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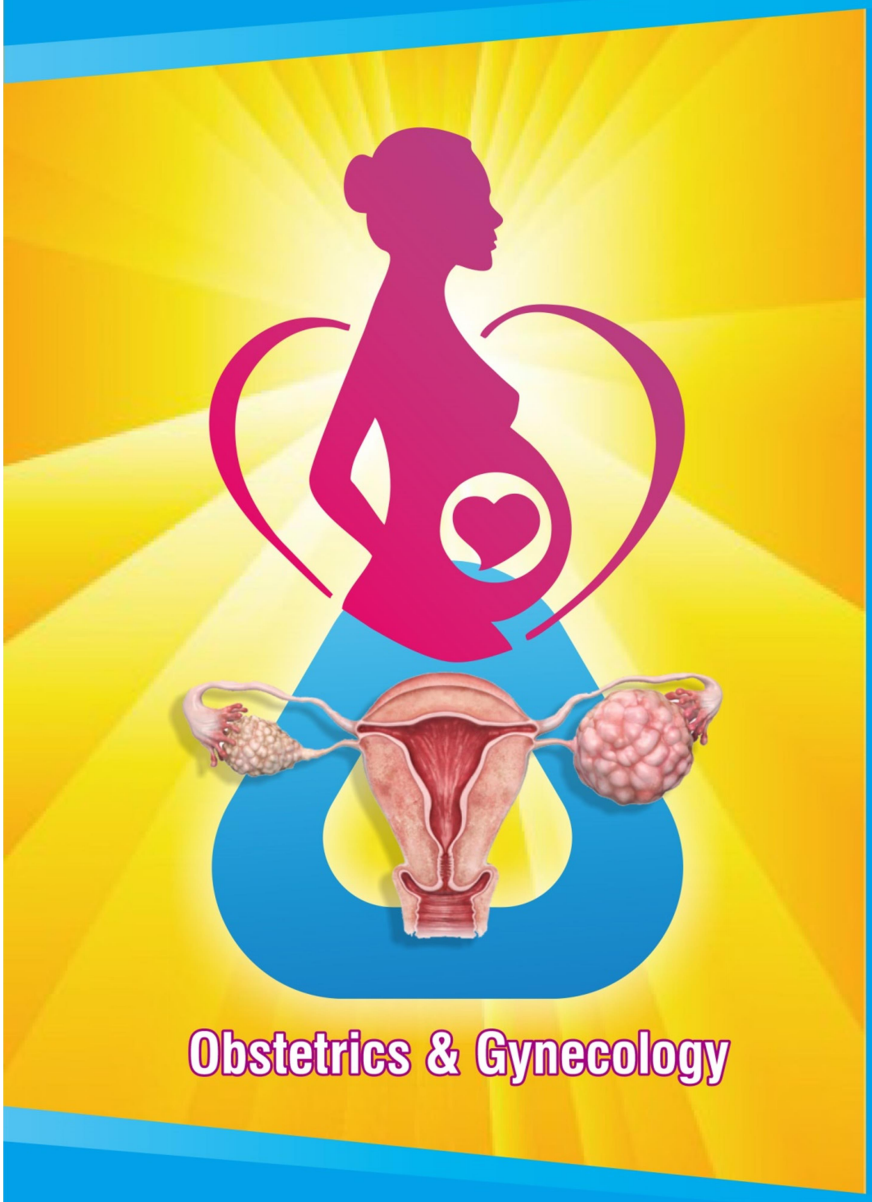




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# Editorial Team

## EDITORIAL



## RESEARCH ARTICLE



## CASE REPORT



## LITERATURE REVIEW

**Editorial**

# Obstetrics and Gynecology in Indonesia and Its Challenges in the Near Future

***Noroyono Wibowo***

Indonesia's vast and various characteristics of its social, economic, and geographic conditions affect variations in service needs in the field of Obstetrics and Gynecology, which bring about several great challenges to face.

There has not been standardized electronic medical record system utilized by all obgyn practitioners in Indonesia. This leads to difficulty in access to real-time actual data about issues around OBGYN. In the absence of real-time accurate data, the issues put on the table is merely an assumption or an estimation. Thus, prioritization of problem solving is almost impossible, neither distribution of task force which serve as think tank centre for specific issues. As surveillance towards each disease is practically non-existent, disease management is performed impromptu rather than organized.

Being shackled by global mindset and concurrently forgetting local wisdom. One should not forget that variations in response to therapy and disease patterns are influenced by local behaviour, nutrigenomic, epigenetic, and environment. The preference of curative management instead of prevention, leading to insignificant decline in mortality and morbidity.

Big data will soon be a prerequisite in managing diseases, therefore understanding the use and the interpretation of artificial intelligence is imperative. In obstetrics, cases of Great Obstetrics Syndrome (GOS), consisting of preeclampsia, preterm labor, intrauterine growth restriction (IUGR), and gestational diabetes will remain dominant in services, followed by autoimmune and cardiac abnormalities. In gynecology, Polycystic Ovaries (PCO), endometriosis, myoma, and menstrual disorders will remain major issues, followed by the alternation between ovarian and endometrial malignancy.

*Perkumpulan Obstetri Ginekologi Indonesia* (POGI) has to stress the fact that humans, through their reproductive nature, are the main assets of the country, hence they have to be the main subject in drafting the state budget. Indeed, a nation with poor reproductive function, quality, and results will soon or later vanish, if not colonized.

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**Research Article**

# Characteristic of Midwives who Refer Complex Obstetrics Cases

## *Karakteristik Bidan yang merujuk Kasus Obstetri Komplek*

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## Abstract

**Objective:** To identify reasons for referring and characteristics of midwives who have an independent practice and its relation with the complication that manifested from the cases.

**Methods:** Descriptive analytic case-control. Medical records of patients referred directly to RSCM in January 2016-July 2017 were obtained, then information about midwives and obstetric cases, along with its complications, were collected. Interview and analysis of six characteristics of midwives were conducted. Characteristics analyzed were age, education, training, duration of work experience, number of patients ever treated, also distance and travel time of the referral process.

**Results:** All midwives refer due to inadequate facilities. There is a statistically significant correlation between duration of work experience and number of patients that has been managed, with the complication that manifested from referred cases, with OR 7.036 and 6.032, respectively.

**Conclusions:** Midwives refer due to inadequate facilities, and so patients can be treated immediately. Characteristics that affect midwives in referring are: duration of work experience and number of patients that has been managed. It is necessary to re-evaluate the position of midwives who practiced independently in BPJS, refresher programs, and monitoring by relevant agencies. A larger number of samples and data combination of midwives' and patients' characteristics in referral cases are needed for further research. Confounding and external factors are identified first in order to do a thorough analysis.

**Keywords:** characteristics, complicated cases, midwives, emidwives who practiced independently, referral, referral system.

