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Reference Values of Fetal Mechanical PR Interval and Heart Rate-Corrected Fetal Mechanical PR Interval: Influence of Fetal Sex, Heart Rate, Gestational Age, and Maternal Age

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ABSTRACT

Background: Mechanical PR Interval (MPRI) is an important parameter in the fetus as a surrogate for PR interval. Normal values of MPRI have been reported with controversial effects of Fetal Heart Rate (FHR) and Gestational Age (GA). However, the effect of HR-correction on PR interval is unknown.

Objectives: This study aimed to obtain the reference values of fetal MPRI in a large series of normal fetuses by pulsed-Doppler fetal echocardiography. This was done to determine the influence of fetal sex, Heart Rate (HR), GA, and maternal age on MPRI and to calculate the novel HR-Corrected Mechanical PR Interval (CMPRI) to investigate whether HR-correction of PR interval can decrease the influence of HR.

Materials and Methods: This cross-sectional study was performed on 516 consecutive normal singleton fetuses. By extrapolation from Bazett's formula, we corrected the MPRI for HR. Impact of fetal sex, HR, and GA on MPRI and CMPRI was studied. Mean ± standard deviation, 5th, 50th, 95th, and 99th percentiles of MPRI and CMPRI were also calculated. Then, the data were entered into Stata, version 12 and analyzed using t-test, ANOVA, and linear regression.

Results: Reference values of MPPR and CMPRI were provided in four GA groups; i.e., 14 - 18, 19 - 22, 23 - 26, and 27 - 38 weeks. Fetal sex and maternal age had no influence on either MPRI or CMPRI. After adjustment for fetal sex, GA, and maternal age, there was a 0.14-millisecond (ms) decrease in MPRI and a 8.06-ms increase in CMPRI for every single increase in FHR. Additionally, adjusted linear regression model indicated a 0.43-ms increase in MPRI and a 2.53-ms increase in CMPRI per gestational week. The results of paired t-test showed no significant difference between fetal MPRI and neonatal PR interval.

Conclusions: This study provided reference values for MPRI and CMPRI in fetus from 14 to 38 weeks of gestation from the 5th to the 99th percentile. The results also revealed significant correlations between both FHR and GA and MPRI and CMPRI. Furthermore, HR correction of MPRI did not add any advantage in terms of HR-independency of mechanical PR interval.

1. Background

Fetal Mechanical PR Interval (MPRI) is an important parameter in the fetus as a surrogate for PR interval. Prolonged MPRI may occur in fetuses born to mothers with Ribonucleoprotein (RNP) autoantibodies, such as those with systemic lupus, Sjogren syndrome, and rheumatoid arthritis (1). Progressive fetal atrioventricular block may result in complete heart block, which can lead to fetal demise in 15 - 30% of cases (2). Early prenatal diagnosis and timely treatment of atrioventricular conduction disturbance can be life-saving in certain, but not all, conditions (3-5). Fetal MPRI can be measured either by tissue Doppler or

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gated pulsed Doppler echocardiography with or without inclusion of isovolumic contraction time. For gated pulsed wave Doppler, two methods of "mitral valve-aorta" and "superior vena cava-ascending aorta" have been used (6-9).

There are contradictory reports regarding the influence of Fetal Heart Rate (FHR) and Gestational Age (GA) on fetal MPRI (10-13). Ethnic variations in PR interval have been also reported after birth (14, 15). However, to the best of our knowledge, no studies have been conducted on the effect of heart rate correction on PR interval.

2. Objectives

This study aims to 1. investigate the reference values of MPRI in a very large series of normal Iranian fetuses by gated pulsed Doppler fetal echocardiography (mitral valve-aorta method), 2. determine the impact of GA and FHR on MPRI, and 3. calculate the novel heart rate-Corrected Mechanical PR Interval (CMPRI) to investigate whether heart rate-correction of PR interval can decrease the influence of heart rate.

3. Materials and Methods

3.1. Study Population

This cross-sectional study was performed on 516 consecutive pregnant women with healthy singleton fetuses referred to the Fetal Echocardiography Center between January 2015 and January 2016. They were referred by obstetricians or perinatologists with any indication of fetal echocardiography (16, 17).

