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Estimating Gestational Age From Maternal-Fetal Heart Rate Coupling Parameters

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ABSTRACT Maternal and fetal heartbeat couplings are evident throughout fetal development. Most of the published work, however, did not consider maternal physiological factors such as Heart Rate Variability (HRV), and did not investigate the interrelationships of maternal-fetal coupling parameters. The aims of this study are to investigate whether: 1) maternal-fetal Heart Rate (HR) coupling (λ-based) parameters are associated with fetal development, and 2) fetal gold standard Gestational Age (GA) can be estimated using maternal-fetal HR coupling and variability of various recording lengths. The study considered Electrocardiogram (ECG) signals from 60 healthy pregnant women with no records of fetal abnormalities. HRV and λ parameters at various Maternal:Fetal coupling ratios were calculated, and stepwise regression was utilized to create generalized linear regression models considering various lengths of recorded signals (1 and 5 min) to produce a robust estimate of fetal age. Cross-validation performances were evaluated by the mean square root of the average of squared errors (mRMSE) between age values estimated by the proposed models and gold standard GA identified by Crown-Rump Length (CRL). Effect of Fetal Behavioral States (FBSes) on proposed models with different recording lengths was considered to examine the highly nonstationary nature of signals. We found that HR coupling strength for a specific ratio is not constant throughout gestation. Results showed that ratios of 2:3 and 2:4 were common between the proposed models. The value of λ[2:3] was found to be positively correlated with GA, while λ[2:4] had a negative correlation. Compared with gold standard GA identified by CRL, the proposed regression model resulted in mRMSE of 2.67 and 3.69 weeks for the recordings of 5 and 1 min, respectively. However, when FBS was considered, both models produced lower estimation errors. Fetal GA can be more reliably estimated by a multivariate model incorporating fetal and maternal HR coupling and HRV parameters using 5 min of ECG signals.

INDEX TERMS Biomedical signal processing, electrocardiography, fetal development, fetal heart rate, gestational age, heart rate variability, linear models, pregnant women.

NOMENCLATURE

LMP	Last Menstrual Period
GA	Gestational Age
CRL	Crown-Rump Length
FHR	Fetal Heart Rate
FHRV	Fetal Heart Rate Variability
HRV	Heart Rate Variability
MHR	Maternal Heart Rate
HR	Heart Rate
ECG	Electrocardiogram
FBS	Fetal Behavioral States
MMHR	Mean value of Maternal Heart Rate
FMHR	Mean value of Fetal Heart Rate
MSDNNHR	Standard Deviation of NN intervals in Maternal Heart Rate
FSDNNHR	Standard Deviation of NN intervals in Fetal Heart Rate
MRMSSDHR	Root Mean Square of Successive Differences between normal Maternal heartbeats

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FRMSSDHR	Root Mean Square of Successive Differences between normal Fetal heartbeats
One-Min model	One-Minute model
Five-Min model	Five-Minutes model
mRMSE	mean Root Mean Square Error
bpm	Beats per minute

I. INTRODUCTION

The American College of Obstetricians and Gynecologists provided guidelines for estimating the due date based on ultrasonography and the Last Menstrual Period (LMP) in pregnancy [1]. Up to the first trimester of pregnancy, ultrasound measurement of the embryo is considered to be the most accurate method to confirm Gestational Age (GA) [2], [3]. Measurements of the Crown-Rump Length (CRL) of the fetus earlier in the first trimester of pregnancy are more accurate [4], [5] with an error of ±5–7 days [6], [7]. Beyond the first trimester, the accuracy of the CRL to assess fetal development decreases. One of the main challenges when confirming GA using CRL-based methods or standard ultrasonography techniques in general is being subject to human errors and requiring good clinical practice administered by highly-skilled technicians [8], which might not be feasible in low- and middle-income settings. Therefore, a more robust approach is required to estimate the GA.

It has been reported in the literature that Fetal Heart Rate (FHR) and its variability have estimated fetal growth as an alternative GA [9]. One advantage of this method is that it does not require expensive equipment nor heavy training, making it suitable for countries with limited income [10]–[12]. An early study reported insignificant difference in accuracy of estimated GA from FHR in early pregnancies when compared with CRL method [13]. A recent study estimated the GA using ultrasound fetal biometrics [14]. Another study used a learning method for classification and regression to assess fetal age by Fetal Heart Rate Variability (FHRV) measures [15]. These studies, however, did not consider maternal physiological factors such as Heart Rate Variability (HRV).

Maternal and fetal beat-by-beat heart couplings were reported to be evident throughout fetal development [16], [17]. Recent studies reported the casual influences of fetal on Maternal Heart Rate (MHR) and vice versa throughout fetal development, which showed that developing autonomic nervous system function played significant roles in maternal-fetal heartbeat synchronizations and its directionalities [18], [19]. It is still unknown, however, whether maternal-fetal heartbeat coupling parameters are associated with fetal development and the potential interrelationships. Limitations in recent fetal development studies include, but are not limited to, estimating fetal growth without considering maternal physiological factors, as well as the lack of the explanation of the specific mechanism leading to maternal-fetal Heart Rate (HR) coupling.

In our preliminary study [20], we showed that it is possible to estimate the GA by using maternal-fetal HR coupling strengths with fetal and maternal HRV parameters using ECG signals recorded for 10 min. Moreover, a previous study reported that an Electrocardiogram (ECG) recording period of 5 min is appropriate to determine HRV features [21]. However, there have been no studies to look at the effect of the signals' recording length on fetal development estimation, which is an important issue due to the highly nonstationary nature of fetal ECG and its coupling strengths with the maternal ECG signal.

During the development of the fetus in the utero, biological rhythm is developed and is gradually harmonized by the central nervous system [22], [23]. This results in distinctive Fetal Behavioral States (FBSes) that correspond to four categories: quiet and active sleep, as well as quiet and active awake (i.e. states 1F, 2F, 3F and 4F, respectively). After 36 weeks of gestation, FBSes can be identified by the simultaneous occurrence of specific FHR patterns (i.e. differences in short-term FHRV [24]) in normally developing fetuses [25].

