# **Pregnancy and Diabetes Disease History: Correlated?**

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#### Abstract

**Objective:** Pregnancy, gestational diabetes and induced hypertension are frequently observed in practice among the pregnant women, but their relationships are not well realized. The article aims to develop the relationship of pregnancy on diabetes, hypertension and some other related parameters.

**Methods:** The targeted response 'the number of pregnancies' is heteroscedastic, which is not stabilized by any suitable transformation. It is modeled herein using joint generalized linear models under both the log-normal and gamma distributions.

Results: It is derived herein that diabetic women (P=0.0053) become pregnant earlier than normal women. Mean pregnancy is positively linked to glucose level (P=0.0013) and age (P<0.0001), while it is negatively linked to their joint interaction effect Glucose\*Age (P=0.0003). It is partially positively linked to body mass index (BMI) (P=0.1129) and free of triceps skin-fold thickness (TST) (P=0.2747), while it is negatively linked to their joint interaction effect TST\*BMI (P=0.0039), and it is also positively linked to TST\*Age (P<0.0001). In addition, mean pregnancy is negatively linked to insulin level (P=0.0170) and diabetes pedigree function (DPF) (P=0.0890). Variance of pregnancy is positively linked to glucose level (P=0.1061) and diastolic blood pressure (DBP) (P=0.0657), while it is negatively linked to their joint effect Glucose\*DBP (P=0.0125). Variance of pregnancy is negatively linked to TST (P<0.0001) and positively linked to DPF (P=0.0309), while it is negatively linked to the interaction effect TST\*DPF (P=0.0985), and positively linked to DBP\*TST (P= 0.0006). In addition, variance of pregnancy is negatively linked to insulin level (P=0.0871), while it is partially positively linked to the interaction effect Insulin\*DBP (P=0.1652), but free of BMI (P=0.7468).

**Conclusions:** It is concluded that mean pregnancy is well related to the diabetic functions such as glucose & insulin levels, diabetes history, DPF, BMI, while pregnancy's variance is well related to the diabetic functions and hypertension parameter DBP. Diabetes women become pregnant more earlier than normal women.

**Keywords:** Body mass index (BMI); Diastolic blood pressure (DBP); Gestational diabetes; Joint generalized linear gamma models (JGLMs); Pregnancy; Triceps skin fold thickness (TSFT).

# Introduction

For pregnant women, hypertensive and gestational diabetes mellitus (GDM) disorders are general pregnancy complications all over the world. Pregnancy, GDM and hypertension are commonly observed among pregnant women, but their inter-relationships are not well established. Pregnant women with GDM have insulin resistance pre-pregnancy and during pregnancy. Commonly, they are diagnosed with GDM between 24 and 28 weeks of gestation applying a glucose tolerance test [1-3]. GDM is explained as any dysglycemia that occurs for the first time during pregnancy, which is a global public health problem [3,4]. GDM is one of the principal morbidity and mortality of mother and the infant over the world [5-7].

Generally, GDM mothers are always at high risk of growing preeclampsia, gestational hypertension and caesarean section [4,6,7-9]. Beside these, females with a GDM history are always at higher risk of growing type 2 diabetes and cardiovascular diseases later on [1,7,8-11]. Children born from GDM mothers are at high risk of being macrosomic, and they may suffer from many congenital abnormalities along with having higher propensity of growing neonatal hypoglycaemia, type 2 diabetes, cardiovascular diseases in their later life [7-12]. The pregestational diabetes and GDM prevalence has been increasing globally [5,8,11,13]. In pregnancies with diabetes complications, the diabetic intrauterine condition could cause placental dysfunction along with hormonal alterations, guiding to disease development [1,2,10,12,14]. Therefore, it is significant for healthcare policy makers to feel the GDM and cardiovascular burdens for in advance detection and further intervention.

