QTc Interval Changes in Preeclampsia vs. Normal Pregnancy: A Systematic Review and Meta-Analysis

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Pregnancy induces significant adaptations in the cardio-autonomic nervous system, with additional cardiac stress in preeclampsia potentially impacting ventricular repolarization. Despite the widespread use of QT-prolonging drugs during pregnancy, the extent of heart rate (HR)-corrected QT (QTc) interval changes during normal pregnancy and preeclampsia remains unclear. This study aimed to quantify changes in QTc interval across different trimesters of normal pregnancy and third-trimester preeclampsia. Eight databases were systematically searched from their inception to January 13, 2025. Any type of study design, except case reports/series, reporting QT interval and HR or RR interval, and/or QTc interval for at least one trimester were included. Those reporting at least two trimesters or one trimester with nonpregnant controls were pooled in meta-analyses using random-effect models to calculate pooled mean differences (MD) across trimesters. Data from 57 studies (6,686 participants) were included with 33 studies (5,153 participants) pooled in meta-analyses. Compared with nonpregnant individuals, QTc intervals increased across trimesters of normal pregnancy and in third-trimester preeclampsia. Meta-analyses revealed significant increases in QTc interval during first (MD = 10.0 msec), second (MD = 20.2 msec), and third trimesters (MD = 23.0 msec) compared with nonpregnant individuals. Furthermore, preeclampsia increased the QTc interval by 21.7 msec during the third trimester compared to normal pregnancy. No publication bias was detected, and the overall quality scores of most studies were fair ($n = 23$) or poor ($n = 33$). A significant QTc interval lengthening throughout normal pregnancy was identified, and to a greater extent during preeclampsia. The arrhythmogenicity in third-trimester preeclampsia with a known risk for QTc interval prolongation, especially with using QT-prolonging drugs, warrants further investigation.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Pregnancy and preeclampsia induce significant cardiovascular adaptations that can affect ventricular repolarization. However, the extent of QTc interval changes during normal pregnancy and preeclampsia remains unclear.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ What are the changes in the QTc interval during different trimesters of normal pregnancy and preeclampsia?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ In this systematic review, which included 57 studies and 6,686 individuals, there was significant QTc interval lengthening throughout the trimesters of normal pregnancy, with an additional QTc interval increase in patients with preeclampsia during the third trimester.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ The significant QTc interval lengthening during pregnancy—further amplified in preeclampsia—may be concerning, especially in pregnant individuals with known risk factors for QTc interval prolongation. Further, well-designed studies are needed to assess the arrhythmogenicity in third-trimester preeclampsia, especially with using QT-prolonging drugs.

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Pregnancy induces significant adaptations in the cardio-autonomic nervous system leading to structural left ventricular remodeling that can prolong ventricular repolarization.[1] Moreover, there is a 10-to-20-fold increase in estrogen and progesterone concentrations, which affect cardiac ion channels responsible for ventricular repolarization.[2,3] In addition to these physiological changes, drugs that prolong cardiac repolarization, such as ondansetron and selective serotonin reuptake inhibitors (SSRIs), are commonly used during pregnancy.[4,5]

Preeclampsia, a condition affecting approximately 6–8% of pregnancies worldwide, is a leading cause of maternal and fetal morbidity and mortality.[6] With increased cardiac workload due to hypertension, concentric ventricular hypertrophy and electrophysiological alterations are common and can exacerbate preexisting arrhythmias or even induce *de novo* arrhythmias.[6] In addition, changes in circulating hormones and electrolytes with increased sympathetic neural outflow can also impact ventricular repolarization.[7,8]

The QT interval on a surface electrocardiogram (ECG) serves as a biomarker for ventricular repolarization that portends the risk of arrhythmia and torsade de pointes (TdP), which can lead to sudden cardiac death. Therefore, evaluating the QT interval plays a critical role in both clinical practice and drug development. Prolongation of the heart rate (HR)-corrected QT (QTc) interval beyond 500 milliseconds (msec) is associated with a two- to threefold increase in the risk of TdP, with each 10-msec increment contributing to a 5 to 7% exponential rise in risk.[9]

While studies have reported QTc interval lengthening during normal pregnancy and preeclampsia, others have observed shortening or no significant changes in QTc interval.[10–12] Therefore, the exact magnitude of QTc interval alterations across different trimesters of pregnancy remains unclear. This systematic review and meta-analysis aimed to quantitatively assess changes in QTc interval length during each trimester of pregnancy with and without preeclampsia. Identifying the magnitude of QTc interval changes may inform the monitoring and management of pregnant individuals, especially in preeclampsia where multiple risks of QTc interval prolongation are expected.

MATERIALS AND METHODS

The study protocol was registered before the start of the study in the International Prospective Register of Systematic Reviews (PROSPERO, CRD42023427889). The methodology adhered to the reporting guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)[13] and Meta-analysis of Observational Studies in Epidemiology (MOOSE).[14] Detailed PRISMA reporting can be found in Table S1.

Search strategy

Eight databases (Embase, PubMed/Medline, Scopus, Web of Science, APA PsycINFO, Cochrane CENTRAL, Academic Complete, and CINAHL Complete) were systematically searched from their inception to November 30, 2023. The search was updated on April 18, 2024 and January 13, 2025 which identified four additional studies.[15–18] Backward citation analysis using Google Scholar and manual screening of the reference lists of relevant studies were also performed to identify additional literature.[19] The detailed search strategy is provided in Tables S2–S7.

Eligibility criteria

We included any type of study design except case reports/series that (i) reported QT interval and HR or RR interval, and/or QTc interval for at least one trimester during pregnancy in either normal pregnant or preeclamptic individuals; (ii) reported the trimester (or gestational age) at which QT interval and HR or RR interval, and/or QTc interval were measured; (iii) were published in English; and (iv) had full text available. Conference abstracts and animal studies were excluded.