To estimate GA, date of the mother's last menstrual period or the report of the first-trimester fetal ultrasound was used. In case of discrepancy between these two, the latter was taken into account. Fetuses of women were enrolled if the mother had no history of collagen vascular disease, consumed no medications with effects on the conduction system of the fetus or heart rate, had no history of a prior pregnancy with fetal or postnatal atrio-ventricular conduction abnormality, and had no positive test for anti-ro and anti-la antibodies. Further inclusion criteria were appropriate acoustic window for fetal echocardiography and completely normal fetal heart examination on echocardiography. Mothers' informed consents were obtained.

Totally, 22 fetuses were followed into the neonatal period and their fetal MPRI and neonatal PR interval were compared. The effects of heart rate and GA on MPRI and CMPRI were investigated, as well.

3.2. Echocardiography Protocol

3.2.1. Fetal Mechanical PR Interval (MPRI)

All fetal echocardiographies were performed by a single experienced pediatric cardiologist using a SonoAce X8 OB/GYN Ultrasound System (Samsung Medison Company). We obtained 5-chamber view on all fetuses with the ventricular septum in the vertical position. In doing so, we inserted the ultrasound beam of the gated pulsed wave Doppler in the left ventricular outflow tract in the mid-way between the aortic valve and mitral valve to simultaneously record the Doppler flow pattern of both inlet and outlet of the Left Ventricle (LV). The angle of the insonation beam with the flow of mitral and aortic valves was less than 20 degrees. To measure the PR interval, we measured the time interval between the onset of the A wave to the onset of the aortic flow at a sweep speed of 360 Hz.

3.2.2. Heart Rate-Corrected Fetal Mechanical PR Interval (CMPRI)

Based on the prior studies on the effect of FHR on MPRI and inspired by the original concept of heart rate-correction of QT interval, we calculated the novel index of heart-rate-corrected fetal mechanical PR interval. We also extrapolated the widely used Bazett's formula for rate-correction of QT interval (i.e., QTC = QT / √ RR) for heart-rate correction of PR interval in the fetus (18):

3.3. Statistical Analysis

Continuous variables were reported as mean ± Standard Deviation (SD). Shapiro-Wilk test was used to assess the normal distribution of MPRI and CMPRI. Then, t-test and one-way ANOVA were used to compare the means of MPRI and CMPRI in different gestational and maternal ages in both sexes. Additionally, linear regression model was also used to assess the association between MPRI and CMPRI, and independent variables. Paired t–test was also employed to compare MPRI and CMPRI to their normal electrical PR interval in the study population. The means of MPRI and CMPRI were reported with 95% Confidence Interval (CI). All data analyses were performed using Stata 12 (Stata Corp, College Station, TX, USA).

3.4. Ethical Considerations

This study was performed in accordance with the ethical standards of the Research Ethics Committee of Tehran University of Medical Sciences as well as the latest revision of Helsinki declaration (19). The study was also approved by the Research Ethics Committee of Tehran University of Medical Sciences. Informed consent was obtained from all participants.

4. Results

This study was conducted on 516 fetuses with normal fetal echocardiography. The fetuses were divided into four GA groups of 14 - 18, 19 - 22, 23 - 26, and 27 - 38 weeks. The 5th, 50th, 95th, and 99th percentiles of MPRI according to FHR and GA have been shown in Tables 1 and 2.

4. A. The effect of "fetal sex" on "MPRI" and "CMPRI":

Unadjusted linear regression model showed that MPRI was 15.46 milliseconds longer in male fetuses (P = 0.035, 95% CI: 1.07 - 29.85). However, after adjusting for FHR, maternal age, and GA, there was no significant difference between male and female fetuses (P = 0.455, 95% CI: -5.52 - 12.30). Neither unadjusted nor adjusted regression models showed any significant effects of sex on CMPRI (P = 0.645, CI: -1.85 - 1.14 and P = 0.342, CI: -2.18 - 0.76, respectively).

