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Modeling Pregnancy Induced Hypertension among Pregnant Woman in Jimma University Specialized Hospital

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Abstract: *Many longitudinal studies generate a dataset having two or more longitudinal repeated biomarkers measurement, which often depend on each other. In Gestational hypertension study the two important markers are gestational systolic blood pressure (GSBP) and diastolic blood pressure (GDBP) are collected simultaneously from a pregnant woman every visit. In such studies, evolution of the biomarkers over time and the association between them are commonly of interest.*

The aim of the analysis was to determine joint evolution and association of pregnancy induced systolic and diastolic blood pressure over time and determining their associated risk factors. The association among the two sequences is captured by correlated normal random effects included to account correlation between two outcomes

In this study, we propose a joint random-effects model which enables two or more longitudinal repeated biomarker measurements to be modeled together while taking account of association between them. We apply these methods to a pregnancy induced hypertension among antenatal care follow up pregnant woman in Jimma University specialized hospital.

Under joint analysis, two aspects of the relation were investigated: the association between the evolutions and the evolution of association. Results of the joint model suggested a very strong association between the evolutions of GSBP & GDBP and a slowly decreasing evolution of the association over gestational age. Sex of fetus, family history of pregnancy induced hypertension, gestational age, age of mother and number of Gravida are identified as associated risk factors.

Joint model is able to address the same questions as separate model with more accuracy by addressing additional questions that may be of great interest to the researcher, such as the association of evolution and the evolution of association of the responses.

Keyword: *pregnancy induced hypertension; gestational hypertension; joint modeling; joint evolution; mixed model; systolic blood pressure; diastolic blood pressure*

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I. Introduction

Pregnancy–Induced Hypertension (Gestational hypertension): is new hypertension presenting after 20 weeks of gestation in a woman without prior hypertension or other features of eclampsia (NHBPEG, 2000). It is usually defined as systolic blood pressure of at least 140 mmHg and/or diastolic blood pressure of at least 90 mmHg (Cnossen, *et al.*, 2006).

Hypertensive disorders of pregnancy [HDP] affect 5-10% of all pregnancies worldwide and cause a substantial maternal and prenatal morbidity and mortality (Bergstrom, (2001). It is believed that 10-15% of maternal mortality in developing countries is due to HDP (Al Ghamdi, *el al.,* 1999). Incidence and prevalence of PIH vary from one country to another and might have genetic predisposition. Among African-Americans ,it is 6.4% of deliveries; in Sweden 1.5% of pregnancies (Al Ghamdi, *el al.,* 1999); in West-Africa 0.64 per 100 (Prual, *et al.*,2001); in South Africa HDP is number one cause of maternal deaths {20%} (Moodley,*et al*.,1998).

In Ethiopia, these disorders were pointed out as major causes of maternal and prenatal morbidities and mortality (Teklu, *et al.,* 2006, Abate, *et al*., 2006). Study done in Jimma university referral hospital reported an overall prevalence of HDP, 8.48%, where 95% is due to PIH. Severe preeclampsia was the most common hypertensive disorder of pregnancy accounting for 51.9% of the cases followed by eclampsia which contributed for 23.4% of the cases (Zenebe, *et al.,* 2011)..

Many longitudinal studies involve collecting data on more than one outcome from a given subject repeatedly in time. These outcomes may be of similar or disparate types, and a variety of scientific questions may be of interest, depending on the application. For example, (GSBP and GDBP, longitudinal measure and

time to event), However, statistical modeling of such data poses several challenges that cannot be addressed by separate analysis. First, there is a possibility to be a correlation between the outcomes in addition to the correlation due to repeated measures over time. Second, the variability for each response is likely to be different. Further, one may be interested in their joint evolution rather than their individual evolution. A broad objective of joint modeling is to provide a framework within which questions of scientific interest pertaining to systematic relationships among the multiple outcomes and between them and other factors (treatment, dose, etc.) may be formalized. Response measured repeatedly on the same unit or individual are correlated because they contain a common contribution from that unit (Fieuws and Verbeke, 2005). Separate analyses would not able to examine the correlation or association between the two outcomes. Therefore, it is more desirable to jointly modeling of two outcome variables together (Williams, 2001).

