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Effectiveness of a Standardized Clinical Management Protocol for Spontaneous Preterm Birth in Twin Pregnancies on Maternal and Perinatal Outcomes: A Retrospective Study

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Abstract

Purpose

Spontaneous preterm birth (sPTB) occurs in 40–45% of twin pregnancies and is a leading cause of adverse perinatal outcomes. Single-modality interventions have shown inconsistent effectiveness. This study evaluated a standardized clinical management protocol for sPTB prevention in twin pregnancies.

Methods

This single-center retrospective study reviewed medical records of 150 women with twin pregnancies who delivered between January 2024 and June 2025. Based on the antenatal care model actually received, participants were divided into the study group (standardized protocol, n = 75) or control group (routine antenatal care, n = 75). The protocol included biweekly transvaginal cervical length measurements (14–24 weeks), fetal fibronectin screening at 22–24 weeks, structured patient education, psychological support, individualized nutritional counselling, and prespecified hospitalization criteria. The primary outcome was sPTB incidence (delivery at 28 to < 37 weeks); secondary outcomes covered gestational age at delivery, maternal and neonatal complications, NICU admission, and hospitalization costs.

Results

The sPTB incidence was significantly lower in the study group than in the control group (21.3% vs. 40.0%; $P = 0.013$), with a 46.8% relative reduction. Deliveries before 32 weeks were markedly reduced ($P = 0.008$), and mean gestational age at delivery was significantly prolonged ($P < 0.001$). Neonates in the study group had higher birth weights, lower NICU admission rates, shorter hospital stays, and lower hospitalization costs (all $P < 0.05$). Maternal postpartum hospital stay was also shorter in the study group ($P < 0.001$). No protocol-related serious adverse events were reported.

Conclusion

A standardized clinical management protocol integrating serial cervical monitoring, fetal fibronectin (fFN) screening, education, psychological support, and nutritional counselling significantly associated with lower sPTB and improves perinatal outcomes in twin pregnancies.

What does this study add to the clinical work

This retrospective study demonstrates that a standardized multidisciplinary management protocol integrating serial cervical monitoring, fetal fibronectin screening, structured patient education, psychological support, and nutritional counselling reduces spontaneous preterm birth by 46.8% in twin

pregnancies compared with routine antenatal care. The protocol offers a clinically implementable, cost-effective framework that outperforms single-modality interventions and provides a practical risk-stratification tool using combined cervical length and fetal fibronectin.

1. Introduction

Twin pregnancies have become increasingly prevalent worldwide, largely because of the expanding use of assisted reproductive technologies and advanced maternal age [1]. In China, recent multicenter studies have indicated that preterm birth occurs in more than 58% of twin gestations, imposing substantial burdens on neonatal intensive care resources [2]. Spontaneous preterm birth (sPTB) constitutes 40–45% of all preterm deliveries in twin pregnancies, with particularly severe sequelae for deliveries before 32 weeks, including respiratory distress syndrome, intraventricular hemorrhage, and neurodevelopmental morbidity [3].

Despite the magnitude of this problem, effective preventive strategies for sPTB in twin pregnancies remain elusive. Pharmacological interventions, including vaginal progesterone, have demonstrated inconsistent results in unselected twin populations. The EVENTS trial revealed no reduction in sPTB before 34 weeks with early vaginal progesterone [4], whereas an updated individual patient data meta-analysis suggested modest benefits limited to short-cervix subgroups [5]. Mechanical interventions, including cervical pessary and cerclage, have similarly failed to demonstrate consistent efficacy in recent randomized trials [6, 7]. A recent factorial trial directly comparing cerclage, a pessary, and adjunctive progesterone in short-cervix twins suggested that cerclage may be preferable for extremely short cervices, but the addition of progesterone conferred no additional benefit [8]. Current international guidelines differ substantially regarding routine biomarker screening and intervention strategies in asymptomatic twin pregnancies [9].

