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Original Research

Fetal Cardiac Function Shifts Following Tocolytic Therapy With Nifedipine or Magnesium Sulfate: A Comparative Doppler-Based Prospective Assessment

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Abstract

Background: To compare short-term changes in fetal cardiac function following tocolytic therapy with nifedipine or magnesium sulfate ($MgSO_4$) in pregnancies complicated by threatened preterm labor. **Methods**: This prospective observational study included 316 singleton pregnancies between 32–34 weeks of gestation presenting with threatened preterm labor at a tertiary perinatology clinic. Women received either oral nifedipine (n = 280) as first-line tocolysis or intravenous $MgSO_4$ (n = 36) when nifedipine and indomethacin was contraindicated. Fetal echocardiography was performed within 2 h before initiation and 2–4 h after cessation of tocolysis. Mitral and tricuspid E and A velocities, E/A ratios, left and right myocardial performance indices (MPI), and fetal heart rate (FHR) were recorded. Pre-and post-treatment changes, as well as between-group differences, were analyzed. Receiver operating characteristic (ROC) curves were constructed to assess the discriminative performance of cardiac indices. **Results**: A total of 316 pregnant women were included in the analysis, with 280 receiving nifedipine and 36 receiving $MgSO_4$. Baseline demographic and clinical characteristics were comparable between groups, except for a slightly higher gestational age and longer duration of tocolysis in the $MgSO_4$ group. In the nifedipine group, post-treatment mitral and tricuspid E/A ratios increased significantly, accompanied by a small but statistically significant decrease in left ventricular MPI and a significant decrease in FHR. In the $MgSO_4$ group, E/A ratios increased significantly after treatment, whereas individual E and A wave velocities and MPI showed no significant changes. In both groups, FHR decreased significantly after treatment. ROC analyses demonstrated limited to moderate discriminative performance of individual cardiac parameters in distinguishing pre- and post-tocolysis states. **Conclusions**: Both nifedipine and $MgSO_4$ were associated with short-term alterations in fetal diastolic filling parameters following tocolysis. Nifedipine additionally showed a small but statistically significant decrease in left ventricular myocardial performance index (MPI). All observed changes remained within physiologically acceptable ranges for late gestation, supporting the fetal cardiac safety of both agents when used for tocolysis. **Clinical Trial Registration**: The study has been registered on https://clinicaltrials.gov/ (registration number: NCT06904534; registration link: https://clinicaltrials.gov/study/NCT06904534?cond=NCT06904534&viewType=Card&rank=1).

Keywords: preterm labor; tocolysis; fetal echocardiography; myocardial performance index; magnesium sulfate

1. Introduction

Preterm birth, defined as delivery before 37 completed weeks of gestation, is the leading cause of death in children under 5 years of age, affecting an estimated 13–15 million births annually worldwide [1,2]. This persistent global burden highlights the need to optimize the management of threatened preterm labor. The primary goal of tocolytic therapy is to gain time for antenatal corticosteroids, *in-utero* transfer, and fetal neuroprotection when indicated [3–5]. These benefits should be achieved without imposing additional maternal or fetal risk.

Calcium channel blockers, particularly oral nifedipine, are widely used as first-line tocolytics. They are considered more effective and better tolerated than β-adrenergic agonists in delaying delivery for at least 48 h [3–6]. Nifedipine inhibits transmembrane calcium influx in myometrial cells and reduces uterine contractility. It may also cause systemic vasodilation and changes in maternal hemodynamics, although several Doppler studies suggest that short-term nifedipine tocolysis does not significantly alter uteroplacental or fetal arterial flow [7,8]. Nevertheless, its effect on fetal cardiac function, particularly diastolic filling indices, remains incompletely defined.

Magnesium sulfate ($MgSO_4$) is currently used mainly for fetal neuroprotection rather than as a first-line tocolytic [9,10]. International guidelines recommend $MgSO_4$ before anticipated very preterm delivery (28–32 weeks) to reduce the risk of cerebral palsy [9]. Magnesium sulfate acts as a non-specific calcium antagonist and readily crosses the placenta. It may cause maternal vasodilation and neuromuscular depression. Reviews describe a generally favorable benefit–risk profile, but note concerns about fetal heart rate (FHR) patterns and short-term cardiovascular adaptation [10].

Over the past two decades, fetal echocardiography has evolved beyond structural assessment. It is now also employed for detailed functional evaluation of the fetal heart. Doppler-derived myocardial performance index (MPI) and atrioventricular inflow E/A ratios are non-invasive markers of global ventricular performance and diastolic function [11–13]. These parameters have been applied in growth restriction, maternal disease, and other high-risk conditions. However, data comparing the acute effects of different tocolytic strategies on fetal cardiac function remain limited. Most studies have focused on the use of nifedipine alone in heterogeneous populations [3–8]. Direct comparisons with $MgSO_4$ in real-world clinical settings are rare.