The scope of this work is to propose a novel approach to estimate the GA based on ECG signals from healthy pregnant women with no records of fetal abnormalities. The study takes into account various lengths of the recorded signals used in the model, which is vital when estimating fetal development because fetal ECG and its coupling strengths are highly nonstationary with the maternal ECG signal.

In this paper, a novel multivariate regression approach is proposed for estimating the GA based on two key tools: maternal and fetal HRV features, and maternal-fetal HR coupling parameters. The generalized linear regression model combines maternal-fetal heartbeat coupling parameters with maternal and fetal HRV features to produce a robust estimate of fetal age. The model utilizes a stepwise regression algorithm that automatically adds to or removes from the model linear term for each parameter to determine a final model. A key point highlighted in this study is the contribution of maternal-fetal HR coupling strengths at various ratios for correctly estimating the physiological development of the fetus.

The remainder of the paper is organized as follows. The proposed methodology for obtaining a reliable estimate of fetal GA employing the multivariate regression approach based on maternal and fetal HRV features in conjunction with maternal-fetal HR coupling parameters at various ratios is discussed in Section II. The results are presented in Section III, and analyzed in Section IV. Lastly, conclusions and directions for future work are presented in Section V.

II. METHODS

A. PARTICIPANTS AND ECG SIGNAL PROCESSING

Datasets of abdominal ECG signals from 60 healthy pregnant women with no records of fetal abnormalities were obtained from Tohoku University Hospital (36 samples, 60%) and Kanagawa Children's Medical Center (9 samples, 15%) in

Japan, in addition to Children's National Hospital in the US (15 samples, 25%). The study protocols were approved by the Tohoku University Institutional Review Board (IRB: 2015-2-80-1) and Children's National Hospital IRB with appropriate institutional agreements. Written informed consent was obtained from all subjects. All experiments were performed in accordance with relevant guidelines and regulations. The GA and maternal age ranges for the three databases are: 20–39.3 weeks and 20–40 years (Tohoku University Hospital), 23.6–37.3 weeks and 25.8–40.8 years (Kanagawa Children's Medical Center), and 20–37 weeks (Children's National Hospital), respectively. The maternal age information for the Children's National Hospital dataset is not included herewith because it is not permitted to share this patient information under the IRB.

Twelve channel abdominal signals were recorded bipolarly from the electrodes placed on the maternal abdomen and sampled every 1 ms (1 kHz sampling) with 16 bit resolution. ECG signals were obtained for a period of at least 10 min with the participant in the supine position. To separate fetal ECG from the composite abdominal signal, a combination of maternal ECG cancellation and blind source separation with a reference was employed [26]. Detailed description of experimental set up can be found in our previous study [27]. In brief, the linear combination of mutually orthogonal projections of the heart vector was used to subtract the maternal ECG component. Blind source separation was accomplished via a neural network method by an iterative calculation from reference signals with resemblance to the target signal. Maternal and fetal QRS peak locations were detected by a custom-made MATLAB [28] routine program.

B. MATERNAL AND FETAL HEART RATE VARIABILITY

HRV features [21], [29] including the mean value of maternal or fetal HR (MMHR or FMHR), standard deviation of NN intervals in maternal or fetal HR (MSDNNHR or FSDNNHR), and root mean square of successive differences between normal maternal or fetal heartbeats (MRMSSDHR or FRMSSDHR) were estimated from the recorded ECG signals.

C. PHASE COUPLING

The coupling or synchronization between R-peaks of maternal and fetal ECG signals was estimated by phase coherence method [30], in which the instantaneous phase time series was calculated using

$$\varphi(t_k) = \frac{2\pi\,(t - t_k)}{(t_{k+m} - t_k)} + 2\pi\,k \tag{1}$$

where t and t_k are the time values of R-peaks in the fetal and maternal ECG signals, respectively, and m is the number of maternal heartbeats. The relative phase $\Psi(t_k)$ in the time window of t_w with respect to maternal ECG signal was calculated using the formula

$$\Psi(t_k) = \frac{\varphi(t_k) \mod 2\pi}{2\pi} \tag{2}$$

The phase coupling index λ was defined by [31]

$$\lambda(t_k) = \left\| \frac{1}{N} \sum_{j=k-N/2}^{k+N/2} e^{i\,\Psi(t_j)} \right\|^2 \tag{3}$$

where N is the number of heartbeats in time window of $t_k - t_w/2 \leq t_j < t_k + t_w/2$, λ ranges from 0 to 1, with $\lambda = 1$ being the highest synchronization. $\Psi(t_k)$ and respective λ values were computed for multiple Maternal:Fetal $(m : n)$ heartbeat ratios, where n is the number of fetal heartbeats. In this study, $m : n$ coupling ratios associated with maternal beats of 1, 2 and 3; and corresponding fetal beats of 2, 3 and 4 were investigated (i.e. the considered $m : n$ ratios are 1:2, 1:3, 2:3, 2:4, 3:4 and 3:5), and N was set to 70.

D. MULTIVARIATE REGRESSION MODELS AND STATISTICS

The generalized linear regression model combines maternal-fetal heartbeat coupling parameters with maternal and fetal HRV features to produce a robust estimate of fetal age. Two multivariate linear models were generated using MATLAB's `stepwiseglm`. These models were based on different lengths of the input ECG signals and considered various HRV-based and coupling-based variables. We refer to the proposed models as the One-Minute (One-Min) model and the Five-Minutes (Five-Min) model.

The employed stepwise regression algorithm initially starts with a model that contains only a constant (intercept) term. The algorithm then automatically adds to or removes from the model linear term for a variable based on deviance of the model (i.e. the change in the deviance that results from adding or removing the term) as the criterion. The linear term for a variable is added to the model if the p-value of the F-statistic –given the newly-added and the existing terms in the model– is less than the threshold value (i.e. $p < 0.05$). In summary, the stepwise regression algorithm automatically adds to or removes from the model linear term for each variable in a forward and backward process (based on deviance of the model as the criterion) to determine a final model.

