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Research Article
Correlation Between Fibrinogen Level with Placenta Infarct to Missed Abortion

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Abstract

Background and Objective: Missed abortion is a failed pregnancy due to the death of the embryo conception product or a fetus. This research aims to identify the correlation between fibrinogen level on pregnancy and the age of the conception product during abortion, abortion progress and appearance of placental infarct on missed abortion cases. **Materials and Methods:** The research method used is a cross sectional analysis. The study was done in Budi Mulia Maternal Hospital and Network Hospital in Makassar city. The study sample is patient with early pregnancy, whom after the researchers do anamnesis, physical examination, supporting examination (blood fibrinogen level and ultrasonography) showed the potential for missed abortion, the sampling was done since March, 2017. The data was analyzed using version 17.0 of SPSS. **Results:** The study resulted that there were significant increases of fibrinogen ($p = 0.015$) on missed abortion during 6th-10th week pregnancy, that had been measured since the beginning of the last menstruation period and on fibrinogen level increased on early pregnancy according to the ultrasonography (64.3%) ($p = 0.007$). **Conclusion:** The abnormally elevated pregnancy fibrinogen concentration during abortion age is equivalent to hypercoagulation that has potential on abnormal hyper coagulability, tend to create thrombosis.

Key words: Missed abortion, fibrinogen, placental infarct

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Missed abortion is a failure of pregnancy continuity of a pregnancy due to the death of conception product of embryo or a fetus that was seen during ultrasonography examination when the mother's gestational age is less than 20 weeks without any signs of life[1] marked by the absence of fetal heartbeat and that the whole abnormal conception product still be obstructed inside the womb[2]. The pregnancy itself is a unique combination, although it is not a disease, it often causes complications due to physiological changes[3]. Various thrombolytic cases show that pregnancy can undergo hemostasis capacity changes into hypercoagulation that has the potential to trigger thrombosis due to coagulation and fibrinolytic system dysregulation as the response of pregnancy that can cause complications such as abortion in early pregnancy, intra-uterine fetal death and hypertension abnormality at the end of pregnancy[4]. Hypercoagulation is a set of blood coagulation disturbance that happens due to the change of equilibrium of hemostatic system, because of the increase of more fibrinogen pro-coagulation level to proportion along with the decrease of fibrinolysis and anti-level of protein[3].

The previous study by Cunningham *et al*.[4] found that the average fibrinogen grown level of non-pregnant women was 200 mg dL^{-1}. On normal pregnancy, the fibrinogen increases along with the increasing gestational age on about 300 mg dL^{-1} or 50% from the range[5,6] of 200-400 mg dL^{-1}. Then, the fibrinogen level progressively increases until the end of pregnancy into the average level of 450 mg dL^{-1} from 300-600 mg dL^{-1} with the critical score >700 mg dL^{-1}.

Furthermore, the hormonal changes that happen in pregnancy and thrombosis risk factors can trigger the instability of coagulation factors and fibrinolysis that cause the haemodynamic change in haemostasis system of pregnancy[7]. Along with the increasing gestational age, if the increasing pro-coagulation level reaches the abnormal level, it will trigger thrombosis (the abnormal blood coagulation) from normal coagulation status to abnormal hypercoagubility[3]. The thrombosis changes haemodynamic uteroplacental vascular circulation into abnormality, such as the risk factor of ischemial infarct, perfusion deficit and placental insufficiency that end with fetal death[6]. The thrombosis impairment on pregnancy outcome can causes fetal death and abortion at the end[8]. In the same case, the disturbance of a chronic blood flow of uteroplacental vascular causes retardation of growth and fetal death if the disparity is weight[9].

It was predicted that the change of increasing fibrinogen activity most likely causes disturbance of coagulation factor balance, anti-coagulation and fibrinolytic in pregnancy that can undergo changes into hypercoagulation state with the hypercoagulable capacity and its capability tends to trigger thrombosis, vascular occlusion and ischemic infarct. By this change, they cause placental insufficiency and the death of conception product. This study is conducted to identify the the correlation between fibrinogen level with placenta infarct to missed abortion until it addresses pregnant woman to fatal death and thus the result of the correlation can contribute a particular and new handling of the fatal death in woman pregnancy.