4. B. The effect of "maternal age" on "MPRI" and "CMPRI":

Neither unadjusted nor adjusted linear regression model revealed any correlations between maternal age and MPRI or CMPRI (unadjusted MPRI: P = 0.665, 95% CI: -0.17 - 0.11; adjusted MPRI: P = 0. 792, 95% CI: -0.16 - 0.12; unadjusted CMPRI: P = 0.67, 95% CI: -1.07 - 1.67; fetal

Table 1. 5th to 99th Percentiles of Mechanical PR Interval (MPRI) in Milliseconds (ms) based on Gestational Age and Fetal Heart Rate in 516 Healthy Singleton Iranian Fetuses

Gestational Age (weeks)	5th percentile (ms)	50th percentile(ms)	95th percentile(ms)	99th percentile(ms)
14 - 18	96.67	109.33	124.50	132.00
19 - 22	99.00	111.00	125.00	129.67
23 - 26	93.33	112.50	124.00	131.33
27 - 38	101.00	115.00	133.67	137.00
Fetal Heart Rate (bpm)	**5th percentile**	**50th Percentile**	**95th Percentile**	**99th Percentile**
≤ 134	101.00	114.00	137.00	137.00
135 - 139	100.00	113.00	124.00	124.00
140 - 144	99.00	113.67	129.00	132.00
145 - 149	99.00	112.00	130.33	133.00
150 - 154	97.33	110.00	122.00	132.00
155 - 159	95.33	110.00	117.33	127.67

Abbreviations: bpm, beats per minute

Table 2. 5th to 99th Percentiles of Corrected Mechanical PR Intervals (CMPRI) in Milliseconds (ms) based on Gestational Age and Fetal Heart Rate in 516 Healthy Singleton Iranian Fetuses

Gestational Age (weeks)	5th percentile (ms)	50th percentile(ms)	95th percentile(ms)	99th percentile(ms)
14 - 18	580.27	673.87	798.81	839.07
19 - 22	541.69	688.26	789.33	895.57
23 - 26	528.70	662.80	820.83	874.12
27 - 38	501.64	680.93	795.28	848.70
Fetal Heart Rate (bpm)	**5th percentile**	**50th Percentile**	**95th Percentile**	**99th Percentile**
≤ 134	383.86	528.70	663.08	663.08
135 - 139	506.25	587.19	655.96	660.13
140 - 144	546.73	641.59	731.52	749.80
145 - 149	590.19	671.63	774.81	805.17
150 - 154	620.69	705.96	786.80	843.24
155 - 159	657.31	760.01	876.61	909.72

Abbreviations: bpm, beats per minute

sex, gestational age, and maternal age adjusted CMPRI: P = 0. 834, 95% CI: -0.95 - 0.77).

4. C. The effect of “FHR” on “MPRI” and “CMPRI”:

The correlations between FHR and MPRI and CMPRI have been presented in Tables 3 and 4. The unadjusted linear regression model showed a 0.18-millisecond (ms) decrease in MPRI and a 7.84-ms increase in CMPRI for every unit of increase in FHR. After adjustment for fetal sex, GA, and maternal age, there was a -0.18-ms decrease in MPRI and a 8.06-ms increase in CMPRI for each unit of increase in FHR (Figures 1 and 2 and Table 5).

4. D. The effect of “fetal GA” on “MPRI” and “CMPRI”:

Unadjusted linear regression model showed a 0.45-ms increase in MPRI and a 1.10-ms decrease in CMPRI for every unit of increase in fetal GA. After adjustment for fetal sex, heart rate, and maternal age, there was a 0.43-ms increase in MPRI and a 2.53-ms increase in CMPRI (Figures 3 and 4 and Table 5).

4. E. Comparison of fetal MPRI to neonatal electrical PR interval:

The results of paired t-test showed no significant difference between fetal MPRI and neonatal electrical PR interval measurements (105.68 ± 14.80 versus 106.18 ± 13.57; P = 0.679).