In general, the motivation behind this study is to address the following major research questions:

- ☞ Does the rate of change (slope) of GSBP have an effect on rate of change on GDBP?
- ☞ Which factors predict the evolution of pregnancy induced Systolic and Diastolic blood pressures in pregnant women under separate and joint modeling?

III. Methodology

3.1 Data source and its Description

Under this study the latest data from retrospective cohort follow up of pregnant woman under ANC, who have followed at least four visits from January 2013 to January 2014 in Jimma University Specialized Hospital, were used. JUSH located in south west of Ethiopia in Jimma town 340 KM form Addis Ababa.

Inclusion and exclusion

The data was extracted from the follow up of woman which contains history, obstetric, gynecologic, epidemiological, laboratory and clinical information. Women with preexisting proteinuria or chronic hypertension, defined as BP 140/90 or antihypertensive therapy that preceded pregnancy or first appeared before 20 wk of gestation were excluded

Seven covariates were used for joint analyses. Two of these covariates are continuous (age of mother &gestational age) while sex of fetus, family history of PIH/PE and diabetes mellitus of mother are categorical and the rest two are discrete covariates (number of Para and Gravida).

3.3 Statistical Methods of Data Analysis

3. Linear Mixed Effect Model

The general linear mixed effect model viewed as a combination of models from a two stage analysis where: The first stage assumes that Yi satisfies a linear regression model,

$$Y_i = Z_i\beta_i+\varepsilon_i \qquad (0)$$

where Z_i is an appropriate design matrix. This model shows how the response evolves over time for the i^{th} subject where β_i is a p- dimensional vector of unknown subject specific regression coefficients and ε_{ij} is a vector of the residual component , j=1,2,3,4,.....n_i. Usually assumed to be normally distributed with mean zero and covariance matrix R_i. .

In mixed-effects models, response variables are assumed to be a function of fixed effect, non-observable random effect, and error term *(*Laird and Ware, 1982). When both the fixed and the random effects contribute linearly to the response, the model is called linear mixed-effects model.

$Y_i= Z_i(K_i\beta + b_i) + \varepsilon_i = Z_iK_i\beta + Z_ib_i+ \varepsilon_i$ $_{i=1,2}$.....S Where $Z_iK_i = X_i$ and the final model becomes

$Y_i=X_i\beta + Z_ib_i+ \varepsilon_i$ where (1)

$\boldsymbol{Y_i}$ –is the n_i x 1 response vector for i^{th} subject: $Y_i= (Y_{i1},Y_{i2},.....Y_{ini})$

$\boldsymbol{Z_i}$ –is a $n_{\times}$ q matrix of known covariates, $\boldsymbol{X_i}$ –is a $n_{\times}$ p design matrix for the fixed effects

β --is a $p_{\times 1}$ dimensional vector unknown parameter for fixed effect, $\mathbf{b_i}$ -- is $q_{\times 1}$ dimensional vector of unknown random effects

$\boldsymbol{\varepsilon_i}$ -is $n_i\times 1$ error vector $\varepsilon_i \sim N(0, \Sigma_i)$, often $\Sigma_i = \sigma^2 I_{ni}$ $\mathbf{b_i} \sim N(0, G)$ i.e:- $\mathbf{b}_i$ vector of subject-specific random effects which has a q-variate normal density with mean vector 0 and a variance-covariance matrix G

In this model, $X_i\beta$ is the mean response which is fixed effect and Z_ib_i incorporates the random effect part. The Z_ib_i can viewed as the true individual level of GSBP or GDBP trajectories after they have been adjusted for the overall mean trajectory and other fixed effects.

