Joint modeling of longitudinally measured pregnancy induced systolic & diastolic 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. For example, in Gestational hypertension study the two important markers, gestational systolic blood pressure (GSBP) and diastolic blood pressure (GDBP) are collected simultaneously from a pregnant woman every visit time. In such studies, evolution of the biomarkers over time and the association between them are commonly of interest.

Often Univariate analyses using a mixed effects model are performed and are well developed for a single outcome variable. However, separate models are overly simplified because they do not consider the association between two components of such data and so produce misleading conclusions.

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. 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. Besides, correlation of error terms is given a great consideration.

Both Separate and joint modeling results are consistent. But, fit statistics shows that joint modeling with uncorrelated error is the best to fit the data. 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.

Key word: pregnancy induced hypertension; gestational hypertension; joint modeling; joint evolution; mixed model; systolic blood pressure; diastolic blood pressure.

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As thesis research advisors, we herby certify that we have read the thesis prepared by Abdulfeta shafi our guidance, which is entitled "**Joint modeling of longitudinally measured pregnancy induced systolic & diastolic hypertension among pregnant woman in Jimma University specialized hospital**", in its final form and have found that (1) its format, citations, and bibliographical style are consistent and acceptable and fulfill university and department style requirements; (2) its illustrative materials including tables and figures are in place; and (3) the final manuscript is satisfactory to the graduate committee and is ready for submission to the university library.

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As the members of the board of examiners of MSc thesis open defense examination, we certify that we have read and evaluated the thesis and examined the candidate. Hence, we recommend that the thesis be accepted as it fulfills the requirements for the degree of Master of Science in Biostatistics.

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List of Acronyms

AIC:	Akaike information criteria
ANC:	Antenatal care
AOE	Association of the evolution
AR:	Autoregressive
BIC:	Bayesian information criteria
BMI:	Body mass index
CI:	Confidence interval
DBP:	Diastolic Blood Pressure
M/GDBP:	Mean/ Gestational diastolic blood pressure
GH:	Gestational Hypertension
M/GSBP:	Mean/ Gestational systolic blood pressure
HDP:	Hypertensive Disorder Pregnancy
HELLP:	Haemolysis Elevated Liver Enzyme and Low Platelet Count
ICMR:	Indian Council Medical Research
JUSH:	Jimma University Specialized Hospital
LMM:	Linear Mixed Model
LMP:	Last menstrual period
MDG:	Millennium Development Goal
ML:	Maximum Likelihood
MMR:	Mother Mortality
NHBPEG:	National Heart Blood Pressure Education Group
NHLBI:	National Heart Lung and Blood Institution
NIH:	National Institution of Heart
OR:	Odds Ratio
PE:	Preeclampsia
PIH	Pregnancy induced hypertension
PPH	Post-partum hemorrege
WHO	World Health Organization
WK	Week

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CHAPTER ONE

1. INTRODUCTION

1.1 Back ground

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). When pregnancy induced hypertension accompanied by proteinuria, the disorder is termed as preeclampsia and Eclampsia (more severe form of Pre-eclampsia) defined as seizures in a pregnant woman with preeclampsia and subsequently diagnosed convulsive disorder confirmed by significant proteinuria greater than 2^+ or 300mg of protein. When preeclampsia develops in women with chronic (preexisting) hypertension, the classification of disease is chronic (preexisting) hypertension with superimposed preeclampsia.

PIH is one of the most common cause of maternal mortality around the world whereby it contribute up to 8% of all maternal death (WHO and World Bank, 1997). Globally half a million women die each year as a result of pregnancy and childbirth. Of these deaths, 50% occur in Africa, about 42% in Asia, about 4% in Latin America and Caribbean and less than 1% in the developed countries (WHO, 2001). It is well documented that 95% of the approximately 350,000 maternal deaths occurring annually worldwide are in low-resourced, developing countries (WHO, 2011). Over half of the maternal mortality worldwide occurs in six countries: India, Nigeria, Pakistan, Afghanistan, Ethiopia, and Democratic Republic of the Congo (Hogan, *et al.,* 2010). The most common direct causes are post-partum hemorrhage (25%), sepsis (13%), unsafe abortions (13%), pre-eclampsia and eclampsia (12%), and obstructed labor (8%). Between 75 and 50 thousand women are thought to die annually from complications resulting from pre-eclampsia and eclampsia (Ridge, *et al,* 2010; Tukur, 2009; WHO, 2011).

Hypertensive disorders of pregnancy [HDP] affect 5-10% of all pregnancies worldwide and cause a substantial maternal and prenatal morbidity and mortality (Bergstrom, (2001), Sibai, (2002)). 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 the United Kingdom hypertension in pregnancy is the most frequent cited cause of death (Magee, *et al.,* 1999, Brown, *et al.,* 2001). In Zimbabwe, hypertension complicates about 15% of pregnancies delivered at Harare Maternity Hospital (Mahomed, *et al.,* 1998). Pre-eclampsia/eclampsia, commonest causes of high maternal and infant mortality and morbidity rates in Malawi (Sungani,*et al*., 1998).

In Ethiopia, these disorders were pointed out as major causes of maternal and prenatal morbidities and mortality (Teklu, *et al.,* 2006, Mekbeb, *et al*., 1991, 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). Another study by Endeshaw and Berhan, (2015), using three university teaching hospitals in south west region of Ethiopia also revel the burden of this disorder where they found Preeclampsia, eclampsia and other type of HDP account 49.4%, 44.4%, and 6.2% of prenatal mortality, respectively.

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. Hence, a statistical model that jointly represents these relationships is an appropriate framework in which these questions may be addressed. A number of approaches to joint modeling of multiple outcomes, where some or all of the outcomes are ascertained longitudinally, have been proposed. 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. To ensure valid inferences, joint models must appropriately account for the correlation among the outcomes. Response measured repeatedly on the same unit or individual are correlated because they contain a common contribution form that unit (Fieuws and Verbeke, 2005). Modeling the true correlation

structure become significant in the presence of missing values and when the number of observations per subject is not large. Measures of GSBP and GDBP are highly related and changes in either often affect changes in the other. 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).

There are different general approaches for joint modeling longitudinal observations with differing outcome. However; none of these approaches answers the question of how the evolution of one is related to the evolution of another response (Fieuws and Verbeke, 2004). A flexible solution is to model the association between the different responses using random effects. In a joint-modeling approach using mixed models, random-effects are assumed for each response process and by imposing a joint multivariate distribution on the random effects; the different processes are associated. This approach has many advantages and is applicable in a wide variety of situations. Indeed, the approach allows joining models for responses of the same response type as well as models for responses of different types (Laird and Ware, 1982)

Under this study a mixed model approaches was used, which allows the longitudinal examination of gestational systolic and diastolic blood pressure of pregnant woman over time. It provides a flexible and powerful tool for the analysis of data with complex covariance structure. A mixed model has two types of components, the systematic or fixed, or the mean model component and the random component (McCulloch *et al.,* 2008). The fixed component is a sub-model representing the contribution by fixed effects and the random component represents the contribution by random effects. A fixed effect is an effect where all levels of the variable are contained in the data and the effect is universal to the entire target population (Der and Everitt, 2006). These unobserved effects are then included in the model as random variables, or equivalently called, random effects. A random effects model means that the levels of the factor variable in the data being modeled comprise a random sample of levels in the target population.

1.2. Statement of problem

Pregnancy induced hypertension is growing health problem in both developed and developing country that complicates pregnancy. It contributes to develop coronary heart disease, stroke, heart failure and kidney disease.

Even though, obstetrician, gynecologist, midwives and different health professionals have tried their best to control different pregnancy complication and pregnancy induced hypertension in pregnant woman, there are many different questions which will be raised. That is, how the change in gestational age leads to change in systolic and diastolic blood pressure pattern on different covariate and what are common risk factor associated with pregnancy induced blood pressure.

In our country, to the best knowledge of the researcher, there were no much published literatures that documented on this area except the studies about determinants of pregnancy induced hypertension based on cross-sectional study by using multiple regression and logistic regression. Determinant factors that progress systolic and diastolic blood pressure overtime were analyzed to show their influence on pregnant woman's blood pressure. In addition, almost all research on this area has been done without considering the correlations within and between subject specific random effects. So, the purpose of this thesis is to fill this gap.

Now, in longitudinal data analysis with two or more outcomes measured repeatedly, there is a correlation between them besides correlation due to repeated measures over time. So, their separate modeling of the systolic and diastolic outcomes may not be appropriate in this case. The two outcomes are biologically correlated or mutually influential. Consequently, Joint modeling of the two responses incorporates all information simultaneously and provides valid and efficient inferences (Fieuws and Verbeke, 2004). An interest then lies in how the evolution of GSBP is related to the evolution of GDBP, as well as how the association changes over time. Therefore, cross-sectional study and separate modeling would not be able to examine the association or evolution of the two outcomes evolves over time, but joint modeling did.

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?

1.3. Objective of the Study

1.3.1. General objective

The main objective of this study was to investigate the joint evolution and association of pregnancy induced systolic and diastolic blood pressure among pregnant woman in Jimma University Specialized hospital.

1.3.2. Specific Objective

- Explore the mean evolution of pregnancy induced GSBP and GDBP of pregnant woman.
- Fit a separate mixed effect models for longitudinally measured pregnancy induced GSBP and GDBP with significant associated risk factor.
- To identify direction of association of evolution and evolution of association over time
- Joint modeling pregnancy induced systolic and diastolic blood pressure and identifying the associated factor for the progress of GSBP and GDBP.
- Finally make comparison to identify the best model.

1.4. Significance of the study

The finding of this study will be helpful in developing an effective antenatal care policy and awareness creation for pregnant woman. Specially, helps to identify influential risk factors for joint and separate evolution of systolic and diastolic blood pressure in pregnant woman. Ultimately,

- It highlights how the pregnancy induced systolic and diastolic blood pressure related
- It helps to show how different groups of pregnant woman respond to different risk factors.
- To improve health care services related to PIH, Pre-eclampsia and eclampsia.
- It can be used as references for those who want to apply joint and separate modeling techniques for two longitudinally measured continuous data.
- To take prior care for associated risk factors of PIH and PE.

CHAPTER TWO

2. REVIEW OF LITERATURE

2.1. Factors Associated With Pregnancy Induced Hypertension and Related Study

Research on PIH has been unlimited as a result of its growing prevalence, but to date the etiology remains unknown, however, a number of risk factors have been identified (Roberts & Lain, 2002). These risk factors for hypertensive pregnancy (preeclampsia and gestational hypertension) include maternal, paternal, genetic, environmental and/or obstetric factors. Reportedly, primiparas are known to be at markedly greater risk of preeclampsia than multiparas (Chesley,1984). Preeclampsia is reported to complicate 25-30% of nulliparous pregnancies, it is more common in nulliparous women than in multiparous women and as such the first pregnancy is understood to be a risk factor for preeclampsia (Serhal, *et al*., 2003). Lack of leisure-time physical activity early in pregnancy (Marcoux, *et al.,* 1989), the use of barrier contraceptives (Klonoff- Cohen, *et al*., 1989), young maternal age (Saftlas, *et al*., 1990), and partner change (Duckitt & Harrington, 2005); have all been reported to amplify the risk of PIH or preeclampsia.

Ganesh, *et al.* (2010) used Univariate Analysis to identified risk factors and reported pre-pregnant Body Mass Index (OR=8.65), History of Diabetes (OR=11.0), History of Renal Disease (OR=7.98), Family History of hypertension (OR= 5.4), history of pre eclampsia in earlier Pregnancy (OR-9.63) and multiple pregnancy (OR=4.85). Multiply Logistic Regression analysis revealed that the pre-pregnancy Body Mass Index (OR-7.56), History of Chronic Hypertension (OR-6.69), History of Diabetes (OR-8.66), History of renal disease (OR=5.6) Multiple Pregnancy (OR-5.73) are the significant risk factors of Pregnancy induced hypertension.

Hypertensive disorders of pregnancy especially preeclampsia occurs more frequently in young primigravidae, first pregnancy from a new partner, in mothers of over 35 years of age, preexisting hypertension, hydatidiform mole, multiple pregnancy(twin pregnancy), and in maternal diabetes (Lloyd, *et al*., 1999). Long inter-pregnancy interval (Basso, *et al*., 2001), familial history (Dawson, *et al.,* 2002) and obesity (Mohamed K, *et al*., 1998, Wolf, *et al*., 2001)

are also associated risk factors for HDP. A study in Saudi Arabia between 1992 and 1993 showed that 30.3% were primigravidae and 46% were grandmultipara (Al Ghamdi, *et al*., 1999). While a similar study at Umtata General Hospital (UGH) between January 1993 and December 1994 indicated 27.3% of the hypertensive patients were teenagers, 18.3% were mothers of over 35years and 42.9% were primigravidae (Buga, *et al*., 1999). In Denmark, Basso established that long inter-pregnancy interval was associated with higher risk of preeclampsia in women with no previous history of HDP (Lloyd, *et al.,* 1999).

In South Africa, a study at Tygerberg Hospital and Stellenbosch University revealed results similar to those established by Basso. Also, the result revealed that prim gravidity had a threefold increased risk for the development of pre-eclampsia (Verwoerd, *et al*., 2002). In Norway, a similar study concluded that long intervals between pregnancies, rather than change of partner, were associated with higher risk of pre-eclampsia (Verwoerd, *et al*., 2002). Multiple pregnancies (twining) is another risk factor for pre-eclampsia as confirmed in previous studies (Dawson, *et al.,* 2002, Lszczynska-Gorzelak, *et al.,* 2000, Basso and Olsen, 2001).

A study done by Cronje and Grobler, (2003) showed that the prevalence of hypertensive disorder in pregnancy varies with socioeconomic status, pre-existing renal condition and essential hypertension. In similar study by Assis TR *et al*., (2008) identified several risk factors for hypertensive disorders in pregnancy and these can be related to regional and ethnic factors. Prim parities, obesity, non-white race, previous preeclampsia, age above 30 years as it occurs in chronic hypertension are some of the risk factor. Another by Ros *et al.,* (1998), Revealed that the following risk factors were significantly associated with pregnancy induced hypertension: type 1 diabetes (odd ratio = 5.58, 95% confidence interval 2.72-11.43), gestational diabetes (odds ration = 3.11, 95% confidence interval 1.61-6.00) and twin birth (odds ration = 4.17, 95% confidence interval 2.30-7.55.

A study done by Bodole, (1992), on the Maternal and Prenatal mortality of Pregnancy induced hypertension groups were significantly higher than that of the group without pregnancy. The result reveals that pathogenesis of Pregnancy induced hypertension was positively related to age, Prim parity, multiple pregnancy, labor, posture intensity, maternal Education level, body status, hereditary and various complications during pregnancy.

In a US national hospital discharge survey, higher mortality from preeclampsia and eclampsia was reported among women of African ancestry compared with European Americans, but only one-third or less of the difference could actually be attributed to the higher prevalence (Tucker ,*et al.,* 2007). Deaths from preeclampsia/eclampsia were 3 times higher in African Ancestry women compared with Europeans (MacKay *et al.,* 2001). In the UK Maternal Death Review for the period 2006-2008, 22 deaths occurred as a result of preeclampsia and eclampsia. Despite being a minority group, 6 of these deaths were Africans and the authors noted: "Black African women seem particularly susceptible to aggressive forms of preeclampsia (Cantwell, *et al.,* 2011).

Zenebe, *et al.,* (2011) used hospital based prospective cross-sectional study from April 1, 2009 to March 31, 2010 in JUSH, Southwest Ethiopia, to study hypertensive disorder of pregnancy and its associated socio-demographic and other risk factors. The result shows the overall prevalence of hypertensive disorders of pregnancy was 8.5%. Severe pre-eclampsia accounted for 51.9% of the case followed by eclampsia 23.4%. Residential area of the mothers (urban/rural) was found to have statistically significant association with severity of the disorder. Most (66.5% and 74.7%) of the mothers were nulliparous and had antenatal care follow up during the index pregnancy, respectively.

