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Causes of Miscarriage: Evidence from Logistic Regression Analysis

Nasir Elmesmari*

University of Benghazi, Benghazi-Libya
Email: nasir.elmesmari@uob.edu.ly

Abstract

The unexpected end of a pregnancy before the birth is called Miscarriage. The miscarriage rate among pregnant women is about 15 to 20%. The first step in emotional recovery is to gain a better understanding of miscarriages. Next, it's important to identify the factors that can elevate the risk of miscarriage. The objective of this study was employing a logistic regression model to evaluate the impact of various factors, including maternal age, embryo weight, chronic conditions, the number of previous miscarriages, and the embryo's gender. Our analysis reveals that when we control for these characteristics, the findings based on the data sample show that maternal age, chronic conditions, and the number of previous miscarriages have statistically significant impact on the incidence of miscarriage.

Keywords: Pregnancy; Miscarriage; maternal age; chronic conditions; Logistic regression; Binary data.

1. Introduction

Miscarriage is often misunderstood by many women, and health care providers, and misconceptions about miscarriage are widespread. For example, women might believe miscarriage is rare, that it could be caused by lifting heavy objects or previous contraceptive use, or that there are no effective treatments to prevent a miscarriage [8]. Such misconceptions can be damaging, leaving women and their partners felling at fault and not seeking treatment and support. Miscarriage can also lead to isolation, since many women might not tell their family, close friends, or even their partner about the loss of their pregnancy [17].

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* Corresponding author.

Couples have voiced concerns over unsympathetic routine clinical care by healthcare provider [2].Women and their partners who have had a miscarriage generally want to understand what causes the miscarriage, and what needs to be done to prevent miscarriage from occurring again as well as the likelihood of subsequent pregnancy resulting in a healthy baby [7]. Couples might be given diverse pinions by different health care professionals, which can exacerbate their distress. There are also debates over definitions, causes, and consequences, and cost of miscarriage.

Women presenting for the early pregnancy scan very often do not have any symptoms that may alert them to the possibility of pregnancy failure [6]. The miscarriage or the biochemical pregnancy loss is pregnancy loss, which occurs from positive urinary or serum human chorionic gonadotropin, however, before ultrasound detection of pregnancy less than weeks [1].

2. Research Objective and Hypotheses

Miscarriage can occur for various reasons. For instance, genetic abnormalities, maternal health issues, and cardiovascular diseases are recognized causes of miscarriage. Additionally, lifestyle choices, diet, smoking, and alcohol consumption are potential risk factors. Some studies have identified obesity as an independent risk factor for miscarriage [9]. Maternal age of 35 or older significantly contributes to the likelihood of miscarriage. There may also be a gender bias in spontaneous abortions, suggesting that female fetuses might be more vulnerable to miscarriage than male ones. A history of previous miscarriages and chronic health conditions can further elevate the risk.

The objective of this study is to see if these characteristics are statistically significant of miscarriage.

Table 1: Research Hypotheses

Null Hypothesis	**Alternative Hypothesis**
H_0: maternal age is not a statistically significant for miscarriage	H_1 : maternal age is a statistically significant for miscarriage
H_0 : Number of previous miscarriages is not a statistically significant for miscarriage	H_1 : Number of previous miscarriages is not a statistically significant for miscarriage
H_0: Wieght of embryo is not a statistically significant for miscarriage	H_1: Wieght of embryo is a statistically significant for miscarriage
H_0: Chronic conditions is not a statistically significant for miscarriage	H_1: Chronic conditions is a statistically significant for miscarriage
H_0 : Gender is not a statistically significant for miscarriage	H_1: Gender is a statistically significant for miscarriage

3. Miscarriage

Is the natural death of a fetus before it is viable, usually in the first 20 weeks of pregnancy. Medically termed spontaneous abortion, miscarriage is one of the most common pregnancy related issues [1]. The American college

of obstetricians or gynecologists (ACOG) estimates that about 15% to 20% of clinically recognized pregnancies end up in miscarriages [7]. Although, it is common, it can be an extremely traumatic and devastating experience. Many women may even have miscarriage before they know they are pregnant or before it has been confirmed by a health-care provider [2].