It is clear from the previous articles that pregnancy is associated with diabetes and cardiovascular diseases. Many articles have focused on the relationships of pregnancy with gestational diabetes and induced hypertension using metaanalysis, simple correlation, which are not supported with suitable statistical analyses [1,5,7,11,14]. Consequently, the research has not good faith on these previously published articles. The current article aims to examine the relationships of pregnancy with diabetic functions such as glucose & insulin levels, diabetes history, DPF, BMI, hypertension parameter DBP, age, TST based on a real data set related to gestational women at least 21 years old. The article considers the following hypotheses.

- Is there any relationship of pregnancy with diabetic functions and induced hypertension parameters?
- If it is affirmative, what is the probable relationship?
- How do the diabetic functions and hypertension parameters affect pregnancy?

The current article examines the above hypotheses by considering some sections such as materials & methods, statistical analysis & results, discussions and conclusions. The real data and statistical methods used in the article are described in the materials & methods section. Necessary results related to the above hypotheses and interpretations are described in the remaining sections.

### **Materials & Methods**

#### Materials

The paper examines the above stated hypotheses using real data of 768 gestational American (Pima Indians) women at least 21 years old, which was extracted by the National Institute of Diabetes and Digestive and Kidney Diseases. One can finds the data set in the UCI Machine Learning Repository, which includes nine observational characters such as number of pregnancies, age, DBP (mm Hg), TST (mm), 2-hours serum insulin ( $\mu$  U/mI) (Insulin), BMI, plasma glucose concentration over 2 hours in an oral glucose tolerance test (Glucose), DPF, diabetic history subject type (DHST) (1=non-diabetic, 2=diabetic). Here number of pregnancies is a discrete variable, and diabetic history of sample unit type is an attribute character, but the remaining are continuous variables. It is pointed out here that DPF is a function that predicts diabetes likelihood based on family history.

#### **Statistical Methods**

The considered gestational data are physiological, while most of the responses may be heteroscedastic in nature. In the current study, 'the number of pregnancies' is the interested response variable, which is of discrete nature. During the whole gestational period of a female, all the fractional pregnancies, known as miss-carriage (known as natural abortions), or some induced abortions [please see 15-17] may be assumed to have some fractional numerical values, say 0.5. So, all the pregnancy values are increased by some fractional numbers, say 0.5 (herein), which is simply known as origin shifted by 0.5. This practically true assumption that the discrete variable 'the number of pregnancies' may be considered as a continuous variable. It is identified herein that the number of pregnancy's variance is non-constant, which should be modeled by stabilizing the variance using a suitable transformation, but it is not always stabilized under a suitable transformation [18]. It is well-known that a continuous positive equal variance dependent variable can be modeled either by the gamma, or the log-normal distributed model [19]. For a nonconstant variance continuous positive dependent variable, modeling can be done by using joint generalized linear models (JGLM) adopting the gamma, or the lognormal distributed model [20,21]. JGLMs is well illustrated in the book by Lee KW [20] et al., and Das RN [22]. The response 'the number of pregnancies' is modeled herein properly by JGLMs, which have been shortly presented in the recent articles by Das RN et al. [23,24] and for ready reference, they are shortly illustrated herein.

**Log-normal distributed JGLMs:** For a positive heteroscedastic random response  $Y_i$  (=the number of pregnancies) with  $E(Y_i) = \mu_i$  (mean) and  $Var(Y_i) = \sigma_i^2 \mu_i^2 = \sigma_i^2 V(\mu_i)$  say, where  $\sigma_i^2$ 's are dispersion parameters and V (=) explains the variance function, the log transformation  $Z_i = log(Y_i)$  is usually adopted to stabilize the variance  $Var(Z_i) \approx \sigma_i^2$ , while the variance may not be stabilized always [18]. In order to derive an improved model, JGLMs for the mean and dispersion are considered. Under log-normal distribution, JGL mean and dispersion models (with  $Z_i = logY_i$ ) are as follows:

 $E(Z_i) = \mu_{\tau_i}$  and  $Var(Z_i) = \sigma_{\tau_i}^2$ ,

 $\mu zi=x_i^t \beta$  and log ( $\sigma zi2$ )=  $g_i^t \gamma$ ,

where  $x_i^t$  and  $g_i^t$  are the explanatory variables vectors linked to the regression coefficients  $\beta$  and  $\gamma$ , respectively.