$$Var(Y_i)=Var(Z_ib_i) +Var(\varepsilon_i)=Z_iGZ_i`+ \Sigma_i \qquad (2)$$

3.4 Joint Model for Two Continuous Outcomes

Linear mixed model given above can be easily extended to bivariate response variables by further stacking the data and defining a specific variance-covariance structure for the random effects. Consider for modeling the two

response variables (Y^1 and Y^2) over time and incorporating random intercepts and slopes in order to model the correlations over time between responses. Maximum likelihood estimation (MLE) is used to estimate parameter. Let $y_{ij}{}^k$ represent the jth observation from ith subject, for the kth response variable, where i = 1, …,S , j= 1, …, $n_i{}^k$, and k = 1, …, K. For this thesis k is 1 and 2. Also, define $N_k=\sum_{i=1}^{s} n_i{}^k$ and $N=\sum_{k=1}^{K} N_k$.The vector $y_i{}^k = [y_{i1}{}^k, y_{i2}{}^k \ . \ .. \ . \ .y_{ini}{}^k]$ then represents the $n_i{}^k$ observation of the kth response variable from the ith subject the vector $Y_k = [y_1{}^k, y_2{}^k, \ \ldots Y_s{}^k]'$ represents the N^k observation from the kth response variable across all subjects. Finally, the vector $Y= [Y^1, Y^2 \ldots Y^k]$ represents N observation across all response variables and subjects.

In modeling two response variables, the linear mixed-effects models for each response variable for subject i taken at time t can be specified as (Fieuws and Verbeke, 2004).

$Y_i{}^1(t)=\mu^1(t)+a_i{}^1+b_i{}^1(t)+\varepsilon_i{}^1(t) \qquad Y_i{}^2(t)=\mu^2(t)+a_i{}^2+b_i{}^2(t)+\varepsilon_i{}^2(t)$ (3)

Where $\mu^k(t)$ refers to the average evolution (of the kth response over time) and is a function of the fixed effects. The subject specific random intercepts $a_i{}^k$ and slopes $b_i{}^k(t)$ describe how the subject specific profiles deviate from the average profile for the kth response and changes over the time. The two response trajectories are joined together by assuming a joint distribution for the vector of random-effects, b_i, such as

$b_i=\begin{bmatrix} a_i{}^1 \\ b_i{}^1 \\ a_i{}^2 \\ b_i{}^2 \end{bmatrix} \sim N(0,G)$ Where the variance-covariance matrix for the random effects, G, has the following structure:

$$G=\begin{bmatrix} \sigma_{a1}^2 & \sigma_{a1b1} & \sigma_{a1a2} & \sigma_{a1b2} \\ \sigma_{b1a1} & \sigma_{b1}^2 & \sigma_{b1a2} & \sigma_{b2b1} \\ \sigma_{a2a1} & \sigma_{a2b1} & \sigma_{a2}^2 & \sigma_{a2b2} \\ \sigma_{b2a1} & \sigma_{b2b1} & \sigma_{b2a2} & \sigma_{b2}^2 \end{bmatrix} \quad \text{special case of } G=\begin{bmatrix} \sigma_{a1}^2 & \sigma_{a1b1} & 0 & 0 \\ \sigma_{a1b1} & \sigma_{b1}^2 & 0 & 0 \\ 0 & 0 & \sigma_{a2}^2 & \sigma_{a2b2} \\ 0 & 0 & \sigma_{b2a2} & \sigma_{b2}^2 \end{bmatrix} \quad (4)$$

The error components for each response, which are independent of the random effects, can be taken to be uncorrelated (σ_{12} =0) and not associated with the random effects, such that the error components are defined:

$$\begin{bmatrix} \varepsilon_i{}^1 \\ \varepsilon_i{}^2 \end{bmatrix} \sim N\left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \sigma_1^2 & \sigma_{12} \\ & \sigma_2^2 \end{bmatrix}\right) \qquad (4.1)$$

Assuming σ_{12} =0 implies that, conditional on the random-effects, both response trajectories are independent. The assumption of conditional independence could alternatively be relaxed and the random errors could be taken to be dependent by allowing for a nonzero co-variances between the errors components ($\sigma_{12} \neq 0$).