To generate the proposed regression models, the full dataset of 60 subjects was randomly divided into two parts. The two halves of the datasets (i.e. Subjects#1–30 and Subjects#31–60) consider different time segments of the maternal and fetal ECG signals when preparing the training and testing datasets. This has been adopted to increase reproducibility and overcome possible data dependency. Figs. 1 and 2 show flowcharts of the proposed regression models.

In the One-Min model, each of the recorded maternal and fetal ECG signals were divided into 10 segments (each segment has a length of one minute). To prepare the training data for the One-Min model, the first time segment (i.e. 0–1 min) of the ECG signals were considered for half of the datasets (i.e. Subjects#1–30), and the last time segments that are complete in length (i.e. 8–9 min) were considered for the remaining half of the datasets (i.e. Subjects#31–60). Note that the last complete time segment in this model was considered

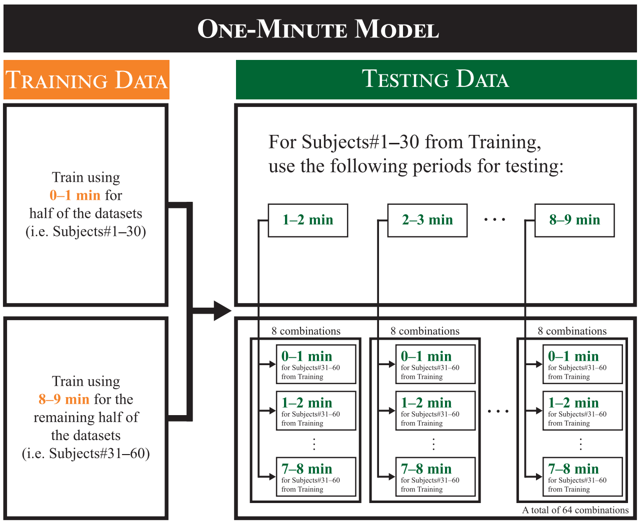

FIGURE 1. Flowchart for the One-Min model. Min, minute.

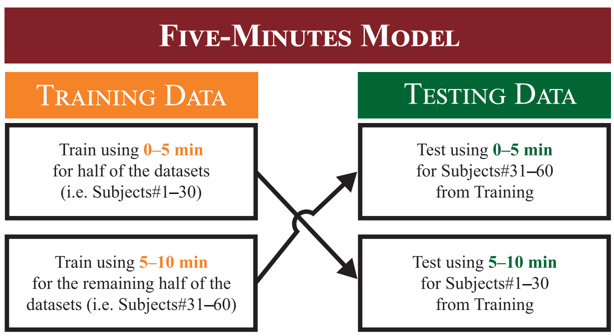

FIGURE 2. Flowchart for the Five-Min model. Min, minutes.

to be minute 8–9 rather than minute 9–10. That is because some datasets did not have an exact length of 10 min, which made the length of the last segment unequal to 1 min, exactly. In addition, the value of λ did not span the total length of the last segment due to windowing. To prepare the testing data for the One-Min model, all minute segments were considered except those used in training. In other words, each of the remaining segments (i.e. minute 1–2, minute 2–3, . . ., up until minute 8–9) for Subjects#1–30 from training was combined with the eight different segments (i.e. minute 0–1, minute 1–2, . . ., up until minute 7–8) for Subjects#31–60 from training, one at a time. This summed up to a total combination of 64 testing datasets for the One-Min model. Throughout this study, the results associated with the 64 combinations were averaged to obtain a single final result for the One-Min model. This approach was adopted in this model to eliminate systematic bias and establish a fair representation of the data.

The Five-Min model, on the other hand, considered a more straightforward approach. Half of the datasets (i.e. Subjects#1–30) considered the first time segment (i.e. 0–5 min) of the maternal and fetal ECG signals, and the remaining half (i.e. Subjects#31–60) considered the last time segment (i.e. 5–10 min) when preparing the training data. For testing data, the 30 subjects that were selected for the first segment category in training (i.e. Subjects#1–30) were considered for the last segment category (i.e. 5–10 min) in testing. Likewise, the remaining half of the datasets (i.e. Subjects#31–60) were considered for the first segment category (i.e. 0–5 min) in testing.

Results are presented in the next section and include different values calculated for the regression of each set of variables: the t-statistic of a single variable and the F-statistic of the group of variables versus a constant model and their associated p-values, the Pearson Correlation Coefficient (r), and the adjusted Coefficient of Determination (R^2). Cross-validation was repeatedly used for validation. The estimation error was defined as the mean Root Mean Square Error (mRMSE) between age values estimated by the proposed models and gold standard GA identified by CRL. Effect of FBSes on proposed models with different recording lengths was considered to examine the highly nonstationary nature of signals.

III. RESULTS

A. MATERNAL AND FETAL HEART RATE COUPLING

Fig. 3 shows an example of maternal and fetal HR time series signals for 10 min and their coupling patterns as defined by the relative phase (Ψ) with coupling strength (λ) at a ratio of 2:4 (i.e. considering 2 and 4 heartbeats in the maternal and fetal ECG signals), respectively. It can be depicted from the figure that occasional strengthening of λ appears between 6–9 min for this particular subject.

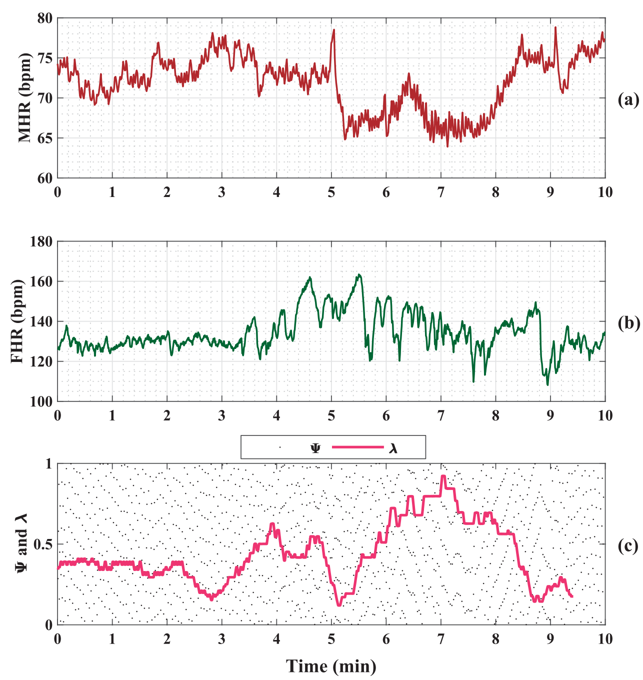

FIGURE 3. An example of a 29 week pregnant woman, including: (a) MHR, maternal heart rate, (b) FHR, fetal heart rate, and (c) Ψ, relative phase and λ, coupling strength, both at a ratio of 2:4. bpm, beats per minute; Min, minutes.