Against this background, we conducted a prospective observational study in pregnancies with threatened preterm labor between 32 and 34 weeks of gestation. The study compared short-term Doppler-derived fetal cardiac changes before and after nifedipine or $MgSO_4$ therapy. We assessed mitral and tricuspid E/A ratios, MPI, and FHR. By focusing on a pragmatic cohort in which $MgSO_4$ was reserved for women with contraindications to first-line agents, this study aims to provide clinically relevant data on fetal cardiac safety and hemodynamic adaptation. To our knowledge, this is the first prospective study to directly compare the acute Doppler-derived functional cardiac effects of nifedipine and $MgSO_4$ in fetuses using a standardized protocol, a single blinded operator, a strict pre–post treatment time window, and complementary receiver operating characteristic (ROC) analysis. This approach allows a focused assessment of short-term fetal cardiac adaptation to two commonly used tocolytic regimens under real-world clinical conditions.

2. Materials and Methods

2.1 Study Design and Setting

This prospective observational study was conducted between January 2025 and July 2025 at the Department of Perinatology, Şanlıurfa Training and Research Hospital, a tertiary referral center for high-risk pregnancies in Southeastern Turkey. Ethical approval was obtained from the Ethics Committee of Harran University in December 2024 (Approval No: HRÜ/24.21.07), prior to participant recruitment. The study was registered at https://clinicaltrials.gov/ (NCT06904534) on 23 March 2025. Written informed consent was obtained from all participants prior to inclusion, and the study was performed in accordance with the principles of the Declaration of Helsinki.

All fetal echocardiographic examinations were performed prospectively by the same experienced perinatologist who was blinded to the tocolytic regimen. These examinations were conducted within a predefined and narrow time window before and after treatment to minimize inter-observer variability and temporal bias. As this was a prospective observational study with a pragmatic design, no formal a priori sample size calculation was performed. All eligible patients meeting the inclusion criteria during the study period were included.

2.2 Study Population

The study population consisted of singleton pregnant women between 32 and 34 weeks of gestation presenting with threatened preterm labor. Patients were evaluated and assigned to treatment groups based on the availability and appropriateness of tocolytic agents, following standard perinatology protocols. All enrolled participants completed both pre-treatment and post-treatment fetal echocardiographic assessments. There was no missing data for the primary Doppler parameters, including in the $MgSO_4$ group (n = 36). Maternal–fetal tolerance was evaluated through continuous maternal vital sign monitoring, assessment of maternal symptoms (e.g., hypotension, tachycardia, flushing), daily cardiotocography, and serial ultrasonographic evaluation. Tocolytic therapy was continued only in the absence of clinically significant maternal or fetal intolerance. During the study period, approximately 1200 women were managed for threatened preterm labor at our institution, of whom 316 met the inclusion criteria and were enrolled in the present analysis (**Supplementary Fig. 1**).

2.3 Nifedipine Group (n = 280)

Participants with no contraindications to calcium channel blockers were administered oral nifedipine. The regimen included a 20 mg loading dose, followed by 10 mg every 6 h for up to 48 h, depending on uterine activity and maternal-fetal tolerance.

2.4 Magnesium Sulfate ($MgSO_4$) Group (n = 36)

Patients in this group were selected due to clinical contraindications to both nifedipine and indomethacin (Endol). These contraindications included:

- Maternal hypotension (systolic blood pressure $<$90 mmHg).
- Persistent maternal tachycardia ($>$120 bpm).
- Pre-existing cardiac arrhythmias or valvular heart disease.
- Maternal asthma or bronchospastic disease [contraindication to non-steroidal anti-inflammatory drugs (NSAIDs)].
- Oligohydramnios [amniotic fluid index (AFI) $<$5 cm], which limits NSAID use due to the risk of fetal ductus arteriosus constriction and renal impairment.
- History of gastrointestinal ulcers or active gastrointestinal (GI) bleeding.
- Allergic reaction to NSAIDs or calcium channel blockers.

In such cases, $MgSO_4$ was administered both for its tocolytic effects and fetal neuroprotection, especially in cases where early preterm delivery ($<$34 weeks) remained likely. The dosing protocol included a 4 g intravenous loading dose over 30 minutes, followed by 1 g/h maintenance infusion