MATERIALS AND METHODS

A cross sectional analysis had been done to figure any correlation between the increasing pregnancy fibrinogen level and the conception product age on abortion and the progress of abortion with the appearance of placental infarct on missed abortion. The resesrch location is at Budi Mulia Mother and Child Hospital as well as Networking Hospital of Obstetry and Gynecology Department, Medical Faculty, Hassanudin University, Makassar south Sulawesi province. The research is conducted on March, 2017 to August, 2017. The research design is cross sectional analysis. The variables of research are:

- Independent variable that includes fibrinogen level during abortion
- Dependent variable that involves conception product age on an abortion, the progress of abortion and the appearance of placental infarct on missed abortion
- Intermediate variable that includes patophysiology thrombosis mechanism and vascular congestion due to dysregulation of coagulation-fibrinolysis system on pregnancy haemostasis
- Moderator variable that involves C Protein, S Protein, anti Thrombin III
- Controlled variable that includes gestational age based on 1st day of last menstrual period >6 to <10 weeks, fetus >10 to <20 of age, ultarsonography examination: Embryo >6 to <8 of age, Fetus >8 to <20 of age
- Confounder variable and random variable that includes Gene/polymorphism, hormonal, infection). Population is every mother with early pregnancy who come for antenatal examination to the hospital where research is held

The samples are mother with early pregnancy who fulfilled the inclusion and exclusion criteria. The data are taken from mothers with early pregnancy who had experienced missed abortion and agreed to join the research. This study takes 3 cc vein of blood sample to examine the fibrinogen. During curretage, the placenta was taken and stored into a pot that contained formal dehyde with subject's identity before the placenta was sent to the Histopathology Anatomy Laboratory. The blood serum fibrinogen level measurement was done according to the laboratory standard operational procedure of clinical Pathology Departement Wahidin Sudirohusodo Central Hospital Makassar by using Sysmex CA-1500 analyser. This study used SPSS program to analyze the statistical data. To evaluate the correlation, the study used χ^2 chi-square test with significance $\alpha = 5\%$. The result can be significant if the $p<0.05$. The probability analysis used the relative risk test with confidence interval of 95%.

RESULTS

This study classifies the samples into 6 classification as in Table 1. The researchers think that it is necessary to classify the samples according to the social status and the reproduction status in order to easily identify which woman social status has undergone missed abortion.

During the research, the researchers collected 38 blood fibrinogen tested samples and placenta histopathology test. The risk distribution on reproduction age and occupation did not show plenty of differences with the highest number of educational level is barchelor degree. Reproduction status is mostly embryo conception product, early abortion and first-time abortion.

The researchers used the limit of 375 mg dL^{-1} to analyze the correlation between the normal and abnormal increasing level of fibrinogen, where the researchers got the distribution rate above 375 mg dL^{-1} that is 469.85±76.63 mg dL^{-1} from 24 of 38 patients and the distribution rate below 375 mg dL^{-1} that is 327±38.22 mg dL^{-1} from 14 of 38 patients with no significant correlation ($p = 0.09$). The analysis of the correlation between normally and abnormally increasing fibrinogen level on age limit of conception product when abortion happened more than 10 weeks gestational age and the distribution rate was 459.88±86.25 mg dL^{-1} from 23 of 38 patients. Besides, the age of conception product during abortion was less than 10 weeks gestational age and the shape of embryo distribution rate was 389.59±91.61 mg dL^{-1} from 15 of 38 patients. Thus, statistically, there is no any significant correlation as it can be seen through the distributed Table 2.

There are some results that can be stated in this analysis of correlation and these can be identified in Table 3.