3.4.3. Association of the Evolution (AE)

One of important question that may be addressed with a joint mixed-effects model is how the evolution of one response is associated with the evolution of another response. Joint evolution is the gradual change biological correlated response variable over time.

$$rE= \frac{Cov(b_1,b_2)}{\sqrt{Var(b_1)}*Var(b_2)} = \frac{\sigma_{b1,b2}}{\sqrt{\sigma_{b1}^2}*\sigma_{b2}^2} \qquad (7)$$

3.4.4. Evolution of the Association (EA)

A similar idea that may be investigated using a joint mixed effects model is how the association between the responses evolves over time ("evolution of the association"). Assuming uncorrelated errors, the marginal correlation between the two responses as a function of time is given by (Fieuws and Verbeke, 2004):

$$r_m(t)=\frac{Cov(Y_j{}^1(t),Y_j{}^2(t))}{\sqrt{Var(Y_j{}^1(t))}\sqrt{Var(,Y_j{}^2(t))}} = \frac{\sigma_{a1,a2}+t\sigma_{a1,b2}+t\sigma_{a2,b1}+t^2\sigma_{b1,b2}}{\sqrt{\sigma^2{}_{a1}+2t\sigma_{a1,b1}+t^2\sigma^2{}_{b1}+\sigma_1{}^2}\sqrt{\sigma^2{}_{a2}+2t\sigma_{a2,b2}+t^2\sigma^2{}_{b2}+\sigma^2{}_2}} \qquad (8)$$

Assuming correlated errors, the marginal correlation between the two responses as a function of time is

$\frac{\sigma_{a1,a2}+t\sigma_{a1,b2}+t\sigma_{a2,b1}+t^2\sigma_{b1,b2}+\sigma_{12}}{\sqrt{\sigma^2{}_{a1}+2t\sigma_{a1,b1}+t^2\sigma^2{}_{b1}+\sigma_1{}^2}\sqrt{\sigma^2{}_{a2}+2t\sigma_{a2,b2}+t^2\sigma^2{}_{b2}+\sigma^2{}_2}}$= Two observations can be made from equation (8). First, notice that when t= 0 the marginal correlation reduces to $r_m(t) = \frac{\delta_{a1a2}}{\sqrt{\delta^2{}_{a1}+\delta^2{}_1}\ \sqrt{\delta^2{}_{a2}+\delta^2{}_2}}$ which is essentially the correlation between the two random intercepts. If fact, when the error components are small, the closer the marginal correlation at t= 0 approximates the correlation between the random intercepts. Also, as t increases $r_m(t)$ converges to rE for the case with uncorrelated errors, and $r_m(t) = \frac{\delta_{a1a2}+\sigma_{12}}{\sqrt{\delta^2{}_{a1}+\delta^2{}_1}\ \sqrt{\delta^2{}_{a2}+\delta^2{}_2}}$ for the case of correlated errors, which indicates that the absolute value of the marginal correlation at t= 0 cannot be higher than the correlation between the random intercepts (Fieuws, et al. 2004).

3.4.6. Model Comparisons

The most commonly known model comparison criteria (AIC) (Sakamoto, 1986), (BIC) (Laird and Ware, 1982) and Log-likelihood ratio test were used.

AIC = -2log L + 2p BIC=-2log L + P*log (N), Where, -2 log L is twice the negative log-likelihood value for the model P: - is the number of estimated parameters. N: - is the total number of observations used to fit the model. Smaller values of AIC and BIC reflect an overall better fit.

IV. Results

4.1 Basic information and Descriptive Statistics

Under this study, 97 women having gestational hypertension with minimum of four and maximum of nine visits for systolic and diastolic blood pressure during ANC with seven covariates were used. Basic information on each variable are given below in table

Table 1 Percentages of each category's and Mean with StDev for GSBP and GDBP

S. No	Variable	Categories	Percentag	Systolic	Diastolic
				Mean (StDev)	Mean (StDev)
1	Gender	Male	55.10	145.1556(15.65891)	87.96358(7.831829)
		Female	44.90	140.0725(16.91583)	85.69565(8.376987)
		Total	100%		
2	Diabetes mellitus	Yes	22.44	144.1705(15.32926)	88.50388(7.487619)
		No	77.56	142.7211(16.69566)	86.54474(8.283283)
		Total	100%		
3	Family history PIH/PE	Yes	26.53	146.7682(14.188)	88.38411(7.323807)
		No	74.47	141.5363(16.97114)	86.47486(8.387879)
		Total	100%		
4	Age of mother	≤ 20	25.77	142.9313(17.29259)	85.54198 (8.280895)
		20-25	34	141.7168 (16.62044)	85.27746(7.830576)
		25-30	32	140.949(17.44691)	85.11465(8.654307)
		30-35	8.23	141.3462(12.45453)	85.96154(8.368898)
		Total	100%		
5	Gravida	Primi	30	140.9434(11.82153)	85.22013(6.51335)
		Multiple	70	142.1517(16.97784)	85.42415(8.196896)

4.2 Individual profile plot of GSBP and GDBP over Gestational age

The individual profile plot shows, some women's have systolic and diastolic blood pressure measures that are consistently higher or lower than those of other women's, indicating the presence of a subject specific random effect.