## *Abstrak*

***Tujuan:*** *Mengetahui alasan rujuk dan karakteristik bidan yang berpraktik mandiri serta hubungannya dengan kasus komplikatif yang dirujuk ke RSCM.*

***Metode:*** *Deskriptif analitik kasus kontrol. Data diambil dari rekam medis pasien yang dirujuk langsung ke RSCM di bulan Januari 2016 hingga Juli 2017, kemudian informasi mengenai data bidan dan kasus obstetri beserta komplikasinya dikumpulkan. Dilakukan wawancara dan analisis enam karakteristik bidan. Karakteristik yang dianalisis yaitu usia, pendidikan, pelatihan, lama waktu berpraktik, jumlah pasien yang pernah ditangani, serta jarak dan waktu tempuh proses merujuk.*

***Hasil:*** *Keseluruhan bidan merujuk karena fasilitas yang tidak memadai. Terdapat hubungan yang bermakna antara waktu praktik dan jumlah pasien yang pernah ditangani, dengan kasus komplikatif yang dirujuk langsung ke RSCM, dengan nilai OR 7,036 dan 6,032.*

***Kesimpulan:*** *Bidan merujuk karena fasilitas tidak memadai dan agar pasien langsung ditangani. Karakteristik bidan yang mempengaruhi dalam merujuk yaitu lama waktu praktik dan jumlah pasien yang ditangani. Perlu dilakukan evaluasi ulang mengenai kedudukan bidan yang berpraktik mandiri di BPJS, program penyegaran bidan, serta monitoring oleh instansi terkait. Perlu penelitian lanjut dengan sampel lebih banyak serta menggabungkan karakteristik bidan dan pasien pada kasus-kasus rujukan. Faktor perancu dan eksternal diidentifikasi terlebih dahulu agar analisis dilakukan menyeluruh.*

***Kata kunci:*** *bidan yang berpraktik mandiri, karakteristik bidan, kasus komplikatif rujukan, sistem rujukan.*

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## INTRODUCTION

Maternal mortality is still a problem that has received considerable attention from the Indonesian Government. Initially, through 5th goal of the Millennium Development Goals (MDGs) program, the government tried to reduce maternal mortality to 102 deaths in 100,000 live births. From 2003 to 2007, maternal mortality decreased to 228 deaths, but from 2008 to 2012, unfortunately maternal mortality was again increased to 359 deaths per 100,000 live births.[1] The latest data obtained in 2015 found there were 190 maternal deaths per 100,000 live births[2], which was far from MDG's target. in the present time, the Indonesian Government follows a United Nations (UN) program, which is the goal 3 of Sustainable Development Goals (SDG)[3], so the maternal mortality would fall to 70 deaths.

From a medical point of view, the most common causes of maternal death are divided into bleeding, infection, unsafe abortion, eclampsia, and prolonged labor.[4-8] The most common cause of maternal death is postpartum hemorrhage.[9] These five problems in pregnancy have complications that could cause death if it is not properly managed.

To avoid the occurrence of further complications, excellent and appropriate management are needed where a good referral system supports. The Indonesian Government has established a referral system, where a health service facility can refer a case of pregnancy that can not be managed or not in its competences ,to a health facility that has more authority to manage a more complicated case. This referral system is structured in stages, starting with primary health services with general practitioners and dentists as their health workers, specialists in secondary health services, and sub-specialists in tertiary health services.[10]

A few years ago, midwives, as one of the health workers trained in the scope of maternal and child health, are still part of the primary service, along with general practitioners and dentists.[10] However, the latest referral system prepared by the agency that organized the social security called BPJS, do not include midwives in the referral system.[11] Midwives, in general, should only refer to general practitioners or dentists who work in primary facilities.[12] The new referral system is qcomplicated for midwives because the regulations regarding the position of midwives are not clearly explained. The referral system for emergency cases originating from the midwife's independent practice is not clearly explained in the referral system prepared by the BPJS.

Dr. Cipto Mangunkusumo hospital as the tertiary health facility and also as the national referral center (Type A Hospital according to the Decree of the Minister of Health of the Republic of Indonesia Number 1204/MENKES/SK/X/2004), until now still receives referrals directly from midwives which skips the referrals to primary and also secondary health services. According to data from 2013, the Emergency Room (ER) of Obstetrics and Gynecology in RSCM which is located on the 3rd floor, was receiving approximately 250 referrals from midwives who were practicing independently. Among those referrals, there are a quite number of cases with complications that may appeared due to the delay in making a decision to refer, the delay in referral processes and delay in management.

Complications could be prevented if the mother could perform a good antenatal care and the could recognize the initial signs of a problem in pregnancy and also work as its authority, which are primary survey and stabilization of the emergency cases properly and appropriately recognize these cases as referral cases.[13, 14] In addition, it is also necessary to outline some characteristics that influence a midwife's decision in referring a case directly to the emergency room of Cipto Mangunkusumo Hospital. Therefore this study is conducted to determine the reasons in referring cases and characteristics of those midwives who were practicing independently, as well as their relationship with the manifested complication.

## METHODS

A case-analytic descriptive design was conducted for this study. Data was taken from January 2016 to July 2017. Subjects were all midwives who practice independently and have referred any case of preeclampsia, Premature Rupture of Membranes (PROM) and bleeding and/or its complications to RSCM Jakarta from January 2016 to July 2017 who meet the inclusion and

exclusion criteria. Inclusion criteria include: all midwives who are practicing independently; refer one or all cases of preeclampsia, PROM, as well as bleeding and/or its complications such as eclampsia, infection, and hemorrhagic shock from January 2016 to July 2017; refer directly to Cipto Mangunkusumo Hospital that has skipped primary or secondary service facilities; and willing to participate in research and fill out informed consent. Whereas for exclusion criteria: if there is no reference letter attached to the medical record. Subjects were taken by consecutive sampling. Analysis of six characteristics of midwives was conducted, which were divided into two types of characteristics, demographic and geographic characteristics. The demographic characteristics were age, education, training, duration of work experience, and number of patients that has been managed. While the geographic characteristics were distance and travel time of referral process. Then all analyzes were carried out using SPSS 20.0.

## RESULTS

In the study conducted in January 2016 until July 2017, there were 1,351 cases of preeclampsia, PROM, and bleeding referred to RSCM. Ninety-five of these cases referred directly from midwives who were practicing independently. Based on inclusion and exclusion criteria, tthere were 82 cases from different midwives which have an independent practice. Of the total of 82 cases, there were 29 cases of preeclampsia (35.3%), 40 cases of PROM (48.8%), and 13 cases of bleeding (15.9%); among those cases, 28 of the cases (34.1%) were with complication and 54 cases (65.9%) were not.