In women who are under the age of 35, the risk is about 10% while in those over the age 40 the risk is about 45% Reference [8]. Most women who have a miscarriage go on have healthy pregnancies after a miscarriage. After one miscarriage, the predicted risk of miscarriage in a future pregnancy is usually about 14%. The predicted risk increases to about 26% after two miscarriages and after three miscarriages it increases to about 28% [3].

3.1 Types of Miscarriage

1) Threatened Miscarriage: The woman may experience signs of miscarriage such as bleeding with lower backache, but the loss of pregnancy has not yet occurred.

2) Incomplete miscarriage: Where some of the tissue from the pregnancy has been expelled from the uterus, but some remain [4].

3) Complete miscarriage: Where all of the tissue from the pregnancy are expelled from the body.

4) Missed carriage: Where the embryo dies but the body does not bound expel the pregnancy tissue and no symptoms such as bleeding or pain are experienced.

5) Recurrent Miscarriage: Which is the occurrence of multiple consecutive miscarriages.

6) Septic Miscarriage: Where tissue from a missed or incomplete miscarriage become infected [8].

3.2 Causes of Miscarriage

Most women blame themselves from miscarriage, but most miscarriage happens from reasons that are beyond control. In most cases, there is no way to prevent a miscarriage and nothing to done right would have stopped it Reference [21]. The risk of miscarriage could be increase by various nongenetic reasons including:

1. Age, the risk of miscarriage about 20% for women at age 35, and the risk about 40% if the age is 40 and the risk would be increase till 80 % if the age was 45.

2. Previous miscarriages, women with a history of two or more consecutive miscarriages face a greater likelihood of experiencing future miscarriages

3. Chronic conditions, women with ongoing health issues, like uncontrolled diabetes, are at greater risk of experiencing a miscarriage.

4. Uterine or cervical problems, weak cervical tissue or specific uterine disorders might heighten the chances

of miscarriage [10].

5. Smoking, alcohol and illicit drugs, pregnant women who smoke are more likely to experience miscarriage compared to non-smokers. Additionally, excessive alcohol consumption and the use of illegal drugs further heighten this risk.

6. Weight, both underweight and overweight conditions have been associated with a higher risk of miscarriage.

7. Invasive prenatal examinations, tests such as chorionic villus sampling and amniocentesis, which are used for genetic diagnosis during pregnancy, slightly increase the risk of miscarriage [18].

4. Data and sample size

Data in this study were recorded and collected from Al-Marj Teaching Hospital which located in east coast of Libya from 2011- 2016, this data included 199 women with 119 cases of miscarriages and 80 cases not miscarriage. Other information also was recorded like maternal age, weight of embryo, Chronic conditions, number of previous miscarriages and gender of embryo. The minimal sample size for multiple logistic regression is the minimum number of observations needed to execute the logistic regression model. The factors involved in determining sample size include statistical power, predictor variables, smallest proportion of binary cases, effect size, and standard error, making sample size estimation for multiple logistic regression a complex effort. Peduzzi, Concato, Kemper, Holford and Feinstein (1996) contend that minimal sample size is defined as n = 10k/p, where k represents the number of predictor variables and p denotes the smallest proportion of binary cases in the population, with (1) indicating that the event occurred and (0) indicating that the event did not occur [14, 15]. Additionally, if the calculated number of observations is less than 100, it is recommended that the sample size be increased to 100 [19]. Based on our dataset, the proportion of binary cases resulted in 119 (1's) and 80 (0's), resulting in the value of 80 as the smaller binary proportion. Table (2) shows that the minimum sample size of five predictors which is

Table 2: Logistic Regression Sample Size n = 10k/p

	k	p		n
constant	Predicted variables	Binary case Proportion	Calculated Sample Size	Adjusted Sample Size
10	5	80/199	124.37	125
10	2	80/199	49.75	100

In this study, we have two models (Full model with five predictors and reduced model with two predictors), so the minimal sample size for five predictors model is 125 and the minimal sample size for two predictors model is 50 and rounded up to 100, given that the calculated sample size is less than 100.

5. Logistic regression

Logistic regression is a technique for modeling the relationship between multiple independent variables and a binary categorical dependent variable [14]. Use of logistic regression is an appropriate statistical analysis technique when the dependent variable has two possible outcomes. It is often used to address research objectives associated with establishing a classification system for determining group membership [11].

The other names of this model are the logistic model or logit model, examines the relationship between a categorical dependent variable and one or multiple independent variables, and estimates the possibility of occurrence of an event [14]. There are two models of logistic regression, binary logistic regression and multicategories logistic regression.