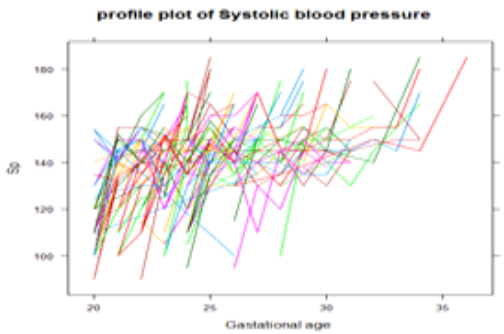

Figure 1a individual profile plot of GSBP

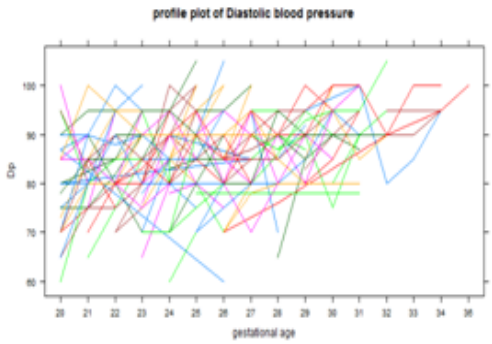

Figure 1b individual profile plot of GDBP

Table 2 Bivariate random effect model (correlated & uncorrelated error) parameter estimate

Uncorrelated error						correlated error					
Para	Estimate	Standard Error	Pr > |t|	Lower	Upper	Para	Estimate	Standard Error	Pr > |t|	Lower	Upper
β_{10}	131.27	61.4768	0.0340	91.53	171.0009	β_{10}	131.27	53.8182	0.0156	25.1119	237.43
β_{11}	5.7375	2.8449	0.0451	0.1257	11.3492	β_{11}	5.5522	13.5900	0.6833	-21.2544	32.3589
β_{12}	8.1238	3.0612	0.0086	2.0855	14.1620	β_{12}	-2.6567	2.9094	0.3623	-8.3956	3.0821
β_{14}	-26.0672	10.2041	0.0114	-46.1951	-5.9392	β_{14}	-26.9455	10.9571	0.0148	-48.5587	-5.3322
β_{15}	11.3384	2.5529	<.0001	6.3027	16.3742	β_{15}	8.0161	1.8921	<.0001	4.2838	11.7483
β_{16}	43.5156	20.3254	0.0336	3.4232	83.6080	β_{16}	42.7490	19.6338	0.0307	4.0208	81.4772
β_{19}	-0.3478	0.1280	0.0072	-0.6002	-0.09538	β_{19}	-0.2565	0.09978	0.0109	-0.4533	-0.05967
β_{111}	1.1138	0.4248	0.0094	0.2759	1.9517	β_{111}	1.4967	0.3558	<.0001	0.7949	2.1986
β_{112}	-1.6263	0.8455	0.0559	-3.2940	0.04138	β_{112}	-0.8032	0.6516	0.2192	-2.0884	0.4821
β_{113}	-0.2672	0.1451	0.0670	-0.5534	0.01891	β_{113}	0.4225	0.4571	0.3564	-0.4791	1.3242