Based on a brief interview conducted by the researcher, the entire midwife (100%) referred, due to inadequate facilities. In addition, according to the authority of midwife that has been mentioned in the Regulation of the Minister of Health of the Republic of Indonesia number 28 in 2017, the midwives should immediately refer to primary facility. But unfortunately, they immediately refer to RSCM because the assumption that by referring directly to Cipto Mangunkusumo Hospital, patients could be immediately managed. Distribution data of demographic characteristics of midwives who practice independently are attached in table 1.

**Table 1.** Demographic Characteristics of Midwives who Practice Independently who Refer the Complicated and Non-complicated Cases to Dr. Cipto Mangunkusumo Hospital

| Midwives' Characteristics | Non-complicated (N = 54) | Complicated (N = 28) | N = 82 (%) |
|---|---|---|---|
| **Age (y.o)** | | | |
| < 36 | 37 (68.5) | 18 (64.3) | 55 (67.1) |
| ≥ 36 | 17 (31.5) | 10 (35.7) | 27 (32.9) |
| **Education** | | | |
| ≤ D3 | 42 (77.8) | 22 (78.6) | 64 (78) |
| > D3 | 12 (22.2) | 6 (21.4) | 18 (22) |
| **Training** | | | |
| Never | 17 (31.5) | 9 (32.1) | 26 (31.7) |
| APN/PONED/etc | 29 (53.7) | 16 (57.1) | 45 (54.9) |
| APN + PONED | 8 (14.8) | 3 (10.8) | 11 (13.4) |
| **Duration of practice (years)** | | | |
| < 11 | 43 (79.6) | 10 (35.7) | 53 (64.6) |
| ≥ 11 | 11 (20.4) | 18 (64.3) | 29 (35.4) |
| **Number of patients** | | | |
| < 50 | 40 (74.1) | 9 (32.1) | 49 (59.8) |
| ≥ 50 | 14 (25.9) | 19 (67.9) | 33 (40.2) |

Data on the distribution of geographic characteristics of midwives who practice independently are attached in table 2 below.

**Table 2.** Geographic Characteristics of Midwives who Practice Independently who Refer the Complicated and non-complicated Cases to Dr. Cipto Mangunkusumo Hospital

| Midwives' Characteristics | Non-complicated (N = 54) | Complicated (N = 28) | N = 82 (%) |
|---|---|---|---|
| **Distance and travel time** | | | |
| < 10 km & < 60 minutes | 32 (59.2) | 19 (67.9) | 51 (62.2) |
| ≥ 10 km & ≥ 60 minutes | 22 (40.8) | 9 (32.1) | 31 (37.8) |

Bivariate analysis is presented using Chi-square. This analysis aims to see the relationship between midwife's characteristics and cases with complication, and also to see the magnitude of probability value that presented with Odd Ratio (OR). The p-value of bivariate analysis that <0.05 shows a significant correlation between midwife's characteristic and complicated cases. From all of the analysis, the characteristic that significantly related to complicated cases are duration of work experience and number of patients that ever handled during their work period. Result of bivariate analysis are shown in table 3 and 4.

**Table 3.** Relationship between Demographic Characteristics of Midwives who Practice Independently and Complicative Cases

| Midwives' Characteristics | Non-complicated | | Complicated | | *P-value* | OR (CI 95%) |
|---|---|---|---|---|---|---|
| | N | % | N | % | | |
| **Age (y.o)** | | | | | | |
| < 36 | 37 | 68.5 | 18 | 64.3 | 0.699 | OR= 1.209 |
| ≥ 36 | 17 | 31.5 | 10 | 35.7 | | (CI95% 0.462-3.167) |
| **Education** | | | | | | |
| ≤ D3 | 42 | 77.8 | 22 | 78.6 | 0.934 | OR = 0.955 |
| > D3 | 12 | 22.2 | 6 | 21.4 | | (CI 95% 0.315 – 2.889) |
| **Training** | | | | | | |
| Never | 17 | 31.5 | 9 | 32.1 | 1.000 | OR=0.970 |
| APN/PONED/etc | 29 | 53.7 | 16 | 57.1 | | (CI 95% 0.364-2.582) |
| APN +PONED | 8 | 14.8 | 3 | 10.8 | | |
| **Duration of practice (years)** | | | | | | |
| < 11 | 43 | 79.6 | 10 | 35.7 | 0.001 | OR=7.036 |
| ≥ 11 | 11 | 20.4 | 18 | 64.3 | | (CI 95% 2.543-19.472) |
| **Number of patients** | | | | | | |
| < 50 | 40 | 74.1 | 9 | 32.1 | 0.001 | OR = 6.032 |
| ≥ 50 | 14 | 25.9 | 19 | 67.9 | | (CI 95% 2.220-16.391) |

**Table 4.** Relationship between Geographic Characteristics of Midwives who Practice Independently and Complicative Cases

| Midwives' Characteristics | Non-complicated | | Complicated | | *P-value* | OR (CI 95%) |
|---|---|---|---|---|---|---|
| | N | % | N | % | | |
| **Distance and travel time** | | | | | | |
| <10 km & <60 minutes | 32 | 59.2 | 19 | 67.9 | 0.446 | OR = 0.689 |
| ≥10 km & ≥60 minutes | 22 | 40.8 | 9 | 32.1 | | (CI 95% 0.264-1.801) |

From the results of the bivariate tests that have been done before, it is known that from the six variables, there are two demographic characteristics, duration of experience and the number of patients that have been managed, which are related to the number of cases with complication that referred directly to RSCM. Then a multivariate analysis is performed on these variables.

From the multivariate analysis, there is a significant relationship between the duration of practical experience and the number of complicated cases with p=0.011. Then there is also a statistically significant relationship between the number of patients that has been managed by midwives and the number of complicated cases that referred directly to Cipto Mangunkusumo Hospital, with p=0.031. From these two variables,

shows that the most dominant variable in referring directly the cases with complication to RSCM is the number of patients that have been managed by midwives, where the p-value of this variable is greater than other variables, which is p=0.031. Therefore, the number of patients that have been handled by midwives more than or equal to 50 patients, would more often refer a case with complication to the hospital as many as 0.294 times compared to midwives who have managed fewer than 50 patients during their experience in independent practice.