5.1. Binary logistic regression

Binary logistic regression is typically used when the dependent variable is dichotomous and the independent variables are either continuous or categorical. Moreover, the dependent variable can take only two values (1 or 0) that indicate to success and fail respectively [20]. Now let variable y follows Bernoulli distribution with parameter π and the formula is:

$y_i = B_0 + B_1 x_i + \epsilon_i$ and $E(y_i) = b_0 + b_1 x_i = \pi_i$,

The expected value of (y = 1) is $E(y_i) = (y_{i=1})$, but there are some challenges when carrying out this linear model like:

1- Error terms are not normally distributed (binary).

2- Nonconstant variance of errors over all observations

$$v(y_i) = \pi_i(1 - \pi_i)$$

$$= (b_0 + b_1 x_i)(1 - b_0 - b_1 x_i)$$

3- Limit of expected value $0 \leq E(y_i) \leq 1$ in fact this is not true because $-\infty \leq b_0 + b_1 x_i \leq \infty$ For these reasons the variable y distributed logistic distribution.

$$P(y_i = 1) = \pi_i = \frac{e^{B_0 + B_1 x_i}}{1 + e^{B_0 + B_1 x_i}} \qquad (1)$$

$$P(y_i = 0) = 1 - \pi_i = \frac{1}{1 + e^{B_0 + B_1 x_i}} \qquad (2)$$

The Odds ratio is $\frac{\pi_i}{1-\pi_i} = e^{B_0 + B_1 x_i}$ the probability of the event (y=1) will occur over the probability of the event (y = 0) will not occur. However, if we take the natural logarithm for both sides will get:

$$\log\left(\frac{\pi_i}{1-\pi_i}\right) = B_0 + B_1 x_i$$

This called the OLS-type equation where allow to apply linear regression [15].

5.2. Multicategories logistic regression

This model will be used if the dependent variable has more than two possible values (more than two categories), there are two type of this model which are nominal logistic regression and ordinal logistic regression [12].

5.2.1. Nominal logistic regression

Suppose the dependent variable y has j number of categories and $\pi_1, \pi_2, \dots, \pi_j$ are probabilities corresponding to categories 1, 2,…,j where $\pi_1 + \pi_2 + \cdots + \pi_j = 1$. If we have base category j then we will have j-1 of equations with different parameters:

$$\log\left(\frac{\pi_1}{\pi_j}\right) = B_{01J} + B_{11J}x_1 + B_{21J}x_2 + \cdots + B_{\rho 1J}x_\rho$$

$$\log\left(\frac{\pi_2}{\pi_j}\right) = B_{02J} + B_{12J}x_1 + B_{22J}x_2 + \cdots + B_{\rho 2J}x_p$$

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$$\log\left(\frac{\pi_{J-1}}{\pi_J}\right) = \mathrm{B_{0J-1J}} + \mathrm{B_{1J-1J}x_1} + \mathrm{B_{2J-1J}x_2} + \cdots + B_{\rho J-1J}x_\rho$$

$$(i = 1, \dots, n, j = 1,2 \dots yij)$$

The maximum likelihood function will be:

$$L(B_{1J}, \dots, \mathrm{B_{J-J}}) = \prod_{i=1}^{n} \begin{bmatrix} y_{i1} & y_{i2} \dots & y_{iJ} \\ \pi_{i1} & \pi_{i2} \dots & y_{iJ} \end{bmatrix}$$

$$\pi_{\mathrm{ij}} = \frac{\exp(\mathrm{x_i B_j})}{1 + \sum_{\mathrm{K=1}}^{\mathrm{J-1}} \exp(\mathrm{x_i B_j})}$$

5.2.2. Ordinal logistic regression

Suppose the dependent variable y has j number of categories $C_1, C_2, \dots., C_j$ such that:

$C_1 \leq C_2 \leq \cdots . \leq C_j$ or $C_1 \geq C_2 \geq \cdots . \geq C_j$

And probabilities $\pi_1, \pi_2, \ldots, \pi_j$ corresponding to 1, 2, …, j where $\pi_1 + \pi_2 + \cdots . + \pi_j = 1$

The cumulative probabilities are the probabilities that the response y falls in category j or below.