Study done by Gedefaw, *et al.,* (2014) in Debre markos referral hospital on maternal assessment of near miss, they found that the most common near-miss events fall under diagnostic obstructed labor, hemorrhage and pregnancy induced hypertension. Obstructed labor, hemorrhage and pregnancy induced hypertension were responsible for 45%, 43% and 38% of near-miss cases, respectively. Using multiple logistic regressions they revealed that distance between residences of the clients and this referral hospital had significant association with maternal near miss case. For instance, those who resided 25 km and far from the Hospital were two times more likely to suffer from near miss events than those who came from less than 25 km (OR = 1.9, 95% CI = 1.17 - 2.94). Birth weights, bad obstetric history, parity, gravidity, ANC follow up were found to have statistically significant association with the occurrence of maternal near- miss events. For instance, those mothers who gave birth to neonate with a birth weight of 4kg and more were three times more likely to develop life threading condition than their counter parts (OR = 3.3, 95% CI=1.9-5.7). Similarly, mothers who had at least one bad obstetric history were two times

more likely to face near miss event(s) than their counter parts (OR = 1.99, 95% = 1.1 -3.3). Prim gravid women have a threefold increased risk for developing preeclampsia (Duley, *et al*., 2002). It also occurs more frequently in the first pregnancy from a new partner; pre-existing hypertension; multiple pregnancy and mothers of over 35 years of age (Basso, *et al*., 2001, Dawson, *et al.,* 2002, and Wolf, *et al*., 2001). It is also established that preeclampsia is associated with family history [daughters of mothers with preeclampsia more affected] and obesity (Sungani, *et al.,* 1999, Thadhan, *et al.,* 1999, Buga, *et al.,* 1999, & Khedun, *et al*., 2000).

2.2. Classification of Hypertensive Disorder of Pregnancy

The National High Blood Pressure Education Program of the NHLBI classifies hypertensive disorders of pregnancy into following categories: gestational hypertension, chronic hypertension, preeclampsia, and preeclampsia superimposed on preexisting hypertension (NHBPEG, 2000)

2.2.1. Chronic Hypertension

Chronic hypertension, also called essential hypertension, is arterial hypertension of unidentified cause. Chronic hypertension is defined by elevated blood pressure that predates the pregnancy, and it is documented before 20 weeks gestation, or is present 12 weeks after delivery (NHBPEG, 2000). Studies have also established an increased risk of chronic hypertension in women, after years of pregnancy complicated with Pregnancy-Induced Hypertension or preeclampsia (Shammas & Maayah, 2000). Similarly, chronic hypertension is associated with increased risks of preeclampsia and abruption placentae, as well as increases in neonatal mortality and morbidity (McCowan, *et al.,* 1996*;* Sibai, 1996). Many individuals with chronic hypertension usually will have a positive family history of hypertension as well as its complications, including congestive heart failure, coronary artery disease, stroke, and renal dysfunction.

2.2.2. Preeclampsia Superimposed on Chronic Hypertension

Superimposed preeclampsia similar to chronic hypertension is associated with significantly increased risks of maternal and fetal death, fetal growth restriction, and placental abruption (August, *et al.*, 2004). The incidence of superimposed preeclampsia in chronic hypertension ranges from 4.7 to 18.4% for mild hypertension (DBP >90 mmHg) *(*Chesley, 1978; Sibai

& Anderson, 1986; Sibai *et al.,* 1983) up to 54% to 100% for severe hypertension (DBP >100 mmHg) (Rey & Couturier, 1994).

2.2.3. Pregnancy-Induced Hypertension

Pregnancy–Induced Hypertension (PIH) is defined as the occurrence of hypertension after 20 weeks of gestation in a woman without prior hypertension (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). When accompanied by proteinuria, the disorder is termed preeclampsia and when it is without significant proteinuria it is termed gestational or transient hypertension (NHBPEG, 2000).

2.2.4. Gestational Hypertension

Gestational Hypertension (GH) is defined as onset of hypertension, (systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg) after 20 weeks of gestation in the absence of significant proteinuria and is generally characterized by good maternal and foetal outcomes (Brown & Buddle, 1995; Davey & MacGillivray, 1988; Helewa, *et al.,* 1997). A rise in blood pressure of at least 25 mmHg systolic or 15 mmHg diastolic during pregnancy, even if the absolute blood pressure level was less than 140/90 mmHg, was also included in past definitions, (National High Blood Pressure Education Group, 1990). Usually in gestational hypertension the hypertension resolves to normal within 3 months postpartum (Brown & Buddle, 1995) although these women may be inclined to essential hypertension later in life. The distinction between preeclampsia and gestational hypertension is made by the presence and magnitude of proteinuria (Seely & Solomon, 2003).

2.2.5. Preeclampsia

Preeclampsia (PE) is an intriguing disease, whose etiology has remained obscure for centuries. Preeclampsia is usually defined as systolic blood pressure of at least 140 mmHg and/or diastolic blood pressure of at least 90 mmHg, accompanied by proteinuria first detected after 20 weeks gestation (Cnossen, *et al.,* 2006). Previously, the definition included a rise in blood pressure from preconception or first trimester values of more than 25–30 mmHg systolic and/or 15 mmHg diastolic (Seligman, 1987).

2.2.6. Eclampsia

Eclampsia which is a rare but more severe form of PIH is defined as seizures in a pregnant woman with preeclampsia in the absence of known or subsequently diagnosed convulsive disorder (Villar, *et al.,* 2006). Eclampsia is the occurrence of generalized convulsions during pregnancy, labour, or within seven days of delivery which is not caused by epilepsy or other convulsive disorders. Eclamptic seizures are relatively rare and occur in less than 1 % of women with preeclampsia (Witlin & Sibai, 1998). Beck and Menezes (1981) established that 7% of deaths due to eclampsia were more attributable to haemolysis, elevated liver enzymes, and low platelet count (HELLP syndrome), a modification of severe hypertension that results in multi organ failure. Normally this stage of the condition would not be reached unless if, the expectant woman has not taken her antenatal visits seriously or in the absence of antenatal visits or late reporting to hospitals.

2.3. Longitudinal Data Analysis

Longitudinal data are a series of measurements of the same event taken from the same individual repeatedly over time. The most unique characteristic of longitudinal data is the ability to directly study change. The primary goal of most longitudinal studies is to characterize the change in response over time and the factors that influence this change (Molenberghs and Verbeke, 2008).

2.3.1. Theory of the Linear Mixed Model

Many longitudinal studies are designed to investigate change over time in a characteristic which is measured repeatedly for each patient (Laird and Ware, 1982). Analyses of multiple observations measured on the same individual over time are different from observations measured on different people. Investigators gather repeated measures or longitudinal data in order to study change in a response variable over time as well as to relate these changes in explanatory variables over time (McCulloch, *et al*., 2008).

In addition, modeling the true correlation structure becomes significant in the presence of missing value and when the number of observations per subject is not large. There are two types of covariates in longitudinal studies in general. There are time invariant or baseline covariates (e.g. gender) and time varying covariates (e.g. weight). The Linear Mixed Model (LMM) has

become the most commonly used tool for analyzing continuous repeated measures data from a sample of individuals in agriculture, biomedical, economical, and social applications. Thus the term `individual' will have different interpretation or meaning for different areas of application. A special case of a linear mixed model is when there are no fixed effects leading to what is called a random effects model (McCulloch, *et al.,* 2008). For example the units may be patients in a longitudinal study where a measurement of biological laboratory markers such as SBP and DBP measures is taken at every month visits. Thus the patient is measured repeatedly giving rise to a cluster of observations from each patient.

The linear mixed-effects model fits the mean response as a combination of population characteristics (fixed-effects) assumed to be shared by all individuals and subject-specific effects (random-effects) that are unique to a particular individual (Nonhlanhla, 2009). By including random-effects in the model, linear mixed-effects models are able to explicitly distinguish between within-subject and between-subject sources of variation. With a linear mixed-effects model, it is not only possible to estimate parameters that describe how the mean responses change over time, but it is also possible to predict how an individual's response trajectories change over time. Mixed-effects models are highly attractive due to their ability to handle missing and unbalanced data reasonably well.

2.3.2. Joint Modeling Approaches

Joint modeling of multivariate outcomes in longitudinal data analysis has been given great deal of attention in the past decades in many studies on a longitudinal outcome during follow-up time. Several approaches for the joint modeling have been proposed by various researchers.

Yasin (2014) used joint random effect model to investigate the joint evolution and association of systolic and diastolic blood pressure measurements of hypertensive patients and identify the potential risk factors affecting the two end points in Jimma University Specialized hospital. Under this study each of the outcomes is analyzed separately using linear mixed model. Then, a joint model is considered to study the joint evolution and identify the potential risk factors affecting the two. For this study fitted statistics showed that the joint model resulted in better fit to the data than the separate models.

Horrocks and van den Heuvel (2009) used a joint longitudinal and GLM model, developed by Wang *et al.* (2000*),* to predict pregnancy in a group of women undergoing treatment for infertility, based on longitudinal adhesion measurements. Li, *et al* (2007) considered a semi-parametric joint model to study the association between bone status in per-menopausal women, being the primary endpoint, and longitudinal hormone levels.

Li (2013) used joint shared parameter model to analyze Stream flow prairies data. Stream flow is of vital importance in semi-arid regions from the perspective of both human and wildlife activities. Accurately predicting stream flow not only helps detect change due to land use or climate variation but also facilitates government regulation. He considered two stations in the same general spatial location. Generally, stream flow on the prairies is dominated by snowmelt and spring rains; there is likely some similarity in flow at the stations, and this depends on the soil and drainage features surrounding the stations. For joint model of stream flow, he proposed permits handling the seasonality by using smoothers and also accounts for the correlation rooted in common random effects.

John (2007*),*in Virginia Common wealth University, used Fels Longitudinal Study data to illustrate both separate and joint mixed-effects modeling strategies. Specifically, jointly modeled longitudinal measures of systolic (SBP) and diastolic (DBP) blood pressure during childhood (ages two to eighteen) were compared between participants who were diagnosed with at least three of the metabolic syndrome risk factors in adulthood (ages thirty to fifty-five) and those who were never diagnosed with any risk factors. On his analysis, he demonstrated the joint model is able to not only answer the same questions addressed as the separate model; it is also able to answer additional important questions about the association in the evolutions of the responses as well as the evolution of the associations. Furthermore, the additional information gained by incorporating information about the correlations between the responses was able to reduce the variability (standard errors) in both the fixed-effects estimates (e.g. differences in groups, effects of covariates) as well as the random-effects estimates.

Yemane (2013) used linear mixed effect model and joint mixed effect model to investigate the joint evolution of pulse rate and respiratory rate of cognitive heart failure patients and identify the potential risk factors affecting the two end points in Ayder referral Hospital of Mekelle University. Linear mixed effects model was fitted for the pulse rate and respiratory rate

outcomes. Furthermore, a joint mixed effects model was fitted for the two end points, and the potential risk factors affecting their joint evolution are identified. Finally, he recommended that, to identify associated effect fitting joint model is better.

Fieuws and Verbeke (2004*)* used a joint random-effects model to evaluate hearing performance at two different frequencies measured repeatedly over time on subjects. The authors specified a bivariate longitudinal model for continuous responses with correlated random intercepts and slopes. Error terms were assumed to be independent conditional on the correlated random effects. The results indicated a discrepancy between the observed data and relations implied by the joint model. However, relaxing the conditional independence assumption by allowing the error terms to be correlated, improved model fit and revealed that the discrepancy was due to inappropriate modeling of the error covariance structure.

Bowman and Manatunga (2005) made inferences about the joint process and discussed the prediction aspect, which is an important part of data application. In their thesis they presented a joint model for a continuous response and an associated event risk that is both conceptually and computationally. The joint model consists of two components: observed HDS scores and computed withdrawal profiles. They also presented a mean estimator for both components of this joint process and estimate covariance parameters, including covariance between the two components. Their model provides inferences about the effect of treatment on serial measures of the joint process and a framework to predict levels of depression from updated patient histories

Thiebaut, *et al*., (2002) used a random-effect bivariate model with correlated stochastic process to investigate the relationship between CD4 and beta-2-microglobulin, two important immunologic measurements in HIV/AIDS research. Another example of joint random-effect models used in psychometric studies is the work by MacCallum, *et al.,* (1997). These authors used a multivariate three-level model specified in a fully Bayesian way to study the relationship between accuracy (binary measurement) and speed of test takers (continuous measurement) on response items clustered within subjects who were nested within groups.

Chakraborty, *et al*., (2003) obtained estimates of the correlation between blood and semen HIV-1 RNA by using a joint random-effects model. Other examples with longitudinal studies can be

found in reference (MacCallum, *et al.,* 1997). All of these examples refer to situations where the number of different outcomes is relatively low. Although the model formulation can be done irrespective of the number of outcomes to be modeled jointly, standard fitting procedures, such as maximum likelihood estimation, is only feasible when the dimension is sufficiently low or if one is willing to make a priori strong assumptions about the association between the various outcomes. Williams (2001) used this approach to model simultaneously growth curves for systolic and diastolic blood pressure, height and BMI. However, such a modeling strategy is restricted to the combination of outcomes of the same type.

CHAPTER THREE

3. 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. It serves as a teaching and referral center for the Jimma area community and adjacent zones. 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.

3.2 Variables

3.2.1 Dependent Variables

The two outcome variables which have been given consideration under this study were; pregnancy induced systolic and diastolic blood pressure of pregnant woman in JUSH from January 2013 to January 2014.

3.2.2 Covariates

Seven covariates were used for either the separate or joint analyses. Two of these covariates are continuous 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). These covariates are described together with their values or codes in Table3.1

Table 3.1: Definition and codes of variable used in joint and separate analysis

S.N	Name	Definitions'	Values /code
1	Age	Age of pregnant women at time of visit	Year
2	Sex	Sex of the fetus	0= Female 1= Male
3	Dm	Diabetes mellitus	0=No 1=yes
4	G.age	Gestational age starting form LMP	In weeks
5	Para	Number of pregnancy greater than 28 weeks	Number
6	Gravida	Total number of pregnancy	Number
7	Fm	Family history of PIH/eclampsia	0= No 1= yes

Age of woman at baseline and gestational age are continuous covariates. Sex of the fetus used as categorical covariates with two levels: Male and Female. Diabetes mellitus used as categorical covariate to see its effect on pregnant woman's blood pressure. Family history of HIP/PE considered as a categorical variable to provide clear evidence of the pattern or evolution of certain diseases in a family of pregnant woman. Finally, Para and Gravida are the two discrete variables which define the number of pregnancy greater than 28 weeks and total number of pregnancy (including abortion and other) woman have before this pregnancy.

3.3 Statistical Methods of Data Analysis

3.3.1 Longitudinal Data Analysis

In longitudinal studies measurements are often collected on different types of outcomes for each subject. These may include several longitudinally measured responses (such as blood values relevant to the medical condition under study) and the time at which an event of particular interest occurs (e.g., death, development of a disease or dropout from the study). These outcomes are often separately analyzed; however, in many instances, a joint modeling approach is either required or may produce a better insight into the mechanisms that underlie the phenomenon under study. The term repeated measures is used to describe both the longitudinal and clustered data. One of the major objectives of statistical analysis is to address variations in the data. For longitudinal data, there are two sources of variations: within-subject variation; the variation in

the measurements within each subject, and between-subject variation; the variation in the data between different subjects. Modeling within-subject variation allows studying changes over time, while modeling between-subject variation allows understanding differences between subjects.

3.3.1.1. Exploratory Data Analysis

Data exploration is a very helpful tool in the selection of appropriate models to visualize the patterns of data relative to research interests. Analyses of longitudinal data compare profiles over time and, indeed, time might be viewed as the primary systematic effect to be investigated. The aim of this process is to understand the data structure and determine the relevant modeling approaches suitable for it. Thus, this study assessed the nature of the data by exploring individual profiles, the average evolution, and correlation structure.

3.3.1.1.1. Exploring the Individual Profile

Exploring the individual profile and plotting response with time was used to show whether there is a noticeable pattern which is common to almost all subjects. Individual profiles plot can also provide some information on within and between subject variability. Plotting observed response over time helps to identify general trends within subjects and change over time.

3.3.1.1.2 Exploring the Mean Structure

Examining mean structure of data was used to see how the mean profile changes over time, which is essential for specifying the functional form of the mean response of the model. To understand the possible relationships among means over time, graphical inspection were used by connecting the average values computed at each time point separately. Under this study unbalanced data was expected and unequally spaced interval, so loess smoothing was used. This gave us some insight how the mean profile evolves over time and help us to choose a fixed-effects structure for the linear mixed model.

