

The Association Between Serial β -hCG Trends and Ectopic Pregnancy Rupture Following Methotrexate Administration

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Background

- Ectopic pregnancy (EP) occurs when a blastocyst implants outside the uterine cavity¹
- EP is diagnosed based on transvaginal ultrasound findings in the context of inappropriately rising serum beta-human chorionic gonadotropin (β -hCG) levels^{1,2}
- EPs can be treated medically with methotrexate (MTX), a folic acid inhibitor with a success rate of 70-90% in single-dose protocol^{1,3,4,5}
- EP rupture is a surgical emergency that is a leading cause of maternal death in the first trimester^{1,3}
- Following MTX, patients must be followed with serial serum β -hCG measurements until β -hCG reaches 0^{1,3}
- Early prediction of MTX failure leading to EP rupture is essential in guiding safe management of EP

Objectives

- Primary:** to assess whether serial trends in β -hCG values are associated with EP rupture in patients treated with MTX
- Secondary:** to identify other potential risk factors for EP rupture

Methods

- Retrospective cohort study of patients followed by Early Pregnancy Assessment Clinic at North York General Hospital between January 2016 and December 2020
- Patients received one dose of MTX following a sonographic diagnosis of EP or pregnancy of unknown location (PUL)
- Collected patient-level data from electronic medical records on demographic data, β -hCG trends, and pregnancy outcomes (rupture vs resolution)
- Out of **433 patients** who were followed by the EPAC between 2016 and 2020, **145 patients** met study inclusion criteria with sufficient data; **12** (8.3%) experienced EP rupture and **133** (91.7%) experienced resolution
- Univariate logistic regression was used to assess associations between rupture status and percent change in β -hCG and patient demographics
- Linear regression was used to calculate slopes for β -hCG trends over time for each patient, which were used to determine percent decreases in β -hCG for any 1-day, 2-day, and 4-day timespan