$$p(y \leq C_j) = \pi_1 + \pi_2 + \cdots . + \pi_j \quad j = 1, 2, \ldots, J$$

For a model with P predictors, it is given by

$$\log\left(\frac{\pi_1}{\pi_2 + . \ldots + \pi_J}\right) = B_{01} + B_1 x_1 + \cdots + B_\rho x_\rho = B_{01} + x'_1 B$$

$$\log\left(\frac{\pi_1 + \pi_2}{\pi_3 + \cdots + \pi_J}\right) = B_{02} + B_1 x_1 + \cdots + B_\rho x_\rho = B_{02} + x'_2 B$$

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$$\log\left(\frac{\pi_1 + \cdots + \pi_{J-1}}{\pi J}\right) = B_{0J-1} + \mathrm{B_1 x_1} + \cdots + B_\rho x_\rho = B_{0J-1} + x'_{J-1} B$$

Or simply

$$\log\left(\frac{p(y \leq C_j)}{1 - p(y \leq C_j)}\right) = B_{0\mathrm{j}} + \mathrm{B_1 x_1} + \cdots + B_\rho x_\rho = B_{0j} + x'_j B$$

Where $p(y \leq C_j) = \frac{\exp(\mathrm{B_{0j} + x'_j B})}{1 + \exp(\mathrm{B_{0j} + x'_j B})}$

The maximum likelihood function will be:

$$L(x_1, \ldots, x_J, B) = \prod_{\mathrm{i=1}}^{n} \left(\prod_{\mathrm{i=1}}^{\mathrm{J}} [\pi_{\mathrm{ij}}]^{y_{ij}} \right)$$

$$= \prod_{\mathrm{i=1}}^{n} \left(\prod_{\mathrm{i=1}}^{\mathrm{J}} \left(\mathrm{P(y_i \leq c_j)} - \mathrm{P(y_i \leq c_{j-1})} \right)^{y_{ij}} \right)$$

6. Goodness of Fit

This is an overall measure of the fit of the logistic model (monotonicity, S-shape) Cases to consider:

6.1. Pearson chi-square test

$$H_0: E(y) = [1 + exp(-x'\beta)]^{-1}$$

$$H_1: E(y) \neq [1 + exp(-x'\beta)]^{-1}$$

Let c = number of distinct combinations of the predictor variables

n_j = number of cases in class j

O_{j1}= observed number of cases in the j^{th} class with outcome 1

O_{j0}= observed number of cases in the j^{th} class with outcome 0

The test statistic is:

$$x^2 = \sum_{j=1}^{c} \sum_{k=0}^{1} \frac{(O_{jk} - E_{jk})^2}{E_{jk}} \sim x^2(c - p)$$

Where E_{jk} is expected frequency [15].

6.2. Hosmer-Lemeshow test

Consists of grouping the data into classes (5-10 classes, approximately the same number of cases in each) with similar fitted values (probabilities), and then apply Pearson chi-square test. Hosmer and Lemeshow [12] showed by simulation as:

$$x^2 = \sum_{j=1}^{c} \sum_{k=0}^{1} \frac{(O_{jk} - E_{jk})^2}{E_{jk}} \sim x^2(c - 2)$$

6.3 The ROC Curves and AUC

The area that the receiver operating characteristics curve (ROC) represented as a scatter plot of values ranging between 0 and 1, such that data pairs (x, y) or (1-specificity, sensitivity) (Berrar & Flach,2012). The overall performance of the fitted logistic regression model provided by the area under the ROC curve (AUC) [5].

In AUC curve, data points below the diagonal line dividing the ROC space represent poor model performance (worse than random), while data points above the diagonal line indicate good model performance (better than

random). Higher AUC values suggest better predictability of the fitted model [14].