Table 3. The Correlation between Mechanical PR Interval (in Milliseconds) and Fetal Heart Rate (Beats/Minute) in 516 Healthy Singleton Iranian Fetuses

Gestational Age Groups (Weeks)		Sex (Percent)		Maternal Age (Years)	Mechanical PR Interval (MPRI)					Fetal Heart Rate (Beats/ Minute)	Correlation Coefficient	P valve*
		Female (number, percent)	Male (number, percent)		Mean ± SD	Mean ± 2 SD	Mean ± 3 SD	5% percentile (PR)	95% per-centile (PR)			
Fetal gestational age groups (weeks)	14 - 18	64 (47.4)	71 (52.6)	29.7 (4.9)	109.6 ± 8.8	109.6 ± 17.6	109.6 ± 26.4	96.6	124.4	149.5 ± 7.1	-0.24	0.005
	19 - 22	120 (47.2)	134 (52.8)	30.8 (5.4)	111.0 ± 7.5	111.0 ± 15	111.0 ± 22.5	99	125	148.3 ± 7.7	-0.06	0.379
	23 - 26	26 (50.0)	26 (50.0)	30.2 (4.7)	111.9 ± 8.6	111.9 ± 17.2	111.9 ± 25.8	93.3	124	146.3 ± 8.6	-0.11	0.434
	27 - 38	32 (53.3	28 (46.7)	30.0 (5.3)	115.9 ± 10.2	115.9 ± 17.6	115.9 ± 30.6	101	133.7	143.7 ± 9.9	-0.20	0.13

* P value for the correlation between fetal heart rate and mechanical PR Interval

Table 4. The Correlation between Heart Rate-Corrected Mechanical PR Interval (in Milliseconds) and Fetal Heart Rate (Beats/Minute) in 516 Healthy Singleton Iranian Fetuses

Gestational Age Groups (Weeks)		Sex (Number, Percent)		Maternal Age (Years)	Heart Rate-Corrected Mechanical PR Interval (CMPRI)					Fetal Heart Rate (Beats/Minute)	Correlation Coefficient	
		Female (number, percent)	Male (number, percent)		Mean ± SD	Mean ± 2 SD	Mean ± 3 SD	5% percentile (PR)	95% percentile (PR)		Correlation Coefficient	P valve*
Fetal gestational age groups (weeks)	14 - 18	64 (47.4)	71 (52.6)	29.7 (4.9)	109.6 ± 8.8	109.6 ± 17.6	109.6 ± 26.4	96.6	124.4	149.5 ± 7.1	-0.24	0.005
	19 - 22	120 (47.2)	134 (52.8)	30.8 (5.4)	111.0 ± 7.5	111.0 ± 15	111.0 ± 22.5	99	125	148.3 ± 7.7	-0.06	0.379
	23 - 26	26 (50.0)	26 (50.0)	30.2 (4.7)	111.9 ± 8.6	111.9 ± 17.2	111.9 ± 25.8	93.3	124	146.3 ± 8.6	-0.11	0.434
	27 - 38	32 (53.3	28 (46.7)	30.0 (5.3)	115.9 ± 10.2	115.9 ± 17.6	115.9 ± 30.6	101	133.7	143.7 ± 9.9	-0.20	0.13

* P value for the correlation between fetal heart rate and heart rate-corrected mechanical PR Interval