3.3.1.2. 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,

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

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. The model is completed by specifying the covariance Structure, which can be homogeneous or heterogeneous. Commonly used homogeneous covariance structures are; identity, autoregressive, compound symmetry.

$$Ri = \delta^2 I_{ni}$$

For I_{ni} denoting the identity matrix of dimension n_i. This is so under the strong assumption that all repeated measurements are independent though repeated measurements within the same subject are seldom independent.

The second stage is a multivariate regression model of the form $\beta_i = K_iB + b_i$ which models variability between the subjects with respect to their subject specific regression coefficients, β_i, K_i is a (q × p) matrix of covariates, b_i is are assumed to be independent following a q − dimensional normal distribution with mean zero and general covariance structure D. Substituting for equation $\beta_i = K_iB + b_i$ in above equation, we get the linear mixed model given below.

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.

$Y_i= Z_i(K_i\beta + b_i) + \varepsilon_i = Z_iK_i\beta + Z_ib_i+ \varepsilon_i$ $\quad$ i=1,2 .....S

Where $Z_iK_i = X_i$ and the final model becomes

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

Where

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

$\boldsymbol{Z_i}$ −is a n × q matrix of known covariates

$\boldsymbol{X_i}$ −is a n× 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 $Z_i b_i$ incorporates the random effect part. The $Z_i b_i$ 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. The assumption $var(\varepsilon_i)=\sigma_{ni}^2 I$ can be relaxed by allowing to model non-constant variance or special within group correlation structures. The random effects, b_i, and the with group errors, ε_i are assumed to be independent for different groups and to be independent of each other for the same group. The columns of $\mathbf{Z}_i$ are usually a subset of the columns of $\mathbf{X_i}$.

$$Var(Y_i)=Var(Z_i b_i) + Var(\varepsilon_i)=Z_i G Z_i` + \Sigma_i \quad (2)$$

Random effect b_i is introduced for each subject to incorporate the correlation between the repeated measurements within subject. Since each subject shares the same random effects, the measurements within subject are correlated. Moreover the random effects facilitate subject specific inference.

3.3.1.2.1. Estimation of Fixed Effects

Maximum likelihood (ML) was used to estimate the parameters in this study. The maximum likelihood estimation method finds the parameter estimates that are most likely to occur given the data. The parameter estimates are derived by maximizing the likelihood function, which is a mathematical expression that describes the joint probability of obtaining the data expressed as a function of the parameter estimates (Verbeke, *et al.,*1998).

3.3.1.2.1.1. Maximum Likelihood Estimation

Assume a random sample of S observations is obtained from a linear mixed effect model as defined above, and then the likelihood of the model parameters, given the vector of S observations, is defined as:

$$L=l(\beta, \theta, Y_i)=\prod_{i=1}^{S}\left\{2\pi^{-1/2}|V|^{-\frac{1}{2}}\exp\left(-\frac{1}{2}(Y_i - X_i\beta)'V^{-1}(Y_i - X_i\beta)\right)\right\}$$

Where: - β is a vector of fixed-effects parameters and θ is a vector containing the variance parameters. Given its simplicity in comparison to the likelihood function, the log of the likelihood function is generally used in practice. Its maximized value coincides with that of the likelihood function. The log-likelihood of the model parameters, is defined as

$$\text{Log } L=l(\beta, \theta, Y_i)= -\frac{S}{2}\log(2\pi) - \frac{1}{2}\log|V| - \frac{1}{2}(Y_i - X_i\beta)'V^{-1}(Y_i - X_i\beta)$$

$$=K - \frac{1}{2}\log|V| - \frac{1}{2}(Y_i - X_i\beta)'V^{-1}(Y_i - X_i\beta)$$

Where, $V=Z_iGZ_i'+\Sigma_i$ and $K=-\frac{S}{2}\log(2\pi)$,

K is constant may be ignored in maximization process. The model parameters which maximize the log-likelihood may be determined by maximizing the log-likelihood given in above equation with respect to β and θ. One such method that may be used to maximize the log-likelihood function is the maximum likelihood (ML) method. The ML method first maximizes the log-likelihood with respect to the variance parameters, while treating the fixed-effects parameters, β, as constant. Upon determining the variance parameter estimates, the fixed-effects parameters are then determined by finding the values of β which maximize the log likelihood, while treating the variance parameters as constant. It is important to note, the maximum likelihood approach may produce variance parameters that are biased downwards since they are based on the assumption that the fixed-effects parameters are known (Brown and Prescot, 1999).

Thus, $\frac{\partial l}{\partial \beta}= -X_iV^{-1}X_i\beta+X_i'V^{-1}Y_i$

Then, the MLE of $\widehat{\beta}$ on combining all the information from all the N subjects equals

$\hat{\beta}=(\sum_{i=1}^{S} X_i{}'V^{-1}X_i)^{-1}\sum_{i=1}^{S} X_i{}'V^{-1}Y_i$

3.3.1.2.2. Model Assumption Checking Technique for Separate Linear Mixed Model

Normality assumption of linear mixed model has been assessed by looking at residual errors. It is assumed that the random effects are normally distributed and uncorrelated with the error term. Residual plots has been used to check normality of these effects and to identify any outlying effect categories. Examining the plot of the standardized residuals versus fitted values by any covariates of interest can give a better fitting (Molenberghs and Verbeke,2008).

The assumption of normality for the within-group error has been assessed with the normal probability plot of the residuals by covariates. Similarly, Normality of the random effects has been assessed using Normal Plot of each random effect.

3.4 Joint Model for Two Continuous Outcomes

Joint modeling has received massive attention in recent years, owing to researchers' desire for more insight into their data with a single statistical model. The reason to find this type of analysis is because commonly researchers simultaneously record several kinds of outcomes in their studies. The Univariate mixed effects model can be extended in a relatively straightforward fashion to define a multivariate mixed effects model for longitudinal data by appropriately defining the variance-covariance structure for the random effects. Joint modeling of two or more responses and appropriately accounting between subjects' sources of variability as well as within subject sources of variability in multivariate nature of the data would be more useful than several Univariate models.

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.

Let $y_{ij}{}^k$ represent the j^{th} observation from i^{th} subject, for the k^{th} 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 k^{th} response variable from the i^{th} subject the vector $Y_k = [y_1{}^k, y_2{}^k, \ldots Y_s{}^k,]'$ represents the N^k observation from the k^{th} 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.

Fieuws and Verbeke (2004) were interested in the questions of how the evolution of one outcome is related to the evolution of another outcome ('association of evolutions') and how the association between outcomes evolves over time ('evolution of the association') for longitudinal multivariate data. To get flexible solutions to such questions, they investigated a joint model using a random effects approach. In this approach, random effects were assumed for each outcome and by adopting a joint multivariate distribution for the random effects, the different outcomes were associated.

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).

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

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

Where $\mu^k(t)$ refers to the average evolution (of the k^{th} 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 k^{th} 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:

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

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 as;

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

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 ($\sigma_{12} \neq 0$).

3.4.1. General Approaches

Several methods are available in the literature for jointly modeling longitudinal data. Multivariate marginal models (Galecki, 1994; Molenberghs and Verbeke, 2006), the idea here is to directly specify the joint density $f(y^1, y^2)$ of (Y^1, Y^2).

Second strategy is the conditional models; direct specification of a joint distribution for (Y^1, Y^2) is avoided by factorizing the density in to a product of a marginal and a conditional density.

$$f(y^1,y^2)= \int f(y^1|y^2) f(y^2) dy^2 = = \int f(y^2|y^1) f(y^1) \; dy^1$$

A third strategy is the shared-parameters modeling approach as described earlier, random-effects can be introduced into a model to account for associations in the longitudinal measures. This same idea can be extended to account for additional associations in the multivariate longitudinal data. For the shared-parameters model, define β as a vector of random-effects, common to the model for Y^1 and to model Y^2, and assume independences of both outcomes, conditionally on β. The joint density of (Y^1, Y^2), is then obtained from

$$f(y^1,y_2) = \int f(y^1, y^2|\boldsymbol{B})\, f(\boldsymbol{\beta})\, d\boldsymbol{\beta} = \int f(y^1, y^2|\boldsymbol{B})\, f(\boldsymbol{\beta})\, d\boldsymbol{\beta}$$

Here $f(\boldsymbol{\beta})$ denotes the marginal density of the random effects. The random-effects, **β** is a "shared-parameter" that induces a correlation between $Y^1$and Y^2, through their joint dependence of β .The $Y^1$and Y^2 are conditionally independent given the random-effects β is interpreted as a belief that a common set of underlying characteristics of the individual governs both outcome processes. An advantage of this type of model is that and $Y^1$and Y^2do not needs to be of the same type (e.g. Y^1 could be continuous responses and Y^2 could be binary responses). Another advantage is that the parameters in the joint shared-parameters model have the same interpretations as they do in each of the corresponding "Univariate" models.

3.4.2. Special Case of Variance Covariance Matrix

Special case can now be obtained by making specific assumptions for the variance covariance matrix G. Two such specific variance-covariance structures are described in the following subsections, a complete independence structure and a shared-parameters structure.

Complete Independence: The two response variable could be taken to be completely independent at any point in time, thereby imposing the following structure for G (Howard, 2006):

$$G=\begin{bmatrix} \sigma_{a1}^2 & \sigma_{a1b1} & 0 & 0 \\ \sigma_{a1b1} & \sigma_{b1}^2 & 0 & 0 \\ 0 & 0 & \sigma_{a2}^2 & \sigma_{a2b2} \\ 0 & 0 & \sigma_{b2a2} & \sigma_{b2}^2 \end{bmatrix} \quad (5)$$

Within a response variable, the random intercept and slope induce within-subject correlations in the repeated measures over time, while assuming independence between subjects. Moreover, this model assumes that the two responses are completely independent. The results for the model would be identical, in theory, to fitting two separate random-effect models.

Shared-Parameters: Now that a complete independence structure has been considered for the G matrix one may consider the other end of the spectrum where the two response variables could be taken to be completely dependent. In this case, the two responses essentially "share" the same set of random effect parameters (intercept and slope) (Howard, 2006). When two parameters are

completely dependent, the correlation between them is equal to one. This occurs when the covariance between the parameters is equal to the square root of the product of their respective variances. Most notations, however, define the model with a 2×1 vector of random effects, such as:

$$b_i=\begin{bmatrix}ai\\bi\end{bmatrix}\sim N(0,G), \text{ with } G=\begin{bmatrix}\sigma_a^2 & \sigma_{ba}\\ \sigma_{ab} & \sigma_b^2\end{bmatrix} \quad (6)$$

Clearly, the aforementioned structure imposes strong assumptions on the relationship between the two response variables. It is very unlikely that the two responses would exhibit complete dependence in the association between the random slopes and between the random intercepts. One advantage of this model, when the assumption is tenable, is that it drastically reduces the number of random effects that must be estimated when the number of response variables is large. For models with a large number of response variables, estimation would likely be impossible if the shared-parameters (or alternative approach) were not used.

3.4.3. Association of the Evolution (AOE)

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 ("association of the evolutions"). Joint evolution is the gradual change (develop) of biological correlated response variable from earlier forms to new stage in a changing situation over time. By definition, the correlation between the evolutions for the two random slopes is given by:

$$rE=\frac{Cov(b_{1,}b_2)}{\sqrt{Var(b_1)}*Var(b_2)}=\frac{\sigma_{b1,b2}}{\sqrt{\sigma_{b_1}^2}*\sigma_{b_2}^2} \quad (7)$$

3.4.4. Evolution of the Association (EOA)

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):

$$r_m(t)=\frac{Cov(Y_j{}^1(t),Y_j{}^2(t))}{\sqrt{Var(Y_j{}^1(t))}\sqrt{Var(,Y_j{}^2(t))}}$$

$$=\frac{\sigma_{a1,a2}+t\sigma_{a1,b2}+t\sigma_{a2,b1}+t^2\sigma_{b1,b2}}{\sqrt{\sigma^2{}_{a1}+2t\sigma_{a1,b1}+t^2\sigma^2{}_{b1}+\sigma_1{}^2}\sqrt{\sigma^2{}_{a2}+2t\sigma_{a2,b2}+t^2\sigma^2{}_{b2}+\sigma^2{}_2}} \quad (8)$$

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

$$=\frac{\sigma_{a1,a2}+t\sigma_{a1,b2}+t\sigma_{a2,b1}+t^2\sigma_{b1,b2}+\sigma_{12}}{\sqrt{\sigma^2{}_{a1}+2t\sigma_{a1,b1}+t^2\sigma^2{}_{b1}+\sigma_1{}^2}\sqrt{\sigma^2{}_{a2}+2t\sigma_{a2,b2}+t^2\sigma^2{}_{b2}+\sigma^2{}_2}}$$

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 to

$$r_m(t)=\frac{\delta_{a1a2}+\sigma_{12}}{\sqrt{\delta^2{}_{a1}+\delta^2{}_1}\ \sqrt{\delta^2{}_{a2}+\delta^2{}_2}}$$

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. It may also be noted that as t increases the marginal correlation converges to the correlation between the random slopes, while the variance-covariance parameters of the random effects determine the shape of the marginal correlation function (Fieuws, et al. 2004).

3.4.5. Joint Model Estimation

In the particular context of random-effects models, so-called adaptive quadrature rules can be used (Pinheiro and Bates, 2000), were the numerical integration is centered on the estimates of the random effects, and the number of quadrature points is then selected in terms of the desired accuracy.

To illustrate the main ideas, we consider Gaussian and adaptive Gaussian quadrature, designed for the approximation of integrals of the form

$$\int f(z)\phi(z)dz \qquad (9)$$

For a known function *f(z)* and for ϕ(z) the density of the multivariate standard normal distribution. Therefore first standardize the random effects such that they get the identity covariance matrix. Then, the likelihood contribution for subject i equals

$f_i(y_i|\beta,G,\phi) = \int \prod_{i=1}^{s} f_i(y_i|b_i,\beta,\phi) f(b_i|G)db_i$ where,

- b_i is $q_{\times 1}$ dimensional vector of unknown random effects, $b_i \sim N(0, G)$
- β is a vector of fixed-effects parameters and ϕ is a vector containing the variance parameters

3.4.5.1. Correlation Structures

In longitudinal data analysis, when subjects are followed over time, there is a natural ordering of the data for each subject. Correlation structure are used to model dependence among observations, in mixed-effect model, it is used to model dependency among the within-group errors (Pinheiro, and Bates, 2002). The correlation between two within-group errors ε_{ij} and ε_{ij}' is assumed to depend on some distance between them, and ρ is a vector of correlation parameters. Olkin and Tate (1993) described the serial correlation structures in detail of the linear mixed-effects models; serial correlation structures are used to model dependency in the data observed sequentially over time and indexed by a one dimensional time vector. The general serial correlation model is defined as

Cor (ε_{ij}, $\varepsilon_{ij'}$) =h(ρ), Where h(.)-indicates autocorrelation function

Some of the most common serial correlation structures used in practices includes:

Compound symmetry:-It is the simplest serial correlation structure, which assumes equal correlation among all within-group errors of same subject. The corresponding correlation model is

$Cor(\varepsilon_{ij}, \varepsilon_{ij}') = \rho$

While the compound symmetry correlation model tends to be too simplistic for practical application

General (Unstructured):-The general correlation structure represents the other extreme in complexity to the compound symmetry structure. Each correlation is shown by a different parameter, the correlation function is $h(\rho) = \rho_k$; k = 1,2,. .. .While the general correlation model tends to over parameterized model. It is useful for few observations per subject that leads to precise correlation with observations.

Autoregressive (AR):-Box *et al*., (1994) described the family of correlation structure which includes different classes of linear stationary models: autoregressive models, moving average models, and mixture of autoregressive-moving average models. Autoregressive models express the current observation as a linear function of previous observation plus a homoscadastic noise terms. Let ε_t indexes an observation taken at time t, μ_t indexes a noise term with $E[\mu_t] = 0$, and assumed independent of the previous observations.

$$\varepsilon_t = \phi_1\varepsilon_{t-1} + \ldots + \phi_p\varepsilon_{t-p} + \mu_t \quad |\phi| < 1$$

p is called the order of the autoregressive model, which is denoted by AR(p). There are p correlation parameters in an AR (p) model, given by $\phi = (\phi_1, \phi_2, \ldots, \phi_p)$. The AR (1) model is the simplest and one of most useful autoregressive model. Its correlation function is

$$h(k; \phi) = \phi^k \qquad k = 0,1,\ldots\ldots \text{, where, k-distance between time point}$$

In the First-order autoregressive structure, it is assumed that the correlation between time points decrease as the distances in time increase, this implies that the number of time intervals between pairs of observation increases, the correlation decreases and approaches to zero. Measurements that are closer in time have higher correlation than measurements with longer time between

them. This structure will often be more realistic than the compound symmetry and has the same number of parameters which often makes it more preferable.