Data collection

Two reviewers, independently and in duplicate, conducted title and abstract screening and full-text screening. Any conflicts between the reviewers were resolved through discussion and adjudication by a third reviewer. We used Covidence software (Veritas Health Innovation) to run screening using standardized forms and pre-specified eligibility criteria.[20]

Data extraction

Two authors extracted the following data from the included studies: study design, participant characteristics (sample size, age, weight, body mass index [BMI], and geographic location), pregnancy characteristics (type of pregnancy, parity, gestational age), ECG parameters (QTc, type of correction, HR, QT, QTc dispersion [QTcd], QRS, T_{peak}–T_{end} [*Tp*-*Te*], and presence of TdP), ECG measurements (type of ECG, definition of QT and QTcd, number of ECG and QTc, type of recording [manual or automatic], position of the patient during recording, and presence of resting condition), and presence of confounders that may affect QTc interval (potassium and magnesium abnormalities, diabetes, cardiovascular diseases, kidney or liver diseases, and use of any QT-prolonging medication with known risk to induce TdP).[21] The trimesters were defined according to the American College of Obstetricians and Gynecologists as follows: first trimester (prior to 13 weeks), second trimester (between 14 and 27 weeks), and third trimester (between 28 and 40 weeks). Data extraction was reviewed by two study investigators for accuracy, and any discrepancies were resolved through discussion.

Risk of bias assessment

The quality and risk of bias was assessed by two study investigators using the National Heart, Lung, and Blood Institutes (NHLBI) study quality assessment tools for "observational cohort and cross-sectional studies" and "controlled intervention studies".[22] These tools evaluate internal validity across four key areas of risk: selection bias, information bias, measurement bias, and confounding bias. For observational studies, key criteria include whether the research question was clearly stated, the study population was well-defined, participant recruitment was sufficient, exposures and outcomes were measured using valid, reliable methods, and potential confounding variables were identified and appropriately adjusted for. For controlled intervention studies, additional factors such as randomization methods, blinding of participants and assessors, adherence to intervention protocols, and drop-out rates were considered. Each study was independently dual classified as having a "good" (low risk of bias), "fair" (moderate risk of bias), or "poor" (high risk of bias) quality based on a qualitative assessment of the criteria rather than a numerical scoring system. Any discrepancy was resolved by a third author through discussion and adjudication. Full details regarding scoring are provided in Tables S8 and S9.

Data synthesis and statistical analysis

Statistical analyses were performed using R (version 4.3.2; R Project for Statistical Computing)[23] and RStudio (version 2023.12.0; RStudio, Inc.).[24] All statistical tests were two-sided with α set to 0.05. Descriptive statistics, including median, range, and interquartile range [IQR] (Q25–Q75), were calculated for continuous variables using reported mean or median values.

To quantify the changes between trimesters, meta-analyses (using the meta and dmetar packages)[25] were performed to estimate the pooled weighted mean difference (MD) with a corresponding 95% confidence interval (CI) using a random-effect model with the restricted maximum likelihood estimation method.[26] Studies were categorized based on predefined study-level characteristics, including study design, geographic region, type of ECG measurement, type of recording, type of ECG correction, severity of preeclampsia, onset of preeclampsia, presence of electrolyte imbalances, use of magnesium sulfate in preeclampsia, and overall quality assessment score. A stratified meta-analysis was used to analyze the data within each category if the number of studies in the meta-analysis was higher than 10 to determine the potential source of heterogeneity.[26,27]

To assess the statistical heterogeneity between studies, Cochran's Q test was used with a significance level of $P < 0.05$. Index statistics (I^2) were used to determine the level of inconsistency, categorized as low ($I^2 = 25\%$), moderate ($I^2 = 50\%$), or high ($I^2 = 75\%$).[28] Funnel plots were generated for outcomes with sufficient data (at least 10 studies) to visually evaluate potential publication bias. Additionally, statistical publication bias for each specific outcome was assessed using the Egger test with a significance level of $P < 0.10$.[29]

RESULTS

The search identified 19,177 citations during the three phases, of which 10,374 were removed for duplication. After title and abstract review of 8,803 citations, 145 citations were included for full-text assessment. Additionally, 16 citations were included during manual screening and backward citation analysis. Of the final 161 citations, 57 studies[10,11,15–18,30–80] were included in the systematic review, with 33 articles included in the meta-analyses (**Figure 1**).

