant group, accounting for 63.3% (95% CI: 63.0–63.6%), followed by Hispanic, African American/Black, and Asian patients, while other ethnic groups only constituted 2.8%. For pre-pregnancy body mass index (BMI) distribution, the proportion of overweight patients was the highest (49.2%), followed by those with normal weight (47.5%), and the proportions of underweight and obese patients were both less than 3%.

In terms of medical history, 59.2% of the patients had a personal history of allergy, and 29.6% were complicated with depression. Regarding the timing of AR diagnosis, 80.1% of the patients (n = 4,071) were diagnosed before pregnancy, and only 19.9% (n = 1,012) received the first diagnosis of AR during pregnancy. The 95% CIs of all the above baseline indicators were in a narrow range, indicating that the data exhibited good stability (Table 1).

Table 1
Baseline characteristics of the study population (n = 5,083)

Variables	Characteristics	n	Value / %	95% CI
Age (years)	Mean (33.92)	5,083	—	(33.85, 34.00)
Race/Ethnicity	White	3,218	63.3	(63.0, 63.6)
	Hispanic	620	12.2	(11.9, 12.5)
	African American/Black	564	11.1	(10.3, 10.9)
	Asian	539	10.6	(10.3, 10.9)
	Other	142	2.8	(2.6, 3.0)
Pre-pregnancy BMI	Underweight (< 18.5)	117	2.3	(2.1, 2.5)
	Normal (18.5–24.9)	2,414	47.5	(46.7, 48.9)
	Overweight (25.0–29.9)	2,501	49.2	(49.0, 50.0)
	Obese (≥ 30.0)	51	1.0	(0.9, 1.1)
History of allergy	Yes	3,009	59.2	(58.7, 59.7)
	No	2,074	40.8	(40.3, 41.3)
Time of allergic rhinitis diagnosis	Pre-pregnancy	4,071	80.1	(79.8, 80.4)
	During pregnancy	1,012	19.9	(19.6, 20.2)
History of depression	Yes	1,505	29.6	(29.1, 30.1)
	No	3,578	70.4	(69.9, 70.9)
Medication during pregnancy	Yes	1,698	33.4	(32.9, 33.9)
	No	3,385	66.6	(66.1, 67.1)

Correlation between the Timing of AR Diagnosis and Pregnancy Outcomes

The study subjects were divided into the pre-pregnancy diagnosis group (n = 4,071) and the intra-pregnancy diagnosis group (n = 1,012) according to the timing of AR diagnosis. Comparison of pregnancy outcome indicators between the two groups showed no statistically significant difference in the preterm birth rate (10.4% vs 11.6%, $P = 0.18$), while significant differences were observed in all other pregnancy outcome indicators ($P < 0.05$) (Table 2). Figure 2 intuitively visualizes the intergroup differences in five core pregnancy outcome indicators, consistently demonstrating that pre-pregnancy AR diagnosis was associated with more favorable maternal and neonatal outcomes. The vaginal delivery rate in the pre-pregnancy diagnosis group was significantly higher than that in the intra-pregnancy

diagnosis group, whereas the cesarean section rate was significantly lower, with extremely significant differences for both indicators ($P < 0.001$). Meanwhile, the incidences of low birth weight, neonatal complications, and 1-minute and 5-minute Apgar scores < 7 in the pre-pregnancy diagnosis group were all significantly lower than those in the intra-pregnancy diagnosis group, among which the intergroup difference in the incidence of 5-minute Apgar score < 7 was the most prominent (0.8% vs 4.7%). This indicated that pre-pregnancy diagnosis and intervention of AR could significantly improve the immediate vital signs of neonates.

Table 2
Association between timing of allergic rhinitis diagnosis and pregnancy outcomes (n = 5,083)

Pregnancy outcomes	Pre-pregnancy diagnosis (n = 4,071)	Mid-pregnancy diagnosis (n = 1,012)	*P*-value	OR (95% CI)
Vaginal delivery rate	3,688 (90.6%)	726 (71.7%)	< 0.001	2.64 (2.32, 3.01)
Cesarean delivery rate	383 (9.4%)	286 (28.3%)	< 0.001	0.38 (0.34, 0.42)
Preterm delivery rate (< 37 weeks)	423 (10.4%)	117 (11.6%)	0.18	0.89 (0.79, 1.00)
Low birth weight rate (< 2500 g)	163 (4.0%)	70 (6.9%)	0.002	0.58 (0.49, 0.68)
Neonatal complication rate	1,478 (36.3%)	446 (44.1%)	< 0.001	0.77 (0.72, 0.83)
1-minute Apgar score < 7	313 (7.7%)	165 (16.3%)	< 0.001	0.43 (0.40, 0.47)
5-minute Apgar score < 7	33 (0.8%)	48 (4.7%)	< 0.001	0.15 (0.12, 0.19)

Effects of Different AR Therapeutic Regimens on the Risk of Preterm Birth

The study subjects were divided into the intranasal corticosteroids group (n = 946), oral antihistamines group (n = 1,773), combination therapy group (n = 1,277), and no treatment group (n = 1,087) according to the AR therapeutic regimens during pregnancy. The results showed that compared with the no treatment group, there was a statistically significant difference in the preterm birth rate among patients receiving different AR therapeutic regimens ($P < 0.001$) (Fig. 3 **and** Fig. 4). Specifically, the preterm birth rates in the intranasal corticosteroids group and oral antihistamines group were significantly lower than that in the no treatment group, while the preterm birth rate in the combination therapy group was significantly higher. This suggested that combination therapy for AR during pregnancy may be associated with an increased risk of preterm birth; however, given the univariable analysis and potential confounding by disease severity, this association requires further validation.