Variable selection technique:- To select significant variables, first the main effect and main effect by time interaction were incorporated to the initial candidate model. After that, avoid non significant variables one by one starting from the most non significant terms which is called backward variable selection technique (Pinheiro and Bates, 2002) were used.

3.4.6. Model Comparisons

Model selection technique is one of the most frequently encountered problems in data analysis. In most observational epidemiological studies, investigators frequently attempt to construct the most desirable statistical model using the popular methods of forward, backward, and stepwise regression (Pinheiro and Bates, 2002). Of course knowledge of the subject matter plays an important role in model selection, but if based strictly on the data, model selection is often carried out using one of the automated procedures built into the software, of which the most popular method is perhaps stepwise model selection. These methods pose the problem of the arbitrary selection of the significance levels in allowing a variable to enter into or to be dropped from the model during the selection process (Diggle, *et al*., 1994). There is also the problem of multiple testing that comes with fitting and refitting the model. The issue is made more complicated in the case of repeated or longitudinal data where selecting the best model means not only to select the best mean structure but also the most optimal variance covariance structure for model selection criteria, like AIC, BIC and likelihood ratio test were used (Shah, *et al.,*1997). In this thesis the most commonly known model selection criteria Akaike Information Criterion (AIC) (Sakamoto, 1986), the Bayesian Information Criterion (BIC) (Laird and Ware, 1982) and Log-likelihood ratio test were used.

$$AIC = -2\log L + 2p \qquad BIC = -2\log L + P*\log(N),$$

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.

CHAPTER FOUR

4. 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. A measurement taken after 20 weeks of gestation were used for both outcomes variables. But, those women who develop hypertension before 20 weeks of gestation and women who have chronic hypertension were not included under this study. In addition, those who have admitted to maternity ward for different hypertension complication were excluded.

The age of mother with gestation hypertension range from15 to 35 but, average age equals to 24.65. Most of mother under hypertension were less than 25 years old. Maximum number of the Gravida under this study is eight. Women's having higher Gravida numbers are older than mothers of smaller Gravida number. Mode of Gravida and Para are equal but greater variability exists in Gravida number.

Table 4.0 Summary statistics for covariates

Variable	Min	Mode	Average	Maximum	StDev
Age	15	20	24.65	35	4.65
Gestational age	20	24	25	36	3.26
Para	0	2	1.68	6	1.27
Gravida	1	2	2.85	8	1.46

Out of these hypertensive woman 26 (26.53%) have family history of hypertensive. only about 11(11.34) % of them have diabetes mellitus and about 54(55.10%) have give birth of male neonates. Average of gestational systolic and diastolic blood pressure of woman, who gives birth of male neonate, is greater than that of female neonate. There is a greater variability of these outcomes between individual women as result of gender difference in fetus. (Table 4.1 below)

Mean systolic and diastolic blood pressure of diabetic woman is higher than that of none diabetic. Mean of GSBP and GDBP for diabetic woman is 144.1705(SD=15.32926) mmHg and 88.50388(SD=7.487619) mmHg respectively, with standard deviation in the bracket. But for none diabetic woman is 142.7211(SD=16.69566) mmHg and 86.54474(SD=8.283283) mmHg respectively for systolic and diastolic gestational blood pressure, which is less than from the above. In similar, woman having hypertensive family history are more exposed to gestational hypertensions. Those woman have family history of PIH/PE have 146.7682(SD=14.188) mmHg mean SBP but, those don't have family history of PIH/PE have 141.5363(SD=16.97114) mmHg.

Around sixty percent (60%) of mother under this study were less than 25 years old and 25% were less than 20 years. However, only 8.2% of woman had age greater than 30 years. Besides, average systolic and diastolic blood pressure with their standard deviation for age of mothers less than 20 years is142.9313(SD=17.29259) and 85.54198 (SD=8.280895) respectively .

Table 4.1 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	Yes	22.44	144.1705(15.32926)	88.50388(7.487619)
	mellitus	No	77.56	142.7211(16.69566)	86.54474(8.283283)
		Total	100%		
3	Family history	Yes	26.53	146.7682(14.188)	88.38411(7.323807)
	PIH/PE	No	74.47	141.5363(16.97114)	86.47486(8.387879)
		Total	100%		
		≤ 20	25.77	142.9313(17.29259)	85.54198 (8.280895)
4	Age of mother	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. Separate analysis of gestational systolic and diastolic blood pressure

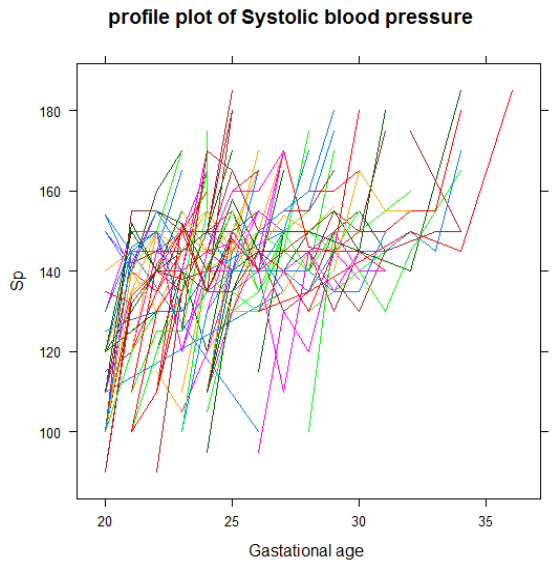
The two jointly measured outcome analyzed separately by using simple linear regression. Next, linear mixed model fitted to specify the true model and to determine the fixed and random effect to model the response variables.

4.2.1. Data exploratory analysis

Exploratory analysis comprises techniques to visualize patterns in the data. Data analysis begins by making displays that expose patterns relevant to the scientific question. Below very important tools were used to visualize patterns of systolic and diastolic blood pressure over gestational age.

4.2.2. 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. This means that two measures on the same individuals are correlated simply because they have the subject effect in common. Also, for a given woman, consecutive measures are more highly correlated than measures several gestational weeks apart, although this is not readily apparent from the profile plots. As show in figure below, the variability of GSBP and GDBP is higher especially at beginning of gestational age. In addition to individual variability, there is a considerable observed difference within subject. Figure (4a and 4b) below confirms that within subject and between subject difference should be given care during model fitting.



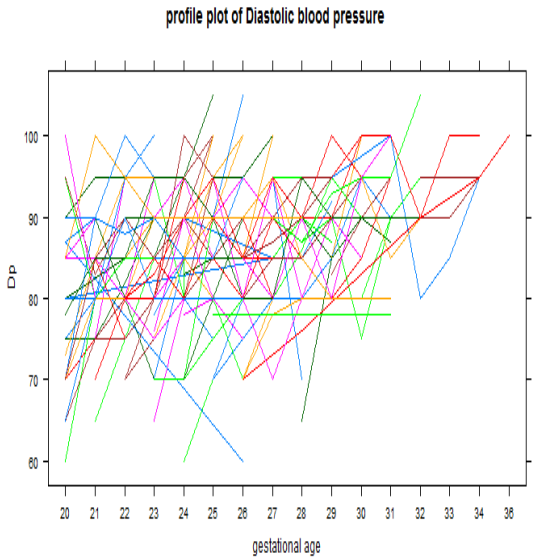
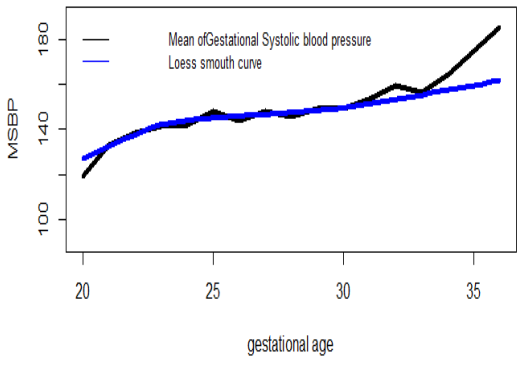


Figure 4.0a individual profile plot of GSBP **Figure 4.0b** individual profile plot of GDBP

4.2.3 Mean profile plot of GSBP and GDBP of pregnant woman

The mean effect profile plot of the longitudinal measured gestational SBD and DBP of pregnant woman shows the rate of change of change over the gestational age is somewhat linear. So, linear gestational age random effect should be included in the model. The rate of increment in GSBP and GDBP increases at higher rate up to the delivery or admission to maternity ward for treatment. The rates of change of changes increase step by step or from week to week. Mean profile plots are given below by using loess smooth curve. However, the variability of consecutive measurement is decreasing over gestational age, this is because, as length of pregnancy increases the difference between consecutive measurements decreases.



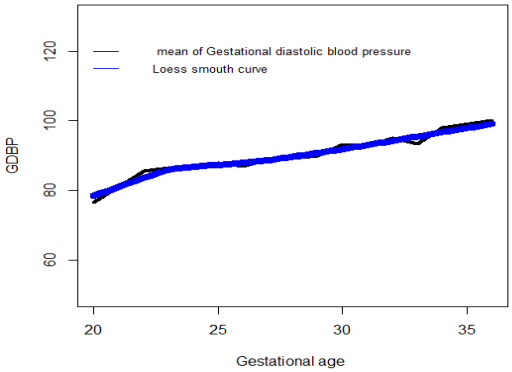
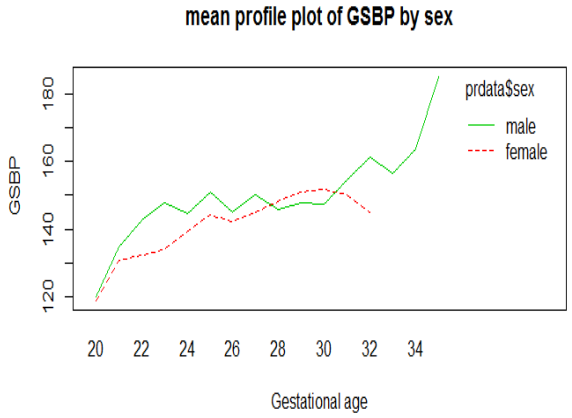


Figure 4.1a Mean profile plot for GSBP **Figure 4.1b** Mean profile plot for GDBP

Now, mean profile plots for different covariates and categorical variables are given below. Even if, Mean profile Plot for discrete and continuous variable are not advisable, here we have plotted mean profile for Gravida and Para to show the effect of primigravidae and null parity under pregnancy induced hypertension.

4.2.4 Mean profile plot by using covariate variables

Different covariate plot were show in figure below. The plot shows that, there is mean difference in profile plot of sex, number of Para, number of Gravida and family history of gestational hypertension.



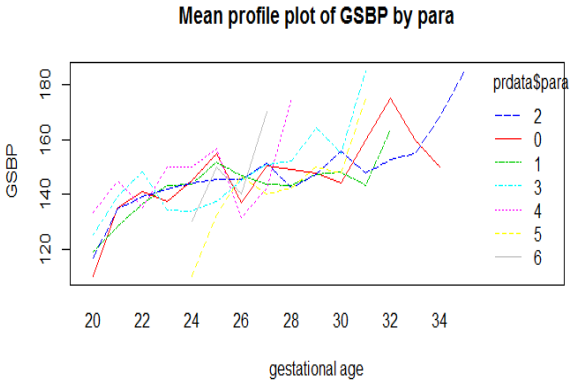


Figure4.2a Mean profile plot of GSBP by sex of fetus

Figure 4.2b Mean profile plot of GSBP by Para

Mean profile plot of gender given above shows, there is mean difference for GSBP between pregnant woman who gave birth of male and female neonate over time. A woman who gave birth of male neonate has higher GSBP as compared with that of female neonate. The right plot shows that woman with less number of Para have higher MSBP compared with that of large number of Para. However, both plots confirm that, as length of gestational age increase the mean systolic blood pressure is increasing in all categories of variables. Similar plots are given for mean profile of GDBP by different covariate in Appendix **II** (Figure 4.2f up to 4.2g).

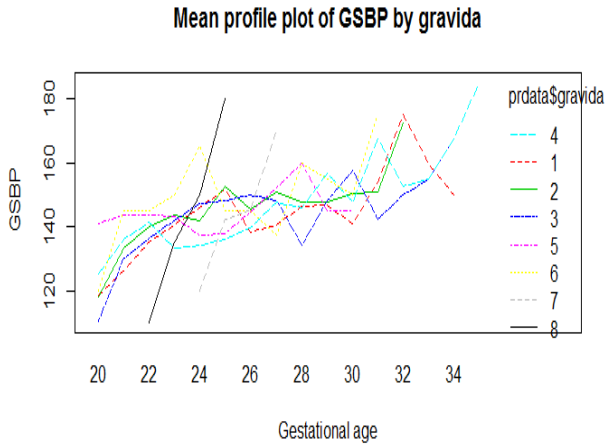


Figure 4.2c The mean profile plot of GSBP by Gravida

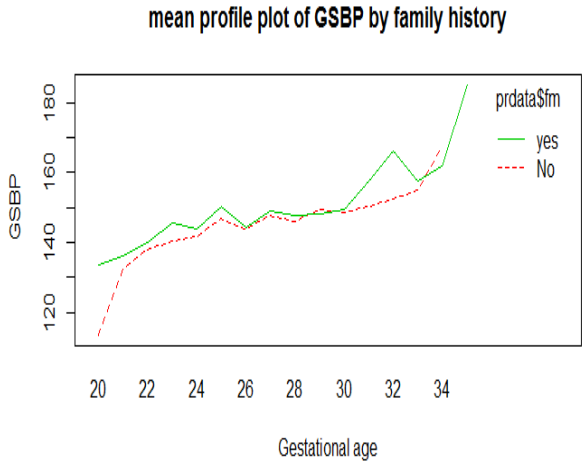


Figure 4.2d The mean profile plot of GSBP by FM

GSBP is increasing over time for both covariates. There is a great difference between categories of Gravida. Woman of family history of gestational hypertension/PE seems to have greater blood pressure. That is, the green (upper) line in the left figure indicates family history of PIH/PE woman had higher MGSBP than her counterpart over time.

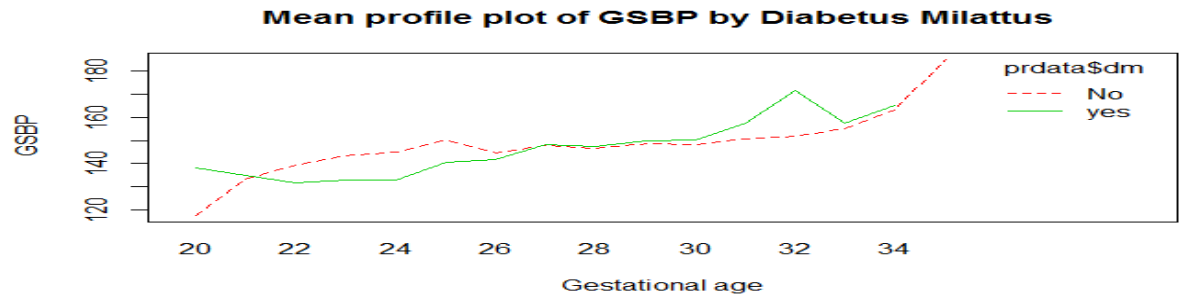


Figure 4.2e Mean profile plot of SBP by diabetes mellitus

The plot shows that diabetes mellitus have no much effect on longitudinally measured pregnancy induced Systolic blood pressure. There is an overlap on the two lines but, profile plot for both increasing up to the end.

4.3 Linear regression model for Gestational systolic blood pressure

Simple linear regression model using base line information without considering any random effect and neglecting any correlation between and within subject were fitted. Both Models without interaction and with interaction terms were fitted and compared below.