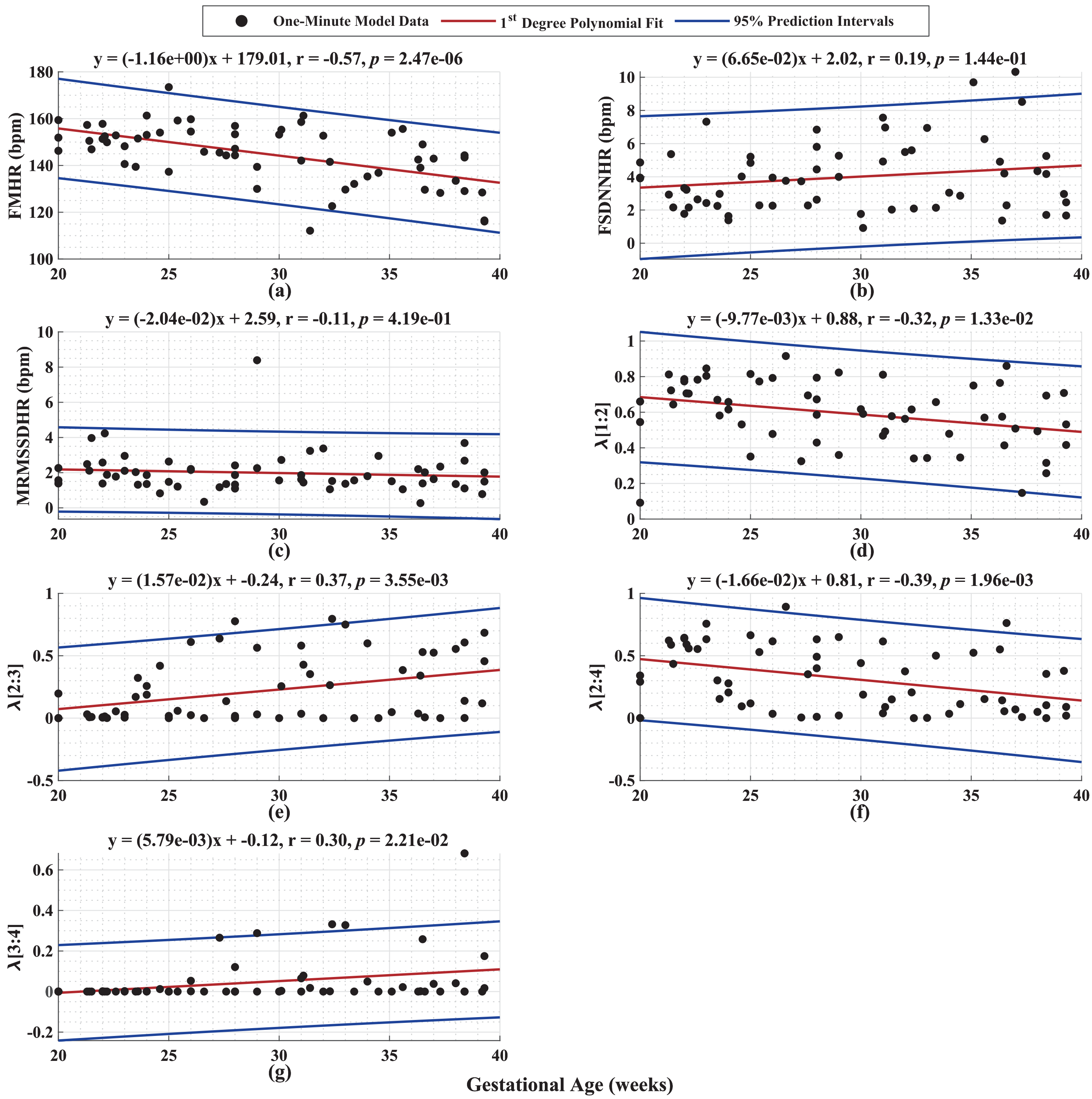

FIGURE 4. Scatterplots of the selected variables by the One-Minute model grouped in two categories: Heart Rate Variability-based variables which include: (a) FMHR, mean value of fetal heart rate, (b) FSDNNHR, standard deviation of NN intervals in fetal heart rate, where NN stands for interbeat intervals from which artifacts have been removed, (c) MRMSSDHR, root mean square of successive differences between normal maternal heartbeats, and coupling-based variables (λ) associated with different Maternal:Fetal heartbeat ratios of: (d) 1:2, (e) 2:3, (f) 2:4, and (g) 3:4. bpm, beats per minute.