Effects of Different AR Therapeutic Regimens on Other Pregnancy Outcomes

To further explore the impact of medication on pregnancy outcomes in patients with AR during pregnancy, the vaginal delivery rate, cesarean section rate, low birth weight rate, incidence of neonatal complications, and incidences of 1-minute and 5-minute Apgar scores < 7 were statistically analyzed among all therapeutic groups (Table 3). By comparing the three key pregnancy outcome indicators among the four treatment groups, it was found that different treatment strategies corresponded to different overall outcomes (Fig. 5). In terms of delivery mode, the combination therapy group had the highest vaginal delivery rate (98.2%) and the lowest cesarean section rate (1.8%), while the opposite was true for the oral antihistamines group, which had the highest cesarean section rate (20.0%); all the above differences were statistically significant compared with the no treatment group ($P < 0.05$). In addition, the low birth weight rate in the combination therapy group was significantly higher than that in the no treatment group ($P < 0.01$), whereas no significant differences were found between the intranasal corticosteroids group, oral antihistamines group and the no treatment group. The incidence of neonatal complications presented a unique distribution: it was the highest in the intranasal corticosteroids group (52.5%), followed by the oral antihistamines group (42.5%) and the combination therapy group (47.7%), and all the three groups had significantly higher incidences than the no treatment group (28.2%).

Analysis of neonatal Apgar scores revealed that compared with the no treatment group, the incidences of 1-minute Apgar score < 7 in the oral antihistamines group and combination therapy group were significantly increased ($P < 0.05$), while no significant difference was observed in the intranasal corticosteroids group. As further shown in Fig. 6, the intranasal corticosteroids group maintained the lowest incidence of abnormal 1-minute and 5-minute Apgar scores among all medication groups, and no significant difference was detected in the incidence of 5-minute Apgar score < 7 among all groups. These results indicated that medication for AR during pregnancy may lead to adverse pregnancy outcomes, especially exerting a significant impact on the low birth weight rate, incidence of neonatal complications and neonatal Apgar scores, while intranasal corticosteroid monotherapy exhibited the most favorable fetal immediate safety profile.

Table 3
Association between treatment modalities for allergic rhinitis and pregnancy outcomes (n = 5,083)

Pregnancy outcomes	Intranasal corticosteroids (n = 946)	Oral antihistamines (n = 1,773)	Combined therapy (n = 1,277)	No treatment (n = 1,087)
Vaginal delivery rate	828 (87.5%)**	1,418 (80.0%)**	1,254 (98.2%)*	1015 (93.4%)
Cesarean delivery rate	118 (12.5%)*	355 (20.0%)**	23 (1.8%)**	72 (6.7%)
Low birth weight rate (< 2500 g)	44 (4.7%)	80(4.5%)	119 (9.3%)**	48(4.4%)
Neonatal complication rate	497(52.5%)**	754 (42.5%)*	609 (47.7%)**	306 (28.2%)
1-minute Apgar score < 7	85 (9.0%)	186 (10.5%)*	142 (11.1%)**	96(8.7%)
5-minute Apgar score < 7	26 (2.7%)	46 (2.6%)	23 (1.8%)	30 (2.8%)

Discussion

Allergic rhinitis (AR) is a common allergic comorbidity in pregnant women, with its incidence among childbearing-aged females rising year by year worldwide [23, 24]. Its impact on maternal and infant prognosis has become a research hotspot in the fields of perinatal medicine and allergyology [25]. Current domestic and international studies have mostly focused on evaluating the fetal safety of a single therapeutic drug, research on the effect of AR diagnosis timing on pregnancy outcomes is limited to small-sample retrospective reports, lacking support from large-sample evidence-based medical data [26, 27]. Moreover, a unified conclusion has not been reached regarding the differential effects of different therapeutic regimens on various pregnancy outcome indicators, and clinical diagnosis and treatment are still plagued by problems such as conservative treatment strategies and blind combined medication use [28, 29]. Against this research background, this multicenter study systematically investigated the effects of AR diagnosis timing and different therapeutic regimens on pregnancy outcomes based on large-sample clinical data of 5,083 pregnant patients with AR from two centers in the United States and China. It was confirmed that pre-pregnancy diagnosis of AR is an independent protective factor for improving maternal and infant prognosis in pregnant patients, and that intranasal corticosteroids, oral antihistamines, combined therapy and other regimens exert distinct effects on pregnancy outcomes. This result fully addresses the core research question of this study regarding the correlation between AR diagnosis and treatment-related factors and pregnancy outcomes in pregnancy, and also verifies the research hypothesis that pre-pregnancy intervention for AR and individualized selection of therapeutic regimens during pregnancy can optimize maternal and infant outcomes. It thus provides important large-sample evidence-based evidence for the standardized diagnosis and treatment of AR during pregnancy.