Table 4.2 Analysis of Variance for linear regression model

Model	Df	Res.Df	RSS	Sum of sq	F	Pr(>F)
No interaction	501	501	104783			
With interaction	496	5	103887	895.81	0.8554	0.511

From table, the first model or simple linear regression without interaction term is the best to fit the data or there is no difference between the two models. General model with interaction is given by:

$GSBP_{ij} = \beta_{10} + \beta_{11}sexi + \beta_{12}agei + \beta_{13}parai + \beta_{14}gravidai + \beta_{15}G.ageij + \beta_{16}fmi +$

$\beta_{17}dm + (\beta_{18}sexi + \beta_{19}agei + \beta_{110}parai + \beta_{111}gravidaij +$

$\beta_{112}G.ageij + \beta_{113}fmi + \beta_{114}dmi) * G.ageij + \varepsilon_{ij}$, where

$GSBP_{ij}$ - is gestational systolic blood pressure for i^{th} subject at j^{th} gestational age

i - is subject, i=1, 2, 3.....97 and **j-** is gestational age in week, j=20, 21, 22.....$n_{ij,}$

β_{10}, β_{11}, β_{12} .....**β_{113}** are fixed effect coefficients.

sex_i - is the sex of neonate of i^{th} mother **age_i** - is the age of i^{th} mother.

$para_i$- number of Para for i^{th} mother **$Gravida_i$ -** the number of Gravida for i^{th} mother.

$G.age_{ij}$ - is j^{th} gestational age for i^{th} mother **fm_i** - family history of hypertension for i^{th} mother.

dm_i- diagnosis of diabetes mellitus for i^{th} mother **ε_{ij}**- is an error of measurement

From the above table 4.2, model without interaction term is best fitting the data. Output of selected model was given in appendix-**I** (Table 4.3). From the table we observe that most of the main effects are significant at 0.05 levels of significance. But, age of mother, number of Para and number of Gravida are not significant at 0.05 levels. Fixed mean effect of Gestational age, sex and family history of gestational hypertension and diabetes Miletus are significant at 0.05 levels of significant.

4.4 Linear mixed model for Gestational systolic blood pressure

4.4.1 Selection of random effect for Gestational systolic blood pressure

The random effect of the pregnancy induced systolic and diastolic blood pressure is the rate that shows, how the rate of change of change in blood pressure over gestational age. From the mean profile plot given above, there is linear relationship between MGSBP and MGDBP with gestational age in week. The random plot of individual slope also confirms the presence of between group differences. So, random intercept and random slope should be included in the model.

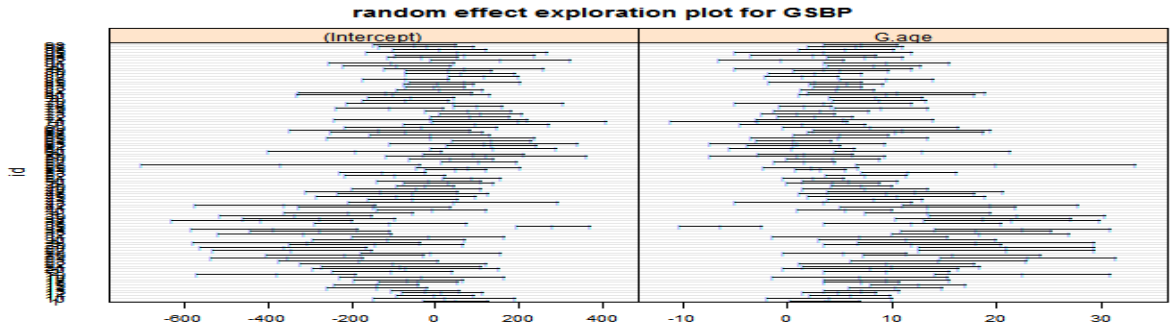


Figure4.3 Random effect exploration for GSBP

For the purpose of more confirmation, six different models have been fit with different random effects. Comparison and selection of random effect have been made by using their AIC information. Consistent conclusion is made to select random effect by using smaller values of AIC. Summary of models are given below

Table 4.4 Selection of appropriate random effect for systolic blood pressure

S. No	Model	Df	AIC	BIC
1	Random intercept w't interaction term in fixed	10	4166.8	4209.1
2	intercept and slope w't interaction term in fixed	12	4151.9	4202.7
3	Random intercept & interaction in fixed	16	4166.1	4233.8
4	intercept & slope interaction term in fixed	**18**	**4148.6**	**4224.8**
5	Random intercept for log(G.age)	21	4154.6	4243.5
6	Random inter. and slope with log(G.age)	16	4177.5	4245.2

From the above table, model with random intercept and random slope with an interaction term in the fixed part is best fitting of GSBP. This model has smaller AIC values as compared with the other. Quadratic slope and log(G.age) didn't improve model fitting and should not be included in the model.

4.4.2. Correlation structure for GSBP

An important difficulty in using longitudinal measurements of the change in response is the need to use models that correctly reflect the variability and dependence between the measurements. As noted above, there are often two aspects of covariance structure in the errors. First, two response measures on the same subject are likely to be more nearly the same than two measures on different subjects. Thus, measures on the same subject are usually positively correlated simply because they share common effects from that subject. Second, two response measures made close in time on the same subject are likely to be more highly correlated than two measures made far apart in time. Different correlation structures have been compared, that the mean and variance covariance structures of the longitudinal measurements of the change in systolic blood pressure can be described by relatively simple models that seem to fit the data well.

Table 4.5 Correlation structure for GSBP

Model	Correlation str.	No. parameter	AIC	LogLik	p-value
1	Symmetric	14	4146.461	-2059.230	
2	ARIMA(q=2)	16	4130.993	-2049.497	0.0001
3	AR(1)	15	**4129.266**	**-2049.633**	**0.6014**
4	Compsymm	13	4161.342	-2067.671	<.0001
5	ARMA(1,1)	16	4130.684	-2049.342	<.0001

**symmetric variance structure * ARIMA -autoregressive moving average of two (p=0, q=2) *AR $_{(1)}$-autoregressive of order one (q=0, p=1) *ARMA- autoregressive of order two (q=1,p=1) *Copmsymm- compound symmetric*

The observed AIC values indicate that three models present a similar fit to the data. Formally speaking, the lowest AIC value (4129.266), indicating the best fit, is obtained for Model 3. However, the AIC value (4130.993 and 4130.684) for Model 2 and 5 are not much different. In addition, it has less number of parameters to be estimated. From the table autoregressive (1) is

the best correlation structure for systolic blood pressure. An autoregressive (AR-1) structure, specified by **type=AR**, allows the correlations to diminish over time (gestational age).

$Corr(yij,yij')=\rho^{|tij-tij'|}$, Where, t_{ij} and $t_{ij'}$ are the observation times (gestational ages) for y_{ij} and $y_{ij'}$. The autoregressive structures express the intra-subject correlations in terms of a single parameter ρ. So, this makes the autoregressive correlation structure is the best correlation structure. Autocorrelation plot given in appendix **II** (Figure 4.4) shows the correlation decrease until lag three and start to increase at lag four.This indicates that, the correlation of measurement decreases as time increases up to some time and finally approaches zero. Because, the scale of increment for systolic blood pressure at j^{th} and $(j+1)^{th}$ time are completely different. General form of selected model is given by:

$$GSBP_{ij}= \beta_{10}+\beta_{11}sexi+\beta_{12}agei+\beta_{13}parai+ \beta_{14}gravidai+ \beta_{15}G.ageij+ \beta_{16}fmi + \beta_{17}dm+$$
$$(\beta_{18}sexi+ \beta_{19}agei+ \beta_{110}parai+\beta_{111}gravidaij + \beta_{112}fmi+ \beta_{113}dmi)*G.ageij + b_{i1}(t)+\varepsilon_{ij}$$

Where: $b_{i1}(t)= (b_{01}+ b_{11}G.agei)$, which is random effect and assumed $b_{1i}(t)\sim N(0,G)$ and (β_{10}, β_{11}, β_{12}----- β_{113}) are fixed effect that describe the mean evolution of gestational systolic blood pressure in the fixed part. But, random effect b_{01} shows how the average of i^{th} subject deviate from overall average and the random effect (b_{i1}) shows the rate of change of change in average for the i^{th} subject.

From the output given in appendix **I** (table 4.5), we observe that all main effect except diabetes mellitus and Para are significant at 0.05 levels of significance. But, Para is significant at 0.1 levels of significance. The interaction term Gestational age by sex, Gestational age by dm, Gestational age by fm, and Gestational age by Para are not significant at 0.05 levels of significance. But, Gestational age by sex and Gestational age by family history are significant at 0.1 level of significant. The rest main effect and interaction terms are significant at 0.05 levels of significance.

Now, there are two main effect and three interaction terms which are insignificant in the model. Hence, these insignificant terms should be removed from the model step by step starting from the most non significant term. Removing diabetes Miletus leads AIC to decrease from 4148.607 to 4146.609. In similar, removing Para, Para by Gestational age and sex by gestational age step by step leads AIC to drop to 4146.461. Similarly, BIC drops from 4218.561 to 4205.75 until all

covariates in the model become significant. P-values at the left shows, all models give the same information about the data. Finally, removing sex by Gestational age interaction terms made the rest variable in the model significant and there are no other variables to be removed from model. Besides, also have less parameter to be estimated. Summaries are given in appendix **I** table (4.6).

Thus, the final reduced linear mixed model for gestational systolic blood pressure is given by:

$GSBP_{ij}= \beta_{10}+ \beta_{11}*sexmale+ \beta_{12}*agei+ \beta_{14}*gravidai+ \beta_{15}*G.ageij$

$+\beta_{16}*fmyes+(\beta_{19}*agei+\beta_{111}*gravidaij+\beta_{11}*fmyes+\beta_{113}*dmyes_i)*G.ageij$

$+ b_{o1}+b_{11}*G.age+\varepsilon_{ij}$, where, $b_{i1}(t)= (b_{01}+ b_{11}G.age) \sim N(0,G)$

Table 4.7 ML estimated parameter of GSBP for separate model

Coefficient	Estimate	Std. Error	DF	t-value	p-value
(Intercept)	132.32867	62.47527	405	-2.118097	0.0348*
sexmale	6.02033	2.67970	94	2.246648	0.0270*
fmyes	42.54721	21.56741	405	1.972755	0.0492*
G.age	11.43068	2.61176	405	4.376624	0.0000*
gravida	-25.93943	10.36790	405	-2.501899	0.0127*
age	8.16295	3.21590	94	2.538312	0.0128*
fmyes:G.age	-1.61511	0.90203	405	-1.790525	0.0741.
G.age:dmyes	-0.30026	0.13941	405	-2.153796	0.0318*
G.age:gravida	1.10219	0.43571	405	2.529609	0.0118*
G.age:age	-0.34958	0.13536	405	-2.582554	0.0102*

**- Significant covariate or factors at 0.05 levels of significance*

The output given above depicts that, the intercept is 132.3 with standard error of 62.5mmHG, which show there is a greater variability at first follow up (beginning of gestational hypertension). The sex of the neonate has significant effect on the gestational blood pressure of the mother. Having male neonate, made to increase the systolic blood pressure of the mother by more than six fold compared with the female neonate. Having family history of PIH/ pre-eclampsia increases the chance of developing gestational hypertension. Woman of hypertensive

family gestational blood pressure is 42.5mmHg greater than that of no family history of gestational hypertension. In simple term, hypertensive family history women's gestational blood pressure is greater than none family history of gestational hypertension woman. Gestational age has significant effect on systolic blood pressure of pregnant woman. As gestational age (in week) increase by one, systolic blood pressure of the pregnant mother increase by 11.4mmHG with standard deviation of 2.6mmHG. In general, as gestational age increase and mother approaches to give birth, her blood pressure increases linearly with gestational age, if she has no internal and external complication. As the age of the mother increases by one, her gestational blood pressure increases by multiple of 8.2 mmHG. But, as number of Gravida increases, the blood pressure of mother decreases. Mother of primigravidae (primiparas) gestational blood pressure is greater than that of multiparas (multigravida) mothers blood pressure. When the number of Gravida increases by one, gestational SBP of mother decreases by 25.9 mmHG, fixing other covariates and factors. But, there is greater variability's (10.36). The interaction of family history hypertension woman by gestational age and diabetes mellitus by gestational age decrease GSBP of the mother by 1.6 and 0.3 respectively. However, the interaction of gestational by Gravida increases GSBP of mother by 1.1. That is, woman of higher number of Gravida has higher GSBP compared with less number of Gravida over gestational age. Lesser is relative term, it excludes primigravidae or primiparas. The interaction term gestational age by age of mother has negative effect on her GSBP. Meaning that, as gestational age increase the MGSBP of older aged mother is less than younger mother under this study (most of mother have age less than 25).

4.5 Linear regression for Diastolic blood pressure

Simple linear regression model without considering any random effect and neglecting any correlation between and within subject have been fitted. Model without interaction and with interaction are fitted and compared.

Table 4.8 Anova for linear regression model for diastolic blood pressure

Model	Res.Df	RSS	Df	Sum ofSq	F	Pr(>F)
Without inter.	501	104783				
With interaction	496	103887	5	895.81	0.8469	0.5169

The anova table, clearly shows that including the interaction term does not significantly affect the fit of the model (F=0.8469, 0.5169) or interaction term doesn't improve model fitting. Therefore, we may conclude that the most parsimonious model is model one. Once, we certain of the interaction terms are not important to the model, we fit linear regression model without interaction terms. Suppose that $GDBP_{ij}$ is gestational diastolic blood pressure of the i^{th} pregnant woman at j^{th} gestational age. Now, general simple linear model for diastolic blood pressure is:

$$GDBP_{ij}= \beta_{20}+\beta_{21}sexi+\beta_{22}agei+\beta_{23}parai+ \beta_{24}gravidai+ \beta_{25}G.ageij+ \beta_{26}fmi$$

$$+ \beta_{27}dm+(\beta_{28}sexi+ \beta_{29}agei+ \beta_{210}parai+ \beta_{211}gravidaij+ \beta_{212}fmi$$

$$+ \beta_{213}dmi)*G.ageij + \varepsilon_{ij} \quad ,\text{Where, } i=1, 2 \ldots 97 \quad \text{and} \quad j= 20, 21,22 \ldots\ldots n_i$$

In output given at appendix **I** (table 4.10) model fitted including interaction, only the three main effects (gestational age, sex and family history of hypertension) are significant at 0.05 levels of significance. But, in case of interaction, only gestational age by sex is significant at 0.1 levels of significant. After removing insignificant terms step by step, the final linear regression model for gestational diastolic blood pressure is given below.

$$GDBP_{ij}= \beta_{20}+\beta_{21}sexmale+ \beta_{25}G.ageij+ \beta_{26}fmyes+ \beta_{27}dmyes+\beta_{28}sexmale*G.ageij + \varepsilon_{ij}$$

From the output sex, Gestational age, family history of hypertension and diabetes Miletus are significant main effect that influences GDBP of pregnant woman. The interaction term sex by Gestational age has significant effect at 0.1 levels of significance.

4.6. Linear mixed model for diastolic blood pressure

4.6.1. Selection of random effect for Gestational systolic blood pressure

The individual confidence interval of linear regression model parameter shows nothing about correlation between the intercept estimates and the slope estimates. Clearly, the plot indicates that a random effect is needed to account for subject-to-subject variability in the intercept and slope.

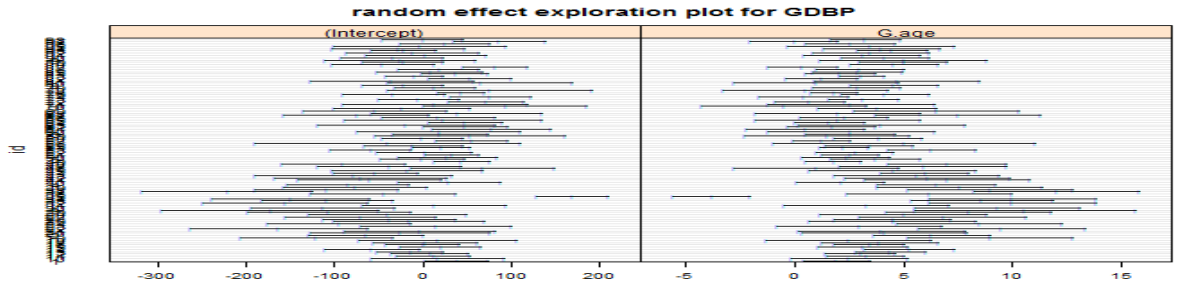


Figure 4.5 The interval plot of intercept and slope for GDBP

The above figure shows, there is greater variability in random intercept and slope. This shows random intercept and slope should be included in modeling gestational diastolic blood pressure. Simple Linear regression is no more important to account subject specific random effect. So, linear mixed model was fitted below to account within and between subject variability.