**Gamma distributed JGLMs:** For the above stated Yi's (=the number of pregnancies), the variance has two elements such as  $V(\mu_i)$  (depending on the mean parameters) and  $\sigma_i^2$  (free of  $\mu_i$ 's). The variance function V (\*) reveals the GLM family distributions. For illustration, if  $V(\mu) = \mu$ , it is Poisson, gamma if  $V(\mu) = \mu^2$ , and normal if  $V(\mu) = 1$  etc. Gamma JGLMs mean and dispersion models are as follows:

$$\eta_i = g(\mu_i) = x_i^t \beta$$
 and  $\varepsilon_i = h(\sigma_i^2) = w_i^t \gamma$ ,

Where  $g(\cdot)$  and  $h(\cdot)$  are the GLM link functions for the mean and dispersion

linear predictors respectively, and  $x_i^t$ ,  $w_i^t$  are the explanatory variables vectors linked to the mean and dispersion parameters respectively. Maximum likelihood (ML) method is applied for estimating mean parameters, while the restricted ML (REML) method is adopted for estimating dispersion parameters,

and these are illustrated in the book by Lee KW, Nelder JA and Pawitan V [20].

#### Statistical analysis & results

## **Statistical analysis**

The dependent variable 'the number of pregnancies' is modeled on the remaining eight independent factors such as glucose & insulin levels, diabetes history, DPF, BMI, DBP, age, TST using JGLMs under both gamma and log-normal distributions. The final number of pregnancies fitted joint model is taken based on the lowest Akaike information criterion (AIC) value that reduces both the predicted additive errors and squared error loss [25; p.203-204]. Following the AIC criterion, gamma model fit (AIC= 3361.795) of the number of pregnancies is better than log-normal fit (AIC= 3478). The final number of pregnancies gamma and log-normal JGLMs analyses outcomes are shown in Table 1. Based on the marginality rule by Nelder JA [26], all the lower order effects such as TST, BMI (in the mean model) (even insignificant) are included in the model as their higher order interaction effects are significant. For better fitting, some partially significant effects such as DPF (in the mean model), TST\*DPF, Insulin\* BMI (in the dispersion model) are included in the model, which are recognized as confounders in Epidemiology [25].

The number of pregnancies (NOP) gamma fitted JGLMs (Table 1) are diagnosed by Figure 1, where Figure 1(a) presents the absolute NOP gamma fitted residuals plot against its predicted values, which is closely a flat straight line, except the left tail, concluding that variance is equal with the running means. The left tail is decreasing due some lower absolute residuals are located at the left boundary. Figure 1(b) presents the NOP gamma fitted mean model (in Table 1) normal probability plot without any fitting discrepancy. Therefore, Figures 1(a) & 1(b) support that the NOP gamma fitted JGLMs are closely true models.

The NOP log-normal fitted JGLMs (Table 1) are diagnosed by Figure 2, where Figure 2(a) presents the absolute NOP log-normal fitted residuals plot against its predicted values, which is closely a flat straight line, concluding that variance is equal with the running means. Figure 2(b) presents the NOP log-normal fitted mean model (in Table 1) normal probability plot without any fitting discrepancy. Therefore, Figures 2(a) & 2(b) support that the NOP log-normal fitted JGLMs are closely true models.