Given the limitations of single-modality interventions, there is a compelling rationale for developing an integrated, standardized clinical management protocol that combines dynamic risk stratification, serial biometric surveillance, structured patient education, psychological support, and targeted therapeutic interventions. Such a multifaceted strategy aligns with the “preterm parturition syndrome” concept, which posits that sPTB arises from multiple pathophysiological pathways that may be simultaneously addressed through comprehensive care [10]. However, limited real-world evidence exists on whether a protocolized, multidisciplinary management approach can reduce the incidence of sPTB in twin pregnancies compared with routine antenatal care.

Therefore, we conducted a single-center retrospective study to evaluate the efficacy of a standardized clinical management protocol for sPTB in twin pregnancies compared with routine antenatal care. The aim of this study was to construct and validate a predictive model for spontaneous preterm birth in twin pregnancies using clinical and ultrasound parameters to further optimize risk stratification and guide clinical decisions.

2. Methods

This single-center retrospective study was conducted at the Department of Obstetrics and Gynecology of Shijiazhuang Fourth Hospital. We reviewed medical records of women with twin pregnancies who delivered between January 2024 and June 2025. The study protocol was approved by the Ethics Committee of Shijiazhuang Fourth Hospital (approval number: 20220046). The study was performed in accordance with the Declaration of Helsinki and reported following the STROBE statement. The flowchart of patient selection and grouping is shown in Fig. 1.

Women with twin pregnancies at 12–14 weeks of gestation were reviewed for inclusion. Inclusion criteria were: (1) gestational age 12–14 weeks at first visit; (2) twin pregnancy confirmed by ultrasonography; (3) delivery at our hospital; and (4) complete medical records available for review. Exclusion criteria were: severe cardiac, hepatic, or renal dysfunction; psychiatric disorders documented in medical records; or transfer to another hospital during pregnancy. Based on the actual antenatal care model received, eligible participants were divided into the study group (those who received the standardized protocol) or the control group (those who received routine antenatal care according to national guidelines). Assignment was determined by attending physician discretion and patient preference.

The standardized protocol received by the study group included: (1) serial transvaginal cervical length (CL) measurements every 2 weeks from 14 to 24 weeks; (2) fetal fibronectin (fFN) screening at 22–24 weeks and when short cervix was detected; (3) structured patient education; (4) psychological support; (5) individualized nutritional counselling; and (6) prespecified criteria for further evaluation or hospitalization (CL ≤ 25 mm, positive fFN ≥ 50 ng/mL, progressive cervical shortening, regular contractions, cervical dilation, or other obstetric indications). The control group received routine antenatal care according to national guidelines.

The primary outcome was sPTB incidence (delivery at 28 to < 37 weeks from spontaneous contractions or preterm premature rupture of membranes). Secondary outcomes included gestational age stratification, pregnancy surveillance indicators, maternal complications, neonatal outcomes, and adverse events.

Statistical analysis

A total of 150 participants (75 per group) were included in the analysis based on the available medical records during the study period. Missing rates of key outcomes were minimal, so complete-case analysis was applied; no imputation was performed for covariates with < 5% missing data. All analyses were conducted using SPSS 22.0. Continuous variables were compared via t-test or Mann-Whitney U test, and categorical variables via chi-square test or Fisher's exact test.

The primary outcome was analyzed by chi-square test and multivariate logistic regression adjusted for maternal age, prepregnancy BMI, parity, chorionicity, mode of conception, history of cervical surgery, and

history of preterm birth. A prediction model combining cervical length and fetal fibronectin was constructed, with subgroup analyses performed. All tests were two-sided, with $P < 0.05$ as the significance threshold, and no correction for multiple comparisons was applied.

3. Results

3.1 Baseline Characteristics

All 150 participants (75 in each group) had complete medical records available for analysis. Table 1 shows the two groups were comparable in age, prepregnancy BMI, parity, chorionicity, mode of conception, prepregnancy comorbidities, history of cervical surgery and preterm birth history (all $P > 0.05$), ensuring comparable baseline conditions.