B. MULTIVARIATE REGRESSION MODELS

The general mathematical formulation of estimated GA (in weeks) by the proposed One-Min and Five-Min models is described as follows

$$GA = Intercept + E_1 \times V_1 + E_2 \times V_2 + \ldots + E_i \times V_i, \quad (4)$$

where $V_1, V_2, \ldots, V_i$ are the selected variables (based on HRV or coupling parameters) by the stepwise algorithm for each of the proposed models for the estimation of GA, and $E_1, E_2, \ldots, E_i$ are the estimated regression coefficients associated with each variable. Figs. 4 and 5 show scatterplots of the selected variables by the One-Min model and the Five-Min model, respectively. Both of the models considered HRV-based as well as coupling-based variables. Table 1 provides a summary of the proposed multivariate regression models including the values of models coefficients for every selected variable. Following (4), the formulas of the estimated

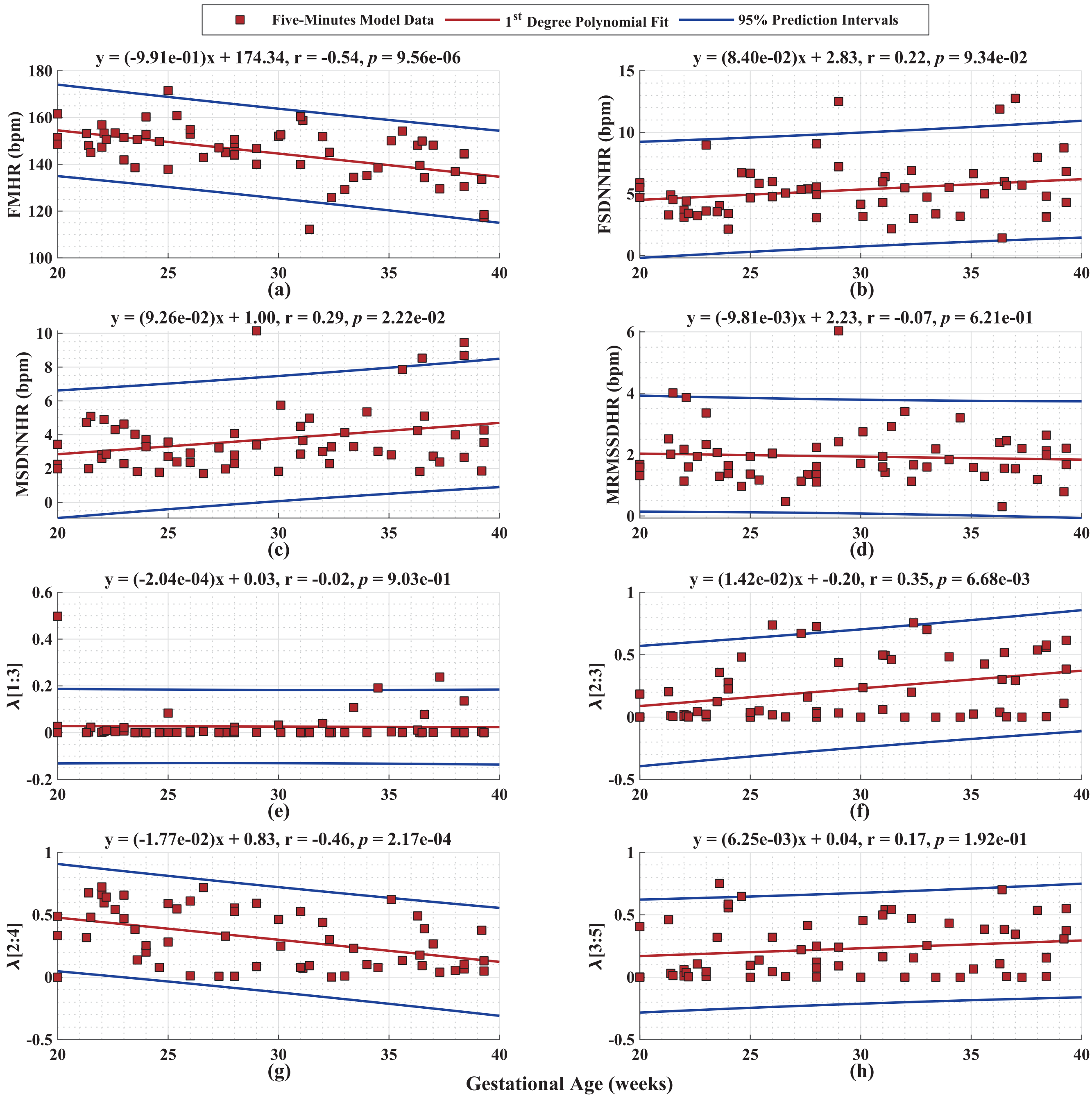

FIGURE 5. Scatterplots of the selected variables by the Five-Minutes model grouped in two categories: Heart Rate Variability-based variables which include: (a) FMHR, mean value of fetal heart rate, (b) FSDNNHR, standard deviation of NN intervals in fetal heart rate, where NN stands for interbeat intervals from which artifacts have been removed, (c) MSDNNHR, standard deviation of NN intervals in maternal heart rate, (d) MRMSSDHR, root mean square of successive differences between normal maternal heartbeats, and coupling-based variables (λ) associated with different Maternal:Fetal heartbeat ratios of: (e) 1:3, (f) 2:3, (g) 2:4, and (h) 3:5. bpm, beats per minute.

GA values by the proposed models are:

$$\begin{aligned} GA_{(\text{One-Min})} = 65.58 &- 0.30 \times FMHR \\ &+ 0.95 \times FSDNNHR \\ &- 0.99 \times MRMSSDHR \\ &+ 28.74 \times \lambda[1:2] \\ &- 13.50 \times \lambda[2:3] \\ &- 29.22 \times \lambda[2:4] \\ &+ 21.12 \times \lambda[3:4], \end{aligned} \tag{5}$$

$$\begin{aligned} GA_{(\text{Five-Min})} = 86.74 &- 0.29 \times FMHR \\ &+ 0.86 \times FSDNNHR \\ &+ 1.32 \times MSDNNHR \\ &- 3.57 \times MRMSSDHR \\ &- 47.08 \times \lambda[1:3] \\ &- 22.53 \times \lambda[2:3] \\ &- 30.94 \times \lambda[2:4] \\ &- 9.24 \times \lambda[3:5] \end{aligned} \tag{6}$$

TABLE 1. Results of stepwise multivariate regression models (One-Minute and Five-Minutes models) for the estimation of gestational age.