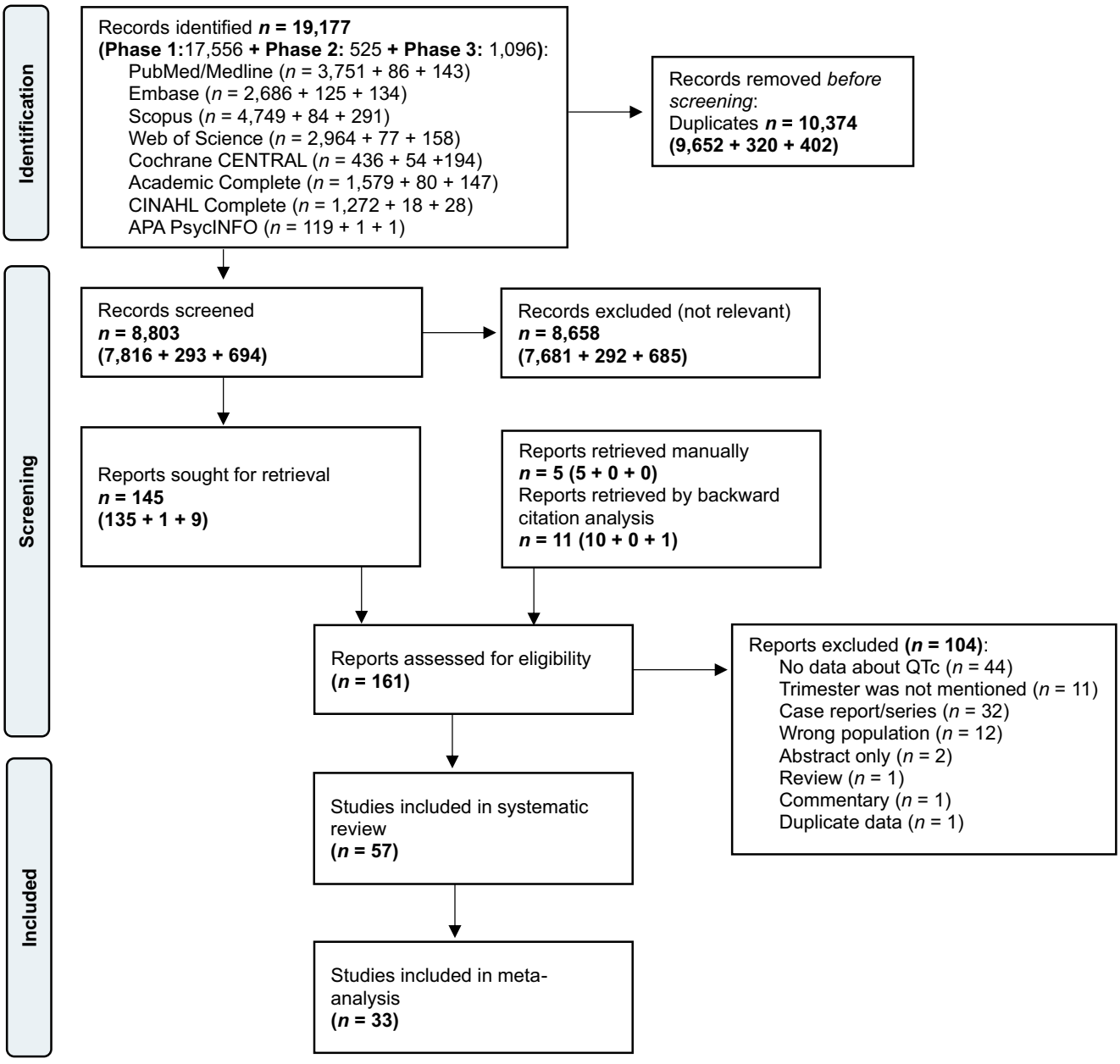


Figure 1 PRISMA flow diagram of study selection and screening.

Table 1 Characteristics of included studies

Parameter	Results
Study design, *n* (%)	
Cross-sectional	40 (70.2%)
Prospective cohort	7 (12.3%)
Retrospective cohort	2 (3.5%)
Control-arm of clinical trial	8 (14.0%)
Trimesters, *n* (%)	
First	19 (33.3%)
Second	24 (42.1%)
Third	52 (91.2%)
Parity, *n* (%)	
Nulliparous	2 (3.5%)
Mixed	20 (35.1%)
Not reported	35 (61.4%)
Type of pregnancy, *n* (%)	
Singleton only	10 (17.5%)
Not reported	47 (82.5%)
Age (years), median (IQR)	27.9 (25.0–30.2)
Weight (kg), median (IQR)	66.8 (56.0–77.0)
BMI, median (IQR)	27.9 (23.1–29.4)
Geographic location, *n* (%)	
North America	6 (10.5%)
Latin America and Caribbean	1 (1.8%)
Middle East and North Africa	15 (26.3%)
South Asia	3 (5.3%)
East Asia and Pacific	23 (40.3%)
Europe and Central Asia	6 (10.5%)
Sub-Saharan Africa	3 (5.3%)
Type of ECG, *n* (%)	
Twelve-lead ECG	45 (78.9%)
Single-lead ECG	3 (5.4%)
Five-lead ECG	1 (1.7%)
High-resolution ECG	1 (1.7%)
Holter ECG	2 (3.5%)
Body surface potential mapping	2 (3.5%)
Not reported	3 (5.3%)
Type of ECG measurement, *n* (%)	
Manual	24 (42.1%)
Electronic	6 (10.5%)
Mixed	1 (1.8%)
Not reported	26 (45.6%)
Type of QT correction, *n* (%)	
Bazett	40 (70.2%)
Hodges	2 (3.5%)
Fridericia	1 (1.8%)
Framingham	1 (1.8%)
Not reported	13 (22.7%)
Reporting resting condition during measurement, *n* (%)	20 (35.1%)
Reporting supine position during measurement, *n* (%)	21 (36.8%)
Defined how QT was measured, *n* (%)	29 (50.9%)
Defined how QTcd was measured, *n* (%)	15 (26.3%)
NHLBI overall quality assessment score, *n (%)*	
Good	1 (1.7%)
Fair	23 (40.4%)
Poor	33 (57.9%)

IQR, interquartile range (Q25–Q75); *n*, number of studies; NHLBI, National Heart, Lung and Blood Institutes; QTcd, QTc dispersion.

Study characteristics

Forty cross-sectional, nine longitudinal cohort, and eight control-arm of clinical trials involving 6,686 individuals (4,912 [73.5%] normal pregnant, 1,236 [18.5%] nonpregnant, and 538 [8.0%] preeclamptic) from 21 countries published between 1949 and 2024 reported data on QTc interval for at least one trimester (**Table 1**). A subset of 33 studies involving 5,135 individuals (3,527 [68.7%] normal pregnant, 1,138 [22.2%] nonpregnant, and 470 [9.1%] preeclamptic) from 15 countries reported QTc interval data for at least two trimesters and were pooled for meta-analyses. The number of participants per study ranged from 20 to 471 (median [IQR]: 90.0 [50.0–151.5]; mean: 117.3). The median [IQR] of mean age of participants was 27.9 [25.0–30.2] years, while the median [IQR] of mean BMI was 27.9 [23.1–29.4]. Most studies (45 studies, 78.9%) used 12-lead ECGs, and the Bazett method was the most commonly used method for QT correction (40 studies, 70.2%). Almost all studies (56 studies, 98.2%) had fair-to-poor overall quality assessment scores (**Table 1**). The details of demographic data and patient characteristics of individual studies and their NHLBI quality assessment scores are available in **Tables S10–S14**.