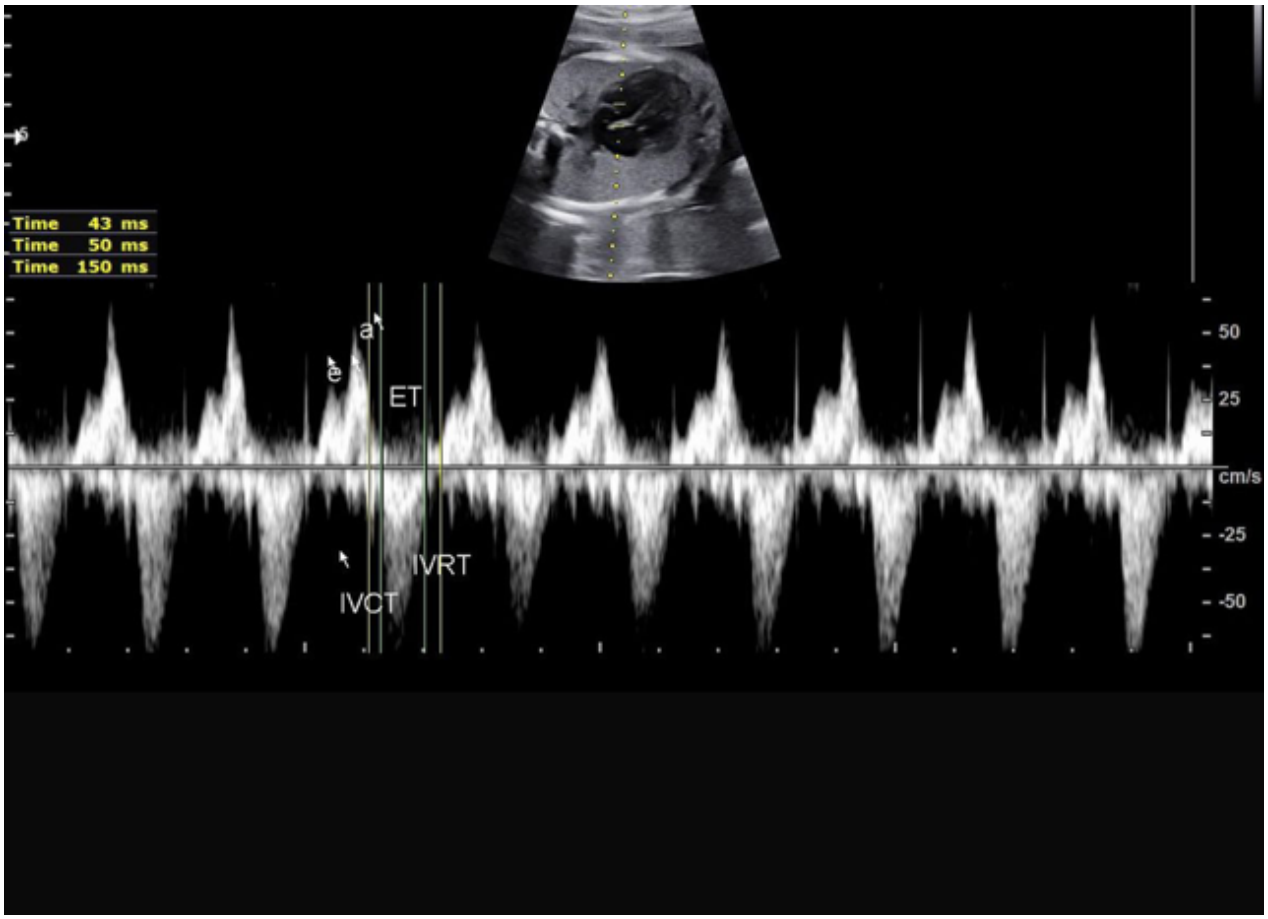

Fig. 1. Representative fetal pulsed-wave Doppler tracing illustrating myocardial performance index (MPI, Tei index) measurement using simultaneous atrioventricular inflow and ventricular outflow recordings. Identification of the E and A waves, ejection time (ET), isovolumetric contraction time (IVCT), and isovolumetric relaxation time (IVRT) allows calculation of MPI as (IVCT + IVRT)/ET. Abbreviations: MPI, myocardial performance indices.

for 24–48 h, adjusted based on maternal serum magnesium levels and clinical monitoring.

All patients were monitored closely for maternal side effects, including flushing, nausea, loss of deep tendon reflexes, and respiratory depression. Fetal surveillance included daily cardiotocography and serial ultrasonography.

This group typically included more clinically high-risk, or higher-risk patients, reflecting real-world scenarios where first-line tocolytics are unsuitable or poorly tolerated.

2.5 Exclusion Criteria

- Multiple gestation.
- Major fetal structural or chromosomal anomalies.
- Intrauterine growth restriction (IUGR).
- Pre-eclampsia or hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome.
- Maternal structural cardiac disease is not suitable for $MgSO_4$ use.
- Contraindications to fetal Doppler assessment [e.g., body mass index (BMI) >40 kg/m^2, fetal position preventing consistent cardiac windows].

2.6 Fetal Echocardiographic Assessment

Fetal echocardiographic evaluations were performed using a GE Voluson E8 Expert® system (GE Healthcare, Zipf, Austria) ultrasound device equipped with a 3.5–5 MHz transabdominal transducer. All scans were conducted by a single experienced perinatologist certified in fetal echocardiography and who was blinded to the treatment group.

Cardiac Doppler parameters were recorded within 2 h before initiation of tocolysis and within 2–4 h after cessation of therapy. The following parameters were measured:

- Mitral and Tricuspid E/A ratios.
- Mitral and Tricuspid inflow velocities (E and A waves).
- Left and Right Ventricular Myocardial Performance Index (MPI) (Fig. 1).
- Fetal Heart Rate (beats per minute).