Feature	Estimate	SE	t-Stat	p-value ($\times 10^{-2}$)	F-test	Statistics
One-Minute Model						
Intercept	65.58	7.72	8.49	2.14×10^{-9}	F-Stat = 9.05	r = 0.74
FMHR	-0.30	0.05	-6.08	1.43×10^{-5}	p-value = 2.96×10^{-7}	R^2 (Adjusted) = 0.49
FSDNNHR	0.95	0.28	3.34	0.15		*mRMSE* (Model) = 4.33 weeks
MRMSSDHR	-0.99	0.50	-1.97	5.46		*mRMSE* (Validation) = 5.50 weeks
λ[1:2]	28.74	10.76	2.67	1.01		
λ[2:3]	-13.50	6.07	-2.23	3.04		
λ[2:4]	-29.22	9.57	-3.05	0.36		
λ[3:4]	21.12	8.60	2.46	1.75		
Five-Minutes Model						
Intercept	86.74	7.56	11.48	9.46×10^{-11}	F-Stat = 14.71	r = 0.83
FMHR	-0.29	0.05	-6.40	4.90×10^{-3}	p-value = 7.03×10^{-11}	R^2 (Adjusted) = 0.65
FSDNNHR	0.86	0.21	4.11	14.20		*mRMSE* (Model) = 3.58 weeks
MSDNNHR	1.32	0.35	3.83	35.08		*mRMSE* (Validation) = 4.55 weeks
MRMSSDHR	-3.57	0.71	-5.04	0.62		
λ[1:3]	-47.08	12.67	-3.72	50.46		
λ[2:3]	-22.53	5.28	-4.26	8.69		
λ[2:4]	-30.94	6.25	-4.95	0.86		
λ[3:5]	-9.24	3.42	-2.70	936.44		

SE, standard error; FMHR, mean value of fetal heart rate; FSDNNHR, standard deviation of NN intervals in fetal heart rate; NN intervals, interbeat intervals from which artifacts have been removed; mRMSE, mean root mean square error; MRMSSDHR, root mean square of successive differences between normal maternal heartbeats; λ, coupling strength; MSDNNHR, standard deviation of NN intervals in maternal heart rate. The equations for the One-Min and Five-Min models are:

$$\begin{aligned} GA_{(\text{One-Min})} &= 65.58 - 0.30 \times FMHR + 0.95 \times FSDNNHR - 0.99 \times MRMSSDHR \\ &\quad + 28.74 \times \lambda[1:2] - 13.50 \times \lambda[2:3] - 29.22 \times \lambda[2:4] + 21.12 \times \lambda[3:4], \\ GA_{(\text{Five-Min})} &= 86.74 - 0.29 \times FMHR + 0.86 \times FSDNNHR + 1.32 \times MSDNNHR - 3.57 \times MRMSSDHR \\ &\quad - 47.08 \times \lambda[1:3] - 22.53 \times \lambda[2:3] - 30.94 \times \lambda[2:4] - 9.24 \times \lambda[3:5]. \end{aligned}$$

The regression equation was obtained using multivariate linear regression employing the stepwise algorithm to account for the use of multiple variables per fetus.

Statistics for the t-test on the regression model vs. constant model showed significance of the models ($p < 0.05$). Training mRMSE (i.e. model) between the estimated and gold standard GA of 4.33 and 3.58 weeks were produced by the One-Min and the Five-Min models, respectively.

C. VALIDATION OF MODELS

Cross-validation scheme was repeatedly used to validate the proposed models for estimating the GA against gold standard age identified by CRL. The One-Min and the Five-Min models produced mRMSE of 5.50 and 4.55 weeks, respectively. Fig. 6 shows the significant correlation between gold standard GA identified by CRL and estimated values by the proposed models. The r values for the One-Min and the Five-Min models were 0.74 and 0.83, respectively. Additionally, Fig. 7 presents the Bland–Altman plots which validate that estimated GA values by the proposed models are within the Limits of Agreement (LoA) (i.e. $\pm1.96\times$SD). The estimated bias (i.e. mean differences) and LoA for the One-Min model are -6.10×10^{-15} and ±7.97 weeks, respectively. The Five-Min model, on the other hand, results in estimated bias and LoA of -4.26×10^{-15} and ±6.53 weeks, respectively. Moreover, mean differences between gold standard GA identified by CRL and estimated GA values for every age group (20–39 weeks) are plotted in Fig. 8.

D. EFFECT OF FETAL BEHAVIORAL STATES ON PROPOSED MODELS

The two FBSes considered in this study were classified based on FHR analysis reported in [24]. Only ECG data of healthy fetuses from the 36th week onward (sample size = 11 datasets) were considered because their FHRV becomes sufficiently higher and suitable to identify behavioral states [32]. Fig. 9 shows a scatterplot of the mean values of fetal R-R intervals (FMRR) and the corresponding standard deviation (FSDRR) with respect to behavioral states 4F (active awake) and 2F (active sleep) for 11 fetuses. Table 2 lists the statistics (FMRR, FSDRR, and FRMSSDRR) of the considered FBSes for the two proposed models, r and the corresponding p-values, in addition to the mean error produced during cross-validation. The One-Min model returned 64 p-values during validation (see Fig. 1), the majority of which were insignificant ($p < 0.05$), and are not shown in this paper due to space limitations. The proposed One-Min and

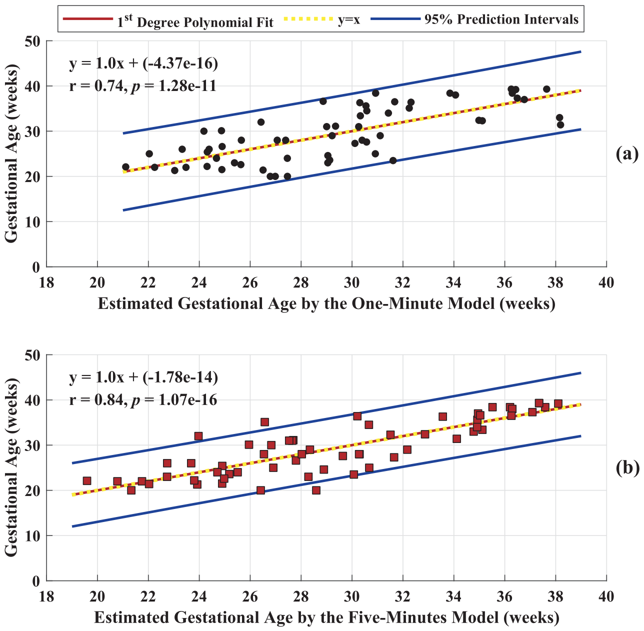

FIGURE 6. Pearson correlation plots between gold standard gestational age identified by crown-rump length and estimated age by the (a) One-Min model, and (b) Five-Min model for 60 healthy fetuses. The linear polynomial fit (regression) line along with the 95% prediction intervals are shown as solid red and blue lines, respectively. The identity line is represented as dotted yellow line.