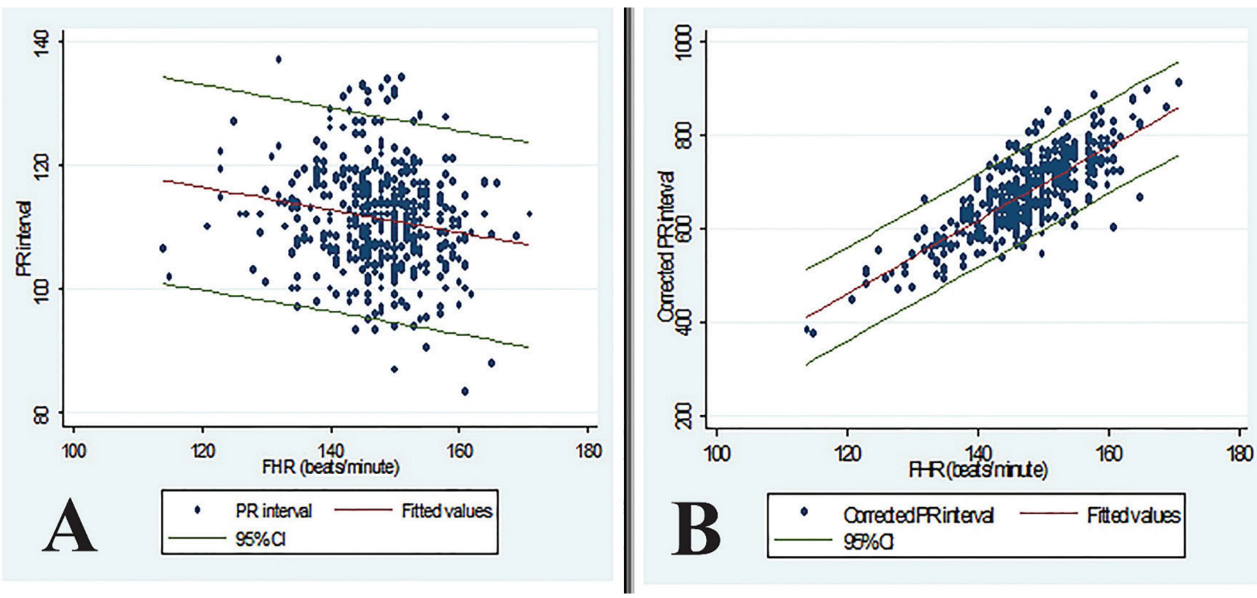

Figure 1. Regression Line and 95% Confidence Interval for the Correlation between Mechanical PR Interval (Figure A) and Heart-Rate Corrected Mechanical PR Interval (Figure B) and Fetal Heart Rate in 516 Healthy Singleton Fetuses

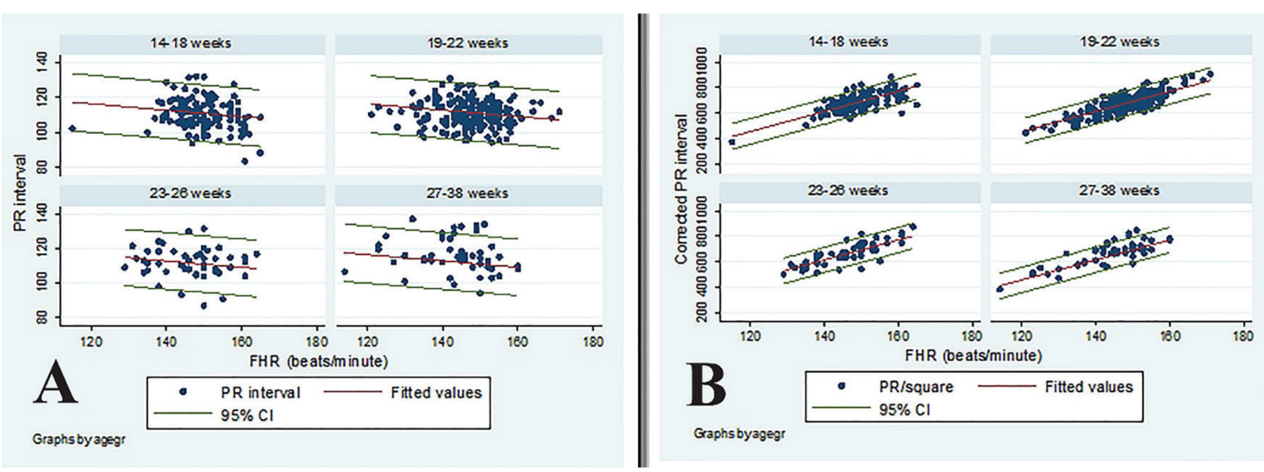

Figure 2. Regression Line and 95% Confidence Interval for the Correlation between Mechanical PR Interval (Figure A) and Heart-Rate Corrected Mechanical PR Interval (Figure B) and Fetal Heart Rate in 516 Healthy Singleton Fetuses according to the Four Gestational Age Groups of 14 - 18, 19 - 22, 23 - 27, and 28 - 38 Weeks

5. Discussion

This study provided reference values for fetal mechanical PR and CMPRI in the largest population of healthy fetuses studied in four GA groups from 14 to 38 weeks of gestation. The results revealed that fetal sex and maternal age had no effects on MPRI or CMPRI.