2.7 Outcome Measures

Primary outcomes included pre- and post-treatment changes in fetal cardiac Doppler indices. Secondary out-

Table 1. Demographic and clinical characteristics of the study population (N = 316).

Characteristic	Nifedipine group (n = 280)	$MgSO_4$ group (n = 36)	*p* value
Age (years)	26.9 ± 3.8	27.8 ± 4.6	0.201
Gestational age (weeks)	33.0 ± 0.5	33.2 ± 0.4	0.022*
Gravidity, median (IQR)	2 (2–3)	2 (2–3)	0.943
Parity, median (IQR)	1 (1–2)	2 (1–2)	0.015
Body mass index (kg/m^2)	28.1 ± 3.3	28.7 ± 3.0	0.301
Previous preterm birth (%)	25	31	0.472
Presence of comorbidity (%)	30	25	0.535
Duration of tocolysis (hours)	35.8 ± 6.2	42.1 ± 4.7	<0.010*

Note: Continuous variables are presented as mean ± SD or median (interquartile range, IQR), as appropriate.

Gravidity and parity were non-normally distributed on Shapiro-Wilk testing ($p < 0.050$) and are therefore presented as median (IQR) and compared using the Mann-Whitney U test.

*Statistically significant at $p < 0.050$.

Abbreviations: $MgSO_4$, magnesium sulfate; N, number of samples.

comes involved comparative ROC analysis to assess the discriminative performance of these parameters for detecting treatment-induced cardiac shifts.

2.8 Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive data were expressed as the mean ± SD for continuous variables, and percentages (%) for categorical variables. Normality of continuous variables was assessed using the Shapiro-Wilk test. Gravidity and parity were not normally distributed (Shapiro-Wilk $p < 0.050$) and are therefore presented as median with interquartile range (IQR) and compared between groups using the Mann-Whitney U test.

- Independent-sample *t*-tests and Chi-square tests were used for between-group comparisons.
- Paired-sample *t*-tests were employed for pre- and post-treatment intragroup comparisons.

ROC analysis was conducted to evaluate the diagnostic performance of each parameter, and the Youden Index was used to determine optimal cut-off values. ROC analyses were performed to evaluate the discriminative ability of fetal cardiac parameters between pre- and post-tocolysis measurements. Optimal cut-off values were determined using Youden's index. Area under the curve (AUC) values are reported with 95% confidence intervals.

Given the limited sample size of the magnesium sulfate group, 95% confidence intervals for AUC values in this group were estimated using non-parametric bootstrap resampling with 20,000 iterations.

Covariates included in the propensity score model were selected based on both clinical relevance and preliminary univariate screening ($p < 0.10$). Variables entered into the logistic regression model for estimation of the propensity score included maternal age, gestational age, body mass index, gravidity, parity, and duration of tocolysis.

- Sensitivity analyses: To assess robustness against confounding by indication, we performed (i) multivariable linear regression with pre–post change (Δ) in each cardiac index as the dependent variable and treatment group as the main predictor, adjusting for maternal age, gestational age, BMI, gravidity, parity, comorbidity, prior preterm birth, and duration of tocolysis; and (ii) inverse probability of treatment weighting (IPTW) using a propensity score for $MgSO_4$ exposure. The propensity score was calculated using a logistic regression model including maternal age, gestational age, BMI, gravidity, parity, and duration of tocolysis as covariates. Covariate balance before and after IPTW was assessed using standardized mean differences (SMD <0.10), with detailed balance diagnostics provided in **Supplementary Table 1**.

A graphical representation illustrating covariate balance before and after IPTW weighting has been added as **Supplementary Fig. 2**.

3. Results

A total of 316 pregnant women with threatened preterm labor were included in the study, of whom 280 received nifedipine and 36 received $MgSO_4$. Baseline demographic and clinical characteristics of the study population are summarized in Table 1.

No statistically significant differences were apparent between the nifedipine and $MgSO_4$ groups with respect to maternal age, body mass index, gravidity, history of previous preterm birth, or presence of maternal comorbidity (all $p > 0.050$). Parity was also significantly higher in the $MgSO_4$ group compared with the nifedipine group ($p = 0.015$). Gestational age at the time of evaluation was slightly higher in the $MgSO_4$ group compared with the nifedipine group ($p = 0.022$). The duration of tocolysis was significantly longer in the $MgSO_4$ group than in the nifedipine group ($p < 0.010$).

Table 2. Intragroup changes in fetal cardiac function parameters before and after tocolysis.

Table 2a. Nifedipine group (n = 280).