The output given above depicts that, the intercept for systolic blood pressure is 131.27 with standard error of 61.47mmHG, which show there is a greater variability at first follow up (beginning of gestational hypertension). The sex (β_{11}) of the neonate has significant (positive) effect on the GSBP of mother. Having male neonate made to increase the SBP of the mother by more than five and half fold compared with the female neonate. Because, naturally Male neonates have high involvements in increasing mother blood pressure as compared to their counterparts. Having family history of hypertension (β_{16}) increases the chance of increasing gestational hypertension. Woman of hypertensive family of PIH/PE has greater Bp than her counterpart. Gestational age (β_{15}) has significant effect on SBP of pregnant woman. As gestational age (in week) increase by one, SBP of the pregnant mother increase by 11.34mmHG. As the age (β_{12}) of the mother increases by one year, her SBP increases by multiple of 8.14 mmHG. But, as number of Gravida increases, the blood pressure of mother decreases. Mother of primigravidae (primiparas) SBP is greater than that of multiparas (multigravida) mothers blood pressure. When the number of Gravida (β_{14}) increases by one, gestational SBP of mother decreases by 26.07 mmHG, fixing other covariates and factors. But, there is greater variability's (10.2). The interaction family history of hypertension by gestational age (β_{112}) and diabetes mellitus by gestational age (β_{113}) decrease GSBP of the mother by 1.63 and 0.26 respectively. However, the interaction of gestational by Gravida (β_{111}) increases GSBP of mother by 1.1.

Table.3. Diastolic case parameter estimation for uncorrelated and correlated Error

Para	Estimate	Standard Error	Pr > |t|	Lower	Upper	Para	Estimate	Standard Error	Pr > |t|	Lower	Upper
β_{20}	60.3679	32.7959	0.0672	-125.06	4.3230	β_{20}	59.1816	26.8825	0.0289	6.1551	112.21
β_{21}	13.2631	10.3249	0.2005	-7.1032	33.6293	β_{21}	12.4542	9.0114	0.1686	-5.3210	30.2294
β_{22}	3.4726	1.6391	0.0354	0.2393	6.7058	β_{22}	-1.3802	1.3596	0.3113	-4.0621	1.3017
β_{24}	-10.4722	5.2527	0.0476	-20.8332	-0.1111	β_{24}	-9.1664	4.7608	0.0557	-18.5573	0.2245
β_{25}	5.8948	1.3786	<.0001	3.1755	8.6141	β_{25}	2.9431	0.9088	0.0014	1.1505	4.7357
β_{26}	19.5450	11.164	0.0816	-2.4768	41.5669	β_{26}	21.3785	8.3814	0.0115	4.8460	37.9111
β_{28}	-0.4434	0.4356	0.3101	-1.3027	0.4159	β_{28}	-0.4805	0.3004	0.1114	-1.0731	0.1121
β_{29}	-0.1416	0.0693	0.0424	-0.2782	-0.00487	β_{29}	-0.03329	0.04648	0.4747	-0.1250	0.05839
β_{211}	0.4384	0.2211	0.0488	0.002252	0.8745	β_{211}	0.4512	0.1635	0.0063	0.1287	0.7738
β_{212}	-0.7410	0.4677	0.1148	-1.6635	0.1815	β_{212}	-0.2753	0.2986	0.3578	-0.8643	0.3137

In similar way, the estimated intercept (β_{20}) for GDBP is 60.13 with standard deviation of 31, which shows t existence of greater variability at beginning of GDBP but less than that of GSBP. The intercept and standard deviation of GDBP is almost half of that of GSBP. Sex (β_{21}) is not significant at 0.05 levels of significance. However, age of mother has an effect on her GDBP. As the age (β_{22}) of mother increase her GDBP increase by 3.4. When the number of Gravida (β_{24}) increases by one, GDBP decreases by 10.5. Completing one week in gestational age (β_{25}) and beginning of the next new week, in average increase DBP more than five and half folds. Gestational age has positive effect on mother's blood pressure. In average after completion of one, her DBP increases by 5.8. In other way, having positive family history of hypertension (β_{26}) increases gestational hypertension by 19.5 folds. Sex by gestational age (β_{28}) have estimated value of -0.445, which shows the GDBP decline more faster for male neonate over gestational age. The estimated difference in slope -0.14 is highly significant, indicating that the response is declining overtime more quickly for the age of mother. In reverse, interaction of gestational age with Gravida (β_{211}) increases the gestational GDBP by 0.43 and family history of hypertension by gestational age (β_{212}) made the GDBP to decline by 0.74.