7. Analysis

Based on data available we have five factors maybe contribute to miscarriage incidence, these factors are maternal age, number of previous miscarriages, weight of embryo, chronic conditions, and gender of embryo. Binary logistic regression model is a technique for evaluating the relationship between these five independent variables and a binary dependent variable. This model is an appropriate statistical technique for addressing the relationship when the dependent variable has only two possible outcomes [14,1]. Logistic regression is often used to address research objectives associated with establishing a classification system for determining group membership [11]. The Microsoft Windows R platform (R Core Team, 2019) was selected as the computer software for executing the analysis and the results as the following:

Table 3: Statistical Significance of Logistic Regression Coefficients for full model

Variable	Estimate	Std. Error	z-value	p-value
Intercept	- 2.815	0.9569	-2.942	0.00327
Maternal age	0.0576	0.02961	1.945	0.05176
Previous miscarriages	0.9476	0.3966	2.390	0.01687
Weight of embryo	-0.00006	0.00013	-0.465	0.64188
Chronic conditions	1.8880	0.4203	4.492	0.00000
Gender of embryo	-0.2684	0.3336	-0.804	0.42112

This model (Full Model) has AIC coefficient = 227.37 as estimator of prediction error, and a Hosmoer-Lemeshow test with P-value = 0.559 which means that all predictor variables are more effective than the null model [12]. As we can see in (Table3) the contribution of the factors weight and gender of embryo is not significant (P-value > 0.05), so we should drop these factors and apply the rest of factors in the next model (Reduced Model):

Table 4: Statistical Significance of Logistic Regression Coefficients for reduced model

Variable	Estimate	Std. Error	z-value	p-value
Intercept	- 3.008	0.92057	-3.268	0.00108
Maternal age	0.0569	0.02871	1.983	0.04742
Previous miscarriages	0.9441	0.39334	2.400	0.01638
Chronic conditions	1.8870	0.41704	4.525	0.00000

The AIC coefficient for reduced model is 224.22 which indicate that this model is better than the full model, and Hosmoer-Lemeshow test with P-value = 0.608 which shows all predictor variables are more effective than the null model.

Using classification confusion matrix to measure the performance of the model and see how well classifier is preforming, the confusion matrix for full model (using all predictor variables) in table 5 shown the predictive accuracy of the logistic model [16].

Table 5: Classification Confusion Matrix of full model

Predicted			
Actual	Yes	No	% Correctly predicted
Yes	82	38	68.33% Sensitivity
No	24	55	69.62 % Specificity
Overall % correct			68.84 % Overall
Sensitivity = 82/(82+38) = 68.33% ; Specificity = 55/(24+55) = 69.62 %			

The elements of confusion matrix are predicted values for the cross classification of the observed values for the dependent variable and the predicted values at the default cut-off point which is 0.5. So, predicted value of response variable > 0.5 classified as a women with miscarriage which coded as 1 and predicted value of response variable ≤ 0.5 classified as a women with no miscarriage which coded as 0. It is known that the ability to correctly predict a class 1 as sensitivity and the ability to correctly predict 0 as specificity. In table 5 the overall correct prediction of 68.84% that indicates an improvement over a 50% level of chance. A fitted model with superior classification performance is shown by higher percentages of sensitivity and specificity.

Table 6: Classification Confusion Matrix of Reduced model

Predicted			
Actual	Yes	No	% Correctly predicted
Yes	79	41	66 % Sensitivity
No	22	57	72.2 % Specificity
Overall % correct			68.34 % Overall
Sensitivity = 79/(79+41) = 66 % ; Specificity = 57/(22+57) = 72.2 %			

The confusion matrix of the reduced model which is after dropping non-significant predictor variables shown in table 6. I noticed that there is no different in the overall accuracy for both models (68.88% in full model and 68.34% in reduced model). This finding is a good indication that the reduced model is preforming well.