QTc interval changes during normal pregnancy

Using any type of QT correction, the median [IQR] of the mean QTc interval for nonpregnant individuals in 20 studies was 398 [380–406] msec. During normal pregnancy, the median [IQR] of mean QTc interval was 408 [391–420] msec in 20 studies during the first trimester, 427 [400–432] msec in 23 studies during the second trimester, and 416 [404–425] msec in 51 studies during the third trimester. This pattern of change remained consistent when the analysis was limited to the Bazett correction, with slightly higher values observed (**Table 2**, **Figure 2**). None of the studies reported an occurrence of TdP.

Meta-analyses confirmed these increasing QTc intervals across normal pregnancy trimesters. Compared to nonpregnant individuals, QTc interval increased significantly by 10.0 msec during the first trimester (95% CI: 6.3 to 13.7; $P < 0.001$; I^2: 0%) in six studies, 20.2 msec during the second trimester (95% CI: 12.0 to 28.4; $P < 0.001$; I^2: 83%) in 11 studies, and 23.0 msec during the

Table 2 ECG parameters changes across different trimesters of normal pregnancy and preeclampsia

ECG parameter	Nonpregnant		First trimester—normal pregnancy		Second trimester—normal pregnancy		Third trimester—normal pregnancy		Third trimester—preeclampsia	
	N	Median (IQR)	*N*	Median (IQR)	*N*	Median (IQR)	*N*	Median (IQR)	*N*	Median (IQR)
HR, bpm	20	77 (73–83)	18	83 (80–84)	18	88 (85–93)	45	90 (86–94)	12	84 (81–91)
QT, msec	15	350 (346–368)	15	350 (332–371)	16	350 (341–364)	33	347 (338–360)	6	376 (365–395)
QTc_{All}, msec	20	398 (380–406)	20	408 (391–420)	23	427 (400–432)	51	416 (404–425)	11	442 (420–449)
QTc_{B}, msec	11	405 (400–411)	14	413 (400–422)	12	429 (413–437)	37	419 (404–429)	9	442 (432–452)
TpTe, msec	2	67	3	76	2	73	11	72 (65–78)	4	81 (76–83)
QRS, msec	10	80 (80–85)	8	82 (77–87)	12	80 (76–83)	21	80 (72–83)	4	82 (74–87)
QTcd, msec	—	—	1	24	—	—	12	57 (36–67)	4	40 (28–64)

bpm, beat per minute; HR, heart rate; IQR, interquartile range (Q25–Q75); msec, millisecond; *N*, number of studies; QTc_{All}, corrected QT by any type of correction; QTc_{B}, corrected QT by Bazett method; QTcd, QTc dispersion; TpTe, Tpeak–Tend.

third trimester (95% CI: 12.3 to 33.3; $P < 0.001$; I^2: 97%) in 17 studies (**Figure 3a-c**). Compared to the first trimester, the QTc interval was significantly higher in the second (MD: 13.7 msec; 95% CI: −0.0 to 27.3; $P = 0.05$; I^2: 79%; 7 studies) and third (MD: 13.4 msec; 95% CI: 0.7 to 26.0; $P = 0.04$; I^2: 92%; 13 studies) trimesters (**Figure S1**). However, there was no significant difference in QTc interval between the third and second trimesters (MD: 3.7 msec; 95% CI: −1.7 to 9.0; $P = 0.17$; I^2: 83%; 16 studies) (**Figure S1**).

Subgroup analyses in normal pregnancy

Subgroup analyses were performed for QTc interval changes between the second and third trimesters in normal pregnant and nonpregnant individuals which had at least 10 studies. None of the subgroup analyses significantly reduced heterogeneity in any comparison (**Table S15**, **Figures S2–S16**). Interestingly, subgrouping by geographic location revealed a significant difference in the pooled MD in QTc interval changes during the second and third trimesters. Two studies from Sub-Saharan Africa[50,74] and one study from North America[69] showed a lower pooled MD during the second trimester (5.2 and 7.7 msec, respectively) compared to other regions, which ranged from 16.4 to 27.2 msec. Moreover, these studies showed negative pooled MD during the third trimester (−7.5 and −4.0 msec, respectively) compared to positive MD in other regions, which ranged from 11.7 to 33.9 msec (**Table S15**, **Figures S2 and S9**).

The QT correction methods were not significantly different during the second or third trimester (**Table S15**, **Figures S7 and S15**). However, the ECG recording methods showed a significant pooled MD during the third trimester. Specifically, electronic recording resulted in a slightly lower pooled MD compared to manual recording during the third (−4.0 vs. 9.2 msec) trimester. When the recording method was not specified, the pooled MD was higher (29.7 msec) than that of either method during the third trimester (**Table S15**, **Figures S8 and S16**).