Results

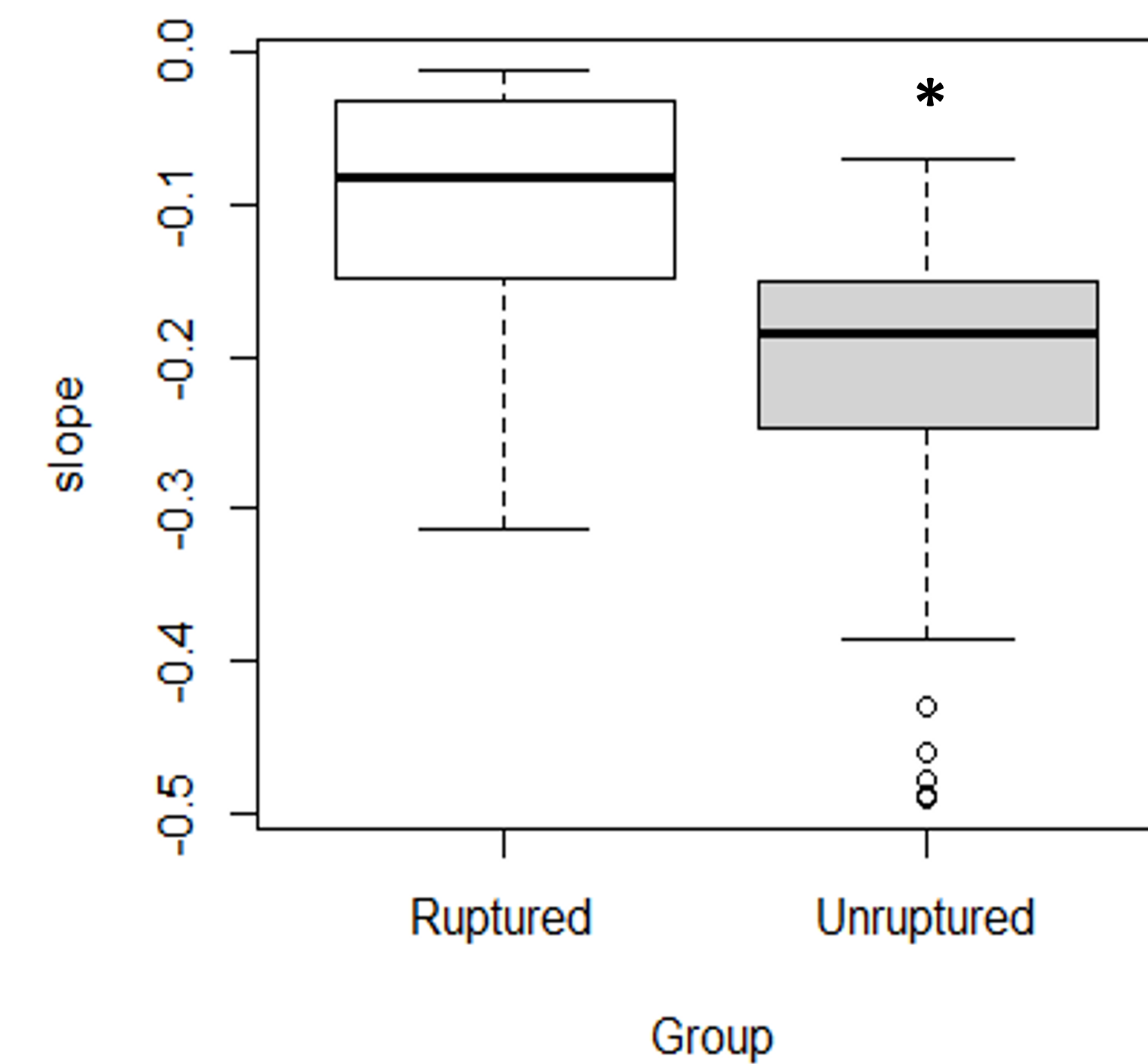


Figure 2. Box plot demonstrating the slope of β -hCG decline between rupture and unruptured groups. The rupture group (median slope: -0.08) had a slower median rate of β -hCG decline compared to the resolution group (mean slope: -0.19), $p=0.001$

Characteristic	Rupture	Unruptured	P-value
	Median (min, max)	Median (min, max)	
Available raw data† (rupture, n=4 ; unruptured, n=20)			
% decrease in β-hCG	24.4 (17.7, 30.2)	35.3 (-8.1, 77.2)	0.0434
Interpolated data‡ (rupture, n=7 ; unruptured, n=133)			
% decrease in β-hCG	20.1 (0.3, 42.7)	35.4 (-40.6, 87.1)	0.0339
Extrapolated data* (rupture, n=10 ; unruptured, n=133)			
% decrease in β-hCG	18.9 (0.3, 42.7)	35.4 (-40.6, 87.1)	0.0450

Table 2. T-test comparing percent decrease in β -hCG between day 4 and 7 for rupture and unruptured groups. Across all three groups, there was a significantly greater percent decrease in β -hCG in the unruptured group compared to the rupture group. † Patients who had raw β -hCG values for day 4 and 7. ‡ Includes patients who did not have an exact day 4 or 7 but had β -hCG ranges extending beyond day 7, and thus could interpolate day 4 and/or 7 values. * Includes patients who had β -hCG day ranges that did not extend to day 7, and thus had day 4 and/or 7 values extrapolated.

Characteristic	Rupture (n = 12)		Unruptured (n = 133)	
	median	(min, max)	median	(min, max)
Age (years)	32.0	(27, 38)	33.0	(16, 45)
Parity	n (%)		n (%)	
0	8	(66%)	84	(63%)
1	2	(17%)	34	(26%)
≥2	2	(17%)	15	(11%)
Gravidity				
1	4	(33%)	47	(35%)
2	4	(33%)	44	(33%)
3	2	(17%)	22	(17%)
≥4	2	(17%)	20	(16%)
History of spontaneous abortion				
Yes	5	(42%)	29	(23%)
No	7	(58%)	95	(77%)
History of ectopic pregnancy				
Yes	0	(0%)	12	(10%)
No	12	(100%)	114	(90%)
Location of current EP				
Right	6	(55%)	51	(45%)
Left	5	(45%)	43	(38%)
Undetermined	0	(0%)	19	(17%)

Table 1. Comparison of baseline demographics between rupture and resolution groups. No statistically significant differences in baseline demographics were identified between the two groups.