Parameter	Before treatment	After treatment	p	Cohen's d
Mitral E (m/s)	0.50 ± 0.07	0.52 ± 0.06	<0.001*	0.31
Mitral A (m/s)	0.66 ± 0.08	0.63 ± 0.07	<0.001*	–0.40
Mitral E/A	0.77 ± 0.16	0.84 ± 0.14	<0.001*	0.43
Tricuspid E (m/s)	0.48 ± 0.06	0.50 ± 0.07	<0.001*	0.30
Tricuspid A (m/s)	0.63 ± 0.07	0.61 ± 0.08	0.002*	–0.27
Tricuspid E/A	0.77 ± 0.14	0.83 ± 0.14	<0.001*	0.41
Left ventricular MPI	0.38 ± 0.05	0.37 ± 0.06	0.033*	–0.18
Right ventricular MPI	0.40 ± 0.06	0.39 ± 0.07	0.070	–0.15
Heart rate (bpm)	142 ± 8	138 ± 7	<0.010*	–0.53

*Statistically significant at $p < 0.050$.

Table 2b. $MgSO_4$ group (n = 36).

Parameter	Before treatment	After treatment	p	Cohen's d
Mitral E (m/s)	0.50 ± 0.07	0.53 ± 0.06	0.055	0.46
Mitral A (m/s)	0.65 ± 0.08	0.62 ± 0.09	0.139	–0.35
Mitral E/A	0.78 ± 0.14	0.87 ± 0.13	0.009*	0.67
Tricuspid E (m/s)	0.49 ± 0.06	0.52 ± 0.07	0.055	0.46
Tricuspid A (m/s)	0.63 ± 0.08	0.60 ± 0.09	0.139	–0.35
Tricuspid E/A	0.79 ± 0.12	0.88 ± 0.15	0.005*	0.68
Left ventricular MPI	0.41 ± 0.04	0.40 ± 0.05	0.352	–0.22
Right ventricular MPI	0.45 ± 0.05	0.44 ± 0.06	0.399	–0.18
Heart rate (bpm)	137.00 ± 10.00	132.00 ± 9.00	<0.010*	–0.53

Note: Values are presented as the mean ± standard deviation (SD). Paired-samples t-tests were used for within-group comparisons.

*Statistically significant at $p < 0.050$.

Abbreviations: bpm, beats per minute.

In the nifedipine group, significant intragroup changes were observed in several fetal cardiac diastolic parameters following tocolysis (Table 2). Mitral E velocity increased significantly after treatment ($p < 0.001$), while mitral A velocity decreased ($p < 0.001$), resulting in a significant increase in the mitral E/A ratio ($p < 0.001$). Similarly, tricuspid E velocity increased ($p < 0.001$), tricuspid A velocity decreased ($p = 0.002$), and the tricuspid E/A ratio showed a significant increase ($p < 0.001$). Although left and right ventricular MPI values appeared numerically similar, the effect size for left ventricular myocardial performance index (LV MPI) was slightly greater than that for right ventricular myocardial performance index (RV MPI), explaining the presence of statistical significance for LV MPI but not for RV MPI.

The left ventricular MPI demonstrated a small but statistically significant decrease after nifedipine administration ($p = 0.033$), whereas the change in right ventricular MPI did not reach statistical significance ($p = 0.070$). FHR decreased significantly following nifedipine treatment ($p < 0.010$).

In the $MgSO_4$ group, the changes in individual mitral and tricuspid E and A wave velocities did not reach statistical significance ($p > 0.050$ for all). However, both mitral and tricuspid E/A ratios increased significantly after treatment ($p = 0.009$ and $p = 0.005$, respectively), indicating altered diastolic filling patterns (Table 2).

No significant changes were observed in left or right ventricular MPI following $MgSO_4$ administration ($p = 0.352$ and $p = 0.399$, respectively). A significant reduction in FHR was observed after treatment ($p < 0.010$).

ROC analyses were performed to evaluate the ability of fetal cardiac parameters to discriminate between pre- and post-tocolysis measurements.

In the nifedipine group, ROC analysis demonstrated modest discriminative performance for individual cardiac parameters, with area under the curve (AUC) values ranging from 0.58 to 0.64 (Table 3). Fetal heart rate showed the highest AUC (0.64), whereas heart rate demonstrated high sensitivity but low specificity.

In the $MgSO_4$ group, ROC analysis revealed AUC values ranging from 0.63 to 0.70 (Table 4). The mitral E/A ratio exhibited the highest discriminative performance (AUC = 0.70). Overall, ROC findings suggested limited to moderate classification ability of individual fetal cardiac parameters in distinguishing pre- and post-treatment states.

Table 3. Receiver operating characteristic (ROC) analysis of cardiac parameters in the nifedipine group.

Parameter	AUC (95% CI)	Cut-off	Sensitivity	Specificity	Youden's J
Mitral E (m/s)	0.59 (0.54–0.63)	0.51	0.61	0.55	0.16
Mitral E/A	0.62 (0.58–0.67)	0.75	0.71	0.49	0.20
Tricuspid E (m/s)	0.58 (0.54–0.63)	0.50	0.50	0.64	0.14
Tricuspid E/A	0.62 (0.57–0.66)	0.78	0.63	0.58	0.21
Fetal heart rate (bpm)	0.64 (0.59–0.68)	≤143.00	0.79	0.45	0.23

Note: ROC analysis was performed to evaluate the discriminative ability of fetal cardiac parameters between pre- and post-tocolysis measurements.
Optimal cut-off values were determined using Youden's index (J = sensitivity + specificity – 1).
Abbreviations: AUC, area under the curve.