## DISCUSSION

We found 1351 obstetric cases including preeclampsia, PROM, and bleeding both antepartum and postpartum hemorrhage, referred to RSCM, where 95 cases of them (7.03%) referred directly by midwives who work independently. The number is significantly smaller compared to the data from Department of Obstetrics and Gynecology in 2013 that stated 14% of cases were referred by midwives who practice independently. It shows that the BPJS referral system in 2016 were running better compared to 2013. From 95 midwives who referred the cases, there are 82 midwives who met the research's inclusion criteria. The data distribution of obstetric cases that are referred were 29 cases of preeclampsia (35.3%), 40 cases of PROM (48%) and 13 cases of bleeding (15.9%). The main reason of all referral were due to inadequate facilities in their practice. Of all cases that are referred, there were complications that manifest such as eclampsia, intrauterine infection, and hypovolemic shock. The total number of complications that appeared from those referred cases was 28 cases (34.1%). Then the demographic and geographic characteristics of the midwives who refer those cases with manifested complication were seen and analyzed. There are five demographic characteristics analyzed, which are age, education, trainings that have been participated, duration of practical experience and the number of patients ever treated during that have been managed. While the geographic characteristics that are analyzed are the distance and travel time oin the process of referring.

Of the overall characteristics mentioned above, a correlation between each characteristic and complication that manifested from the cases is examined. Based on age, it is found that there is no statistically significant relationship with the number of complication that appeared from the referred cases. This finding is on the contrary to the research conducted by Wahyuningsih and colleagues which stated that there was a relationship between the characteristics of midwives in the form of age, years of service, and education of midwife with the accurate decision in referring a patient.[15]

Similar to age, years of service, education, along with motivation and attitude influence the performance of midwives in referring the obstetric emergency cases[16]. It is also inconsistent with the idea that the possibility of an individual's performance will decline along with increased age of a midwife. They would have more experience or skill in performing their duties.

Besides that, there is also no statistically significant relationship between education of a referring midwife and the complication that were appeared from the cases referred directly by the midwives to Cipto Mangunkusumo Hospital. The statement from above previous researches is also inconsistent in this study. The lowest education for a midwife who can have an independent practice is a midwife who has taken diploma degree which is D3. Whereas midwives who have studied higher than D3 degree can be called as a professional midwives and can also work as a manager, educator, and educational contributor to other midwives.[17] Based on the result of this research, it can be said that the midwives' decision in referring a patient is not affected by their educational degree.

Regarding the characteristic of trainings that have been participated, there were no significant association with the complication that appeared from its cases. In this study, there are 26 midwives who stated that they had never attended any training during their practical period and 56 midwives had participated in any training. (From 56 midwives who had attended any training, all midwives who have participated in a training stated that they attended the PONED training. Only 11 midwives participated in any other additional trainings other than PONED. This trainings include Normal Delivery Care (Asuhan Persalinan Normal - APN), Midwifery

Update (MU), Obstetric Neonatal Emergency Management Training (Pelatihan Penanganan Gawat Darurat Obstetric Neonatus - PPGDON), Basic Life Support (Bantuan Hidup Dasar - BHD), Contraception Training Update (CTU), and others. PONED and APN training aim to enable the midwife to provide health services according to established standards. However, based on the result, there were no strong relationship between the trainings that have been attended with the number of complication that arose from the referred cases. The weak relation between both parameters showed that the midwives' ability of making decision in referring a patient is not solely depend on the trainings that have been participated by themselves.

Based on the duration of work experience, there was a significant relationship with the number of complications that were appeared, where p=0.001 with OR 7.036 and a CI 95% of 2.543-19.472 were obtained. This could be interpreted that midwives with more than or equal to 11 years of practical experience would 7.036 times more in referring a case with already manifested complication. This is inversely proportional to the initial thinking of the researcher, where a longer period of work experience will make a midwife to refer less number of the cases that complication has appeared because the experience of the midwife can figure out which cases should be referred immediately so that the complication would not manifest before the arrival at the referring hospital. Based on interview with several midwives who have referred directly to Cipto Mangunkusumo Hospital, the midwives knew that the conditions of the patients were in need of the better facilities so that they would like their cases to be bypassed and managed directly at the tertiary health center (Cipto Mangunkusumo Hospital) rather than being firstly managed in the Regional General Hospital (RSUD) or secondary health center, according to the pathway that has been established by BPJS. There are also external factors that influence this condition, such as patients who come to the midwife is already in a complicated state, or prefer to come to the midwife because there is a high level of trust in midwives with a long working period. In addition, these patients were not performing their ANC routinely in the midwife, so the history of their pregnancy is not known. Thus they only refer patients when they believe that they are unable to provide any further management. There is also the possibility that midwives with a longer working experience have surfeited and causing a decrease in performance, which could lead to reduced awareness for their patient's conditions. Thus resulting in lateness in referring these patients and eventually a complication manifests. Therefore, refresher trainings or re-trainings are needed.

Based on the number of patients that has been managed during their work period, there is also a significant relationship with the number of patients with a complication that manifested, where p=0.001 with an OR of 6.032 and a CI 95% of 2.220-16.391. This shows that midwives who have managed more than or equal to 50 patients, are 6.032 times more often to refer a case which a complication would appeared. This result is also not in line with the initial thought of the researcher, where the number of cases that were managed has a directly proportional direction to the knowledge of midwives in referring patients[18]. Based on the results of this study, several possibilities that led to differences in results from initial thinking could be thought. One of which is the midwives' believe that they could manage a case due to the number of patients that they have had during their work period, even though the case had to be referred in the beginning. However, when they handled these cases and turned out that there were no any improvement, then the midwives referred those patients directly to Cipto Mangunkusumo Hospital.

As for the geographic characteristics such as distance and travel time to referral hospital, there was no statistically significant relationship with complication that manifested. This is on contrary to a statement in this study that said patients who have been delayed to seek medical assistance or any delay in referral process are one factor that could significantly affect the maternal mortality rate. [19] In addition, time and distance are also factors that contribute to the referral process.[20,21] The distance and travel time to the referred health facility affect the outcome of labor.

The multivariate analysis found two independent characteristics of midwives that could be accounted for. The number of patients that have been managed and the

duration of midwife's work experience, where the p-value of both variables was <0.25. The multivariate analysis aims to get the best model in determining or predicting the parameters of midwives' characteristics who refer the case whose complication has manifested to Cipto Mangunkusumo Hospital in 2016-2017. The results of analysis through logistic regression revealed that there are two final variables of midwives' characteristic that are influential in referring the cases, which complication has been developed, are duration of their work experience, and the number of patients that they have been managed. Furthermore, logistic regression analysis is carried out to find the most dominant variable in the referral of case with the complication has arised. The scale of influence between variables is indicated by the odds ratio (Exp (B)), where the largest Exp (B) is in the variable number of patients. This means that midwives who have been handled more than or equal to 50 patients, would more often refer cases with a complication to the hospital as many as 0.294 times compared to midwives who have only managed fewer than 50 patients during their work experience.

This study has limitation in analyzing the relationship between several demographic or geographic characteristics and the complication developed from a case. This is due to many external factors and confounding factors of research that need to be analyzed further. In addition, the small number of samples may not be representative of the characteristics of midwives who practice independently around Indonesia. However, this research shows that although the number of referral from midwife is less than the number in 2013, there are still a lot of midwives that are practicing in independent practice who refer cases directly to Cipto Mangunkusumo Hospital, which does not comply with the BPJS referral system. And finally, it can be seen that there are two characteristics of midwives, which are duration of their work experience and the number of patients contribute to the number of complication that manifested from cases.