Table 1: Sample frequency distribution according to the social status and reproduction status

	Missed abortion	
Sample characteristic	n = 38	%
Age (year)		
Post-reproduction (> 35)	17	44.7
Reproduction (> 18-<35)	21	55.3
Education (graduated)		
Bachelor degree	26	68.4
Non-bachelor degree	12	31.6
Occupation (main)		
Government official	15	39.5
Housewife	23	60.5
Conception product (first day of last menstrual period)		
Embryo >6 to <10	23	60.5
Fetus >10 to <20	15	39.5
Abortion progress		
Early >6 to <8	31	81.6
Late >8 to <20	7	18.4
Abortion frequency (nominal)		
Repeated >1 time	15	39.5
First time = 1 time	23	60.5

Table 2: Mean distribution of fibrinogen concentration on missed abortion according to the normal value of laboratory and gestational age (first day of last menstrual period) using A mann Whitney test $p<0.05$

	Fibrinogen concentration			
Mean distribution clinical determinant	n (38)	Mean (mean)	Range (Range±SD)	p-value
Clinical pathology lab of Wahidin Sudirohusaodo Central Hospital*				
Abnormal above 375 mg dL^{-1}	24	469.85	±76.63	0.09
Normal below 375 mg dL^{-1}	14	327.22	±38.22	
Gestational age (First day of last menstrual period)				
Under 10 weeks	23	389.59	±91.61	0.646
Below 10 weeks	15	459.88	±86.25	

*Maximum value limit 375 mg dL^{-1} clinical pathology lab of Wahidin Sudirohusaodo Central Hospital

Table 3: Correlation of fibrinogen concentration with conception product, abortion type and placental infarct on missed abortion using statistic analysis : χ^2 chi-square test

Fibrinogen concentration on abortion age	Concentration level >375 mg dL^{-1}	%	<375 mg dL^{-1}	%	p-value	RR	CI 95%
***Conception product**							
Embryo <10 weeks	11	45.8	12	85.7	0.015	0.535	0.329-
Fetus >10 mgg	13	54.2	2	14.3			0.868
****Abortion type**							
Early <8 mgg	5	20.8	9	64.3	0.007	0.324	0.135-
Late >8 mgg	19	79.2	5	35.7			0.775
*****Placental infarct**							
Infarct (+)	17	60.7	11	39.3	0.715	0.662	0.140-
Infarct (-)	7	70.0	3	30.0			3.123

*First day of last menstrual period, **Ultrasonography, ***Histopathology. $\alpha = 5\%$, $p<0.05$

Table 3 has 4 interpretation of the correlation as follows:

- The correlation between the distribution of fibrinogen level indicates that the concentration rate is according to the operational limit determinant 375 mg dL^{-1} with the age of abortion and the shape of embryo in less than 10 weeks gestational age and fetus more than 10 weeks gestational age according to 1st day of last menstrual period. Besides, the type of early abortion is less than 8 weeks of gestational age and late abortion is more than 8 weeks according to ultrasonography on missed abortion using the X^2 chi-square statistic test
- The correlation is statistically significant as $p = 0.015$ and relative risk = 0.535 on confidence interval of 95% (0.32-0.86) after analyzing the correlation of abnormally increasing fibrinogen level above 375 mg dL^{-1} and embryo (45.8%) as well as fetus (54.2%) compared with the normally increasing fibrinogen level below 375 mg dL^{-1} with 85.7% embryo and 14.3% fetus in missed abortion
- The correlation between normally increasing fibrinogen level below 375 mg dL^{-1} with 85.7% embryo and 14.3% fetus on missed abortion is statistically relevant by $p = 0.015$ and relative risk = 0.535 on confidence interval of 95% (0.32-0.86)
- The correlation between abnormally increasing fibrinogen level above 375 mg dL^{-1} with the type of 20.8% early abortion and 79.2% late abortion compared to the normally increasing fibrinogen level below 375 mg dL^{-1} with the type of 64.3% early abortion and 35.7% late abortion in missed abortion, is statistically relevant ($p = 0.007$). The relative risk = 0.324 and the confidence interval is 95% (0.135-0.775)