Table 4. Variance of random effect

δ_1	10.7586	0.5654	<.0001	9.6432	11.8739	δ_1	11.6404	0.4234	<.0001	10.8054	12.4755
δ_2	4.6117	0.2128	<.0001	4.1920	5.0314	δ_2	5.4078	0.2087	<.0001	4.9960	5.8195
σ_{12}						σ_{12}	61.598	10.52	<.001	42.972	80.99
δ_{01}	58.3324	10.5913	<.0001	37.4407	79.2241	δ_{01}	66.0414	.	.	.	.
δ_{11}	2.5225	0.4456	<.0001	1. 6435	3.4041	δ_{11}	0.007651	1.2413	0.9951	-2.4409	2.4562
δ_{02}	37.8688	4.9599	<.0001	28.0852	47.6523	δ_{02}	24.2672	.	.	.	.
δ_{12}	1.6389	0.2095	<.0001	1.2.2257	2.0257	δ_{12}	9.719E-7	.	.	.	.

δ_{01}- standard deviation of intercept for GSBP δ_{11}- standard deviation of slope for GSBP δ_{02}- standard deviation of intercept for GDBP δ_{12}- standard deviation of slope for GDBP σ_{12}–covariance between error terms

In the above table, all the variances of the random effects (δ_{01}, δ_{02}, δ_{02}, and δ_{12}) are marginally significant, indicates there is between subjects variability.

4.3. Evolution of association (EA) and association of evolution (AE)

Association of evolution for GSBP and GDBP is typically derived from the correlation matrix of the random effects. Joint analysis of response used to show AE (equa.7) and EA (equa.8). Based on the output given AE for GSBP and GDBP is **0.75**. This positive value suggests that there is a great association between the two.

Table 5 Correlation matrix for joint evolution

		GSBP		GDBP	
		Intercept	**Slope**	**Intercept**	**Slope**
GSBP	**Intercept**	1.0000000	-0.9910898	0.7126446	-0.7019257
	Slope	-0.9910898	1.0000000	-0.7370341	**0.7451846**
GDBP	**Intercept**	0.7126446	-0.7019257	1.0000000	-0.9910898
	Slope	-0.7370341	0.7451846	-0.9910898	1.0000000

Marginal correlation plot at each gestational age have been used to show EA for response variables'. The marginal correlation plot given below shows that, EA (equa.8) between the two responses is decreasing over gestational age

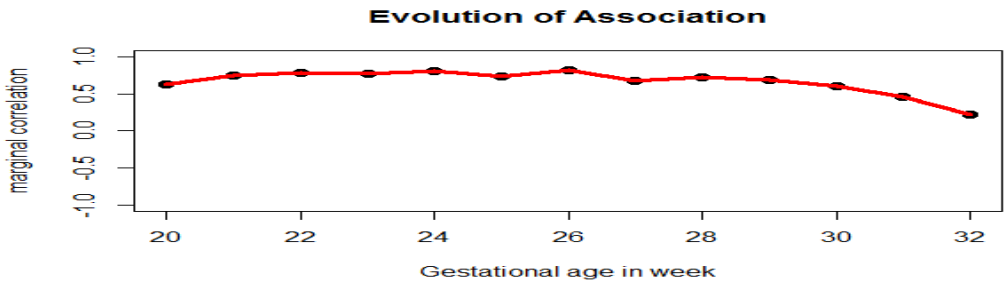

Figure 4. Evolution of the association for response variables over gestational age

V. Conclusions

Joint modeling of two biologically correlated responses gives additional information than separate analysis. That is, association of evolution and evolution of association. Joint analysis with uncorrelated error output for AE shows that, the two responses are strongly positive. But, their EA is decreasing over time.

VI. Recommendation

Pregnant woman should have ANC follow up until her delivery to take care of her life and fetus. This may reduce preterm delivery rate, low birth rate and severity, induction caesarean and instrumental delivery.
Under this study only seven variables had been considered. Further studies should be needed including covariates like interval of pregnancy, multiple pregnancies, body mass index of mother,...etc.

The joint modeling of outcomes involved in a disease process is also able to address the same questions as separate model with more accuracy by addressing additional questions that may be of great interest to the researcher, such as the AE and the EA of the responses.

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