4.6.2. Linear mixed effect model for Diastolic blood pressure

Different model that account within subject and between subjects were fitted and Comparisons have been made to select best model by combining AIC, BIC and the number parameters to be estimated. These models were fitted by using gestational age and log of gestational age with different random effect. Log of gestational age is included because; the mean profile plot seems logarithmic graph. Comparisons of models are given below.

Table 4.11 Summary for selection of random effect

Time variable	Model with	Df	AIC	BIC	logLik
Gestational age	Random intercept	16	3417.910	3485.629	-1692.955
With interac.	**Ran.intr and slope**	**18**	**3396.976**	**3473.160**	**-1680.488 ***
Gestational age	Random intercept	16	3430.415	3498.134	-1699.207
Without interac.	Rand.intr and slope	18	3398.752	3474.936	-1681.376
log of gestational	Random intercept	16	3410.938	3478.657	-1689.469
age	Rand. Intr and slope	18	3395.775	3471.959	-1679.887

**linear mixed Model of random intercept and random slope with interaction term in the fixed part*

Based on the anova table output given above, the second model is best fitting compared with the others. Because, the smaller AIC and BIC indicates the model best fit the data. Including random intercepts and slope with gestational age as time covariate improve the model precision.

Assume that $GDBP_{ij}$ is gestational diastolic blood pressure for i^{th} pregnant women at j^{th} gestational age given by week. Its general form is given by:

$$GDBP_{ij}= \beta_{20}+\beta_{21}sexi+\beta_{22}agei+\beta_{23}parai+ \beta_{24}gravidai+ \beta_{25}G.ageij+ \beta_{26}fmi + \beta_{27}dm$$

$$+(\beta_{28}sexi+ \beta_{29}agei+ \beta_{210}parai+ \beta_{211}gravidaij+ \beta_{212}fmi+ \beta_{213}dmi)*G.ageij +b_{i2}(t)+\varepsilon_{ij}$$

Where: $b_{i2}(t)=b_{02} +b_{02}*G.age$. it contains random intercept and slope for linear gestational age effect. It is assumed bivariate normal with mean zero and variance G and independent of error terms. i.e. $b_{2i}(t) \sim N(0,G)$. The vectors (β_{20}, β_{21}, β_{22} .....β_{213}) are fixed effect that describe the average evolution of GDBP. But, (b_{20}, b_{21}) are random effect that shows the individual deviation from average and the rate of change of change over gestational age respectively. The other covariates are as given above. The output for selected model given in the appendix **I** (Table 4.12)

4.6.3. Correlation structure for GDBP

Measurements in longitudinal studies are highly correlated due to subject specific random term. So, this correlation should be accounted and modeled. Obtaining correct correlation is not single trivial for repeatedly measured data. For GDBP different correlation structures have been fitted and compared below.

Table 4.13 Correlation Structure for GDBP

Model	Correlation.str	No.paramtre	AIC	Loglik	p-value
1	Symmetric	13	3389.244	-1681.622	
2	ARIMA(q=2)	16	3344.702	-1656.351	<.0001
3	AR(1)	15	**3338.001**	**-1654.001**	**0.0301**
4	Compsymm	13	3393.395	-1683.698	<.0001
5	ARMA(1,1)	16	3339.881	-1653.941	<.0001

**symmetric variance structure * ARIMA -autoregressive moving average of two (p=0, q=2) *AR $_{(1)}$-autoregressive of order one (q=0, p=1) *ARMA- autoregressive of order two (q=1, p=1) *Copmsymm- compound symmetric correlation structure.*

In similar way to GSBP, the observed AIC value in the above table indicates that, three models present a similar fit to the data. Formally speaking, the lowest AIC value (**3338.001**), indicating the best fitting model is Model 3, which has autoregressive of order one (AR(1)). However, the

AIC values (**3344.702** and **3339.881**) for Model2 and model5 are not too much different when compared with model two. Model with AR (1) correlation structure were fitted.

Next, Insignificant factor, covariate and their interaction term have been removed until significant terms obtained. The estimated parameters for final model using AR (1) correlation structure are given in table below (the right side). Autocorrelation plot of model was given in appendix **II** (Figure 4.6).

Table 4.14 Final model estimated parameters by using maximum likelihood method

Gestational systolic blood pressure			Gestational diastolic blood pressure		
Parameter	Estimate (St. Error)	p-value	Parameter	Estimate (St. Error)	p-value
β_{10}	132.32867(62.47527)	**0.0348***	β_{20}	60.13309(30.999938)	**0.531**
β_{11}	6.02033 (2.67970)	**0.0270***	β_{21}	13.04738 (9.877078)	**0.1897**
β_{12}	8.16295 (3.21590)	**0.0128***	β_{22}	3.41931 (1.563331)	**0.0312***
β_{14}	-25.93943(10.36790)	**0.0127***	β_{24}	-10.22277 (5.027064)	**0.0426***
β_{15}	11.43068 (2.61176)	**0.0000***	β_{25}	5.87596 (1.297091)	**0.0000***
β_{16}	42.54721 (21.56741)	**0.0492***	β_{26}	20.81157(10.519567)	**0.0486***
β_{19}	-0.34958 (0.13536)	**0.0102***	β_{28}	-0.43756 (0.414896)	**0.2922**
β_{111}	1.10219 (0.43571)	**0.0118***	β_{29}	-0.13945 (0.065799)	**0.0347***
β_{112}	-1.61511 (0.90203)	**0.0741**·	β_{211}	0.42981 (0.210853)	**0.0422***
β_{113}	-0.30026 (0.13941)	**0.0318 ***	β_{212}	-0.77872 0.438443	**0.0765**·

***shows significant variable at 0.05 levels of significant*

The result in the above table shows both model contains the same main effect variable but there is a single interaction term different and also not significant at 0.05 levels of significance. Removing it doesn't improve model. So, it is retained as it is.

The estimated intercept for DBP is 60.13mmHG with standard error of 31, which shows the existence of greater variability at beginning of gestational diastolic blood pressure. The age of mother has an effect on her gestational diastolic blood pressure. As the age of mother increase by one year, the gestational diastolic blood pressure of the mother increase by 3.4. When the number of Gravida increases by one, gestational diastolic blood pressure decreases by 10.22. Increasing one week in gestational age, leads to increase diastolic blood pressure more than five folds. Having family history of hypertension, increases gestational hypertension by 20.8. The estimated difference in slope -0.1395 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 increases the gestational diastolic blood pressure.

Table 4.15a Random effect for systolic and diastolic blood pressure

GSBP		**GDBP**	
Random effect	**StDev**	Random effect	**StDev**
b_{1o}	69.291698	B_{2o}	34.308513
b_{11}	2.986793	B_{21}	1.482757
$Cov(b_{1o}, b_{11})$	-204.722	$Cov(b_{2o}, b_{21})$	-49.5762
δ^2 (residual)	10.653227	δ^2 (residual)	4.633760
$Cor(b_{1o}, b_{11})$	-0.989	$Cor(b_{2o}, b_{21})$	-0.975
(phi=Φ): AR(1)	0.4970565	(phi=Φ): AR(1)	0.6461321

From the above table, the standard deviation of random effect for gestational systolic blood pressure is almost twice of standard deviation of gestational diastolic blood pressure. But correlation of random slope and intercept for GSBP and GDBP are almost the same. The parameter estimate for correlation structure for within error (phi=Φ) is 0.5 and 0.65 respectively for GSBP and GDBP. Also, the result shows that, there is greater variability in random intercept and slope in systolic blood pressure. Within subject residual standard deviation for GSBP is greater than GDBP.

4.7. Joint analysis of Gestational systolic and Diastolic blood pressure

In many situations, joint modeling of the multivariate longitudinal profiles is needed or has additional advantages over the separate analyses of the different outcomes. First, the association structure can be of importance. A possible question might be how the association between outcomes evolves over time or how outcome-specific evolutions are related to each other (Fieuws and Verbeke, 2004). In a second situation, the aim can be to improve the results of a discriminate analysis by using more than one longitudinally measured outcome. In another situation, interest may be in comparison of average trends for different outcomes.

A flexible approach is to model the different outcomes jointly by using random-effects models. Random effects models have become the preferred tool to analyze various types of longitudinal data. With these models, the average evolution of a specific outcome is described using some

function of time, and subject-specific deviations from this average evolution are introduced by using so-called random effects (Fieuws and Verbeke,2006). In a joint modeling approach using mixed models, random effects are assumed for each outcome process, and by imposing a joint multivariate distribution on the random effects, the different processes are associated. This approach has many advantages and is applicable in a wide variety of situations. First, the data can be highly unbalanced. For example, it is not necessary that all outcomes are measured at the same time points. Moreover, the approach is applicable in situations where linear, nonlinear, or generalized linear mixed models are used to describe the evolution of the individual outcome processes. Also, models can be constructed joining different types of mixed models.

The joint model assumes a mixed model for each outcome, and these Univariate models are combined through specification of a joint multivariate distribution for all random effects. Obviously, the joint model can be considered as a new mixed model of the form (1), but with a random-effects vector b_i of a higher dimension. Let Θ be the vector containing all parameters (fixed effects parameters as well as covariance parameters), then $li(Y_{1i},Y_{2i}|\Theta)$ refers to the log-likelihood contribution of subject in to the full joint mixed model. Strictly speaking, standard SAS software has been used to obtain parameter estimates for this joint mixed model.

Both outcomes have been analyzed separately (equa.3) by using linear mixed model in previous section. However, separate analysis of mutually dependent events is not much informative. This is why? The two events are measured on the same individual through the time. The subject specific variation and correlation should be accounted. Joint analyses of the two outcomes account the subject specific correlation and variations for gestational systolic and diastolic blood pressure. In this section, joint analysis' of two response variable are given by assuming (i) error terms correlated and (ii) joint analysis by assuming error terms uncorrelated.

Joint analysis has been done by assuming error terms are correlated (equa.4). Because, measurement have been taken at the same subject for both responses. In other way, the random intercept and slope for these responses are correlated instead of independence. Based on this, parameter estimate for significant covariate and factors at 0.05 levels of significance are given below in (Table 16). Table below shows joint analysis of the two responses by assuming error terms are uncorrelated. The second table.17 shows joint analysis of the two responses assuming correlated error terms.

Table 4.16 Estimated parameter for bivariate random effect model with uncorrelated error

Para.	Estimate	Stand. Error	t Value	Pr > |t|	Lower	Upper	Gradient
β_{10}	131.27	61.4768	-2.14	0.0340	91.53	171.0009	-414E-12
β_{11}	5.7375	2.8449	2.02	0.0451	0.1257	11.3492	-902E-13
β_{12}	8.1238	3.0612	2.65	0.0086	2.0855	14.1620	-1.16E-8
β_{14}	-26.0672	10.2041	-2.55	0.0114	-46.1951	-5.9392	-1.34E-9
β_{15}	11.3384	2.5529	4.44	<.0001	6.3027	16.3742	4.603E-9
β_{16}	43.5156	20.3254	2.14	0.0336	3.4232	83.6080	2.67E-10
β_{19}	-0.3478	0.1280	-2.72	0.0072	-0.6002	-0.09538	7.528E-9
β_{111}	1.1138	0.4248	2.62	0.0094	0.2759	1.9517	1.305E-8
β_{112}	-1.6263	0.8455	-1.92	0.0559	-3.2940	0.04138	9.418E-9
β_{113}	-0.2672	0.1451	-1.84	0.0670	-0.5534	0.01891	9.937E-9
β_{20}	60.3679	32.7959	-1.84	0.0672	-125.06	4.3230	-2.6E-9
β_{21}	13.2631	10.3249	1.28	0.2005	-7.1032	33.6293	-773E-12
β_{22}	3.4726	1.6391	2.12	0.0354	0.2393	6.7058	-6.19E-8
β_{24}	-10.4722	5.2527	-1.99	0.0476	-20.8332	-0.1111	-8.01E-9
β_{25}	5.8948	1.3786	4.28	<.0001	3.1755	8.6141	2.039E-8
β_{26}	19.5450	11.164	1.75	0.0816	-2.4768	41.5669	1.213E-9
β_{28}	-0.4434	0.4356	-1.02	0.3101	-1.3027	0.4159	2.588E-8
β_{29}	-0.1416	0.0693	-2.04	0.0424	-0.2782	-0.00487	3.179E-6
β_{211}	0.4384	0.2211	1.98	0.0488	0.002252	0.8745	9.713E-8
β_{212}	-0.7410	0.4677	-1.58	0.1148	-1.6635	0.1815	4.405E-8
δ_1	10.7586	0.5654	19.03	<.0001	9.6432	11.8739	-8.37E-9
δ_2	4.6117	0.2128	21.68	<.0001	4.1920	5.0314	-1.35E-7
δ_{01}	58.3324	10.5913	5.51	<.0001	37.4407	79.2241	5.88E-10
δ_{11}	2.5225	0.4456	5.66	<.0001	1. 6435	3.4041	6.2b92E-8
δ_{02}	37.8688	4.9599	7.63	<.0001	28.0852	47.6523	1.21E-8
δ_{12}	1.6389	0.2095	7.82	<.0001	1.2.2257	2.0257	1.526E-6

δ_{01}- standard deviation of intercept for GSBP *δ_{11}- standard deviation of slope for GSBP*

δ_{02}- standard deviation of intercept for GDB *δ_{12}- standard deviation of slope for GDBP*

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). Estimated value is almost the same as separate analysis. The sex of the neonate has significant (positive) effect on the gestational systolic blood pressure of the mother. Being male neonate, made to increase the systolic blood pressure 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 increases the chance of increasing gestational hypertension. Woman of hypertensive family of PIH/PE Bp is greater than her counter part by 43.5. In simple term, hypertensive family history women's gestational blood pressure is greater than no family history of gestational hypertension woman. Gestational age has significant effect on systolic blood pressure of pregnant woman. As gestational age (in week) increase by one, systolic blood pressure of the pregnant mother increase by 11.34mmHG. In general, as gestational age increase and mother approaches to give birth, her blood pressure increases linearly with gestational age, if she has no internal and external complication. As the age of the mother increases by one, her gestational blood pressure increases by multiple of 8.14 mmHG. But, as number of Gravida increases, the blood pressure of mother decreases. Mother of primigravidae (primiparas) gestational blood pressure is greater than that of multiparas (multigravida) mothers blood pressure. When the number of Gravida 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 and diabetes mellitus by gestational age decrease GSBP of the mother by 1.63 and 0.26 respectively. However, the interaction of gestational by Gravida increases GSBP of mother by 1.1. That is, woman of higher number of Gravida has higher GSBP compared with less number of Gravida over time. Lesser is relative term, it excludes primigravidae and primiparas. The interaction term gestational age by age of mother has negative effect on her GSBP.

In similar way, the estimated intercept for GDBP is 60.13 with standard deviation of 31, which shows the existence of greater variability at beginning of gestational diastolic blood pressure but less than that of GSBP. The intercept and standard deviation of GDBP is almost half of the GSBP given above respectively. Sex is not significant at 0.05 levels of significance. However, age of mother has an effect on her gestational diastolic blood pressure. As the age of mother increase her gestational diastolic blood pressure increase by 3.4. When the number of Gravida increases by one, gestational diastolic blood pressure decreases by 10.5. Completing one week in gestational age and beginning of the new week, leads to increase diastolic blood pressure more than five and half folds. Gestational age has positive effect on mother's blood pressure. In average after completion of one, her diastolic blood pressure increases by 5.8. On the other hands, having positive family history of hypertension increases gestational hypertension by 19.5 folds. Sex by gestational age 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 increases the gestational diastolic blood pressure by 0.43 and family history of hypertension by gestational age made the GDBP to decline by 0.47. At the end of the parameter estimate table below, all the variances of the random effects ($\delta_{01,}$ δ_{02}, δ_{02}, and δ_{12}) are marginally significant, indicates that between subjects variability is not constant for individual pregnant woman. Intercept and slope for both responses have significant difference that induces the subject specific effect for each individual.

Finally, all significant main fixed effects except Gravida have positive influence on GSBP and GDBP. Meaning that, these factors increase both GSBP and GDBP to the higher levels. But, the interaction terms sex by gestational age, number of Gravida by gestational age and family history of PIH/pre-eclampsia by gestational age decreases the two responses by less than one unit over time.