Table 4. ROC analysis of cardiac parameters in the $MgSO_4$ group.

Parameter	AUC (95% CI)	Cut-off	Sensitivity	Specificity	Youden's J
Mitral E (m/s)	0.63 (0.50–0.76)	0.48	0.83	0.44	0.28
Mitral E/A	0.70 (0.58–0.82)	0.78	0.81	0.58	0.39
Tricuspid E (m/s)	0.65 (0.52–0.77)	0.53	0.58	0.81	0.39
Tricuspid E/A	0.69 (0.56–0.81)	0.74	0.89	0.47	0.36
Fetal heart rate (bpm)	0.65 (0.52–0.78)	≤140.00	0.86	0.50	0.36

Note: Given the limited sample size of the $MgSO_4$ group, 95% confidence intervals for AUC values were estimated using non-parametric bootstrap resampling with 20,000 iterations.

Youden's index was used to identify optimal cut-off values for each parameter. Overall, AUC values indicated limited to moderate discriminative performance, supporting the interpretation of these indices as continuous markers of physiological adaptation rather than diagnostic classifiers. After IPTW, all 36 magnesium sulfate observations remained in the weighted analysis, and no cases were excluded during weighting. Covariate balance was achieved with standardized mean differences below 0.10.

Overall, sensitivity analyses support preserved global myocardial performance with both tocolytic regimens.

To assess the robustness of the main findings given non-random treatment allocation and baseline risk differences between groups, sensitivity analyses were performed. These included (i) multivariable linear regression models using the pre–post change (Δ) in fetal cardiac indices as dependent variables, adjusting for maternal age, gestational age, body mass index, gravidity, parity, presence of comorbidity, history of prior preterm birth, and duration of tocolysis; and (ii) inverse probability of treatment weighting (IPTW) based on a propensity score for magnesium sulfate exposure. The detailed results of these sensitivity analyses are presented in **Supplementary Table 2**.

Across both approaches, changes in left and right ventricular myocardial performance indices remained comparable between groups, whereas differences were largely confined to small shifts in atrioventricular E/A ratios.

Effect size analysis using Cohen's d demonstrated moderate magnitude changes in mitral and tricuspid E/A ratios ($d \approx 0.41$–0.68) and fetal heart rate ($d \approx -0.53$) in both treatment groups, whereas the change in left ventricular myocardial performance index after nifedipine was small ($d \approx -0.18$). Cohen's d was calculated using the pooled standard deviation to provide a standardized estimate of effect magnitude across pre–post comparisons.

4. Discussion

This prospective cohort study investigated women with threatened preterm labor between 32 and 34 weeks of gestation. We observed that short-term tocolytic therapy with either nifedipine or magnesium sulfate was associated with subtle but consistent changes in Doppler-derived indices of fetal diastolic filling. Furthermore, this was accompanied by a modest reduction in FHR, LV MPI showed a small but statistically significant decrease in the nifedipine group, whereas no significant change was observed in the $MgSO_4$ group. Our results indicate that the dosing regimens used for both agents are hemodynamically well tolerated by the fetus. Moreover, the use of these agents is associated with physiological adaptation rather than deterioration in cardiac performance.

Our results should be interpreted in the context of the established role of nifedipine as a first-line tocolytic, and the evolving position of magnesium sulfate as a neuroprotective agent rather than a routine uterine relaxant. Large meta-analyses and systematic reviews have consistently demonstrated that nifedipine is at least as effective as, and often superior to, β-agonists and other traditional tocolytics in delaying delivery and improving short-term neonatal outcomes, with a more favorable maternal side-effect profile [3–6]. More recently, Zamani *et al.* [5] reported that nifedipine is superior to ritodrine and nitroglyc-

erine and comparable to magnesium sulfate in prolonging pregnancy, emphasizing that differences between agents are frequently driven by tolerability rather than efficacy alone. Our clinical practice reflects this evidence: nifedipine was used as the default agent, whereas $MgSO_4$ was reserved for women with contraindications to calcium channel blockers or NSAIDs, many of whom were clinically at higher risk. Although most baseline variables were comparable between groups, gestational age, parity, and duration of tocolysis were significantly higher in the $MgSO_4$ group, reflecting the pragmatic and clinically selected nature of magnesium sulfate use. Therefore, direct intergroup comparisons should be interpreted cautiously.