The effect of AR diagnosis timing on pregnancy outcomes is one of the core findings of this study, which is consistent with the preliminary conclusions of previous relevant studies and further supplements evidence from large-sample quantitative analysis [18, 30]. Prior study has indicated that early diagnosis and intervention for AR during pregnancy can reduce the risk of adverse pregnancy outcomes such as cesarean section and low birth weight, yet the independent protective effect and the strength of this correlation have not been clarified due to limited sample sizes [31, 32]. This study confirmed through large-sample data that pre-pregnancy diagnosis of AR can significantly increase the vaginal delivery rate and reduce the incidence of low birth weight, neonatal complications and abnormal Apgar scores, and univariable logistic regression showed that pre-pregnancy AR diagnosis was associated with a lower risk of the aforementioned adverse pregnancy outcomes. This result further deepens and quantifies the preliminary conclusions of previous research [33]. In addition, the finding of no significant difference in preterm birth rate between the pre-pregnancy and intra-pregnancy diagnosis groups in this study is inconsistent with the conclusions of some studies that suggest AR may increase the risk of preterm birth. This discrepancy is presumed to be attributable to the timely and standardized clinical intervention administered to patients in the intra-pregnancy diagnosis group after confirmation of AR in this study, which effectively controlled AR-related symptoms such as nasal obstruction and hypoxia and offset the potential inductive effect of the disease itself on preterm birth. This finding also provides practical evidence for the timely clinical intervention of AR during pregnancy.

Both the Chinese diagnostic and treatment guideline for AR and relevant international guidelines in allergology recommend intranasal corticosteroids as first-line therapeutic agents for AR in pregnancy, with the core evidence being that such drugs feature topical administration with minimal systemic absorption and thus pose a low risk of fetal exposure [21, 34]. The results of this study also confirmed that the intranasal corticosteroids group had the lowest incidence of abnormal 1-minute and 5-minute neonatal Apgar scores among all groups, which fully verified the safety of these drugs for the immediate vital signs of the fetus and was highly consistent with the conclusions of published clinical study [35]. Meanwhile, this study found for the first time that the oral antihistamines group had a significantly lower preterm birth rate than other groups; this finding fills the gap in previous research that failed to focus on the differential effects of different therapeutic regimens on preterm birth risk, and provides new evidence-based support for the selection of therapeutic regimens for pregnant AR patients at high risk of preterm birth [36]. In contrast, the combination therapy group exhibited the dual characteristics of the highest vaginal delivery rate and a markedly elevated low birth weight rate, which breaks the one-sided perception among some clinicians that combination therapy is the optimal option. This finding also suggests that the clinical application of combination therapy for gestational AR requires strict control of indications.

The findings of this study hold important scientific value and clinical practical guiding significance, as they not only fill certain gaps in the research field of gestational AR but also provide direct evidence-based references for clinical diagnosis and treatment decisions. From a scientific research perspective, based on large-sample clinical data, this study for the first time systematically quantified the protective effect of pre-pregnancy AR diagnosis on pregnancy outcomes, clarified the impacts of four mainstream

therapeutic regimens on multi-dimensional pregnancy outcomes including delivery mode, fetal growth and neonatal prognosis, corrected the cognitive biases in the clinical treatment of gestational AR, and enriched the research system on the correlation between gestational AR and pregnancy outcomes. It also provides large-sample evidence-based evidence for the update and improvement of domestic and international clinical guidelines for gestational AR. From a clinical practice perspective, this study constructs a whole-cycle diagnosis and treatment strategy for gestational AR: clinically, AR should be included in the scope of pre-pregnancy screening for childbearing-aged women, and standardized pre-pregnancy intervention should be implemented for diagnosed patients, with pregnancy guidance provided only after symptom control, so as to reduce the risk of adverse pregnancy outcomes. The treatment of gestational AR must follow the principle of individualization: oral antihistamines can be the preferred option for patients at high risk of preterm birth; combination therapy can be cautiously adopted for patients with moderate to severe AR without high-risk factors for low birth weight; intranasal corticosteroids can serve as the basic therapeutic regimen for most pregnant AR patients, especially for those for whom the immediate vital signs of the fetus are a key concern [37, 38]. At the same time, clinicians need to abandon the excessively conservative treatment concept for gestational AR, avoid poor symptom control caused by pure non-pharmacological care alone, and also eliminate the risk of low birth weight induced by blind combined medication.

This study was a retrospective cohort study. Although the large sample size ensured the statistical power of the results, the study design still leaves room for further exploration, and in-depth research can be carried out from multiple aspects for improvement in the follow-up. Specifically, several non-negligible limitations exist in the current analysis. First, although the multicenter design enhances the generalizability of the findings by incorporating participants from two countries with distinct healthcare systems and ethnic backgrounds, potential differences in clinical practice patterns, diagnostic thresholds, and documentation standards between the US and China centers may introduce heterogeneity. Additionally, the unbalanced sample size distribution between the two centers may limit the statistical power for center-stratified analyses; the generalizability of the conclusions to other populations and healthcare settings remains to be verified. Second, this study did not perform stratified analysis based on AR symptom severity, and detailed information including specific drug types, daily dosage, treatment duration and medication adherence was not fully captured, which precludes further exploration of the dose–response relationship between pharmacotherapy and pregnancy outcomes. Third, the present analysis did not adjust for all potential confounding factors, and the influence of unmeasured variables such as environmental allergen exposure intensity and maternal lifestyle habits on the results cannot be completely excluded. Fourth, the present analysis used only univariable logistic regression without adjusting for potential confounders such as maternal age, pre-pregnancy BMI, and history of allergy or depression; therefore, the reported ORs are crude estimates and may be subject to confounding. Based on the findings of this study and the current research status of gestational AR, multicenter, prospective cohort studies can be launched in the future, enrolling pregnant AR patients of different ethnicities and from various regions with complete documentation of information such as disease severity, medication dosage and treatment course. Such studies will further verify the results of