Table 1
Baseline characteristics of the participants in the two groups

Item	Control Group (n = 75)	Study Group (n = 75)	t/χ²	*P* Value
Age (years), mean ± SD	31.16 ± 4.547	30.85 ± 4.161	0.431	0.667
Prepregnancy BMI (kg/m²), mean ± SD	22.849 ± 3.3516	22.451 ± 3.5507	0.707	0.481
BMI classification, n (%)			0.336	0.845
Underweight (< 18.5)	8 (10.7)	8 (10.7)		
Normal (18.5–24.9)	47 (62.7)	50 (66.7)		
Overweight/Obese (≥ 25)	20 (26.7)	17 (22.7)		
Parity, n (%)			0.110	0.740
Primipara	43 (57.3)	45 (60.0)		
Multipara	32 (42.7)	30 (40.0)		
Chorionicity, n (%)			0.066	0.797
Dichorionic diamniotic	67 (89.3)	66 (88.0)		
Monochorionic diamniotic	8 (10.7)	9 (12.0)		
Conception mode, n (%)			0.243	0.622
Spontaneous conception	32 (42.7)	35 (46.7)		
Assisted reproductive technology	43 (57.3)	40 (53.3)		
Prepregnancy diabetes, n (%)			0.207	0.649
Yes	3 (4.0)	2 (2.7)		
No	72 (96.0)	73 (97.3)		
Prepregnancy hypertension, n (%)			0.150	0.699
Yes	4 (5.3)	3 (4.0)		
No	71 (94.7)	72 (96.0)		
History of cervical surgery, n (%)			0.074	0.785
Yes	8 (10.7)	7 (9.3)		
No	67 (89.3)	68 (90.7)		
History of preterm birth, n (%)			0.118	0.731
Yes	5 (6.7)	4 (5.3)		

Item	Control Group (n = 75)	Study Group (n = 75)	t/χ^2	*P* Value
No	70 (93.3)	71 (94.7)		

3.2 Pregnancy Monitoring Indicators

As presented in Table 2, compared with the control group, the study group had a significantly longer cervical length at 18–24 weeks (31.95 ± 5.75 mm vs. 27.45 ± 6.25 mm, $P < 0.001$) and a lower proportion of cervical length ≤ 25 mm (16.0% vs. 33.3%, $P = 0.014$). No significant between-group differences were found in fetal fibronectin positivity rate or genital tract infection rate. The study group had more antenatal visits and fewer antepartum hospitalizations (both $P < 0.001$).

Table 2
Comparison of Pregnancy Monitoring Indicators between the Two Groups

Indicator	Control Group (n = 75)	Study Group (n = 75)	$t/\chi^2/Z$	*P* Value
Cervical length at 18–24 weeks (mm), mean ± SD	27.451 ± 6.2492	31.951 ± 5.7548	-4.587	0.000
Cervical length ≤ 25 mm, n (%)	25 (33.3)	12 (16.0)	6.063	0.014
Positive fetal fibronectin, n (%)	18 (24.0)	9 (12.0)	3.659	0.056
Genital tract infection, n (%)	12 (16.0)	10 (13.3)	0.213	0.644
Number of antenatal visits, mean ± SD	8.16 ± 2.06	11.45 ± 2.575	-8.649	0.000
Number of hospitalizations during pregnancy, median (IQR)	1 (1–2)	1 (1–2)	-4.499	0.000
Note: Although median hospitalizations were identical, distributions differed significantly, with fewer patients in the study group requiring multiple admissions.				

3.3 Primary Outcomes

Table 3 summarizes the primary outcomes. The incidence of spontaneous preterm birth (sPTB) in the study group was 21.3%, significantly lower than 40.0% in the control group ($P = 0.013$), representing a 46.8% relative reduction.