The short-term fetal hemodynamic effects of nifedipine have been examined in several Doppler-based studies. Overall, the findings suggest minimal adverse impact on uteroplacental or fetal circulations. Guclu *et al*. [7] reported that nifedipine tocolysis does not significantly impair placental, fetal cerebral, or atrioventricular Doppler waveforms within the first 24–48 h of therapy. Similarly, Mari *et al*. [8] reported preserved fetoplacental blood flow during maternal nifedipine treatment for hypertension. Extending these observations, our study focused specifically on functional cardiac indices. We observed modest increases in mitral and tricuspid E velocities and E/A ratios following nifedipine administration, LV MPI decreased significantly, while RV MPI remained unchanged. This pattern is most consistent with preserved diastolic relaxation and loading-dependent changes in ventricular filling, rather than subclinical myocardial dysfunction. The modest but statistically significant reduction in FHR observed after tocolytic therapy likely reflects physiological adaptation rather than direct myocardial depression. This adaptation is potentially mediated by autonomic modulation, reduced fetal sympathetic tone secondary to maternal hemodynamic stabilization, or altered loading conditions.

The $MgSO_4$ group is of particular interest because it comprised women with higher clinical risk profiles and contraindications to first-line tocolytics. Current international guidelines recommend $MgSO_4$ primarily for fetal neuroprotection in the setting of imminent preterm birth, based on randomized trials and high-quality reviews demonstrating reduced rates of cerebral palsy and improved long-term neurodevelopmental outcomes [9,10]. Magnesium readily crosses the placenta and may influence fetal neuromuscular tone and cardiovascular function, raising concerns about potential adverse effects on heart rate or myocardial performance. In the present study, despite longer exposure and higher baseline risk, $MgSO_4$ administration was associated with increased atrioventricular E/A ratios and a modest reduction in FHR, without significant changes in MPI. The absence of deterioration in global myocardial performance supports the conclusion that $MgSO_4$, when used within recommended dosing regimens, has an acceptable fetal cardiac safety profile, consistent with previous reports [10]. Importantly, sensitivity analyses using both multivariable regression and IPTW confirmed that the absence of change in LV and RV MPI was robust to baseline risk imbalance and the small sample size of the $MgSO_4$ subgroup, supporting the interpretation of physiologically compatible cardiac adaptation rather than myocardial dysfunction.

From a fetal cardiology perspective, MPI and atrioventricular E/A ratios are well-established tools for functional assessment. The Tei index integrates systolic and diastolic time intervals into a single measure of global myocardial performance and is sensitive to subclinical dysfunction in fetuses at risk for conduction abnormalities, hydrops, growth restriction, or maternal systemic disease [11–13]. In healthy pregnancies, reference ranges demonstrate a relatively narrow, gestation-dependent distribution. In our cohort, both left and right ventricular MPI values remained within expected third-trimester limits; however, LV MPI showed a small but statistically significant decrease after nifedipine treatment, whereas no significant changes were observed in RV MPI in the nifedipine group or in LV and RV MPI in the $MgSO_4$ group. Despite statistically significant shifts in E/A ratios and FHR, this stability suggests preservation of the overall balance between contraction and relaxation, and argues against clinically relevant myocardial stress.

The observed reduction in FHR in both groups merits consideration. A decrease of approximately 4–5 beats per minute, while statistically significant, remains well within the physiological range for fetuses at 32–34 weeks of gestation. This finding likely reflects a combination of reduced uterine activity, diminished maternal and fetal stress responses, and drug-specific cardiovascular effects. Importantly, no Doppler evidence of impaired forward flow or global myocardial dysfunction accompanied this change, supporting its interpretation as a benign physiological adaptation rather than an early marker of compromise.

ROC analyses provided additional context but should be interpreted cautiously. Although certain parameters, particularly the tricuspid E/A ratio in both groups, demonstrated modest discriminative ability for distinguishing pre- and post-treatment states, most AUC values were <0.70. These findings underscore that Doppler-derived cardiac indices in this setting are best viewed as continuous markers of hemodynamic adaptation rather than as binary diagnostic tools. Accordingly, ROC results should be considered exploratory and hypothesis-generating rather than clinically actionable.

Our findings support the continued use of nifedipine as a first-line tocolytic in appropriate candidates, while reinforcing the safety of $MgSO_4$ as a neuroprotective and secondary tocolytic option in women with contraindications to calcium channel blockers or NSAIDs [3–6,9,10]. Routine fetal echocardiography solely for monitoring short-term cardiac effects of tocolysis does not appear warranted based on these data. Instead, targeted assessment may be re-

served for fetuses with pre-existing cardiac disease, growth restriction, or limited myocardial reserve [11–13].

Statistically significant post-treatment changes were observed in mitral and tricuspid atrioventricular inflow patterns, particularly in E/A ratios; in contrast, changes in individual E and A wave velocities—especially in the $MgSO_4$ group—were more modest and did not consistently reach statistical significance. These findings should be interpreted as short-term, load-dependent physiological adaptation in Doppler-derived diastolic filling indices rather than definitive improvement in intrinsic ventricular relaxation. Given the load-dependent nature of these parameters and the influence of FHR and loading conditions, our findings support hemodynamic tolerance to both agents without establishing a specific mechanistic enhancement of myocardial relaxation. Importantly, this study was not designed to demonstrate superiority or infer differential clinical benefit between tocolytic agents, nor to establish long-term fetal or neonatal cardiac outcomes. Rather, it addresses short-term physiological tolerance and safety within routine clinical use. From a clinical standpoint, the observed Doppler changes support hemodynamic adaptation rather than myocardial compromise, suggesting that routine fetal echocardiography solely due to tocolytic exposure is not warranted in otherwise uncomplicated pregnancies.