QTc interval changes in patients with preeclampsia

During the third trimester, the median [IQR] of the mean QTc interval was 442 [420–449] msec in preeclamptic individuals (11 studies) compared to 416 [404–425] msec in normal pregnant individuals (51 studies) using any type of QT correction (**Table 2**, **Figure 2**). Meta-analysis confirmed this increase with a 21.7 msec MD (95% CI: 9.6 to 33.9; $P < 0.01$; I^2: 92.2%) in 10 studies compared with normal pregnancy during the third trimester (**Figure 3d**). None of the subgroup analyses showed a significantly reduced heterogeneity (**Table S15**, **Figures S17–S23**). However, sub-grouping with the severity of preeclampsia showed statistical significance in the pooled MD. Mild preeclampsia showed a pooled MD of 5.9 msec (95% CI: −26.5 to 38.3; $P = 0.26$; I^2: 0%) in two studies, while severe preeclampsia (six studies) exhibited a pooled MD of 34.6 msec (95% CI: 6.7 to 62.6; $P = 0.02$; I^2: 95%). In the studies that did not report severity (four studies), the MD was 14.3 msec (95% CI: 5.7 to 23.0; $P = 0.008$; I^2: 38%) (**Table S15**, **Figure S22**).

The presence of electrolyte disturbances did not show a significant difference in the pooled MD. When electrolyte disturbances were reported, the pooled MD was 31.6 msec (95% CI: −1.9 to 65.1; $P = 0.06$; I^2: 95%) in four studies compared with 18.3 msec (95% CI: −2.6 to 39.1; $P = 0.07$; I^2: 91%) in four studies without electrolyte disturbances. In two studies that did not report the state of electrolyte disturbances, the pooled MD was 12.5 msec (95% CI: −0.8 to 25.8; $P = 0.06$; I^2: 0%) (**Table S6**, **Figure S23**). Regarding specific electrolyte abnormalities, two studies reported hypocalcemia with a prevalence of 40% and 56% in preeclamptic individuals[52,75], while two other studies reported high potassium levels.[48,52] Magnesium abnormalities were not reported in any of these studies. One study reported the use of magnesium sulfate in preeclamptic individuals, which resulted in a significantly higher QTc interval with a 26.9 msec difference compared with non-users.[70]

Other ECG parameters changes during normal pregnancy and preeclampsia

Table 2 shows the results of median [IQR] of other ECG parameters (HR, QT, QRS, TpTe, and QTcd). HR steadily increased significantly throughout normal pregnancy compared to nonpregnant controls, reaching its highest level during the third trimester. However, there was no significant difference between preeclamptic and normal pregnant individuals during the third trimester (MD: 4.4 bpm; 95%

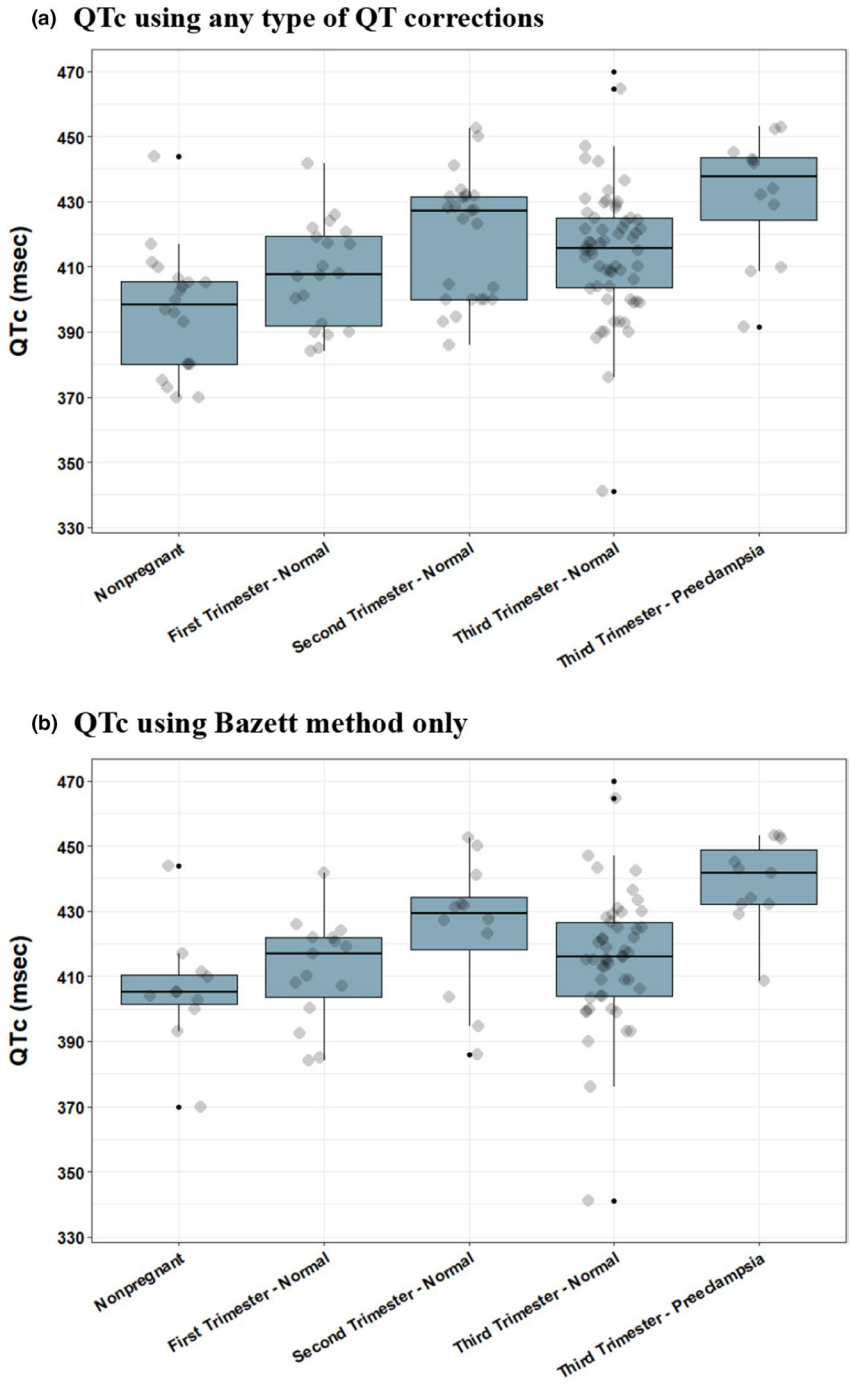


Figure 2 Changes of QTc interval between different trimesters of normal pregnancy and preeclampsia. Box plots show mean QTc intervals (msec) across trimesters of normal pregnancy and preeclampsia using (**a**) all combined methods of QT interval rate correction and (**b**) Bazett-corrected QT intervals.