Table 3
Comparison of Primary Outcome Indicators between the Two Groups

Outcome Indicator	Control Group (n = 75)	Study Group (n = 75)	t/χ^2	*P* Value
Spontaneous preterm birth, n (%)	30 (40.0)	16 (21.3)	6.145	0.013
Gestational age at spontaneous preterm birth, n (%)				
< 32 weeks	13 (17.3)	3 (4.0)	6.996	0.008
32–34 weeks	9 (12.0)	5 (6.7)	1.261	0.262
34–37 weeks	8 (10.7)	8 (10.7)	0.000	1.000
Term delivery, n (%)	45 (60.0)	59 (78.7)	6.145	0.013
Mean gestational age at delivery (weeks), mean ± SD	34.84 ± 2.266	36.32 ± 1.741	-4.485	0.000

Gestational age stratification showed that delivery before 32 weeks was markedly reduced in the study group (4.0% vs. 17.3%, $P = 0.008$), while delivery rates at 32–34 weeks and 34–37 weeks did not differ significantly. The study group achieved a higher term delivery rate (78.7% vs. 60.0%, $P = 0.013$) and a longer mean gestational age at delivery (36.32 ± 1.74 weeks vs. 34.84 ± 2.27 weeks, $P < 0.001$). The Kaplan–Meier curves (Fig. 2) confirmed significantly prolonged sPTB-free survival in the study group (log-rank $P = 0.004$). No miscarriage, stillbirth or intrauterine fetal death was identified in either group.

3.4 Maternal pregnancy outcomes

There were no significant between-group differences in the incidence of premature rupture of membranes, hypertensive disorders of pregnancy, gestational diabetes mellitus, cesarean delivery, postpartum hemorrhage, postpartum fever, or chorioamnionitis (all $P > 0.05$). The mean length of postpartum hospital stay was significantly shorter in the study group ($P < 0.001$). Full maternal outcome data are provided in Table S1.

3.5 Neonatal Outcomes

Neonatal outcomes are detailed in Table 4. Neonates in the study group had significantly higher mean birth weight, lower rates of low birth weight and very low birth weight, lower NICU admission and jaundice rates, shorter hospital stay, and lower total hospitalization costs (all $P < 0.05$). No significant differences were found in the incidence of neonatal asphyxia, transient tachypnea of the newborn, mechanical ventilation requirement, hypoglycemia, sepsis, encephalopathy, intracranial hemorrhage, or meconium aspiration syndrome.

Table 4
Comparison of neonatal outcomes between the two groups

Outcome	Control group (n = 150)	Study group (n = 150)	t/χ²/Z	*P* value
Birth weight (g), mean ± SD	2250.5 ± 520.5	2590.5 ± 400.5	-6.341	< 0.001
Low birth weight (< 2500 g), n (%)	97 (64.7)	52 (34.7)	27.001	< 0.001
Very low birth weight (< 1500 g), n (%)	10 (6.7)	0 (0.0)	10.345	0.001
Neonatal asphyxia (5-min Apgar < 7), n (%)	11 (7.3)	6 (4.0)	1.559	0.212
NICU admission, n (%)	72 (48.0)	39 (26.0)	15.573	< 0.001
Jaundice, n (%)	45 (30.0)	30 (20.0)	4.000	0.046
Transient tachypnea of the newborn (TTN), n (%)	18 (12.0)	10 (6.7)	2.500	0.114
Mechanical ventilation, n (%)	12 (8.0)	5 (3.3)	3.000	0.083
Hypoglycemia, n (%)	20 (13.3)	10 (6.7)	3.600	0.058
Sepsis, n (%)	5 (3.3)	2 (1.3)	1.340	0.247
Encephalopathy, n (%)	2 (1.3)	1 (0.7)	0.330	0.566
Intracranial hemorrhage, n (%)	3 (2.0)	1 (0.7)	1.010	0.315
Meconium aspiration syndrome, n (%)	2 (1.3)	1 (0.7)	0.330	0.566
Neonatal length of hospital stay (days), mean ± SD	5.69 ± 3.82	4.59 ± 2.76	2.875	0.004
Total hospitalization cost for neonates (RMB), median (IQR)	12673.72 (8721.54–16831.72)	10925.60 (7496.74–14573.44)	-2.829	0.005

3.6 Risk Factors and Predictive Model

Multivariate logistic regression analysis identified cervical length ≤ 25 mm at 18–24 weeks (adjusted OR 2.88, 95% CI 1.29–6.45; *P* = 0.010) and positive fetal fibronectin (adjusted OR 2.85, 95% CI 1.15–7.08; *P* = 0.024) as independent risk factors for sPTB in twin pregnancies. The combined prediction model demonstrated good discriminative performance, with an AUC of 0.83 (95% CI 0.76–0.90) (Table S2, Fig S1).