These correlation analysis shows that the level of pregnancy fibrinogen that is abnormally increasing above 375 mg dL^{-1} that turns into coagulation circumstance has the abnormal coagulability feature and becomes a potency to abortion risk factor through thrombosis patophysiology mechanism that has possitive impact (significant) with the fetus environment and can cause intra uterine fetal death if the abortion in gestational age is more than 10 weeks ($p = 0.015$) and thus the potency is 0.5 times greater from the range 0.32-0.86 on the significance level of 95%. It also has positive impact with the type of late abortion with the gestational age above 8 weeks ($p = 0.007$) with the potency 0.3 greater from the range 0.135-0.775 on the significance level of 95% on missed abortion. According to the type of conception product, the fetal abortion is higher than embrionic abortion and the type of abortion is higher on the late abortion than the early abortion.

The analysis of the correlation between abnormally increasing fibrinogen level above 375 mg dL^{-1} has placental infarct as 60.7% and has no placental infarct as 70.0% compared to normally increasing fibrinogen level below 375 mg dL^{-1} with the 39.3% placental infarct appearance and 30% of no placental infarct appearance 30% on missed abortion. So, the correlation is statistically not significant as $p = 0.715$.

These correlation analysis shows that the level of pregnancy fibrinogen that is abnormally increasing above 375 mg dL^{-1} that turns into coagulation circumstance has the abnormal coagulability feature and becomes a potency to abortion risk factor through thrombosis patophysiology mechanism that has negative impact ($p = 0.715$) towards placental infarct as compared to normally increasing fibrinogen below 375 mg dL^{-1} on missed abortion.

DISCUSSION

This study showed that the abnormally increasing fibrinogen level during abortion has positive impact on early abortion when the gestational age is more than 10 weeks and on late abortion when the gestational age is more 8 weeks.

There is not any clinical limitation (determinant) of fibrinogen level rate in abortion age where the death of conception product happens on missed abortion. According to the operational research limit, the researchers use the Wahidin Sudirohusodo Central Hospital lab reference score that is 150-375 mg dL^{-1} from the distribution rate of 262.5±112.5 mg dL^{-1} as compared to the embryo conceptional product age below 10 weeks and fetus above 10 weeks, the onset of last menstrual period (measured form the 1st day of last menstrual period) when the subject came to the antenatal examination. Next, the researchers do the statistic correlation test using Mann Whitney.

Mann Whitney correlation analysis that results two used limits showed that there is an increase of normal and abnormal limit on missed abortion, but the correlation is not significant according to the statistical evidence. This showed that the two barriers' parameter are not adequate for the desired precision level and the relative accuracy wanted on the prediction of the distribution rate score and range of normal and abnormal fibrinogen level premise of this research that lets alone for the correlation coefficient r = 0.4 which needs more sample (minimum 57 samples). This is one of the flaws on this study.

The correlation analysis of abnormally increased fibrinogen level (>375 mg dL^{-1}) during abortion has positive impact on fetal conception product that has statistically significant correlation (p = 0.015) and has positive impact on late abortion that also has statistically significant correlation (p = 0.007). However, it does not have positive impact on placental infarct due to the non-significant correlation (p = 0.715). It means that the fibrinogen level during abortion and fetal conception product and type of late abortion for research hypothesis is accepted. Meanwhile, the correlation with the placental infarct is rejected.

According to Cunningham *et al.*[4], fibrinogen level during early pregnancy is physiologically normal if the increase concentration is from 200-300 mg dL^{-1} or about 50%. Compared to this study, the physiological increase is proved to be lower than the increase with the parameter of fibrinogen level limit 375 mg dL^{-1} towards the conception product during abortion where the distribution rate is 327±38.22 mg dL^{-1} range 289-365.44 mg dL^{-1} and towards the abortion age continuity. The researchers get the distribution rate of 389.59±91.61 mg dL^{-1} range 297.9-481.2 mg dL^{-1}. Besides, from all the case of missed abortion has fibrinogen level elevation is more than physiological raise and the mean rate is 50%.