Table 5. The Correlation between "Fetal Heart Rate and Fetal Gestational Age" and "Mechanical PR Interval and Heart-Rate Corrected Mechanical PR Interval" Using Unadjusted and Adjusted Linear Regression Models

	Mechanical PR Interval						Heart-Rate Corrected Mechanical PR Interval					
	Unadjusted linear regression			Adjusted linear regression			Unadjusted linear regression			Adjusted linear regression		
		95% confidence interval	P value	Regression co-efficient	95% confidence interval	P value	Regression co-efficient	95% confidence interval	P value	Regression co-efficient	95% confidence interval	P value
Fetal heart rate	-0.18	-0.27, -0.09	< 0.001	-0.15*	-0.F24, -0.05	0.002	7.84	7.30, 8.39	< 0.001	8.06*	7.51, 8.62	< 0.001
Fetal gestational age	0.45	0.26, 0.63	< 0.001	0.43**	0.23, 0.62	< 0.001	-1.10	-2.91, 0.71	0.234	2.53**	1.37, 3.69	< 0.001

* Adjusted for gestational age, sex, and maternal age; ** Adjusted for fetal heart rate, maternal age, and sex

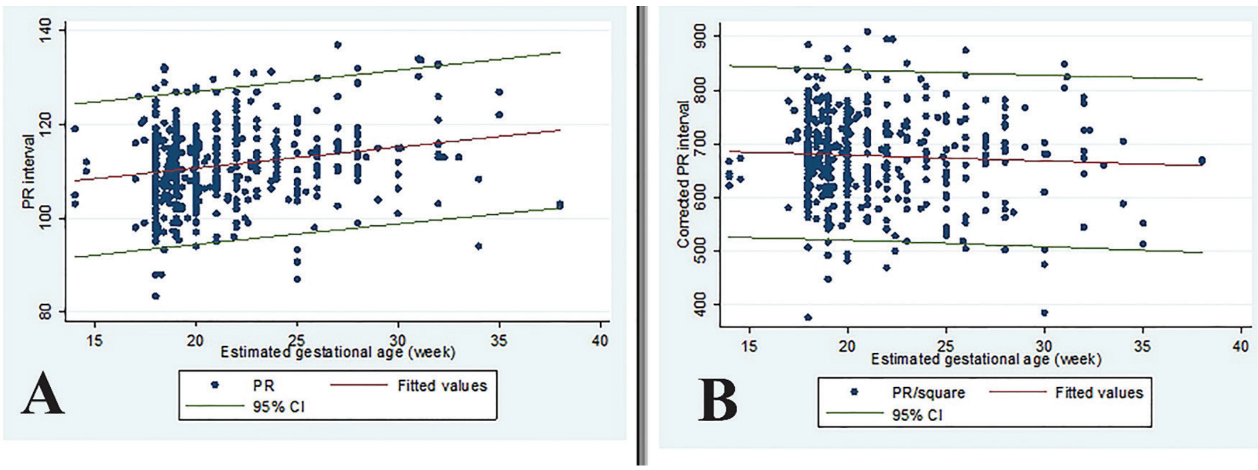

Figure 3. Regression Line and 95% Confidence Interval for the Correlation between Mechanical PR Interval (Figure A) and Heart-Rate Corrected Mechanical PR Interval (Figure B) and Fetal Gestational Age in 516 Healthy Singleton Fetuses