3.7 Adverse Events

No serious adverse events related to the protocol were identified during the study period. Three patients in the study group were recorded to have developed mild vaginal pruritus, which resolved spontaneously without any treatment. No adverse events were identified in the control group.

3.8 Subgroup Analysis

Subgroup analyses stratified by chorionicity, mode of conception, and cervical length at 18–24 weeks showed a consistent trend of lower sPTB incidence in the study group across all subgroups. The low incidence rate observed in the double chorionic amniotic membrane was statistically significant, different conception modes, and both cervical length subgroups. The monochorionic diamniotic subgroup did not reach statistical significance due to small sample size. Full subgroup data are provided in Table S3.

4. Discussion

This single-center retrospective study showed that the standardized clinical management protocol was significantly associated with lower rates of spontaneous preterm birth in twin pregnancies compared with routine antenatal care, with a 46.8% relative decrease in sPTB incidence (21.3% vs. 40.0%, *P* = 0.013) and a 76.9% relative reduction in delivery before 32 weeks (4.0% vs. 17.3%, *P* = 0.008). The standardized protocol was also improved perinatal outcomes including higher birth weight, lower rates of low and very low birth weight, reduced NICU admissions and shorter neonatal hospital stays, with no serious adverse events reported.

The clinical benefit likely arises from concurrent targeting of multiple pathophysiological pathways of preterm parturition syndrome. Serial biweekly cervical length measurements enabled dynamic assessment of cervical remodelling [11, 12]; the longer cervical length and lower short cervix rate in the study group suggest early detection was associated with preserved cervical integrity by mitigating mechanical stress and stretch-induced inflammatory signalling [13], consistent with evidence linking uterine overdistention to proinflammatory cytokine release and impaired progesterone-mediated uterine quiescence [14],[15].

Complementary fetal fibronectin (fFN) screening at 22–24 weeks provided biochemical risk stratification [16, 17]. Positive fFN emerged as an independent predictor of sPTB in our multivariate model (OR 2.848, 95% CI 1.146–7.076; P = 0.024), validating its incorporation into sequential screening algorithms. The psychological support component of the protocol may have contributed to lower observed risk [18]. Chronic stress increases cortisol levels and promotes proinflammatory cytokine release, which can trigger decidual activation and preterm parturition [18]. Although the precise hierarchy of these mechanisms remains to be fully elucidated, the combined CL-fFN prediction model showed good discriminative performance, offering a clinically implementable risk stratification tool [19, 20].

Beyond biomechanical and biochemical surveillance, the protocol's psychological and nutritional components likely contributed to risk reduction through neuroendocrine and metabolic pathways [21].

Cognitive-behavioral and supportive counselling interventions may have mitigated maternal HPA axis activation and cortisol-mediated progesterone withdrawal—a recognized mechanism in stress-induced preterm labor [22]. Individualized nutritional counselling addressing prepregnancy BMI status and gestational weight gain optimization may attenuate metabolic inflammation and insulin resistance, both of which have been implicated in preterm birth pathogenesis through cytokine-mediated decidual activation [23]. The absence of significant between-group differences in gestational diabetes mellitus and hypertensive disorders, despite nutritional intervention, suggests that the benefits of the protocol are relatively specific to sPTB prevention rather than generalized metabolic improvement.

The synergistic interaction of these components aligns with the “preterm parturition syndrome” paradigm proposed by Romero et al. [10], which conceptualizes sPTB as a final common pathway arising from multiple etiologies—including decidual hemorrhage, intrauterine inflammation, uterine overdistension, and stress-mediated activation—that requires simultaneous, multimodal targeting. Our findings empirically support this theoretical framework by demonstrating that an integrated approach outperforms single-modality interventions in a real-world clinical setting.