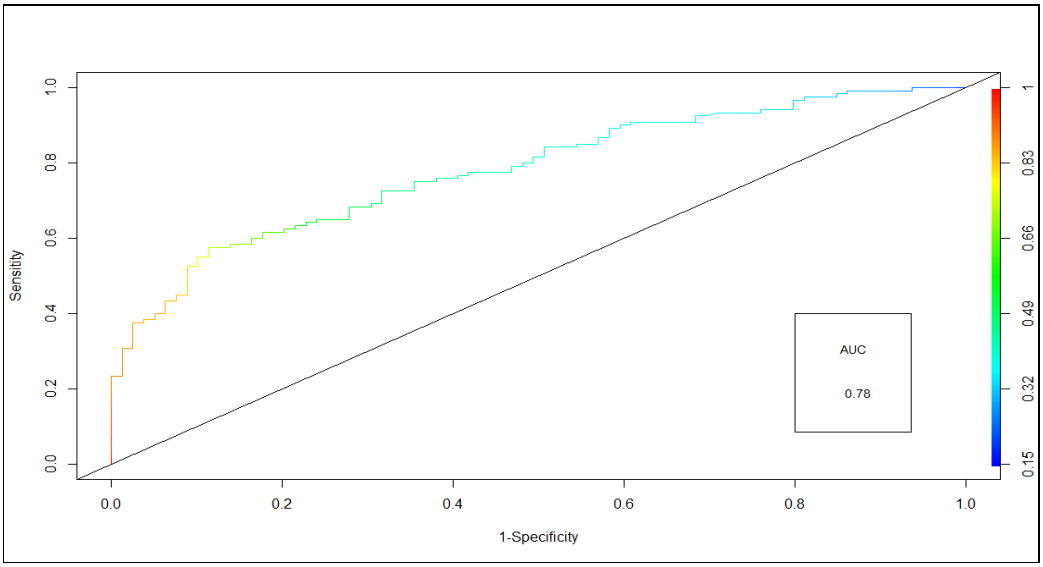

Figure 1 : AUC (78 %) for full model

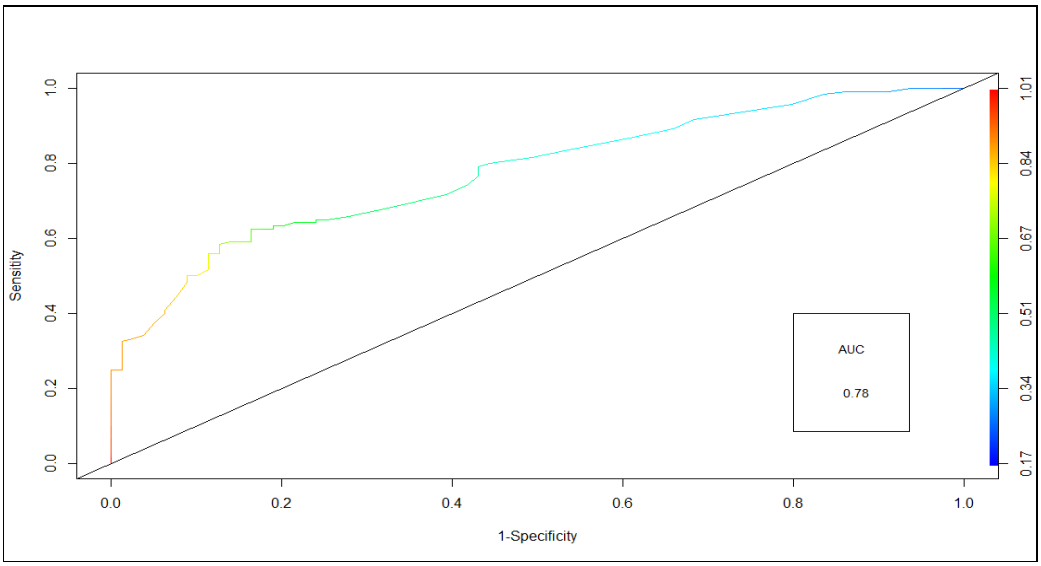

Figure 2 : AUC (0.78 %) for reduced model

Clearly, from Figure 1 and Figure 2 that both AUC curves have data points above the diagonal line, which indicate good models' performance. Consequently, there is no different between the model with all five predictors variables (full model) and the model with three predictors variables (reduced model).