Das RN and Lee KW [21] first focused about the discrepancy of fitting between the gamma and log-normal distributions for heteroscedastic responses. Later on Das and Park [27] and Das [28] have well illustrated the discrepancy of fitting between the gamma and log-normal distributions for homoscedastic and heteroscedastic responses. The current study supports the earlier results by Das RN and Lee KW [21], Das and Park [27] and Das [28]. Here it is noted that the standard error of each of the mean parameters for gamma fitting is smaller than the log-normal fitting, while for dispersion parameters, these situations are mixed. For the normal probability plots, Figure 1(b) and Figure 2(b), it is noted that there are three breaks one at the beginning and two at the ends for Figure 1(b), while for Figure 2(b), there are three breaks one at the beginning, one at the middle, and one at the end. But the two fits are very good showing similar interpretations.

## Results

Summarized NOP analysis findings from both the gamma and log-normal fitted JGLMs are presented in Table 1. It is derived herein that diabetic women (P=0.0053) become pregnant earlier than normal women. Mean pregnancy is positively linked to glucose level (P=0.0013) and age (P<0.0001), while it is negatively linked to their joint interaction effect Glucose\*Age (P=0.0003). It is partially positively linked to BMI (P=0.1129) and free of TST (P=0.2747), while it is negatively linked to their joint interaction effect TST\*BMI (P=0.0039), and it is also positively linked to TST\*Age (P<0.0001). In addition, mean pregnancy is negatively linked to insulin level (P=0.0170) and DPF (P=0.0890). Variance of pregnancy is positively linked to glucose level (P=0.1061) and DBP (P=0.0657), while it is negatively linked to their joint effect Glucose\*DBP (P=0.0125). Variance of pregnancy is negatively linked to TST (P<0.0001) and positively linked to DPF (P=0.0309), while it is negatively linked to the interaction effect TST\*DPF (P=0.0985), and positively linked to DBP\*TST (P= 0.0006). In addition, variance of pregnancy is negatively linked to insulin level (P=0.0871), while it is partially positively linked to the interaction effect Insulin\*DBP (P=0.1652), but free of BMI (P=0.7468).

Table 1: Joint gamma and log-normal Pregnancy fitting mean and dispersion models.

Model	Gamma model fit					Log-normal model fit			
Mean	Covariate	Estimate	Standard error	t-value	P-value	Estimate	Standard error	t-value	P-value
	Constant	-0.7063	0.36621	-1.929	0.0541	-0.7205	0.41234	-1.747	0.0810
	Glucose (GLU)	0.0086	0.00266	3.225	0.0013	0.0057	0.00296	1.914	0.0560
	AGE	0.0583	0.00986	5.916	<0.0001	0.0520	0.01119	4.645	<0.0001
	GLU*AGE	-0.0003	0.00007	-3.624	0.0003	-0.0002	0.00008	-2.402	0.0165
	TST	-0.0098	0.00898	-1.093	0.2747	0.0008	0.00993	0.085	0.9323
	BMI	0.0079	0.00500	1.587	0.1129	0.0103	0.00572	1.804	0.0716
	TST*BMI	-0.0006	0.00020	-2.898	0.0039	-0.0008	0.00022	-3.555	0.0004
	Insulin (INS)	-0.0006	0.00026	-2.391	0.0170	-0.0005	0.00028	-1.904	0.0573
	DPF	-0.1404	0.08244	-1.703	0.0890	-0.1953	0.09061	-2.155	0.0315
	TST*AGE	0.0008	0.00014	5.883	<0.0001	0.0007	0.00016	4.692	<0.0001
	DHST	0.1758	0.06282	2.798	0.0053	0.1720	0.06981	2.464	0.0140
Variance	Constant	-1.9067	0.85358	-2.234	0.0258	-1.7316	0.84779	-2.042	0.0415
	GLU	0.0120	0.00739	1.618	0.1061	0.0133	0.00733	1.817	0.0696
	DBP	0.0226	0.01229	1.843	0.0657	0.0254	0.01223	2.078	0.0380
	GLU*DBP	-0.0002	0.00010	-2.502	0.0125	-0.0003	0.00010	-2.790	0.0054
	TST	-0.0910	0.01921	-4.737	<0.0001	-0.1125	0.01931	-5.824	<0.0001
	GLU*TST	0.0004	0.00011	3.479	0.0005	0.0005	0.00011	4.477	<0.0001
	DBP*TST	0.0006	0.00019	3.439	0.0006	0.0008	0.00019	4.045	<0.0001
	DPF	0.6059	0.28032	2.162	0.0309	0.7538	0.28779	2.619	0.0090
	TST*DPF	-0.0151	0.00913	-1.654	0.0985	-0.0210	0.00958	-2.188	0.0290
	INS	-0.0041	0.00241	-1.713	0.0871	-0.0046	0.00251	-1.833	0.0672
	BMI	0.0027	0.00831	0.323	0.7468	0.0044	0.00819	0.535	0.5928
	INS*BMI	0.0001	0.00007	1.389	0.1652	0.0001	0.00007	1.430	0.1531
AIC		3361,795				3478			