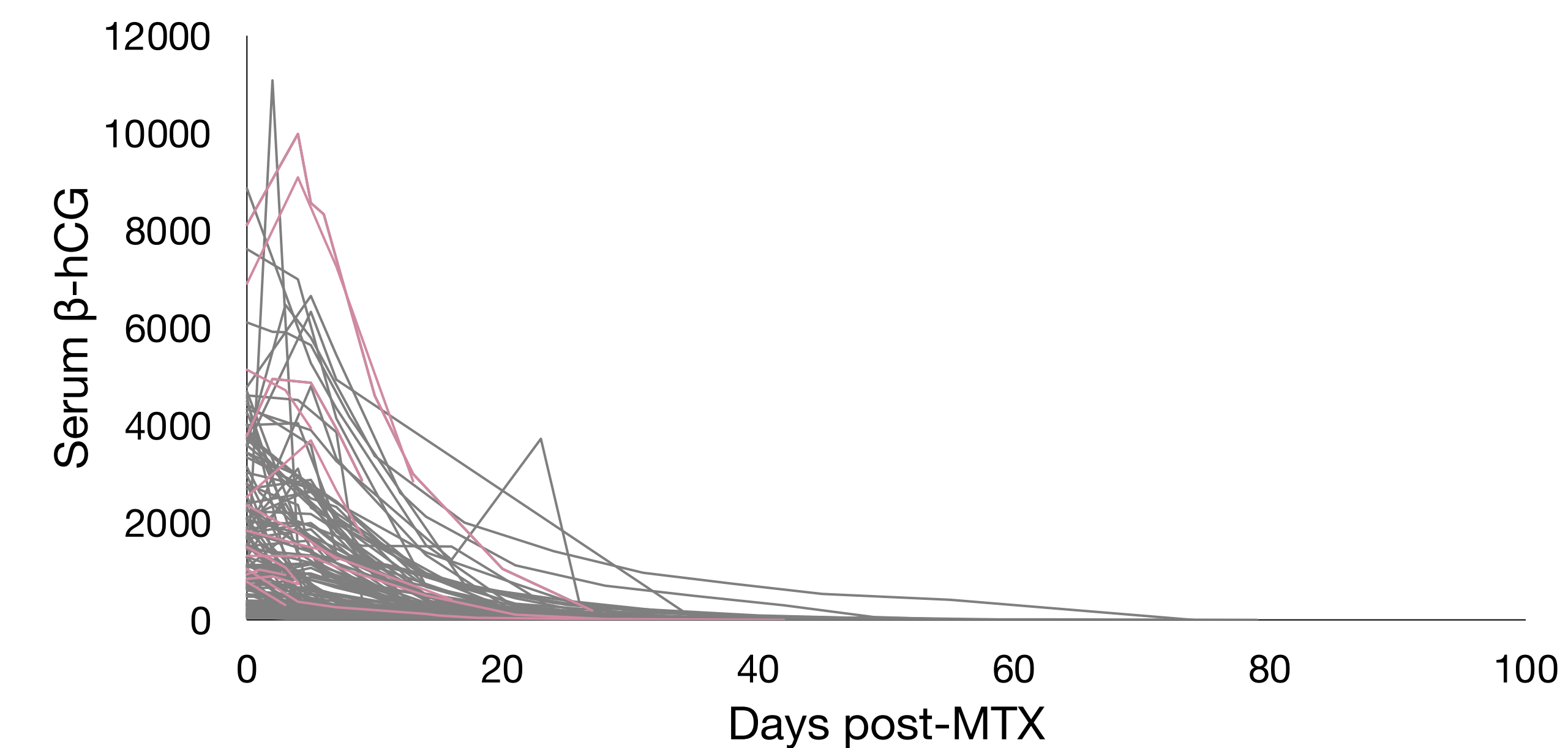


Figure 1. Spaghetti plot of β -hCG values post-MTX (day 0) between rupture (pink, n = 12) and unruptured (grey, n = 133) groups.

		% decrease in odds of rupture	P-value
% increase in any 1-day percent drop	1%	26%	p<0.001
	5%	78%	p<0.001
	15%	99%	p<0.001
% increase in any 2-day percent drop	1%	16%	p<0.001
	5%	59%	p<0.001
	15%	93%	p<0.001
% increase in any 4-day percent drop	1%	11%	p<0.001
	5%	44%	p<0.001
	15%	83%	p<0.001

Table 3. Univariate logistic regression results demonstrating associations between percent increase in percent drop in β -hCG during any 1-day, 2-day, or 4-day interval and percent decrease in the odds of EP rupture. All percent decreases in odds of rupture had p values < 0.001.

- Comparing the groups' percent drops between days 0-4 and days 0-7 using either raw data, interpolated, or extrapolated by regression produced no statistically significant differences, possibly due to this study's small sample size

Conclusions

- Our study describes observed β -hCG trends following MTX treatment for EP management
- Increases in the rate of β -hCG decline post-MTX were associated with decreasing odds of EP rupture
- These data suggest assessment of rupture risk in clinical settings may deviate from standard β -hCG measurement guidelines of 0, 4, and 7 days post-MTX

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