the present research and analyze the dose-effect relationship between the disease and therapeutic drugs. In addition, large-sample randomized controlled trials can be conducted to identify the optimal applicable populations, medication dosages and treatment courses for different therapeutic regimens, thereby providing more precise therapeutic guidance for clinical practice. Meanwhile, long-term follow-up of neonates born to pregnant AR patients up to 1 to 5 years of age can be performed to investigate the impacts of AR diagnosis timing and therapeutic regimens on the long-term growth and development, risk of allergic diseases and cognitive function of neonates, so as to clarify their long-term prognosis [39]. Finally, integrated basic and clinical research can be conducted to further explore the molecular mechanisms underlying the influence of AR on pregnancy outcomes [40], and elucidate the regulatory pathways of nasal mucosal inflammation and maternal hypoxia on placental microcirculation and fetal intrauterine development, which will lay a theoretical foundation for the targeted treatment of gestational AR.

Conclusion

This multicenter retrospective study suggests that the diagnosis timing and therapeutic regimens of allergic rhinitis (AR) are significantly associated with pregnancy outcomes in pregnant patients. Pre-pregnancy diagnosis and standardized intervention for AR are the key to improving maternal and infant prognosis, which can effectively reduce the incidence of adverse pregnancy outcomes such as cesarean section, low birth weight and neonatal complications. There is no absolutely optimal therapeutic regimen for the clinical treatment of gestational AR; intranasal corticosteroids, oral antihistamines and combination therapy each have their own clinical value and applicable scenarios, and clinical selection should be individualized based on patients' disease severity and high-risk factors such as preterm birth and low birth weight. In addition, based on large-sample clinical data, this study fills the evidence-based gap in the correlation between pre-pregnancy diagnosis of gestational AR and pregnancy outcomes, clarifies the differential effects of different therapeutic regimens on pregnancy outcomes, and provides direct clinical evidence for the pre-pregnancy screening, early intervention and whole-cycle standardized management of gestational AR. The conduct of subsequent relevant research will further improve the diagnosis and treatment strategies for gestational AR, and provide more sufficient evidence-based support for the optimization of clinical diagnosis and treatment guidelines and the further improvement of maternal and infant prognosis.

Declarations

Ethics approval and consent to participate

This retrospective study was approved by the Partners Human Research Committee (Partners HealthCare) (Approval No.: 2018P002646) and the Medical Ethics Committee of the Longgang District Maternity & Child Healthcare Hospital of Shenzhen City (Approval No.: LGFYKYXMLL-2024-20). The requirement for informed consent was waived by both committees due to the retrospective nature and the use of de-identified data.

Competing interests

The authors declare no competing interests.

Funding

This research was funded by the Chongqing Science and Health Joint Medical Research Program Youth Project (2024QNXM029) and Project of Science and Technology Research Program of Chongqing Municipal Education Commission (KJQN202500127) and Shenzhen Scienceand Technology Program (JCYJ20230807141908018).

Author Contribution

Tingyu Luo: Writing – original draft; Writing – review & editing. Li Fang: Formal analysis; Writing – review & editing. Yao Yao: Data curation; Funding acquisition. Qiuling Shi: Funding acquisition; Methodology. Cheng Lei: Methodology. Jie Zhou: Formal analysis; Software. Lingling Xiong: Methodology; Writing – review & editing. Yousha Wang: Formal analysis; Writing – review & editing. Zhiling Zeng: Formal analysis; Writing – review & editing. Jinsong Li: Funding acquisition; Methodology. Fan Li: Data curation; Funding acquisition; Project administration; Writing – review & editing.

Data Availability

Our data is available upon request. Please contact the correspondence author for access to the data.