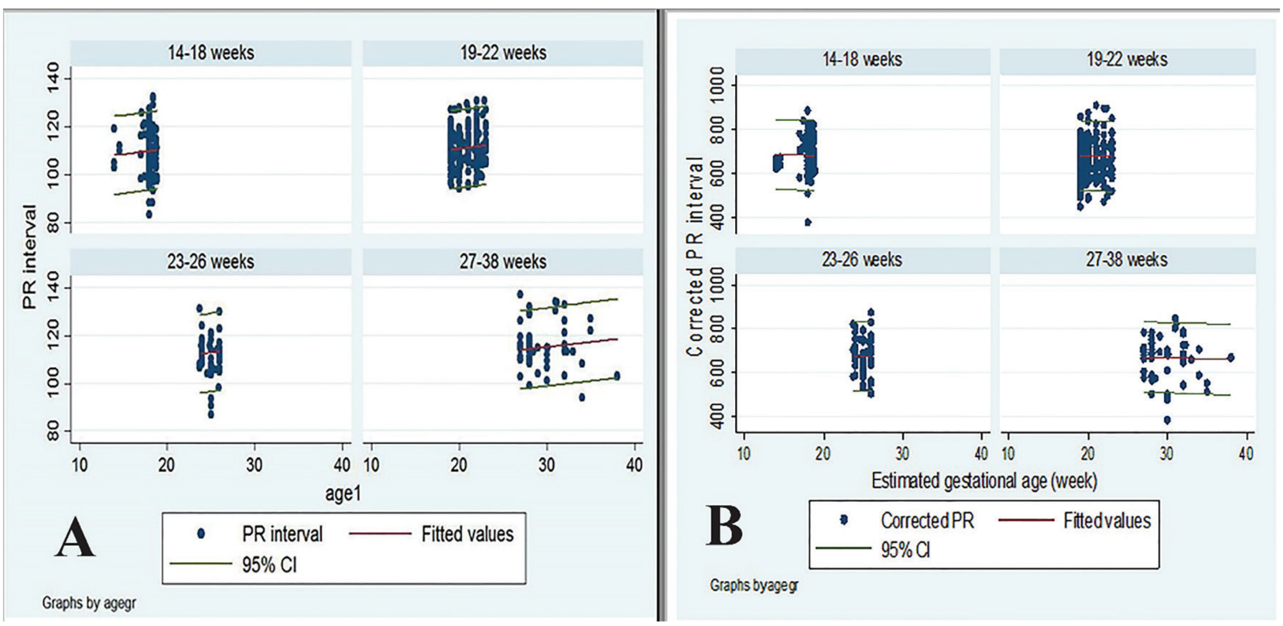

Figure 4. Regression Line and 95% Confidence Interval for the Correlation between Mechanical PR Interval (Figure A) and Heart-Rate Corrected Mechanical PR Interval (Figure B) and Fetal Gestational Age in 516 Healthy Singleton Fetuses According to the Four Gestational Age Groups of 14 - 18, 19 - 22, 23 - 27, and 28 - 38 weeks

Although unadjusted linear regression showed that CMPRI was independent of GA, adjusted linear regression revealed that both MPRI and CMPRI increased with increase in GA. Therefore, on the contrary to QT interval, heart-rate correction of mechanical PR interval did not provide neither heart rate- nor GA-independency of MPRI. Soliman et al. conducted a study on 5757 adults with the mean ± SD age of 58 ± 13 years and reported a significantly lower correlation between heart rate and PR interval in comparison to the correlation between heart rate and QT interval (r = -0.15 versus r = -0.76) (20). This may be explained by different natures of PR and QT intervals. PR interval reflects the time needed for the impulse to reach the ventricles from the atria. On the other hand, QT interval is the total time of depolarization and repolarization of both ventricles.

There is considerable and inexplicable debate on the influence of FHR and GA on fetal MPRI. Many authors have reported that MPRI increased with increasing GA and decreasing FHR, whereas many others have reported conversely. The relevant studies performed in this field during the last decade have been summarized in Table 6. Andelfinger et al. showed that GA had a higher impact on MPRI when measured by "MV-Ao method", whereas a stronger correlation with FHR was observed in

Table 6. Literature Review on Mechanical PR Interval in Normal Fetuses and Effects of Fetal Heart Rate and Gestational Age in Five Previous Studies on a Total of 531 Normal Fetuses (2000 - 2017)*