## CONCLUSION

Ninety-five self-employed midwives referred the obstetric cases (preeclampsia, PROM, and bleeding) directly to RSCM from January 2016 to July 2017, where there was a 50% less number from previous data in 2013, which the total of 267 midwives referred to Cipto Mangunkusumo Hospital. Eighty-two midwives among them agreed to take part in the study. All of them refer their obstetric cases directly because of inadequate facilities. The cases has been referred directly to Cipto Mangunkusumo Hospital and have skipped primary or secondary service facilities in order to be medically treated immediately. More than one third of the cases that are being referred (34.1%) were the complication of the cases that manifested further in the process of referring a patient.

In conclusion, there was a significant relationship between demographic characteristics of midwives who practice independently with the complication manifested from cases that were referred directly to Cipto Mangunkusumo Hospital, which were the duration of midwife's practice and the number of patients that have been managed during the midwife's work period. Based on the duration of experience, 64.3% of midwives who have practiced for more than 11 years were potentially 7.036 times more often in referring a case that a complication has been manifested. Whereas based on the number of patients that were treated during the work period, 67.9% of midwives who managed more than 50 patients were 6.032 times more often in referring a case that a complication has been manifested. For other midwives characteristics such as age, education, trainings that have been participated, as well as distance and travel time to referred hospital, there was no statistically significant correlation with the manifested complication that arose from the referred cases.

A re-evaluation of BPJS referral system is needed regarding the position of midwives who have an independent practice because currently only midwives who practice independently and has collaborated with primary health care facilities or Pratama clinic, could make a referral to a higher health care facilities, according to BPJS referral system. Periodic monitoring and evaluation of midwives, carried out by relevant institutions (Indonesian midwives society, public health care, ministry of health), should be further improved. Good cooperation between health workers at various levels of health care facilities needs to be well established. In addition, refresher programs

for midwives need to be held annually.

Further research could be carried out a form that combining the characteristics of midwives and patient characteristics in referral cases, so they can be identified thoroughly. In analyzing the characteristics of midwives, it is also necessary to identify confounding and external factors that can influence the analytical process. And lastly, larger number of samples is needed in order to represent the population of midwives who practice independently in Indonesia.

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**Research Article**

# Side Effects of Misoprostol Per Rectal for Treating Postpartum Hemorrhage in Vaginal Delivery versus Cesarean Section: What Do We Know So Far?

## *Efek Samping Misoprostol Per Rektal untuk Pengobatan Perdarahan Pascasalin pada Persalinan Normal versus Seksio Sesarea: Apa yang Sudah Kita Ketahui?*

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## Abstract

**Objective:** To compare the incidence and profiles of misoprostol side effects given per rectal for treating postpartum haemorrhage in vaginal delivery versus cesarean section.

**Methods:** A prospective observational study involving 40 women delivered by vaginal birth (VD) and 40 by Cesarean Section (CS) was undertaken in a gynecology ward of a hospital in West Java. The incidence of misoprostol's side effects was identified through patient observation and medical note review. The side effect probability was rated by the panellists of healthcare providers. Patient characteristics and side effect data were summarized descriptively. The incidence rates of misoprostol's side effect between the two groups were compared using Z-test.

**Results:** Thirty-four patients (85.0%) in the VD group experienced side effects, whilst all CS patients reported at least one side effect. There was no significant difference in the proportion of patients having side effects in the two groups (p=0.366). There were 135 and 164 side effects in the VD group and CS group, respectively. There was no discernible difference in side effect profile between the two groups. Gastrointestinal side effects accounted for the most frequent side effects. Regarding the side effect probability, the panellists rated all side effects in VD patients as probable. Meanwhile, around70% of side effects in CS patients were regarded as probable leaving the remaining as definite.

**Conclusions:** High incidence of misoprostol's side effects was documented both in VD and CS patients. The incidence rates and side effect profile between the two delivery modes were quite similar.

**Keywords:** cesarean section, misoprostol, postpartum haemorrhage, side effect, vaginal delivery.

## *Abstrak*

***Tujuan:*** *Membandingkan insiden dan profil efek samping misoprostol per rektal untuk pengobatan perdarahan pascasalin pada persalinan pervaginam versus seksio sesarea.*

***Metode:*** *Penelitian observasional prospektif melibatkan 40 perempuan yang melahirkan melalui persalinan pervaginan (VD) versus 40 pasien melalui Seksio Sesarea (CS) dilakukan di bangsal ginekologi sebuah rumah sakit di Jawa Barat. Insiden efek samping misoprostol diidentifikasi melalui pengamatan pasien dan kajian rekam medis. Probabilitas efek samping dinilai oleh panel tenaga kesehatan. Karakteristik pasien dan profil efek samping dianalisis secara deskriptif. Proporsi insiden efek samping misoprostol antara dua metode persalinan dibandingkan menggunakan uji Z.*

***Hasil:*** *Tiga puluh empat pasien (85,0%) pasien di kelompok VD mengalami efek samping, sementara semua pasien CS melaporkan setidaknya satu efek samping. Tidak ada perbedaan yang signifikan terkait proporsi pasien yang mengalami efek samping di kedua kelompok (p=0,366). Secara keseluruhan terdapat 135 dan 164 efek samping pada kelompok VD dan CS secara berurutan. Tidak ada perbedaan yang nyata dalam profil efek samping kedua kelompok. Efek samping terkait saluran cerna merupakan efek samping yang palings sering ditemukan. Terkait probabilitas kejadian efek samping, panelis menilai semua efek samping pada kelompok VD sebagai "mungkin". Sementara itu, sekitar 70% efek samping pada pasien CS dikategorikan "mungkin" dan selebihnya "sangat mungkin".*

***Kesimpulan:*** *Insiden tinggi efek samping misoprostol ditemukan baik pada pasien VD maupun CS. Proporsi insiden dan profil efek samping cukup seragam pada dua kelompok tersebut.*

***Kata kunci:*** *efek samping, misoprostol, perdarahan pascasalin, persalinan pervaginam, persalinan seksio sesarea.*

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## INTRODUCTION

Primary Postpartum Hamorrhage (PPH) is defined as blood loss from the genital tract of 500 mL or more following a normal vaginal delivery (NVD) or 1,000 mL or more following a cesarean section within 24 hours of birth.[1] PPH contributes significantly to maternal morbidity and mortality. PPH is a leading cause of maternal deaths globally, contributing to a quarter of the deaths annually.[2] In the developed world, PPH is a largely preventable and manageable condition.[3] In developing countries, mortality from PPH remains high and recent studies have shown that PPH causes up to 60% of all maternal death. In Indonesia, PPH is responsible for 43% of maternal death cases.[4]