However, relaxing the conditional independence assumption by allowing correlated errors revealed that the discrepancy was due to the inappropriate modeling of the covariance structure. This indicates that the answer to a question which does not refer to the error structure can highly be influenced by assumptions made on the error components. This is especially surprising for the association of the evolutions, since the covariance parameters for the error components are not used in its calculation.

4.7.1. Evolution of association and association of evolution

The answer to the question how the evolution of the GSBP is associated with the evolution of the GDBP is typically derived from the covariance matrix of the random effects. Estimated Variance covariance matrixes given in appendix **I** (table 17a) depicts that, there is a greater variability in GSBP. The random intercept in GSBP has variance of 3402.67 while GDBP has 1434.046. There is negative covariance between any intercept with random slope. Meaning that, those who have larger intercept encounter lesser random slope. However, covariance between random slopes is smaller than random intercept which is about 12.8 mmHG. Eventually, there is smaller variability in gestational diastolic blood pressure random slope. This is because, when a

gestational age increase and a greater change were observed in GSBP, GDBP shows a little change.

Similarly, joint analysis of response used to show association of evolution (equa.7) and evolution of association (equa.8). Based on the output given below in Table (17b), association of the evolution for gestational systolic and diastolic blood pressure is higher, which is 0.75. This positive value suggests that there is a great association between evolution of GSBP and GDBP

Table 17b Correlation matrix for joint evolution

		GSBP		GDBP	
		Intercept	**Slope**	**Intercept**	**Slope**
	Intercept	1.0000000	-0.9910898	0.7126446	-0.7019257
GSBP	**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 Evolution of association for response variables'. The marginal correlation plot given below shows that, evolution of association (equa.8) between the two responses is decreasing over gestational age. Notice that the association is strongest at week twenty at around 0.65, and this association decreases over time, leveling out at approximately 0.1 after 32 weeks of gestation. This is due to the fact that, the way of increment is not in the same fashion (scale). When GSBP show a great change over time, GDBP shows a little change. Below graph shows evolution of association.

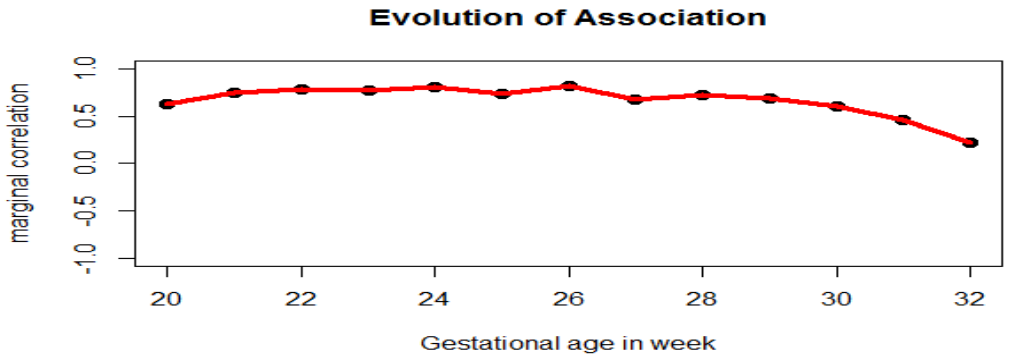


Figure 4.7 Evolution of the association for response variables over gestational age

Using the outlined random effect approach, marginal correlation between two responses as function of gestational age is given above. When *t*=0, marginal correlation simplified as

$\frac{\delta_{a1a2}}{\sqrt{\delta^2{}_{a1}+\delta^2{}_1}\ \sqrt{\delta^2{}_{a2}+\delta^2{}_2}}$. Which implies that absolute value of the marginal correlation at time *t*=0 cannot be higher than the correlation between random intercept. The smaller the measurement error of both response, the closer marginal correlation at *t*=0 approximate the correlation between random intercept. In general, figure shows that the measurements at the beginning of the gestational age are highly correlated. But, to the end of pregnancy or before beginning of birth, the correlation level of the two responses at each point in time decreases. For a little change of diastolic blood pressure, systolic blood pressure shows a greater change.

4.8 Comparison of separate and joint model

Most statistical models for repeated data are restricted to the analysis of one single outcome variable. Those approaches are not flexible when the research question focuses on: (i) association structure of different outcomes (ii) to test homogenous effect of a covariate across different outcomes, (iii) to draw joint inferences about the different outcomes. In order to answer such type of research question, Fieuws and Verbeke (2004, 2005, and 2006) provided detailed explanation on joint modeling.

The two independent Univariate models can be fitted as a joint model with appropriate covariance terms equal to zero. Separate analysis of both outcome i.e. GSBP and GDBP have been done without considering the correlation between random effects. Ignoring this correlation between them make our analysis somewhat biased, inefficient and powerless. The result from separate and joint (correlated error and uncorrelated error) are given in (Table 4.18a and Table 4.18b) below.

Table 4.18a Separate analysis output for systolic and diastolic blood pressure

Systolic blood pressure				Diastolic blood pressure			
Param.	Estimate	(**St. Error**)	**p-value**	**Parameter**	Estimate	(**St. Error**)	**p-value**
β_{10}	132.33	(62.4752)	0.0348	β_{20}	60.13309	(30.99994)	0.0531
β_{11}	6.02033	(2.67970)	0.0270	β_{21}	13.0474	(9.87707)	0.1897
β_{12}	8.163	(3.21590)	0.0128	β_{22}	3.41931	(1.563331)	0.0312
β_{14}	-25.94	(10.3679)	0.0127	β_{24}	-10.2277	(5.027064)	0.0426
β_{15}	11.43	(2.61176)	0.0000	β_{25}	5.875667	(1.297091)	0.0000
β_{16}	42.4914	(21.5674)	0.0492	β_{26}	20.8157	(10.51956)	0.0486
β_{19}	-0.34958	(0.13536)	0.0102	β_{29}	-0.43756	(0.414896)	0.2922
β_{111}	1.0219	(0.43571)	0.0118	β_{211}	-0.13945	(0.065799)	0.0347
β_{112}	-1.61511	(0.90203)	0.0741	β_{212}	0.42981	(0.210853)	0.0422
β_{113}	-0.30026	(0.13941)	0.0318	β_{113}	-0.77872	(0.438443)	0.0765

Table 4.18 b 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
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

Uncorrelated error						correlated error					
Para	**Estimate**	**Standard Error**	**Pr > |t|**	**Lower**	**Upper**	**Para**	**Estimate**	**Standard Error**	**Pr > |t|**	**Lower**	**Upper**
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
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*

Three different analyses have been done for comparison purpose. Separate analysis for two responses and two joint analyses. As we see from the above table 4.18a and 4.18b, parameter estimate for systolic and diastolic blood pressure is almost the same for separate and joint analysis with and without correlated error assumption. Corresponding likelihood and AIC value are 7407.27 and 7467.275 for separate analysis, respectively. A likelihood ratio-test(x^2=84.63,*df* =3) rejects the use of two independent models ($p < 0.0001$). In addition, fit statistics -2 Log Likelihood (6777.4), AIC (6831.4) and BIC (6919.6) in table below indicates that joint modeling with uncorrelated error fits better than the two. Secondly, the estimated standard deviation of joint model with uncorrelated error is smaller as compared with another two models. Since, joint modeling takes in to account of correlation between the two responses. So, joint model with uncorrelated error allow for correct prediction and inference about fixed effects and covariance in the model.

Table 4.20 ML estimates for the covariance parameters in the Univariate model, the bivariate Random effects model with uncorrelated and correlated errors

		Bivariate random model	
	Univariate model	**correlated error**	**uncorrelated error**
-2log likelihood	7407.27	7205.0	6777.4
AIC(smaller is better)	7467.275	7257.0	6831.4
AICC(smaller is better)		7258.4	6832.9
BIC(smaller is better)	7594.241	7342.0	6919.6
δ_1	10.653227	11.6404	10.7586
δ_2	4.633760	4.4078	4.61170
σ_{12}	-	61.598	-
δ_{a1}	69.291698	66.0414	58.3324
δ_{a1a2}	-	6975.29	6739.06
δ_{a2}	34.308513	24.2672	37.8688
δ_{a1b1}	-204.2423	-898.364	-910.709
δ_{a2b1}	-	-285.368	-283.997
δ_{b1}	2.986793	.007651	2.52250
δ_{a1b2}	-	-301.326	-295.630
δ_{a2b2}	-49.4912	-185.872	-173.967
δ_{b1b2}	-	14.3624	12.78858
δ_{b2}	1.482757	9.719E-7	1.638900

In general as we see from table 4.20 given above, AIC for joint modeling with uncorrelated error is less than joint modeling with correlated error as well as Univariate analysis. So, joint modeling with uncorrelated error is besting model. In addition to fitted statistic, almost all variance of random effects are significant as seen in the table 4.19b for join fitted model assuming uncorrelated error. This indicates that subject specific random effect have significant effect in the model.

4.9 Assessing Model assumption

The most useful methods to assess the validity of the assumptions of the model are plots of the residuals vs. fitted values, and the quartile plot of estimated random effects. The primary quantities used to assess the adequacy of assumptions were the within-group residuals which are defined as the difference between the observed response and the within-group fitted values.

Individual specific residual plots for fitted model designates that the residuals are centered at zero. That is, $E(\varepsilon_{ij})=0$ for both GSBP and GDBP shows that normality assumptions of the error term are satisfied. The error terms have centered at mean zero. The horizontal line passes to the centre of the residual vs fitted point. The point above and below horizontal lines are almost constant. But, their variability differs for the two responses Appendix **II** (Figure 4.8a and 4.8b). Since there were no influential observations per individual, that disturbs the normality of within-group error. Besides, the normal plot of residual Appendix **II** (Figure 4.8e and 4.8f) suggests that the distribution of with-in group errors has very little heavier tails than expected under normality, but is also symmetric around zero. Perhaps a mixture of normal distributions or a t-distribution with a moderate number of degrees of freedom would model the distribution of the within-group error more adequately. However as the heavier tails seem to be distributed symmetrically, the estimates of the fixed effects should not change substantially. The heavier tails tend to inflate the estimates of the within-group standard error under the Gaussian model, leading to more conservative tests for the fixed effects, the main conclusion remains unchanged.

The other assumption is that, random effects are normally distributed with mean zero and covariance matrix D and are independent of error term. To assess the validity of these assumptions for gestational systolic and diastolic blood pressure, the most useful methods were plots of the residuals and the fitted values of the estimated random effects. As show in appendix **II** (Figure 4.8c and 4.8d) quartile plot of the random effect seems does not violate the normality assumption of the random effect terms. All random effect satisfies the assumption even if, there are very small extreme values at the tails of the plots.

4.10. Discussion

There are several advantages of using random-effects models for joint modeling purposes. First, the different responses do not necessarily need to be of the same type (continuous or discrete). Second, these models can be easily implemented in standard software, such as SAS procedure MIXED in case of only continuous outcomes, or SAS procedure NLMIXED for the analysis of discrete outcomes or mixed continuous & discrete outcomes. Third, the different responses neither need to be measured at the same time points, nor does one have to assume that the same number of repeated measurements is available for all outcomes. Fourth, the approach gives an

immediate indication of the association between different evolutions. Finally, using some additional computations the evolution of the association can easily be derived from the obtained parameter estimates.

In this paper, a joint model using random-effects was used in a bivariate setting with longitudinally measured continuous outcomes. The two outcomes were tied together by a common distribution for the random intercepts and slopes, implying independence conditional on the random effects. The aim of the joint model was to study the relation between two responses. Two aspects of the relation were investigated: the association between the evolutions and the evolution of the association. Results of the joint model suggested a very strong association between the evolutions and a slowly decreasing evolution of the association

However, relaxing the conditional independence assumption by allowing correlated errors revealed that the discrepancy was due to the inappropriate modeling of the covariance structure. This indicates that the answer to a question which does not refer to the error structure can highly be influenced by assumptions made on the error components. This is especially surprising for the association of the evolutions, since the covariance parameters for the error components are not used in its calculation. In the context of clustered bivariate outcomes, Gueorguieva (2001) introduced conditional dependence by including one response in the predictor for the other response and presented a score test to check the validity of the conditional independence assumption. In another analysis on the same data set (2001b) the conditional dependence was induced by allowing error correlation. It is obvious that the need for scrutinizing the covariance structures depends on the aim of the joint modeling analysis. Two situations should be distinguished. In the first situation, primary interest is in gaining efficiency for the estimation of the mixed effects in the model, in analyzing mixed effects simultaneously or the comparison of different outcomes (as in e.g. References [Gueorguieva (2001), Gueorguieva, & Agresti (2001).]. Although problems might occur due to under- or over parameterization of the covariance structure (Verbeke & Molenberghs (2000)), it is obvious that the interpretation of the mixed- effect parameters themselves remain the same. In the second situation, the covariance structure itself is of interest.

The pregnancy induced hypertension was common at the age of 20-30 years and less than 20. It is more frequent after 20 weeks of gestational age. It had more frequent in primigravidae than

multigravida. This result much with the finding of (Balafair, 2010) al-mukalla University of Yemen. In addition, According to results of research the mean affected age by pregnancy-induced hypertension in JUSH was 24.56 years old, this may be due to early marriage in our society, similar result was found in Yemen research where the mean age affected was 26.5. Regarding the gestational age where pregnancy induced hypertension is more likely to occur, we found that pregnancy induced hypertension is more frequently occurred in a mean 25 gestational weeks but, (Balafair, 2010) results revealed that the mean gestational age is 33 weeks. We get less mean gestational age; it may be early marriage in our society.

Most or around 60% of mothers were young and age less than 25. However, their average systolic and diastolic blood pressure is greater than other age group. This result coincides with founding of (Jasovic-Siveska, *et al.,* 2011). i.e the characteristics' of PIH are bimodal frequency. He identified mostly PIH at young primiparas (younger than 20 years old) and over multiparous (over 35 years old). Gravidity is a strong risk factor of pregnancy induced hypertension as most references talked about, our research was very agreed in this fact and it proved that primigravidae women were more likely to develop pregnancy induced hypertension, similar finding was clarified in UK and Yemen research. This was supposed to go with the theory that during first pregnancy there was an aberrant immune reaction to foreign paternally derived antigens which responsible for the disease. It was examined as positive risk factor for primigravidae woman. This was the same as result obtained by (duley, *et al*, 2002), that is prim Gravida woman had a threefold increased risk for developing preeclampsia. It was also found that, family history [daughters of mothers with preeclampsia more affected] was associated risk factor (Sungani, *et al*., 1999 and thadhan, *et al*., 1999) for PIH. Several epidemiological studies have indicated that a family history of PIH or PE is an independent risk factor for PIH (Kobashi, *et al*., 2001; Qiu, *et al.,* 2003). This study has also established as high risk for PIH among women with a family history of PIH/PE indicating a familial inheritance.

Regarding number of Para during pregnancy our research applied that many cases have no Para (nulliparous) or (primiparas) history during this pregnancies. This can be concluded by the fact that, this society is trapped with young age as discussed earlier. Concerning diabetes mellitus as a risk factor of pregnancy induced hypertension, our research was contraversed with the usual suspect, where we found that diabetes mellitus is not significant covariate that influence PIH.

This reflects one or more of three suspicions, whether only these cases are truly negative for diabetes mellitus; so we need more researches may be through a wide population, or it is really true that this society is negative for diabetes mellitus, and also we need further research. OR, these conditions are not very common in female of this society.

The sex of fetus is another factor associated with the PIH. Male Fetus increases the blood pressure of the mother. This may be due to the weight difference. Normally, i) Male neonates had greater weight compared with female neonate. ii). Male neonate show higher Movement during pregnancy. iii). another possibility is that male fetuses produce something that predispose to PIH that is not produced by females or produced in greater amount by male than females. Our analysis result much with (Naeye and Demers, 1997) study results, undertaken to determine if male and female fetuses had differing environmental effects on their mothers.

CHAPTER FIVE

5. CONCLUSIONS AND RECOMMENDATION

5.1 Conclusions

Under this study three different models were fitted for the two responses. That is Univariate and two (assuming correlated and uncorrelated error) joint models. Joint modeling of these biologically correlated responses gives approximately the same result as separate one. But, the fitted statistics shows that joint modeling with assumption of uncorrelated error between biologically correlated response best fit data. In addition, joint analysis output for association of evolution shows that, the two responses are strongly positively associated for evolution. But, their evolution of association is decreasing over gestational age. Consequently, joint modeling of the two responses gives additional information about joint evolution over the time compared with Univariate analysis. Autoregressive of order one is the best covariance structure for repeatedly measured responses for Univariate analysis and leads to more parsimonies model.