Abbassi-Ghanavati *et al.*[10] research proved that on the referral fibrinogen level of non-pregnant women, the distribution mean is 364.5±131.5 mg dL^{-1} from the range 233-496 mg dL^{-1} and the normal pregnancy on first trimester has distribution mean of 377±133 mg dL^{-1} from the range 244-510 mg dL^{-1}. The change of fibrinogen level in normal pregnancy on early gestational age compared to this study shows similar level of fibrinogen increase, but the incident is different, because at that rate, abortion had already happened.

The statistic test was done by applying correlation analysis between the centration of fibrinogen that has raised abnormally above 375 mg dL^{-1} during abortion age compared to those that have raised normally below 375 mg dL^{-1} with embrional conception product or fetus, the type of abortion-whether it is an early abortion or late abortion and thrombotic arteriole decidua-change along with infarct placenta appearance or vascular congestion without placental infarct.

According to the literature review, in order to determine a hypercoagulation condition, the raise in coagulation component activity especially procoagulation fibrinogen should be signed[11-13]. The raise of fibrinogen level refers to the normal referral scoring with mean rate of 262.5 mg dL^{-1} range 150-375 mg dL^{-1} up to the maximum limit of 375 mg dL^{-1} from the clinical pathology laboratory of Wahidin Sudirohusodo Central Hospital.

To proof whether there is any hypercoagulation state with hypercoagulability status effect (the blood ability to coagulate above normal level) or abnormal hypercoagulable, the clinical pathology signs are the increase of procoagulation fibrinogen level. Thus, the pathology anatomy has the appearance of vascular congestion and placental infarct[14,15].

The research result had proven that there is a correlation between the abnormally raising concentration of fibrinogen during the abortion age with the type of late abortion, when the abortion happen the embryo gestational age is 8 weeks old (CRL-sonography) that causes the death of fetal conception product and ended with abortion. Statistically, it has significant correlation as p = 0.007. The relative risk amount is 0.3 times greater than the range 0.135-0.775 in significance level of 955 and it means that the research hypothesis is accepted.

This result showed the level of abnormally increasing fibrinogen during abortion age has positive impact towards the type of late abortion (the continuity of pregnancy failure), because of the death of fetal conception product in the wob and due to the accumulation of thrombosis pathophysiology

mechanism towards the fetal viability and environment around the fetus. The potential risk is 0.3 times greater. The result had proven analytically the correlation between fibrinogen concentrations that rose abnormally has negative impact on placental infarct during abortion age. Statistically, the correlation is not significant as marked by p = 0.614. Therefore, the research hypothesis is rejected.

Finally, this result also showed that the abnormal raise of the fibrinogen concentration during abortion age does not have absolute power that has potency towards pathophysiology of thrombosis mechanism and placental infarct depends on the hypercoagulation situation whether it has normal or abnormal hypercoagul ability. It is possible that the potency of pathophysiology of congestion mechanism has already done due to none of extensive angiogenesis along with the gestational age when the abortion age is still under eight weeks old and the correlation is statistically not significant (p = 0.614). Over all, it can be simplified that abnormally elevated pregnancy fibrinogen concentration during abortion age that is equivalent to hypercoagulation that has potential on abnormal hyper coagulability tend to create thrombosis.

CONCLUSION AND SUGGESTION

The researchers concluded that the abnormally elevated pregnancy fibrinogen concentration during abortion age that is equivalent to hypercoagulation that has potential on abnormal hypercoagulability, tend to create thrombosis. The thrombosis effect has positive effect on early fetal death on the more than 10 weeks gestational age from the onset of last menstrual period and late abortion above 8 weeks gestational age, but not towards placental infarct on missed abortion. The researchers suggest that the examination of fibrinogen level on early pregnancy is considered in order to prevent hypercoagulable hyper coagulation.

SIGNIFICANCE STATEMENT

This study would like to discover the relationship between the increase of fibrinogen level during pregnancy and conception product age on an abortion, the progress of abortion and the appearance of placental infarct on missed abortion that can be beneficial for the study of Women's health check-up in abortion. Besides, this study will help the researchers to uncover the critical areas of women's abortion that many researchers were not able to explore specifically. Thus, a new methodology of research is welcome to reconsider within this study.

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