Some key women's health organizations including International Federation of Gynecology and Obstetrics(FIGO), World Health Organization (WHO) and Royal College of Obstetricians and Gynecologists have supported the use of injectable uterotonics (i.e. oxytocin, ergometrine) as the first-line treatment for PPH due to their effectiveness and safety evidence.[5-7] Indonesia Society of Obstetrics and Gynecology has released its guideline in PPH management which was in accordance with the aforementioned international organizations.[8] Oxytocin and ergometrine are proven effective and safe in pregnant women even in those with hypertension and preeclampsia. Unfortunately, these drugs should be administered via injection only and require refrigeration to maintain stability. Additionally, their administration needs skilled health care professionals. These features may result in their limited availability particularly in a resource-poor environment such as rural and isolated areas.[9]

Misoprostol, a stable prostaglandin E1 (PGE1) analogue, has been shown to effectively stimulate uterine contractility in early pregnancy and at term. Misoprostol is known as alternative uterotonic agents in a situation where the first-line treatment is not available and feasible[9]. This drug is registered in Indonesia for the treatment of gastric and peptic ulcer. It is not approved yet by the Indonesian National Agency of Food and Drug Control to be used for the prevention and treatment of PPH. However, the use of misoprostol in the management of PPH is quite common among gynecologists. In low resource settings (e.g. developed countries), the use of misoprostol has attracted considerable attention due to its cheaper price, heat stability and longer half-life as opposed to conventional injectable uterotonics being used as the first-line treatment for PPH. In addition, misoprostol can be administered in multiple routes (including oral, buccal, vaginal, sublingual and rectal)supporting its ease of administration and making it more popular in health facilities with limited skilled health care providers. Understandably, misoprostol was added to Essential Medicines WHO Model List for PPH treatment.[10] Nevertheless, the administration of misoprostol poses certain risks to its questionable effectiveness and safety. A systematic review of ten randomized-controlled trials (RCTs) using oxytocin and misoprostol for PPH treatment highlighted that the use of misoprostol as an adjunct treatment to oxytocin conferred no additional benefit for patients.[11] In regards to its safety, misoprostol is frequently associated with some transient side effect such as chills and pyrexia.[12] Moreover, some randomized controlled trials of misoprostol have reported maternal death and severe morbidity presumably linked to its use.[13, 14]

It has been evident that misoprostol should be reserved in certain condition where the first line PPH treatment was impractical. However, the use of misoprostol for PPH treatment in the study hospital was prevalent and not in line with the existing evidence where the access to first-line treatment in the hospital was immediately available. It is of importance to note that the side effects related to misoprostol ranked third of the adverse drug event report in the study hospital. Additionally, little research has been undertaken to evaluate the side effects of misoprostol in two modes of delivery (cesarean versus vaginal delivery). Based on the aforementioned reasons, the study was conducted to compare the incidence and profile of misoprostol side effects in vaginal delivery and cesarean section.

## METHODS

This was a prospective observational cohort study. Subjects were pregnant women admitted to gynecology ward in a district hospital in West Java during the period of June-August 2018. The inclusion criteria were patients undergoing

vaginal delivery or cesarean section who was diagnosed with PPH and received misoprostol via rectal route within 24 hours of delivery. The exclusion criteria were referral patients who delivered in other hospitals, those receiving misoprostol via other routes in addition to per rectal administration and deceased patients. Sampling size was calculated using Slovin's formula as follows:

$$n = \frac{N}{1 + Ne^2}$$

Denote:
n : sample size for each group
N : Population size
e : Margin of error

Sample size for group of vaginal delivery:

$$\frac{n = N}{(1 + Ne^2)} = \frac{40}{(1 + 40 \times 0.05^2)} = \frac{40}{1.1} = 36.36 \sim 40 \text{ patients}$$

Sample size for group of cesarean section:

$$\frac{n = N}{(1 + Ne^2)} = \frac{45}{(1 + 45 \times 0.05^2)} = \frac{45}{1.1} = 40.9 \sim 40 \text{ patients}$$

The principal researcher identified the occurrence of side effects through patient observation and medical note review. The probability of side effects was rated by a panel consisting of gynecologist, midwife and pharmacist. The rating was done using Naranjo algorithm[15] and the consensus among the panel members was used as the final rating. The study was approved by the Human Ethics Committee of the study hospital. Written informed consent was obtained from the patients prior to observation.

Patient characteristics and side effect data were summarized using descriptive statistics. The proportion of misoprostol's side effect incidence between two modes of delivery was compared using Z-test. Statistical data analysis was undertaken using statistical Product and Service Solutions (SPSS) for Windows version 22.0. The level of significance was set at a probability value of $p < 0.05$.

## RESULTS

There were 40 patients observed in each group during this three-month study. Patients' maternal and obstetric characteristics are summarized in Table 1. As seen in Table 1, there was no discernible difference in maternal age and gestational age between the two groups. With regard to parity, patients in CS group tend to have more birth experience with nearly 40% having their third parity compared with 22.5% of those in VD group. Four patients in CS group had comorbidities (i.e. hypertension, human immunodeficiency virus infection, hepatitis B, brain tumour) with only one patient taking regular medicine. Meanwhile, none of the patients in the VD group reported any comorbidities and took any routine medicine.

**Table 1.** Patients' Maternal and Obstetric Characteristics

| Characteristics | Vaginal Delivery Group (N=40 Patients) | Cesarean Section Group (N=40 Patients) |
|---|---|---|
| Maternal age in years (±SD) | 29.05 (±7.172) | 29.58 (±7.510) |
| Gestational age in weeks (±SD) | 37.65 (±1.099) | 36.83 (±2.899) |
| **Parity, N (%)** | | |
| 1 | 15 (37.5) | 10 (25.0) |
| 2 | 16 (40.0) | 15 (37.5) |
| ≥3 | 9 (22.5) | 15 (37.5) |
| Presence of comorbidities, N (%) | - | 4 (10.0) |
| Routine consumption of medicines, N (%) | - | 1 (2.5) |