Figure 1: For the JGL gamma NOP fit (Table 1), the (a) absolute residuals plot against the NOP fitted values, and (b) the normal probability plot for the NOP mean model.

JGL gamma fitted NOP mean ( $\hat{\mu}$ ) model (Table 1) is

# = exp(--0.7063 + 0.0086 Glucose + 0.0583 Age --0.0003 Glucose\*Age --0.0098 TST + 0.0079 BMI -- 0.0006 TST\*BMI -- 0.0006 Insulin --0.1404 DPF +0.0008 TST\*Age + 0.1758 DHST), and the JGL gamma fitted NOP dispersion ( $\hat{\sigma}^2$ ) model (from Table 1) is

*∂*<sup>2</sup> = exp(--1.9067 + 0.0120 Glucose + 0.0226 DBP --0.0002 Glucose\*DBP --0.0910TST + 0.0004 Glucose\*TST + 0.0006 DBP\*TST + 0.6059 DPF -- 0.0151 TST\*DPF -- 0.0041Insulin + 0.0027 BMI + 0.0001 Insulin\*BMI).



Figure 2: For the JGL Log-normal NOP fit (Table 1), the (a) absolute residuals plot against the NOP fitted values, and (b) the normal probability plot for the NOP mean model.

# Discussions

The above JGL gamma fitted NOP analysis outcomes (from Table 1) and the above NOP's mean & dispersion models, the following can be interpreted. Mean NOP is positively linked to DHST (1= non-diabetic, 2= diabetic) (P=0.0053), concluding that diabetic women become pregnant earlier than normal women. Mean NOP is positively linked to glucose level (P=0.0013), interpreting that pregnancy increases as glucose level rises. It shows that diabetic women have higher pregnancy than normal. Mean NOP is positively linked to age (P<0.0001), while it is negatively linked to the joint interaction effect Glucose\*Age (P=0.0003). It shows that pregnancy increases at higher ages, but it is not so high for diabetic women at higher ages as it is negatively linked to the joint effect Glucose\*Age. Therefore, diabetic women have higher pregnancy at younger ages. Mean NOP is partially positively linked to BMI (P=0.1129), interpreting that pregnancy increases as BMI rises, while BMI is also a diabetic factor. It is negatively linked to the joint interaction effect TST\*BMI (P=0.0039), while TST (P=0.2747) is independent of NOP. It concludes that pregnancy is not always so high for obesity women. In addition, mean NOP is positively linked to TST\*Age (P<0.0001), concluding that pregnancy increases with the increase of the joint effect of TST and age. Even though the marginal effect of TST is insignificant with the mean of NOP, its joint effects with BMI and age are significantly associated with the mean of NOP. Therefore, TST has a great role on NOP. Mean NOP is negatively linked to insulin level (P=0.0170), concluding that pregnancy increases as the insulin level decreases. This indicates that pregnancy is higher for the low insulin levels women, and these women are diabetic due to their low insulin levels. Moreover, mean NOP is negatively linked to DPF (P=0.0890), implying that pregnancy increases as DPF decreases.