For both analyses the covariates are equally significant. i.e. significant variables in Univariate case also significant in joint analysis. Sex of fetus, age of mother, number of Gravida, gestational age and family history of hypertension are significant variable on joint and separate analysis. Besides, interaction of sex with gestational age, Gravida with gestational age and family history of hypertension with gestational age were significant risk factors that influence gestation hypertension. Sex of fetus, family history of hypertension/eclampsia, gestational age, and age of mother and interaction of Gravida with gestational age had positive effects on the blood pressure of the mother. However, main effect of Gravida, interaction of family history with gestational age, diabetes Miletus with gestational age and age of mother with gestational age are negatively associated with pregnancy induced hypertension.

5.2 Recommendation

Pregnant woman should have ANC follow up until her delivery. The mothers who have these associated risk factors should have to take care of her life and fetus. This may reduce preterm delivery rate, low birth rate and severity, intervention rate by means of induction caesarean and instrumental delivery.

Under this study only seven variables had been considered. Further studies should be done by including covariates like interval of pregnancy, multiple pregnancies, body mass index of mother, place of residence, obesity , alcohol drinking, contraceptive usage and smoking status.

Governmental and non governmental body should gives awareness for health workers to record all the necessary variables during follow up time to see the change of the disease within and between subjects overtime. Also, University Hospital and other health facilities in the surrounding should give due emphasis for early recognition and management of mothers with HDP. Moreover, improving the obstetric and neonatal care at delivery is essential to improve the maternal and prenatal outcomes of pregnancies complicated by the disorder. So, to reduce the level of prenatal morbidity and mortality in PIH, it is necessary to insist on regular and organized control for every pregnancy. The delivery of hypertensive pregnancy needs to be performed in institutions that can provide intensive care and adequate therapy for the newborn if needed.

Even though, separate model is most common practice for researchers to model several outcomes involved in a disease process, the joint model 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 association of evolution and the evolution of association of the responses. So, using joint model for correlated responses incorporates the direction and rate of changes over time.

Limitation

Under this thesis, only seven covariates have been used. Because, another very important variable are not recorded under ANC follow up card of pregnant woman clearly. There is no organized and specific identity card number common to all PIH women to identify from the other ANC follower and hypertensive woman. This minimizes time and money consumption during data collection. In addition to this, there is no related published paper on this area in our country to the best knowledge of researcher, by using joint modeling to compare and contrast the results of our finding.

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APPENDIX-I

Table 4.3 output for simple linear regression model for systolic blood pressure

coeffeciat	Estimate	Std. Error	t value	Pr(>|t|)
(Intercept)	87.7888	6.2323	14.086	< 2e-16 ***
G.age	2.2501	0.2058	10.934	< 2e-16 ***
sexmale	4.0861	1.3120	3.114	0.00195 **
dmyes	-3.8601	1.6095	-2.398	0.01684 *
fmyes	4.0434	1.5003	2.695	0.00727 **
para	1.0237	1.1426	0.896	0.37074
gravida	0.4151	1.0606	0.391	0.69566

Table 4.5 Separate analysis of systolic blood pressure

Coefficient	Value	Std.Error	DF	t-value	p-value
(Intercept)	-128.3556	64.74705	401	-1.982411	0.0481
G.age	11.27906	2.71519	401	4.154059	0.0000
sexmale	39.71804	19.85732	94	2.000171	0.0484
dmyes	-1.23298	24.51934	401	-0.050286	0.9599
fmyes	45.89027	22.52533	401	2.037274	0.0423
para	29.24372	17.23831	401	1.696438	0.0906
gravida	-46.97053	16.09242	401	-2.918799	0.0037
age	7.60543	3.17256	94	2.397250	0.0185
G.age:sexmale	-1.42367	0.83539	401	-1.704200	0.0891
G.age:dmyes	-0.25018	1.01753	401	-0.245867	0.8059
G.age:fmyes	-1.74922	0.94665	401	-1.847802	0.0654
G.age:para	-1.15384	0.72064	401	-1.601137	0.1101
G.age:gravida	1.93470	0.67480	401	2.867059	0.0044

Table 4.6 summary for variable removing for systolic blood for lmm

Remove	df	AIC	BIC	logLik	Test	L.Ratio	p-v
-none	18	4148.607	4224.791	-2056.303			
-dm	17	4146.609	4218.561	-2056.305	1 vs 2	0.0025382	0.9598
-Para*Gage	16	4147.219	4214.938	-2057.609	2 vs 3	2.6092841	0.1062
-Para	15	4145.840	4209.327	-2057.920	3 vs 4	0.6215800	0.4305

Table 4.10 linear model for DBP

Coefficients	Estimate	Std. Error	t value	Pr(>|t|)
(Intercept)	73.3641	8.6633	8.468	2.75e-16 ***
sexmale	21.5442	10.6368	2.025	0.04335 *
G.age	2.6637	0.3459	7.700	7.26e-14 ***
fmyes	3.9512	1.4874	2.656	0.00815 **
dmyes	3.4290	1.5962	-2.148	0.03217 *

Table 11 Output for gestational diastolic blood pressure

coefficient	Value	Std.Error	t-value	p-value
(Intercept)	50.77915	32.41482	-1.566541	0.1180
sexmale	13.12739	9.98554	1.314640	0.1918
G.age	5.49767	1.36335	4.032462	0.0001
dmyes	-7.53222	12.17623	-0.618601	0.5365
fmyes	23.4521	11.28991	2.077261	0.0384
para	7.96853	8.62062	0.924357	0.3559
gravida	-15.7060	7.96735	-1.971297	0.0494
age	3.17479	1.59273	1.993300	0.0491
sexmale:G.age	-0.44264	0.42055	-1.052531	0.2932
G.age:dmyes	0.28903	0.50711	0.569961	0.5690
G.age:fmyes	-0.88795	0.47478	-1.870230	0.0622
G.age:para	-0.32454	0.35909	-0.903795	0.3666
G.age:gravida	0.65324	0.33207	1.967197	0.0498
G.age:age	-0.12938	0.06734	-1.921472	0.0554

Table 4.17a Variance covariance matrix for joint evolution

		Covariance matrix			
		GSBP		**GDBP**	
		Intercept	**Slope**	**Intercept**	**Slope**
GSBP	**Intercept**	3402.6799	-910.70949	6739.0609	-295.630907
	Slope	-910.7095	3.36544	-283.9971	12.788582
GDBP	**Intercept**	6739.0609	-283.99707	1334.0467	-173.967290
	Slope	-295.6309	12.78858	-173.9673	2.684912

APPENDIX-II

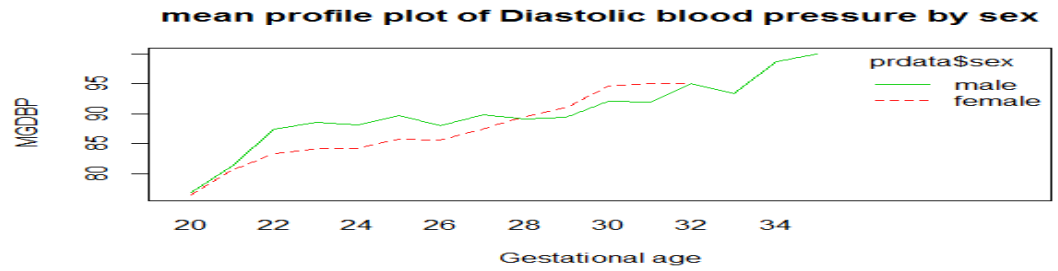
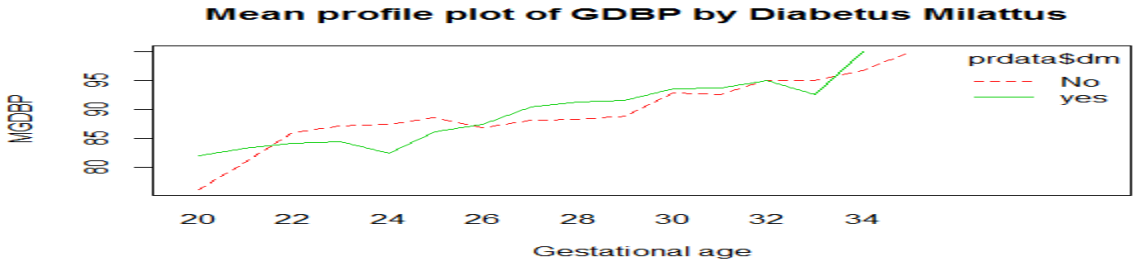
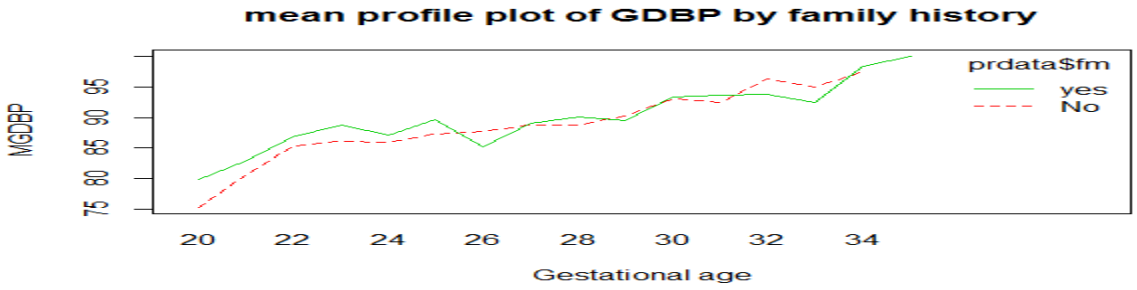


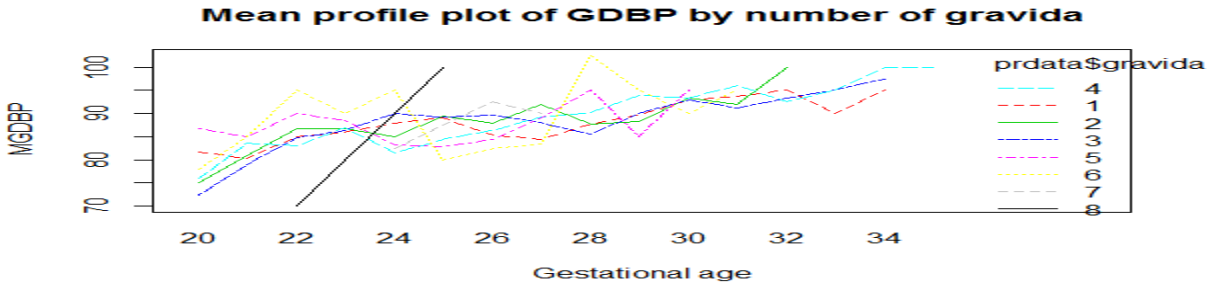
Figure 4.2 (f) Mean profile plot of diastolic blood pressure by sex



4.2(g) Mean profile plot of diastolic blood pressure by Diabetes Mellitus



4.2(i) Mean profile plot of diastolic blood pressure by family history



4.2(j) Mean profile plot of diastolic blood pressure by Gravida

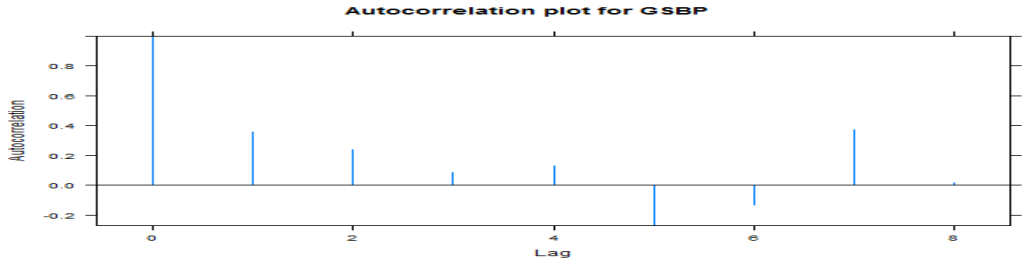


Figure 4.4 Autocorrelation plot for Gestational systolic blood pressure

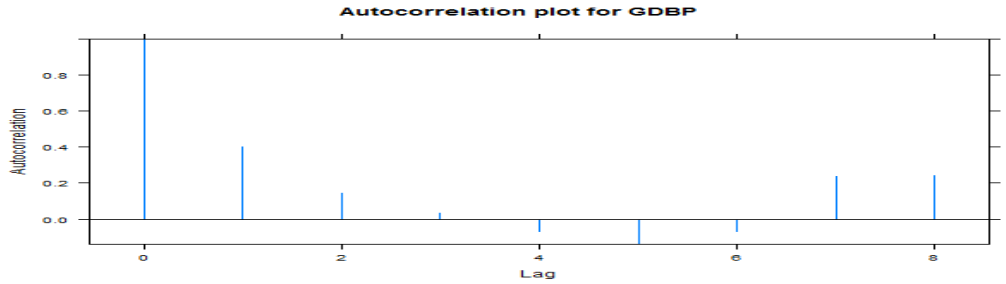


Figure 4.7Autocorrelation plots for diastolic blood pressure

Figure 4.8a Residual vs fitted plot for GBSP Figure 4.8b Residual vs fitted plot for GDBP

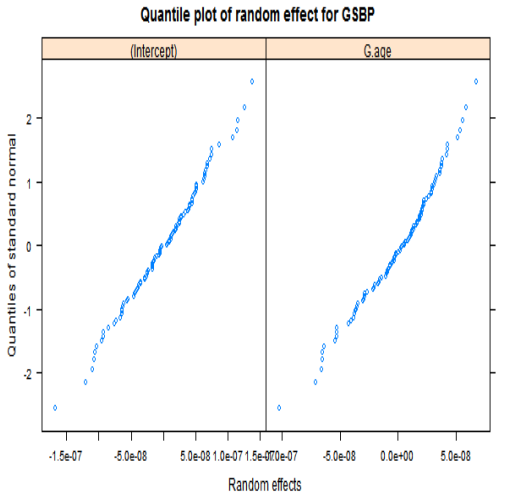


Figure 4.8c quartile plot of random effect for GSBP

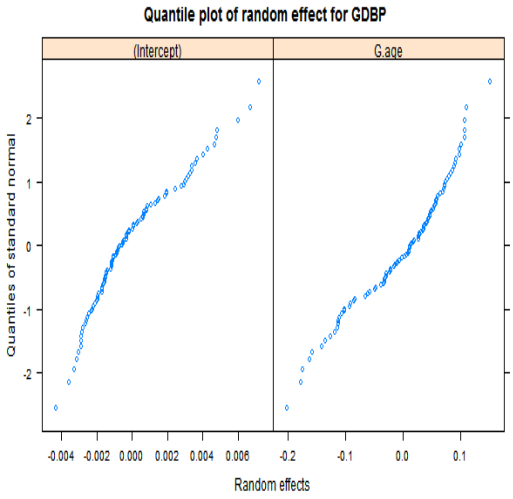


Figure 4.8d quartile plot of random effect for GDBP

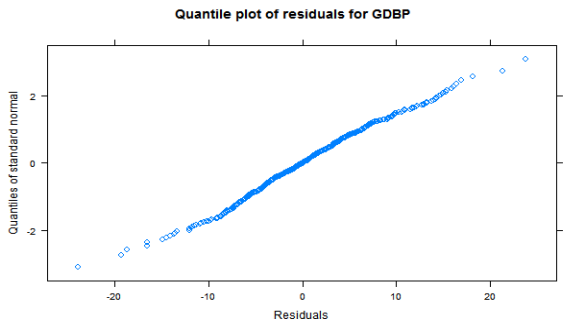


Figure 4.8e quartile plot of residual for GDBP

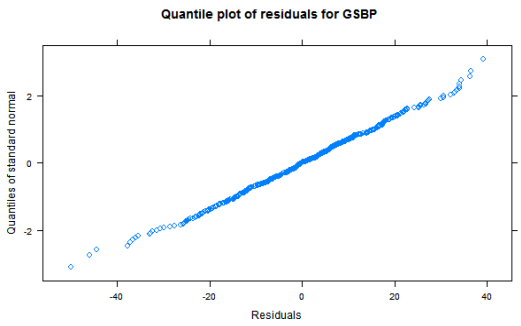


Figure4.8f quartile plot of residuals for GSBP