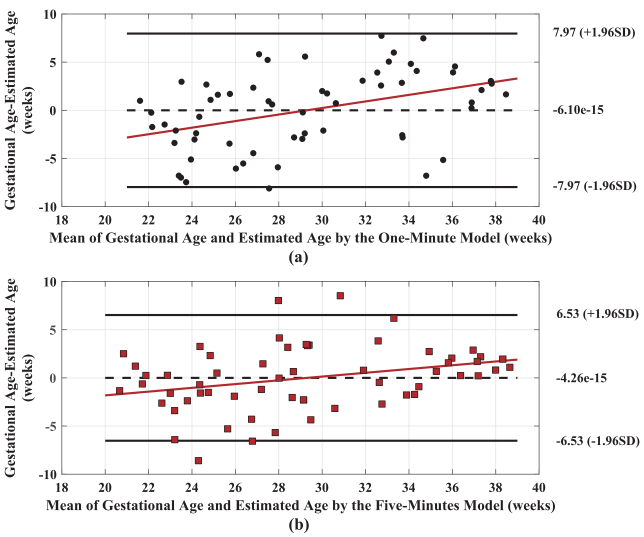

FIGURE 7. Bland–Altman plots for the estimated and crown-rump length-based gestational age by the (a) One-Minute model, and (b) Five-Minutes model (sample size = 60 datasets). Bias is shown as dashed black line, limits of agreement (±1.96×SD) are shown as solid black lines, and regression fit of the differences on the means is represented as solid red line.

Five-Min models produced average error values of 5.09 and 4.75 weeks for behavioral state 4F (active awake), and 3.69 and 2.67 weeks for behavioral state 2F (active sleep), respectively.

IV. DISCUSSION

This study successfully demonstrated that a multivariate regression model based on recorded ECG signals for 5 min could more reliably estimate the GA than that for 1 min of the signal length. The proposed model combined maternal and fetal HRV features with maternal-fetal HR coupling parameters at various ratios. A key point highlighted in this study is the contribution of maternal-fetal HR coupling strengths at various ratios for correctly estimating the physiological development of the fetus. In summary, the results clearly confirmed that utilizing maternal and fetal cardiac parameters produces a robust approach, allowing fetal age to be reliably estimated.

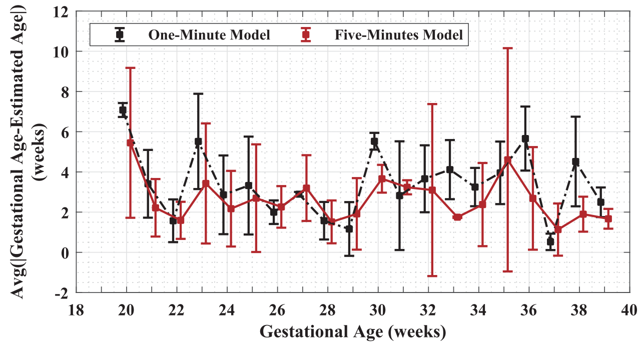

FIGURE 8. The average of the absolute value of the differences between Gestational Age (GA) and estimated age values by the One-Minute and Five-Minutes models vs. GA.

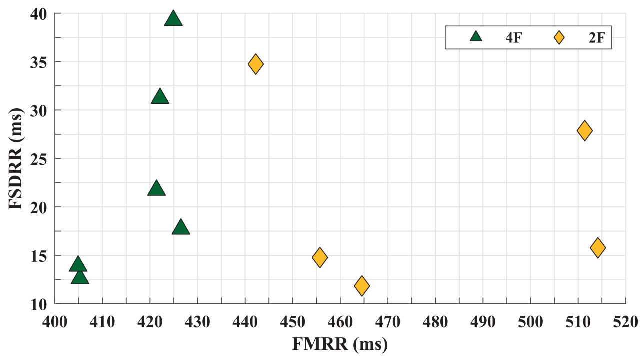

FIGURE 9. Scatterplot of the mean values of fetal R-R intervals (FMRR) and the corresponding standard deviation (FSDRR) with respect to fetal behavioral states 4F (active awake) and 2F (active sleep) for 11 fetuses (sample size for gestational age ≥ 36 weeks is 11 datasets).

The methodology proposed in this paper (including the detection of the adjacent beat-to-beat maternal and fetal R-peaks in the ECG signals as well as the coupling parameters associated with the corresponding HR signal) is fully automated, and is therefore less affected by human errors when compared with LMP and sonography methods. In addition, the proposed technique has the advantage of being easily applied and does not require highly-skilled technicians to administer compared to standard ultrasonography techniques.

The selected variables by the proposed multi-variate stepwise regression models (Figs. 4 and 5) considered maternal as well as fetal HRV parameters, rather than only fetal-based parameters. Moreover, maternal-fetal HR coupling strengths at various ratios contributed to the development of both models, which further confirms the importance of considering

TABLE 2. Statistics of fetal R-R interval, pearson correlation coefficient (*r*), *p*-value, and cross-validation estimation error with respect to fetal behavioral states 4F (active awake) and 2F (active sleep).