**Table 2.** Patients' Pre-and Postpartum Clinical Data

| Clinical Parameters | Vaginal Delivery Group (N=40 Patients) | | Cesarean Section Group (N=40 Patients) | |
|---|---|---|---|---|
| | Prepartum | Postpartum | Prepartum | Postpartum |
| **Temperature, N (%)** | | | | |
| Normal (36.1-37.2 $^0$C) | 40 (100.0) | 5 (12.5) | 37 (92.5) | 1 (2.5) |
| Above normal (>37.2 $^0$C) | - | 35 (87.5) | 3 (7.5) | 39 (97.5) |
| **Pain Scale (5-point), N (%)** | | | | |
| 3 | 40 (100.0) | 40 (100.0) | 39 (97.5) | 39 (97.5) |
| 4 | - | - | 1 (2.5) | 1 (2.5) |
| **Hemoglobin level, N (%)** | | | | |
| 8-12 g/dL | 25 (62.5) | 39 (97.5) | 22 (55.0) | 40 (100.0) |
| 12-16 g/dL | 15 (37.5) | 1 (2.5) | 18 (45.0) | |
| **Hamorrhage volume, N (%)** | | | | |
| >500 mL | - | 40 (100.0) | - | - |
| >1000 mL | - | - | - | 40 (100.0) |

### Side Effects of Misoprostol

All patients in the VD group received misoprostol per rectal 400 mcg given in a single dose. Meanwhile, the majority of CS patients (N=38, 95.0%) was given a higher total dose of misoprostol (i.e. 600 mcg single dose) via rectal route and two patients received total dose 800 mcg divided into two doses (600 mcg followed by 200 mcg). The second dose was given due to persistent hamorrhage despite the administration of first dose. Patients were observed before and after delivery to evaluate the patient's clinical status and identify the presence of misoprostol's side effects. The clinical data are detailed in Table 2.

It can be seen from Table 2 that after delivery the majority of VD patients (87.5%) and nearly all CS patients experienced increased body temperature above the normal range. Both groups showed a similar pattern in pain severity where there was no change in pain scale before and after delivery. Nonetheless, one patient in CS group reported slightly more severe pain (i.e., scale of 4) compared to other patients in both groups. Concerning the hemoglobin (Hb) level, just over 60% of VD patients had Hb < 12 g/dL and the proportion increased enormously to 97.5%. The similar condition was documented in the CS group with all patients having low postpartum Hb level. The high proportion of patients with decreased Hb level could be partly explained due to the volume of blood loss (i.e.>500 mL in the VD group and >1000 mL in CS group).

Thirty-four patients (85.0%) patients in the VD group experienced side effects, whilst all CS patients reported at least one side effect after receiving misoprostol. There was no significant difference in the proportion of patients having side effects in the two groups (p=0.366). Totally, there were 135 and 164 side effects in the VD group and CS group, respectively. The details of side effects of misoprostol in the two study groups can be seen in Table 3. As described in Table 3, gastrointestinal side effects (e.g. nausea, vomiting, diarrhoea) accounted for the most frequent side effects in the two groups. In terms of side effect profile, there was no discernible difference between the two groups. However, abdominal pain and fatigue were observed in CS patients only.

**Table 3.** Side Effects of Misoprostol Per Rectal in Vaginal Delivery and Cesarean Section

| Types of Side Effects N (%) | Vaginal Delivery Group (N=40 Patients) | Cesarean Section Group (N=40 Patients) | *P-value* |
|---|---|---|---|
| Nausea | 31 (77.5) | 34 (85.0) | 0.438 |
| Vomiting | 31 (77.5) | 34 (85.0) | 0.432 |
| Pyrexia | 27 (67.5) | 33 (82.5) | 0.366 |
| Shivering | 20 (50.0) | 23 (57.5) | 0.432 |
| Diarrhea | 10 (25.0) | 8 (20.0) | 0.454 |
| Abdominal pain | - | 2 (5.0) | 0.454 |
| Headache | 16 (40.0) | 29 (72.5) | 0.228 |
| Fatigue | - | 1 (2.5) | 0.477 |

**Z-test was applied to compare the proportion of each side effect occurrence experienced by patients in the group of vaginal delivery versus that of cesarean section.*

Concerning the probability of side effect occurrence, there were slight differences between VD and CS patients. The panellist rated all side effects in VD patients as probable. Meanwhile, more than 70% (N=115/164 ) of the side effects in CS patients were regarded as probable leaving the rest of the proportion as definite. Further, abdominal pain and fatigue, which were absent in VD patients, were rated as definite in CS group.

## DISCUSSION

Misoprostol can be administered through many routes including oral, vaginal, sublingual, buccal or rectal. A pharmacokinetic study comparing the profiles of misoprostol administration in three different routes (i.e. oral, rectal, vaginal) showed that vaginal misoprostol had a greater area under curve (AUC) and circulated in the body longer than the oral route. Rectal misoprostol showed similar profiles to the vaginal route but with lower AUC. Oral misoprostol had a higher peak plasma concentration and more rapid absorption than either vaginal or rectal route highlighting the higher rates of gastrointestinal-related side effects (nausea, diarrhoea) associated with oral misoprostol compared to the vaginal and rectal route. [11, 16] The present study used misoprostol

tablet designed for oral administration instead of the specifically-designed rectal formulation. However, a study done by Khan and colleagues revealed that oral misoprostol tablet can be absorbed by rectal and vaginal route.[16]

It is challenging to compare our findings with other studies despite numerous studies have been done to evaluate misoprostol's side effects. To the best of our knowledge, little research has been done to compare the side effects of misoprostol between VD and CS patients. Regarding the profile of side effect, the results of this present study were in line with the WHO Adverse Reaction Database that the most common frequent adverse events related to misoprostol were as follows: diarrhoea, abdominal pain, nausea, hamorrhage, abortion, vomiting, dyspepsia, flatulence, abortion, vomiting, dizziness, menorrhagia, vaginal hemorrhage and fever.[17] Similarly, pooled data from Cochrane review showed that misoprostol given in treatment doses had increased risk of side effects in comparison to placebo. According to the review, patients taking misoprostol had approximately two-fold risk to experience vomiting and shivering, and three-fold risk of pyrexia. Nevertheless, the reported side effects were transient in nature.[11]

The safety profile of misoprostol in obstetrics is linked to the pharmacokinetic profile of PGE1analogue.[9] In addition to its uterotonic mechanism, misoprostol has shown pharmacologic effects on several organ systems. It can inhibit platelet-activating factors and affects metabolic and physiologic processes.[18] PGE1 like misoprostol acts on the central thermoregulation centres which may explain the incidence of pyrexia in misoprostol use.[19] A systematic meta-analysis done involving 33 trials found that the incidence of pyrexia after administration of misoprostol is largely determined by its dosage and route.[20] That study reported that the highest incidence of pyrexia was noted in sublingual route (15%) with lower rates with the oral (11.4%) and rectal (4%) which was contradictory with our finding showing high incidence of pyrexia more than 60%. In line and colleagues found sublingual route had the highest bioavailability of all administration modes and this route was associated with the highest incidence of side effects compared to other routes.[21] Further, the study underlined vital finding that patients taking misoprostol had the five-time risk of pyrexia as opposed to those given placebo or other uterotonic agents.[20]PGE1 effect on central thermoregulatory system also has an impact on the incidence of shivering. A randomized placebo-controlled trial of misoprostol for PPH prevention reported shivering was more common in the misoprostol group than in that of placebo (19% vs 5% respectively).[22]Corresponding to the result of our study, higher rates of shivering were uncovered in other studies where shivering was documented in 32%-57% of women receiving misoprostol.[13,14] Other common side effects of misoprostol included diarrhoea and nausea which occurred due to the impact of prostaglandin on the smooth muscle of the gastrointestinal tract including increased orocaecal transit time.[23]