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Figures

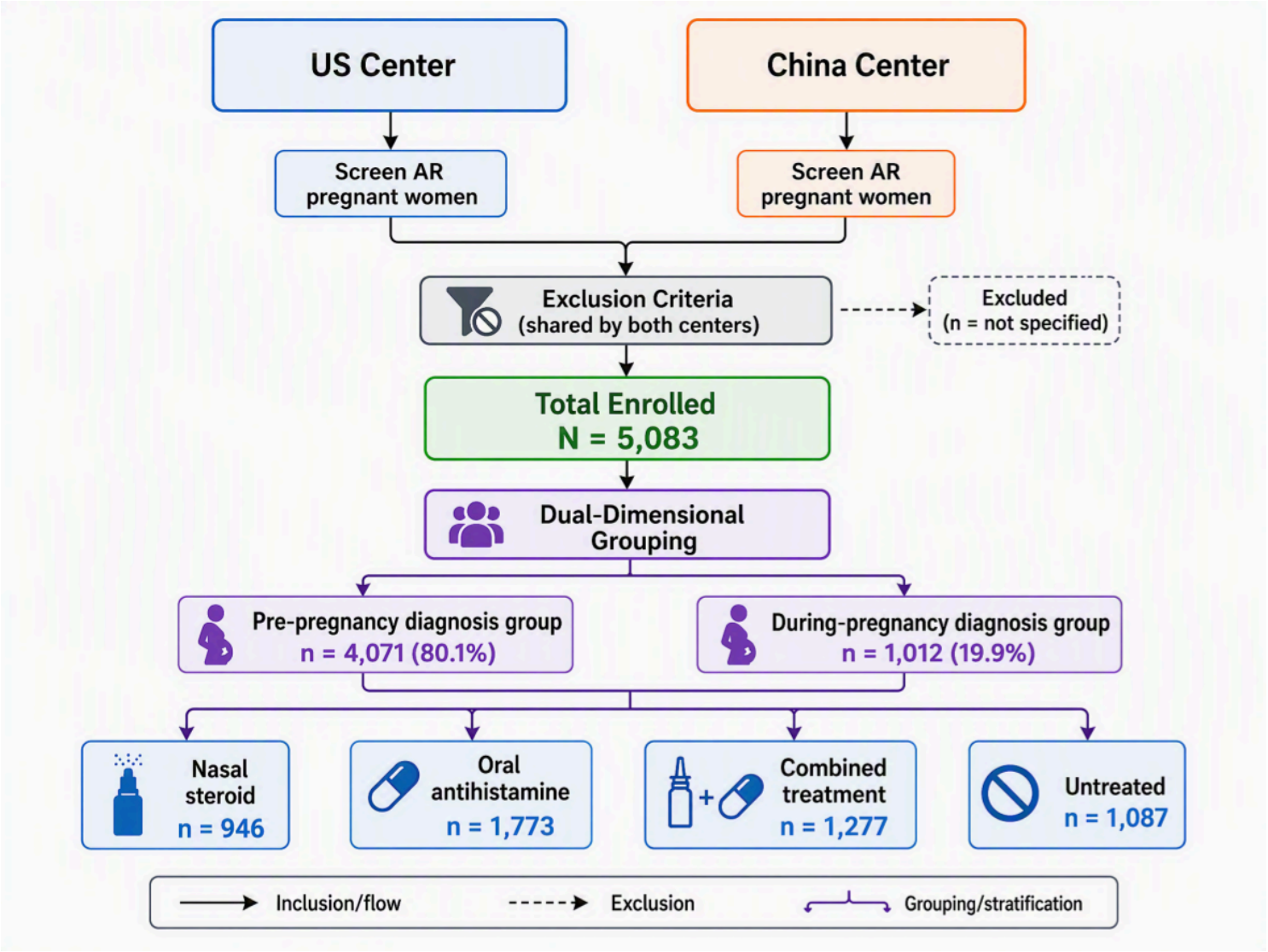


Figure 1

Flowchart of study participant enrollment

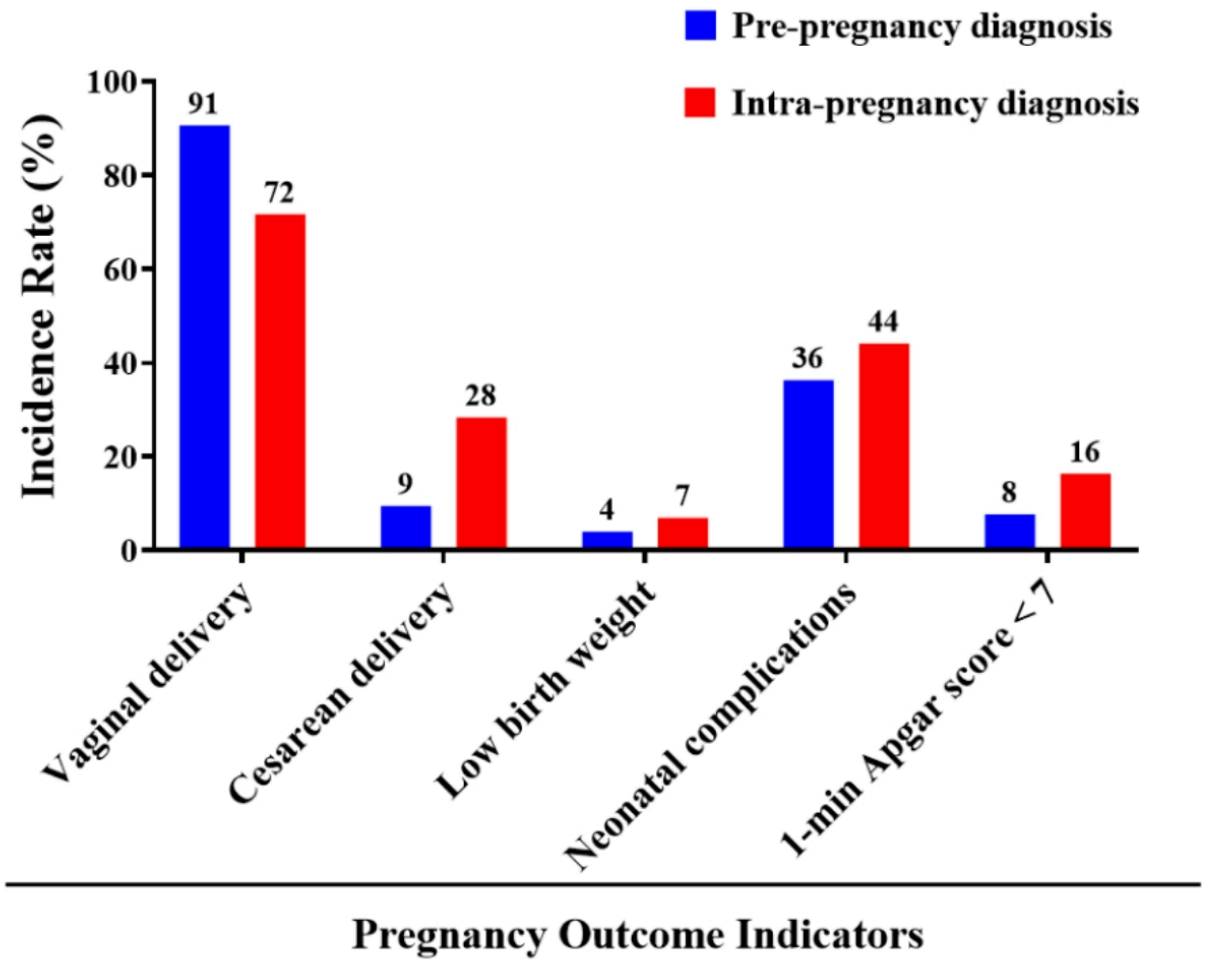


Figure 2

Comparison of major pregnancy outcome indicators between pre-pregnancy and intra-pregnancy AR diagnosis groups.

Treatment modalities	Preterm delivery rate (%)	Pvalue	Hazard Ratio