Limitations

This study has several limitations that should be acknowledged. First, its observational design and nonrandom treatment allocation limit causal inference. Magnesium sulfate was preferentially administered to higher-risk patients with contraindications to first-line agents, introducing potential confounding by indication that must be considered in intergroup comparisons. Second, although the overall cohort size was adequate, the $MgSO_4$ subgroup (n = 36) was relatively small, which may have limited the statistical power to detect subtle changes in MPI, diastolic filling patterns, or rare adverse effects. Third, this analysis focused on short-term hemodynamic changes within hours of tocolysis. Any delayed, cumulative, or dose-dependent effects (particularly for $MgSO_4$), as well as neonatal echocardiographic and long-term neurodevelopmental outcomes, were beyond the scope of this study. Fourth, conventional Doppler-derived indices such as MPI and atrioventricular E/A ratios are inherently load- and angle-dependent and are influenced by FHR and hemodynamic conditions. Although paired-sample analyses were appropriate for the two-time-point design, we did not apply formal heart-rate–adjusted or mixed-effects modeling. Therefore, the observed changes should be interpreted as functional hemodynamic adaptation rather than as definitive evidence of altered myocardial relaxation. In addition, the significantly longer duration of tocolysis and higher parity in the $MgSO_4$ group reflects clinical selection of higher-risk patients, which may itself have influenced fetal cardiac Doppler parameters. Importantly, sensitivity analyses using both multivariable adjustment and IPTW confirmed that the absence of change in left and right ventricular myocardial performance indices was robust to baseline risk imbalance and the small sample size of the magnesium sulfate subgroup. These findings support the interpretation of physiologically compatible cardiac adaptation rather than myocardial dysfunction. However, the inclusion of sensitivity analyses mitigates, at least in part, the impact of nonrandom treatment allocation and sample size imbalance on the main conclusions.

Future studies should aim to disentangle treatment effects from baseline risk through randomized designs or carefully matched cohorts. In addition, they should extend follow-up into the neonatal period, and incorporate advanced functional imaging modalities such as tissue Doppler, speckle-tracking–derived strain, and three-dimensional volumetric assessment [11–13]. In particular, emerging evidence suggests that fetal speckle tracking echocardiography may detect subtle myocardial deformation not captured by conventional Doppler indices and could provide complementary insight in high-risk pregnancies [14–16]. Integrating these techniques with robust perinatal and long-term outcome data may help to identify fetuses who are especially vulnerable or resilient to specific tocolytic regimens. In addition, fetal echocardiographic assessments were deliberately performed within a narrow and predefined pre–post treatment window to capture acute hemodynamic responses. While this approach minimized temporal variability and enhanced internal consistency, it limits insight into delayed or evolving cardiac effects that may occur beyond the immediate post-treatment period. Furthermore, although all examinations were performed by a single experienced operator using a standardized protocol to reduce interobserver variability, subtle measurement-related variability inherent to Doppler-based functional indices cannot be entirely excluded. Finally, as this study focused on pregnancies between 32 and 34 weeks of gestation managed in a tertiary referral setting, the generalizability of the findings to earlier gestational ages or lower-risk populations may be limited.

5. Conclusions

Both nifedipine and magnesium sulfate were associated with short-term, physiologically compatible changes in fetal cardiac diastolic filling parameters following tocolysis. Both agents were associated with shifts in E/A ratios, whereas only nifedipine showed a small but statistically significant decrease in left ventricular MPI. All observed changes remained within normal limits for late gestation, supporting the fetal cardiac safety of both agents when used within recommended clinical regimens.

Availability of Data and Materials

Study data are retained within the hospital's electronic record system and can be accessed upon reasonable request in compliance with institutional policies and confidentiality regulations.

Author Contributions

DT was responsible for the conception and design of the study, data collection, ultrasonographic examinations, statistical analysis, interpretation of results, and manuscript drafting. MH was responsible for the data collection, statistical analysis, and interpretation of results. Both authors contributed to critical revision of the manuscript for important intellectual content. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The present study was conducted in accordance with the principles of the Declaration of Helsinki and internationally accepted ethical standards, and was approved by the Harran University Ethics Committee (Approval No. HRÜ/24.21.07). This prospective observational study was registered with the National Clinical Trial (NCT06904534, registration date: 23 March 2025). Prior to participation, all individuals provided written informed consent and were informed that participation was voluntary and could be discontinued at any stage without penalty. To protect privacy, all study data were anonymized and handled under secure conditions, and no personally identifiable information is included in the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During manuscript preparation, ChatGPT was used exclusively for linguistic editing purposes, such as improving grammar and spelling; it was not involved in the study design, data processing, analysis, or interpretation, and the authors assume full responsibility for the content.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/CEOG48308.

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