Our findings contrast with the largely disappointing results of single-modality interventions in twin pregnancies. Recent systematic reviews and meta-analyses by Conde-Agudelo et al. have shown that vaginal progesterone does not reduce sPTB in unselected twin populations, with benefits confined to short-cervix subgroups [10]. Combined analyses of progesterone, cerclage, a pessary, or acetylsalicylic acid for the prevention of preterm birth in multifetal pregnancies similarly demonstrate the limited efficacy of any single pharmacological or mechanical intervention [24]. Similarly, cervical pessary trials, including the TOPS RCT, failed to demonstrate efficacy in individuals with short cervixes [25, 26], while the evidence concerning cerclage remains inconsistent and procedure specific [26, 27]. The SuPPoRT multicenter trial directly comparing cerclage, a pessary, and progesterone revealed no clear superiority of any single intervention [28]. Unlike single-modality interventions that target only one pathway, our integrated protocol simultaneously addresses multiple components—biomechanical surveillance, biochemical risk stratification, patient education, psychological support, and timely escalation—thus aligning with the multifactorial etiology of sPTB [29].

These results align with emerging evidence supporting comprehensive care models. FIGO good practice recommendations emphasize risk-stratified surveillance and patient-centered interventions [30], and recent cost-utility analyses support universal cervical length screening in twin pregnancies [31, 32]. Our findings extend these principles by demonstrating the clinical efficacy of a fully integrated protocol in a retrospective cohort [33].

Clinically, the protocol fills gaps in current international guidelines by providing an evidence-based framework for standardizing twin pregnancy antenatal care [9]. The combined CL-fFN model offers a practical noninvasive risk stratification tool readily implementable in practice [20], while reduced neonatal hospitalization costs and shorter maternal stays indicate favourable cost-effectiveness [34]. Consistent benefits across natural conception and ART subgroups support broad clinical applicability

[35, 36], reinforcing the paradigm shift from single “magic bullet” interventions toward holistic pathway-oriented prevention strategies [37].

Strengths and limitations

Strengths of this study include the use of a well-defined standardized protocol in a real-world clinical setting, comparable baseline characteristics between groups, and the integrated multidisciplinary approach addressing multiple etiological pathways concurrently[38]. The combined CL-fFN prediction model offers a clinically implementable risk stratification tool.

Limitations include the retrospective, single-center design with relatively small sample size, particularly in the MCDA subgroup, limiting generalizability[3, 39]. The non-randomized allocation based on physician discretion and patient preference may introduce selection bias and confounding by indication; although baseline characteristics were comparable (Table 1), unmeasured confounders cannot be fully excluded. The prediction model was internally validated only and requires external validation in an independent cohort. Additionally, this study evaluated only short-term maternal and neonatal outcomes during hospitalization; long-term neurodevelopmental follow-up is warranted.

5. Conclusion

This retrospective study demonstrates that a standardized multidisciplinary management protocol integrating serial biomarker surveillance, structured patient education, psychological support and targeted therapeutic escalation significantly reduces sPTB and improves perinatal outcomes in twin pregnancies. Its favourable safety profile, consistent effectiveness across key subgroups and potential cost-effectiveness support clinical implementation, challenging the prevailing single-modality intervention paradigm.

Declarations

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Competing interests The authors declare that they have no competing interests.

Authors' contributions Jing Zhang: conceptualization, methodology, formal analysis, investigation, writing of the original draft, supervision, project administration, and funding acquisition. Shan Cao: investigation, data curation, and review and editing of the manuscript. Jie Bai: investigation, data curation, and formal analysis. Meimei Wei: investigation, resources, and validation. All the authors have read and agreed to the published version of the manuscript.

Ethics approval This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics Committee of Shijiazhuang Fourth Hospital (approval number: 20220046). Given the retrospective nature of the study and all the procedures being performed were part of the routine care, the requirement for informed consent was waived by the Ethics Committee.

Consent to participate Not applicable. Informed consent was waived by the Ethics Committee of Shijiazhuang Fourth Hospital due to the retrospective nature of the study and the use of de-identified medical records.