Number	Year	Country	Authors	Number of Healthy Fetuses in the Study	Method of Measurement of Mechanical PR Interval	Mechanical PR Interval Values (Milliseconds)	Any Correlations between MPRI and Fetal Heart Rate?	Any Correlations between MPRI and Gestational Age?	Further Points
1	2000	USA	Glickstein et al.	56 fetuses throughout gestation	Pulsed Doppler (Mitral inflow –Aortic Outflow)	120 ± 2	No	No	
3	2001	Canada	Andelfinger et al.	264 singleton fetuses	Two Doppler methods of mitral-Ao and SVC/ AA including ICT	They presented reference values for 2.5 percentile to 97.5 percentile in seven gestational age groups	Yes, r = 0.23 for FHR for SVC/AA method Yes, r = 0.42 for FHR for MV/ Ao method	Yes, r = 0.50 for GA for SVC/AA method Yes, r = 0.27 GA for MV/ Ao method	No significant differences between the the two sets of values in the two methods. They concluded that GA was the only independent variable that affected PR interval by SVC/AA method.
4	2008	USA	Friedman et al.	They enrolled no control or normal groups for comparison. Their study was performed on 127 fetuses with positive anti-SSA/Ro antibodies	Pulsed Doppler MV/ Ao method	A fixed value of 150 millisecond was defined as the upper limit of normal (based on more than 3 standard deviations of the upper limit of normal).	Not mentioned	Not mentioned	They have referenced the original paper of Glickstein et al. They indicated that occurrence of complete heart block in fetuses of women with positive anti-SSA/ Ro antibodies might be the initial presentation without any prior milder degrees of atrioventricular block.
5	2009	Israel	Rein et al.	109 normal fetuses (13 to 32 weeks, median = 17 weeks)	TVI-based fetal kinetocardiography (FKCG)	Right-sided PR interval = 82 ± 0.32 89 ± 8 Left-sided PR interval=76± 9	Yes (r = 0.25)	No	Right-sided PR interval correlated better with the electrical PR interval in neonated
6	2010	Sweden	Bergman et al.	102 singleton fetuses (17 - 25 weeks of gestation)	Two Doppler methods of mitral-Ao and SVC/ AA excluding ICT	87 (MV-Ao) and 89 (SVC-Ao)	No	Yes (r = 0.25)	

*No studies on mechanical PR interval in normal fetuses were found after 2010.

the "SVC-Ao method" (13).

In the present study, the longest normal MPRI; i.e., the 99th percentile, was 137 ms. However, Acherman et al. reported 153 ms as the 99th percentile for MPRI (1). This may reflect ethnic differences as reported previously (21).

5.1. Conclusion

In summary, this study provided reference values for mechanical PR interval and CMPRI infetuses from 14 to 38 weeks of gestation. The results showed that both MPRI and CMPRI were heart rate- and GA-dependent in the largest series of normal fetuses. Accordingly, MPRI decreased and CMPRI increased with increasing FHR. Indeed, both MPRI and CMPRI increased with increasing GA. Thus, in contrast to heart rate correction of QT interval, CMPRI did not add any advantage in terms of independency of either heart rate or GA. Moreover, sex and maternal age had no influence on MPRI or CMPRI. This study also provided mean ± SD, 5th, 50th, 95th, and 99th percentiles for both MPRI and CMPRI. Values less than the 5th percentile and more than the 99th percentile for GA might indicate the abnormally short and long PR intervals, respectively. Our 99th percentile value in Iranian fetuses was slightly shorter than that in American fetuses.

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Authors' Contribution

Study concept and design: Ehsan Aghaei Moghadam and Elaheh Malakan Rad (the concept of heart rate-correction of mechanical PR and some of the statistical analyses were given by Elaheh Malakan Rad); Acquisition of data: Ehsan Aghaei Moghadam and Maryam Nikoofar; Analysis and interpretation of data: Elaheh Malakan Rad; Drafting of the manuscript: Elaheh Malakan Rad; Critical revision of the manuscript for important intellectual content: All authors; Statistical analysis: Amin Doosti-Irani; Administrative, technical, and material support: all authors; Study supervision: Armen Kocharian and Aliakbar Zeinaloo. Salvador Cruz-Flores: critical revision of article.

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