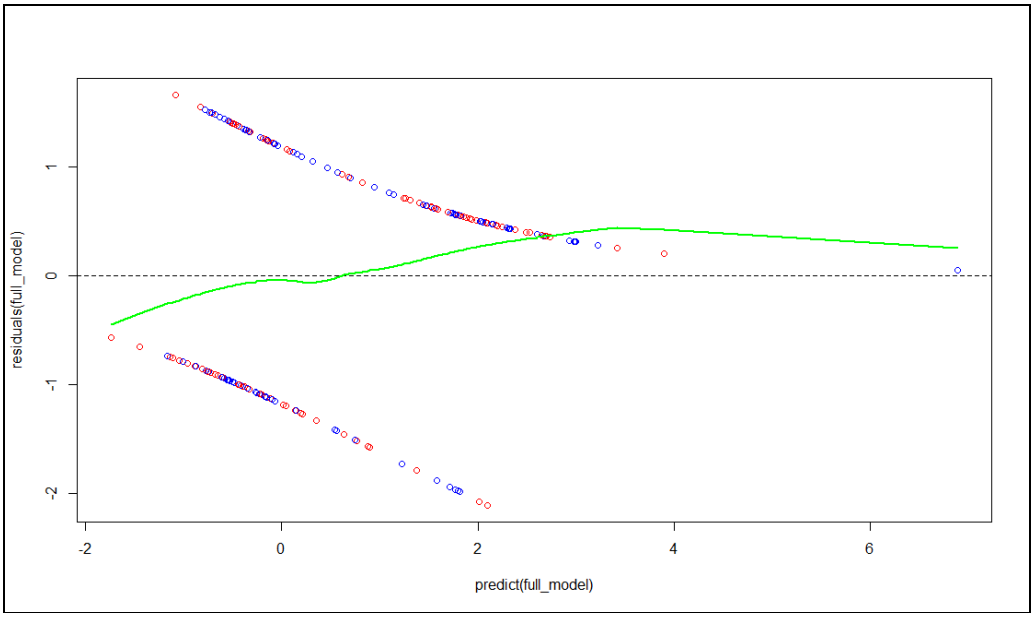

Figure 3: Residual Plot with LOWESS Smoothing for full model

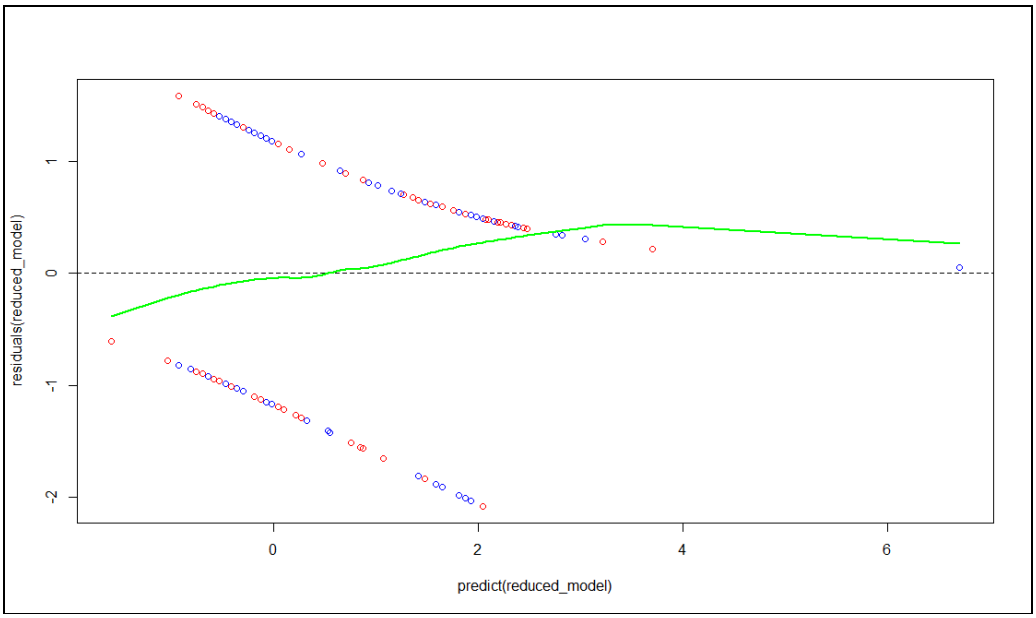

Figure 4: Residual Plot with LOWESS Smoothing for reduced model

From Figures (3 and 4) show Pearson residual plot versus the estimated probability for the model. In these figures, the locally weighted scatterplot smoothing (LOWESS) approximates a line having zero slope and a near zero intercept. We conclude that the adequacy is acceptable for both models.

8. Summary and Conclusion

In this paper we tried to discover the factors that may affect miscarriage using logistic regression, the data available included five factors which are maternal age, previous miscarriages, weight of embryo, chronic conditions and

gender of embryo (full model). Our finding based on the Wald Chi-Square test, there are three factors that are statistically significant classifiers for miscarriage incident. These factors are maternal age, previous miscarriages, and chronic conditions, in fact the pregnancy may affected with these factors as have mentioned in previous studies [2, 3, 6, 7 and 8]. We got the same finding after repeated the analysis with dropping the non-significant factors (reduced model). The limitations of this study include an insufficient sample size, and the study could be enhanced by collecting data with a broader range of variables, particularly genetic information.

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