CI: −4.5 to 13.2; $P = 0.3$; I^2: 91%; 9 studies) (**Figures S24 and S25**). Uncorrected QT interval remained relatively consistent throughout normal pregnancy compared to nonpregnant individuals except for the first trimester which showed a significant decrease (MD: −13.5 msec; 95% CI: −25.9 to −1; $P = 0.04$; I^2: 99%). Preeclampsia did not show a significant difference compared to normal pregnancy during the third trimester (MD: 10.9 msec; 95% CI: −7.2 to 29.1; $P = 0.18$; I^2: 86%) (**Figures S26 and S27**). Similarly, the QRS interval did not show significant changes throughout normal pregnancy or in preeclamptic individuals except for the normal third trimester which showed slightly significantly lower QRS compared with nonpregnant individuals (MD: −4.6 msec; 95% CI: −7.6 to −1.5; $P = 0.009$; I^2: 82%) in 10 studies (**Figures S28 and S29**). None of the meta-analyses showed publication bias (**Figures S30–S36**).

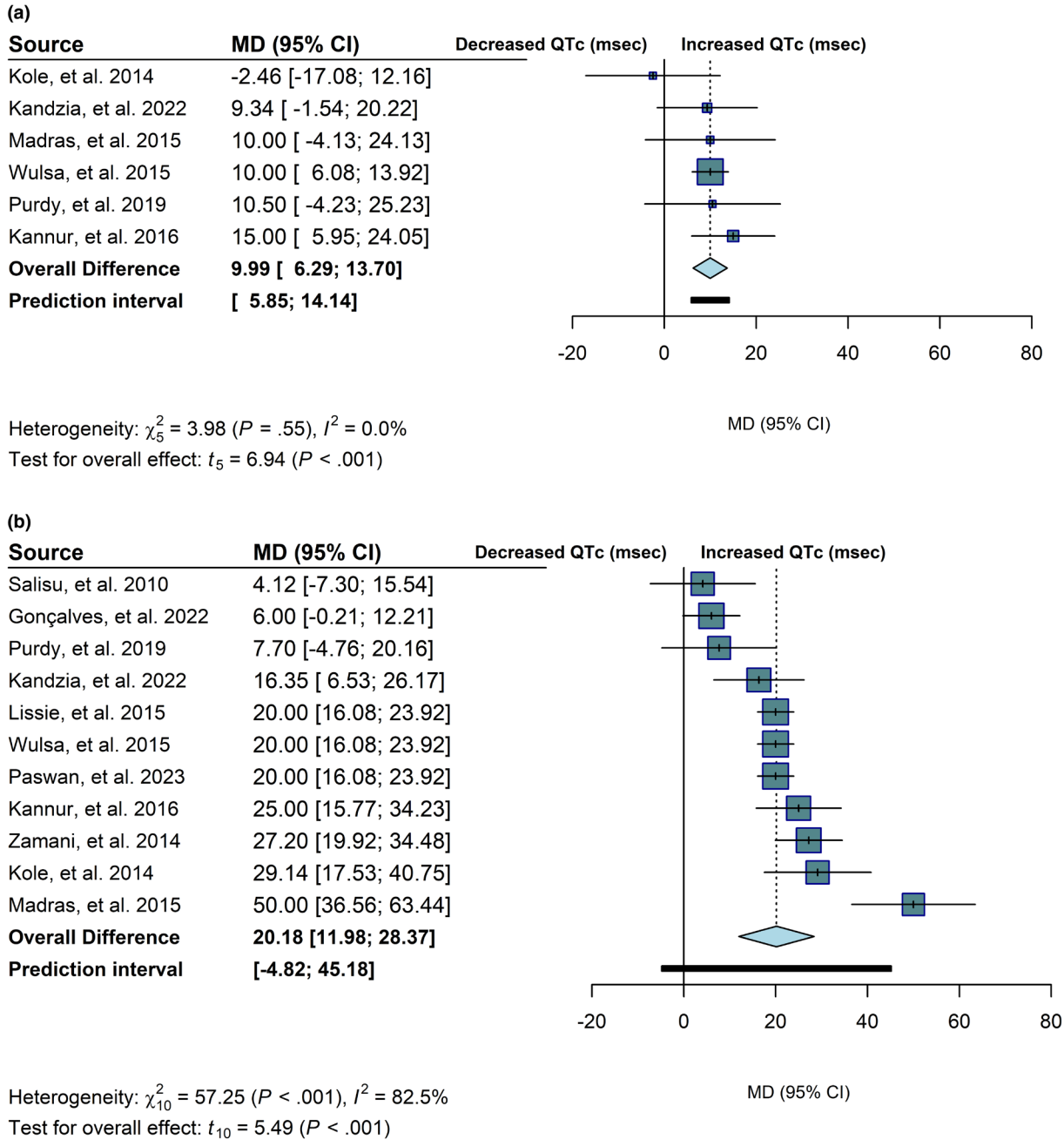


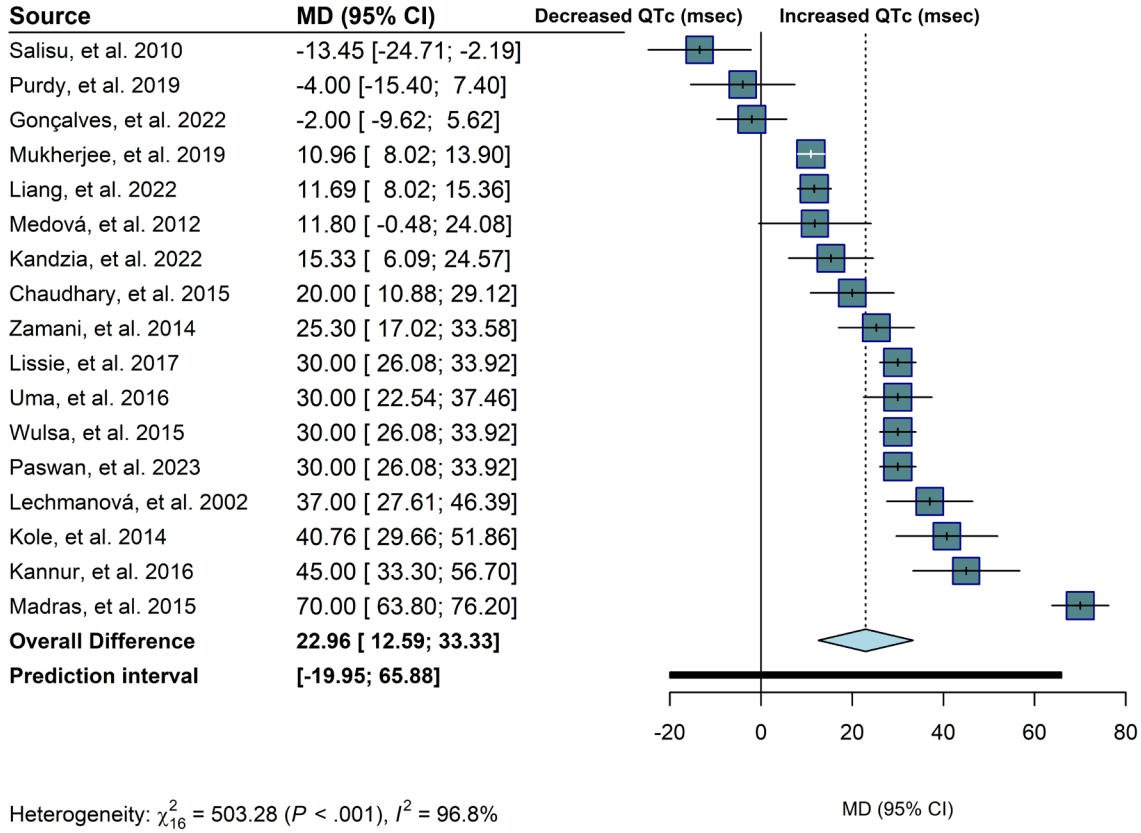
Figure 3 Meta-analyses on the changes of QTc interval between different trimesters of normal pregnancy and preeclampsia. Forest plots show QTc interval changes (msec) between (**a**) normal first trimester vs. nonpregnant individuals, (**b**) normal second trimester vs. nonpregnant individuals, (**c**) normal third trimester vs. nonpregnant individuals, and (**d**) preeclampsia third trimester vs. normal third-trimester individuals. For each study, the blue square and horizontal lines represent the respective point estimate and accompanying 95% CI. The vertical solid line on the forest plot represents the point estimate of the MD of 0. The blue diamonds represent the 95% CI summary of pooled MD. CI, confidence interval; MD, mean difference; msec, millisecond.

DISCUSSION

This systematic review and meta-analysis of 57 studies revealed a significant QTc interval lengthening that increases throughout subsequent trimesters of normal pregnancy, with a 10 msec average increase during the first trimester and 20 msec increase during the second and third trimesters compared with nonpregnant individuals. Preeclampsia further significantly augmented this increase during the third trimester by an additional 20 msec average increase compared with the normal third-trimester pregnancy.

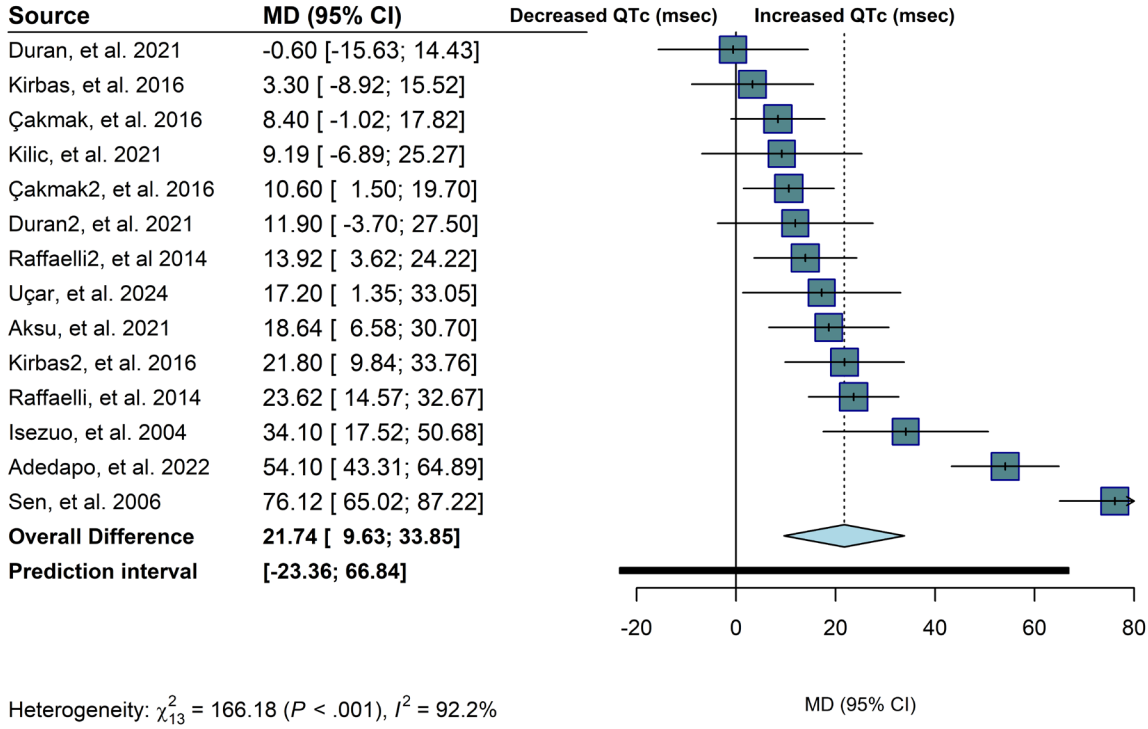
Pregnancy is associated with significant cardiovascular changes affecting ventricular repolarization that may explain the observed QTc interval lengthening, including eccentric hypertrophy that prolongs the time required for repolarization.[1] Additionally, autonomic changes and prolonged sympathetic stimulation can also lengthen the QTc interval. Moreover, the 10-to-20-fold increase in estrogen