Intranasal corticosteroids	7.5	0.012	0.84 (0.74–0.96)
Oral antihistamines	3.9	<0.001	0.42 (0.36–0.49)
Combined therapy	24.1	<0.001	3.290 (2.85–3.80)
No treatment (reference)	8.8	——	1.00

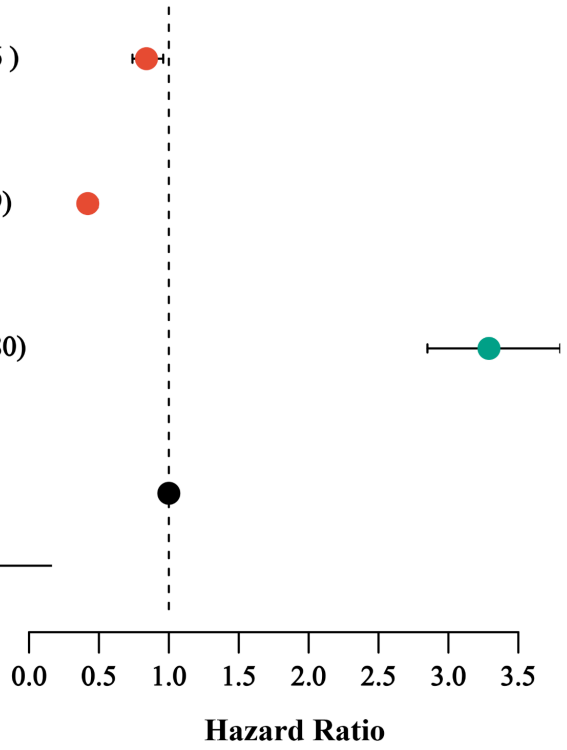


Figure 3

Association between different treatment modalities for allergic rhinitis and the risk of preterm delivery