Consent for publication

Data availability The datasets generated and/or analysed during the current study are available from the corresponding author upon reasonable request.

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Figures

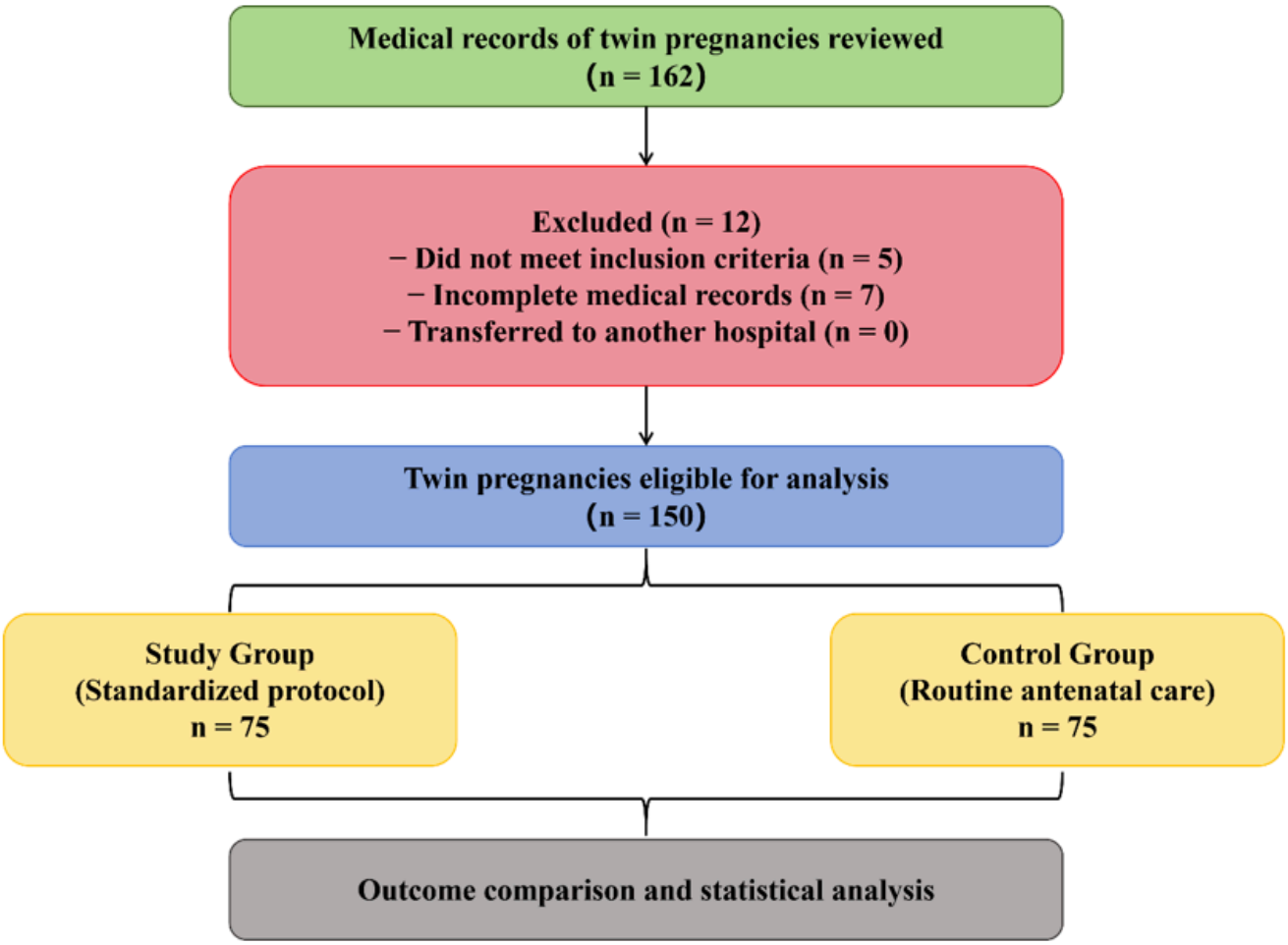


Figure 1

Flowchart of patient selection for the retrospective cohort study.