From the above it is observed that mean NOP is highly associated with the diabetic parameters such as glucose levels, insulin levels, diabetic history of the subjects, BMI and DPF. In addition, mean NOP is associated with joint diabetic parameters such as Glucose\*Age and TST\*BMI. Also it is associated with TST\*Age. But mean NOP is free of hypertension parameter DBP. From these derived results, it can be concluded that mean pregnancy is highly associated with diabetic parameters such as glucose levels, insulin levels, diabetic history of the subjects, BMI, DPF, Glucose\*Age and TST\*BMI. These associations indicate that diabetic women become pregnant earlier than normal women.

Variance of pregnancy is positively linked to glucose level (P=0.1061) and DBP (P=0.0657), concluding that for diabetic and hypertension women pregnancy numbers are highly scattered, while the scatteredness is not so high as the pregnancy's variance is negatively linked to their joint effect Glucose\*DBP (P=0.0125). Variance of pregnancy is negatively linked to TST (P<0.0001), and positively linked to DPF (P=0.0309), implying that pregnancy numbers are

highly scattered for the women with low TST and high DPF values. In addition, pregnancy's variance is negatively linked to the interaction effect TST\*DPF (P=0.0985), and positively linked to DBP\*TST (P= 0.0006), interpreting that pregnancy numbers are highly scattered for the women with low effect of TST\*DPF and high effect of DBP\*TST values. In addition, variance of pregnancy is negatively linked to insulin level (P=0.0871), implying that pregnancy numbers are highly scattered for the women with low insulin level. Moreover, it is partially positively linked to the interaction effect Insulin\*DBP (P=0.1652), but free of BMI (P=0.7468).

Form the above, it is noted that NOP's variance is associated with diabetic and hypertension parameters such as glucose levels, insulin levels, DPF, DBP, Glucose\*DBP, Glucose\*TST, DBP\*TST, TST\*DPF, Insulin\*BMI. It concludes that pregnancy's variance is highly associated with both diabetic and hypertension parameters.

These above outcomes are very little known in the earlier published articles. Most of the outcomes from both in the mean and dispersion models are completely new in the pregnancy study literature. A few earlier articles [1,3,7-14, 29,30] have mentioned the associations of pregnancy numbers with diabetes and hypertension parameters, but the associations have not been established using any suitable statistical modeling. The current paper has established all the associations based on proper modeling, along with model diagnostic checking. The present pregnancy's associations can't be compared with any earlier published article, as there was not any modeling approach of pregnancy study. Present outcomes can be verified using the data set given in the UCI Machine Learning Repository.

#### Conclusion

The associations of pregnancy with diabetes and hypertension parameters are established in the report. All the derived results are verified with similar models and model diagnostic tools. The standard error of the parameters of pregnancy number estimation are very small in both the models, concluding that estimates are stable. Final models are taken based on the lowest AIC value, distributions comparison, and diagnostic checking. Therefore, the research has a complete faith on the present associations. It is hoped that similar pregnancy's associations can be obtained from any source of similar data set that has not been searched herein due to similar data unavailable. This paper has established a complex relationship of pregnancy numbers with diabetes and hypertension parameters. The mean pregnancy model shows many interesting associations of pregnancy with diabetes parameters, while dispersion model shows completely new interesting associations of pregnancy with diabetes and hypertension parameters. All the reported results related to pregnancy's association with diabetes and hypertension parameters are completely new in the pregnancy studies literature, which are helpful to the medical practitioners, researchers and pregnant women. It is concluded that mean pregnancy is well related to the diabetic functions such as glucose & insulin levels, diabetes history, DPF, BMI, while pregnancy's variance is well related to the diabetic functions and hypertension parameter DBP. Diabetes women become pregnant more earlier than normal women.

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