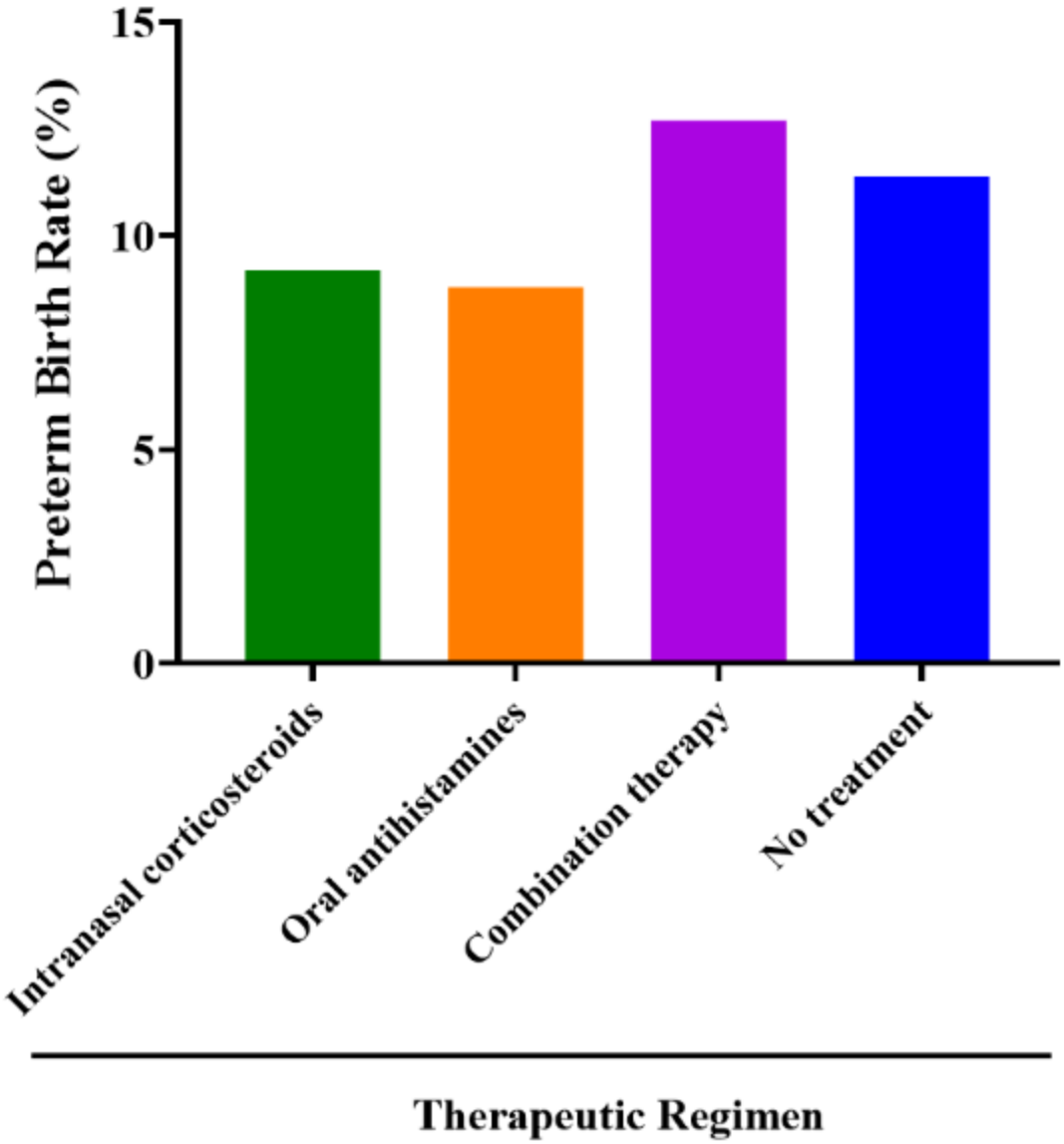


Figure 4

Preterm birth rates in pregnant AR patients receiving different therapeutic regimens.