(c)



Heterogeneity: $\chi^2_{16} = 503.28$ ($P < .001$), $I^2 = 96.8\%$
Test for overall effect: $t_{16} = 4.69$ ($P < .001$)

(d)



Heterogeneity: $\chi^2_{13} = 166.18$ ($P < .001$), $I^2 = 92.2\%$
Test for overall effect: $t_{13} = 3.88$ ($P = .002$)

Figure 3 (Continued)

and progesterone concentrations also impact cardiac repolarization. Estrogen prolongs the QTc interval while progesterone has a protective effect.[2,3] However, the estrogen-to-progesterone ratio shows a U-shaped function during pregnancy peaking during the second trimester.[81] During the third trimester, progesterone increases to a greater extent than estrogen which may partially explain the variability in QTc intervals observed in the systematic review.

Preeclampsia causes over 70,000 maternal deaths and 500,000 fetal deaths globally every year.[6] It is characterized by significant structural and functional cardiac changes that can further impact ventricular repolarization, including concentric hypertrophy with left ventricular thickening, as well as significant electrolyte imbalances such as hypocalcemia.[6,7] Hormonal changes with preeclampsia are inconclusive, with some studies showing that both estrogen and progesterone concentrations decrease[82], while others found an increase in estrogen concentration compared to normotensive pregnant individuals.[83] Our findings showed that preeclampsia significantly augmented QTc interval lengthening with most of the studies' confidence interval exceeding 460 msec. This significant increase in ventricular repolarization may be particularly concerning in this population with higher cardiovascular risks and warrants further investigation to assess potential arrhythmogenicity.

Multiple QT-prolonging drugs, such as ondansetron and SSRIs, are commonly used during pregnancy. However, there is limited data on the effects of these drugs on the QTc interval during pregnancy. Drögemöller *et al*.[47] assessed the effect of intravenous administration of 4–8 mg ondansetron on QTc interval prolongation in 62 pregnant women undergoing elective cesarean surgery. The study found that 14 (23.0%) of the participants showed QTc prolongation after drug administration, defined as a change in the QTc interval from a normal baseline (< 450 msec) to borderline (450–470 msec) or prolonged (> 470 msec), or a change from borderline to prolonged QTc interval. Interestingly, one patient showed unsafe QT prolongation, increasing from 433 msec at baseline to 515 msec after 5 minutes and to 470 msec after 30 minutes post-administration. To our knowledge, there is no available data on the effect of oral administration of ondansetron in early pregnancy or in preeclampsia. Similarly, there is no available data on the effect of any type of SSRIs on the QTc interval during pregnancy or preeclampsia.

The QTc interval displays significant inter- and intra-individual variability, ranging from 360 to 460 msec in nonpregnant individuals. Numerous risk factors, diseases, and medications have the potential to impact the QTc interval.[84] The current study identified substantial heterogeneity in all meta-analyses, which could not be reduced through subgroup analyses. Notably, high heterogeneity has been reported in other systematic reviews examining the QTc interval in different conditions,[85] suggesting that this may be an innate characteristic. However, it is important to acknowledge that the number of studies and sample sizes in the subgroup analyses were limited, which may restrict the validity of their conclusions.

Interestingly, the subgroup analysis by geographic region revealed a significant difference in the pooled MD of QTc interval during the second and third trimesters. Specifically, studies from Sub-Saharan Africa and North America showed lower pooled MD compared with other subgroups.[69,74] This observation may be attributed to the higher percentage increase in progesterone concentrations compared to estrogen during later stages of normal pregnancy reported in Sub-Saharan Africa.[86] However, further research is still needed to confirm this hypothesis.

Study limitations

The majority of the studies had low-to-fair overall quality scores owing to their observational nature. This limits the strength of the final estimates for each trimester, which displays high heterogeneity. Additionally, although the analysis included studies from various geographic regions, the majority were from India and Turkey, which may limit the generalizability of the results across different populations.

CONCLUSIONS

There is significant QTc interval lengthening throughout trimesters of normal pregnancy, and to a greater extent during preeclampsia. The arrhythmogenicity during pregnancy with known risk factors for QTc interval prolongation—especially with the use of QT-prolonging drugs—warrants further investigation, particularly in preeclamptic individuals during the third trimester.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

O.A.A., and B.R.O. wrote the manuscript; O.A.A., J.Z.R., B.R.O., S.K.Q., and J.E.T designed the research; O.A.A., J.Z.R. and B.R.O. performed the research; O.A.A., B.R.O., S.K.Q., and J.E.T analyzed the data.

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