Feature	One-Minute Model		Five-Minutes Model	
	4F	2F	4F	2F
FMRR (Mean±SD)	411.58±15.17*	469.49±17.70	417.51±9.80*	477.61±33.08
FSDRR (Mean±SD)	22.94±8.45	19.29±5.80	22.73±10.51	20.99±9.82
FRMSSDRR (Mean±SD)	7.80±2.99	7.41±1.86	6.28±1.97	7.58±2.47
r	0.52	0.71	-0.89	0.83
p-value	–	–	1.69×10^{-2}	7.89×10^{-2}
mRMSE (Validation) (weeks)	5.09	3.69	4.75	2.67

FMRR, mean value of fetal R-R intervals; R-R intervals, interbeat intervals between all successive heartbeats; FSDRR, standard deviation of R-R intervals in fetal heart rate; FRMSSDRR, root mean square of successive fetal R-R interval differences; *r*, Pearson correlation coefficient; mRMSE, mean root mean square error.
* $p < 0.05$.

maternal influences on fetal development. Indeed, not only do electrophysiological parameters contribute to the estimation of GA, but their interrelations are also a vital element. In addition to this, it is interesting to observe that HR coupling strength for a specific ratio is not constant for all fetal ages; in fact, it varies throughout gestation.

Furthermore, the results of the linear mixed approach presented in Table 1 show that HR coupling (λ-based) variables for different maternal-fetal coupling ratios were also selected as contributing terms to the estimate of the GA. For example, the One-Min model includes λ[1:2], λ[3:4], λ[2:3] and λ[2:4]; in contrast, λ[1:3], λ[3:5], λ[2:3] and λ[2:4] exist in the Five-Min model (also see (5) and (6)).

Considering the coupling ratios that are different between the two models, it is interesting to note that the Five-Min model generally accommodates ratios with higher fetal heartbeats considering the same maternal heartbeat. Consider for example the coupling of fetal heartbeats with 3 maternal beats, the dominant ratio in the Five-Min model is 3:5. In contrast, there exist 4 fetal heartbeats for every 3 maternal beats in the One-Min model, forming a dominant ratio of 3:4. In other words, more fetal heartbeats exist in a fixed window of maternal beats when considering the Five-Min model as compared to the One-Min model. Further, it is notable that coupling with 3 fetal heartbeats (i.e. λ[1:3] and λ[2:3]) is more prevalent in the Five-Min model. A previous study showed that for 5 min recording of magnetocardiogram signals, there exists coordination between maternal and fetal cardiac systems for higher synchronization ratios [16]. It can thus be speculated that coupling with higher fetal heartbeats in the Five-Min model is more prevalent due to longer recording length, and higher FMRR value ($p < 0.05$) in FBS 4F (see Table 2) compared to the One-Min model.

With respect to coupling ratios that are common between the two models, it is notable that λ[2:3] and λ[2:4] appear in the two models (see (5) and (6)). In particular, a positive correlation was found between λ[2:3] and GA, whereas λ[2:4] is found to be negatively correlated with GA in both models (see Figs. 4 and 5). Interestingly enough, including one more fetal heartbeat within the same window of maternal beats flips the direction of the correlation relationship. It is worthwhile noting that FMHR and λ[2:4] (in both models) are higher in younger fetuses compared to more mature ones in this study. This is in line with the results presented in [16] with regards to FHRV. As the fetus develops, FMHR drops causing a decrease in λ[2:4] because, at present, a lower number of maternal heartbeats (every 2 maternal R-peaks) includes 4 fetal beats. In analogy, the correlation trend of coupling variables for the other ratios can be speculated. Furthermore, λ[2:3] is considered a remarkable coupling ratio in the characteristics of maternal-fetal heart rates of pregnant mothers while at rest [33].

The trend lines connecting the mean absolute differences between gold standard GA identified by CRL and estimated GA values by the two models for the different age groups (Fig. 8) clearly show that the overall error produced by the Five-Min model is lower compared to the One-Min model. Additionally, the errors produced by the Five-Min model have lower standard deviation bars around mid-gestation. Moreover, the Five Min model produced higher values of *r* and lower mRMSE (for both of training and validation), suggesting the use of longer recordings which are likely susceptible to allow for the proper conditions to initiate the coupling [16].

An important issue investigated in this paper is the associations of maternal and FHR coupling variables with FBSes. The One-Min and Five-Min models produced lower mRMSE values for behavioral state 2F (active sleep) compared to 4F (active awake). This is as expected due to the highly nonstationary nature of fetal ECG and its coupling strengths in state 4F. The One-Min model produced an average error value of 3.69 weeks for the sleep behavioral state (2F), implying 47.3% error improvement compared with conventional methods [34] used to estimate GA. The lowest error value of 2.67 weeks was produced by the Five-Min model for the same state (i.e. 2F) with error percentage improvement of 61.9% compared with the same conventional method.

The proposed novel approach utilizing longer signal recordings can be easily implemented into a software program to assist physicians in accurately estimating fetal age.

However, the study requires further validation on a large sample size. Nonetheless, the outcomes of this research work would make fundamental as well as translational research outputs for fetal neurological screening and its potential to reduce fetal deaths.

The conducted research activities in this paper addressed some of the barriers associated with estimating the GA in fetal development studies by combining maternal-fetal heartbeat coupling parameters with maternal and fetal HRV parameters. The proposed novel approach is fully automated, does not require heavy computational resources, and can be utilized by nonexperts with little training or limited resources. In addition, it has the potential to detect health issues related to the fetus at early stages of pregnancy. This could possibly reduce obstetric interventions which could have been avoided in an attempt to reduce morbidity and cost savings. Considering the large number of annual births and the high rate of interventions, such improvements could have important implications worldwide.

V. CONCLUSION

The results presented in this paper successfully showed that maternal and fetal physiological parameters including maternal-fetal HR coupling parameters at various ratios and maternal/fetal HRV parameters produce a reliable estimate of the GA utilizing a multivariate regression model based on recorded ECG signals for 5 min rather than 1 min recordings. Further research related to work done as part of this paper include considering the effect of a variety of abnormal developments of human fetuses on the estimated GA for the various cases of heart anomalies and arrhythmias.

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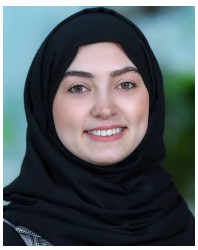

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