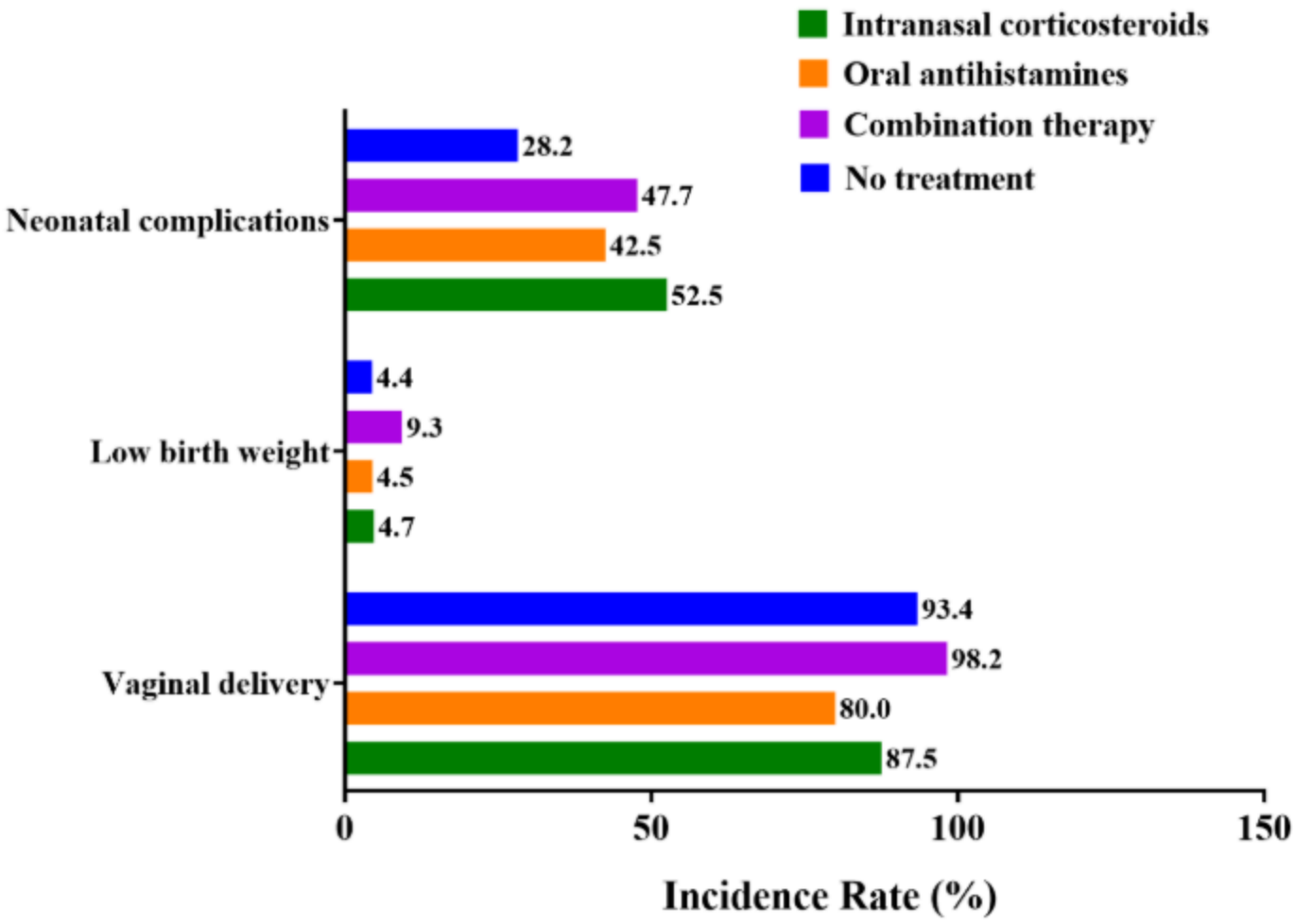


Figure 5

Effects of different AR therapeutic regimens on key pregnancy outcomes

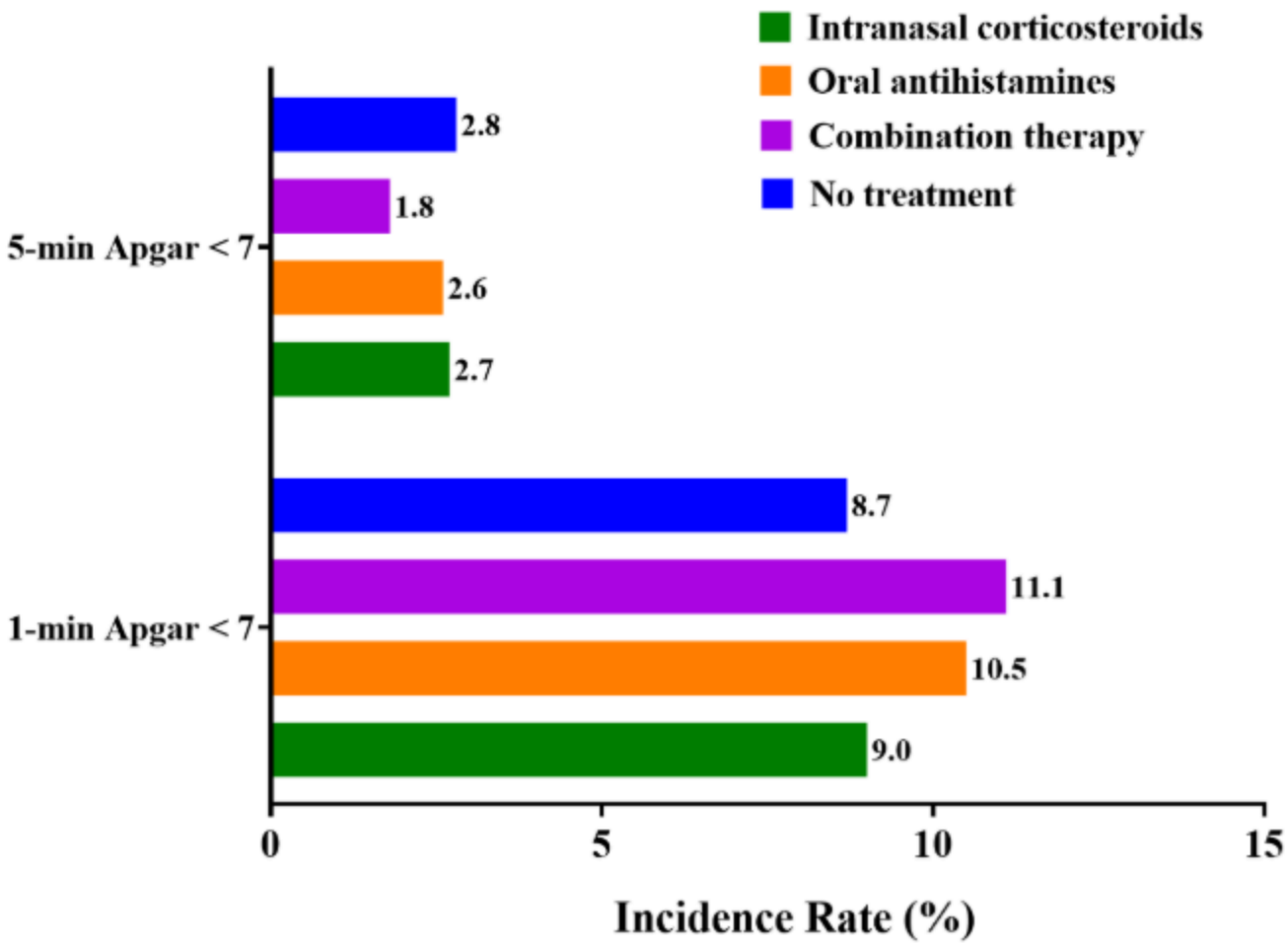


Figure 6

Incidence of abnormal neonatal Apgar scores under different AR therapeutic regimens