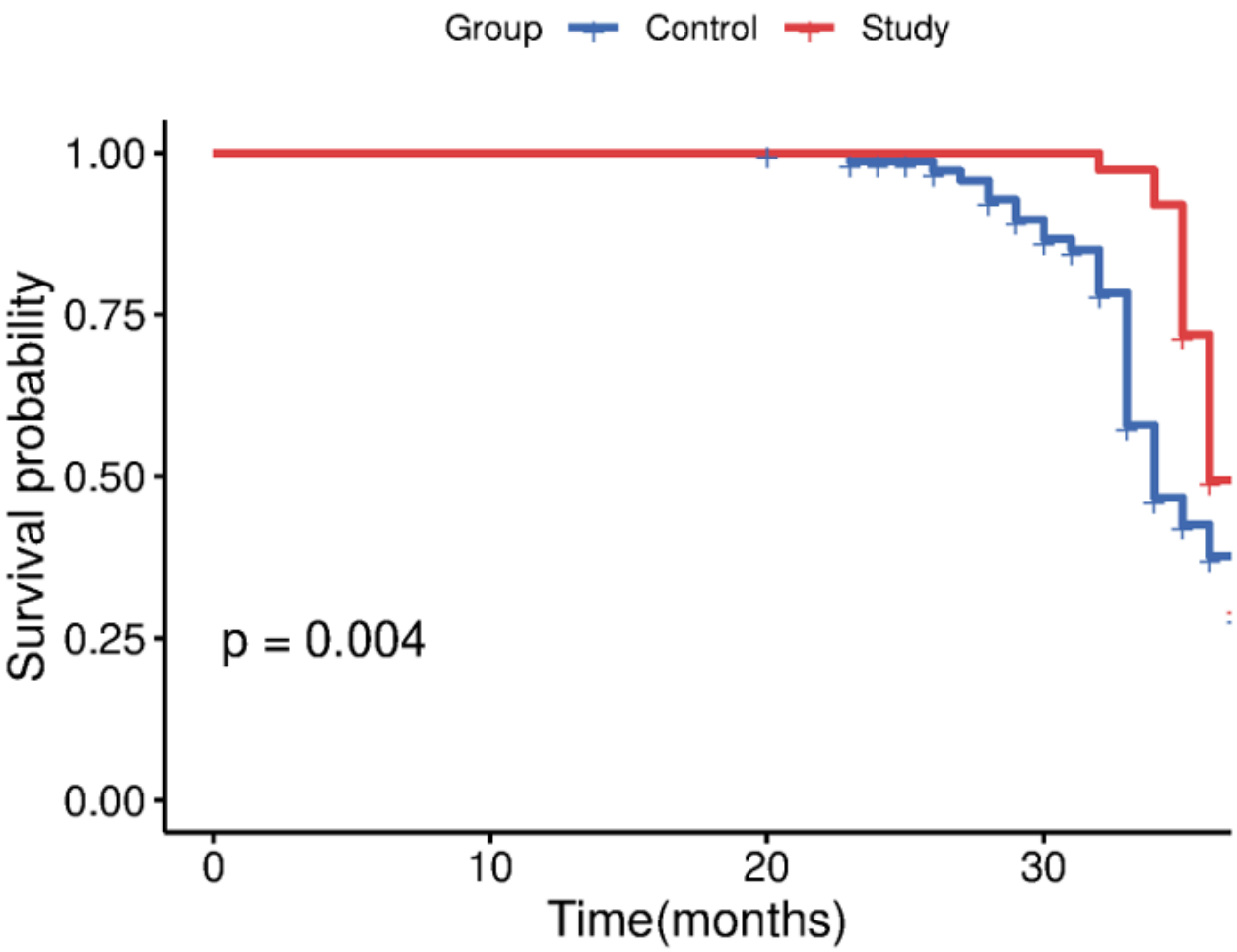


Figure 2

Kaplan–Meier survival curves for spontaneous preterm birth-free survival in the two groups.

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