The current study also revealed that patients in CS group received a higher dose of misoprostol (600 mcg as a single dose and two patients took total dose of 800 mc) than those in VD group (i.e., 400 mcg). A meta-analysis comparing misoprostol 400 mcg vs 600 mcg showed no evidence of using misoprostol with higher dose for reducing blood loss. Moreover, the incidence of pyrexia was higher among women receiving misoprostol compared with those taking other uterotonics. Higher dose of misoprostol (600 mcg) was associated with more incidence of pyrexia than the lower dose (400 mcg).[17] Our study confirmed the finding of the meta-analysis in which CS patients showed higher rate of pyrexia (82.5%) than those in the VD group (67.5%). Further, it has been found that studies reporting maternal death after taking misoprostol, the patients in those studies were administered with higher dose (i.e., ≥600 mcg).[13,14,17] In fact, some trials uncovered significant finding that there was no significant efficacy between misoprostol 400 mcg vs higher doses. Conversely, the findings highlighted the safety concerns pertinent to the use of high dose of misoprostol as the frequency and severity of adverse events were dose-related.[17, 24]

It is quite unfortunate that there is no clinical pathway for PPH management in the study hospital. The findings of this study confirm the existing evidence to obstetricians and gynecologists as to the safety of misoprostol for treating PPH. Further, the results can be used as essential information for the clinicians

to develop clinical pathway in the study hospital to guide them when treating patients with PPH. Nonetheless, there are some limitations in the study. Firstly, this study was conducted in one hospital with modest number of samples which diminished the generalization of the findings. Our findings highlight that more research is required to better understand the rate and pattern of misoprostol's side effects in two modes of delivery. Future studies should include larger sample size with various routes of misoprostol and multiple institutions to provide a broader picture of the side effects and to identify the influence of delivery mode on the side effects. Secondly, the panellists rating the side effect probability were selected for convenience and there was no formal training provided. Nevertheless, the panellists were deemed to have the adequate clinical knowledge and professional experience, and the panellists were asked to read through the Naranjo algorithm prior to the panel meeting. The results might be different if the formal training on how to use the Naranjo algorithm had been provided to the panellists.

## CONCLUSIONS

In summary, the study uncovered high incidence of misoprostol-related side effects both in VD and CS patients and the rate of incidence was not significantly different between the two delivery modes. In addition, there was no discernible difference in the profile of side effects documented in the two groups. This study raises the concern on the importance of judicious use of misoprostol for obstetric and gynecological indications in appropriate clinical settings to ensure its effectiveness and safety. In addition, the frequent occurrence of side effects related to its use requires active pharmacovigilance involving the front-line healthcare professionals particularly doctors, nurses and pharmacists.

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**Research Article**

# Low Vitamin D Levels Increase the Risk of Early Onset Neonatal Sepsis

## *Kadar vitamin D yang Rendah Meningkatkan Risiko Sepsis Neonatal Awitan Dini*

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### Abstract

**Objective:** To identify the association between maternal and umbilical cord vitamin D levels with suspects of Early-Onset of Neonatal Sepsis (EONS) in newborns from mothers with Preterm Premature Rupture of Membranes (PPROM).

**Methods:** This is a retrospective cohort study conducted from January 2017 to Augusts 2018. Data was taken consecutively from medical records and previous study data at Dr. Cipto Mangunkusumo and Persahabatan Hospital, Jakarta.

**Results:** From total of 72 infants from mothers with PPROM, 22 infants (31%) were EONS-suspected and 50 infants (69%) were not EONS-suspected. There was a significant association between maternal and umbilical cord vitamin D levels with EONS.

**Conclusions:** There was a significant association between maternal and umbilical cord vitamin D levels with EONS.

**Keywords:** early-onset neonatal sepsis, preterm premature rupture of membrane, vitamin D.

### *Abstrak*

***Tujuan:*** *Untuk mengetahui hubungan antara kadar vitamin D maternal dan tali pusat dengan risiko tejadinya Sepsis Neonatal Awitan Dini (SNAD) pada bayi dari ibu dengan Ketuban Pecah Dini (KPD).*

***Metode:*** *Desain penelitian kohort retrospektif secara consecutive sampling. Data diambil dari rekam medis dan data penelitian sebelumnya di Rumah Sakit Umum Pusat Nasional (RSUPN) Dr. Cipto Mangunkusumo dan Rumah Sakit Umum Pusat (RSUP) Persahabatan, Jakarta.*

***Hasil:*** *Dari 72 bayi yang dilahirkan dari ibu dengan KPD, 22 bayi (31%) diantaranya diduga mengalami SNAD, sedangkan 50 bayi lainnya tidak mengalami SNAD. Terdapat hubungan yang bermakna antara kadar vitamin D maternal dan tali pusat dengan kejadian SNAD.*

***Kesimpulan:*** *Terdapat hubungan yang bermakna antara kadar vitamin D maternal dan tali pusat dengan kejadian SNAD.*

***Kata kunci:*** *ketuban pecah dini, sepsis neonatal awitan dini, vitamin D.*

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## INTRODUCTION

The common cause (70%) of perinatal death was preterm birth. Preterm neonates often failed to adapt to new environment, causing high morbidity and mortality.[1,2] It was important to decrease neonatal (0-28 days of age) mortality rate because it was contributed to 59% of infant mortality. Indonesian Demographic and Health Survey 2012 showed the neonatal mortality rate during 2012 was 19 per 1.000 live births.[3]Based on RISKESDAS 2007, neonatal sepsis (12%) was one of the common cause of neonatal death during 0-6 days of life besides respiratory disorders (37%), prematurity (34%), hypothermia (7%), icterus neonatorum (6%), and congenital abnormality (1%).[4]

Vitamin D played an important role to modulate the immune system. Vitamin D deficiency was associated with decrease in production of antimicrobial substances. A few studies showed that vitamin D concentration circulated in the umbilical cord was indirectly correlated with newborns susceptibility getting infection.[5]

The incidence rate of preterm premature rupture of membranes was 3-10% from all of

labour, 4% was happened in gestational age less than 34 weeks. Incidence rate of PPROM in Indonesia was approximately 35.7-55.3% from 17.665 labour. PPROM was one of preterm birth cause related to high perinatal morbidity and mortality. Preterm birth was happened in 1 of 10 labor in United State and the number was higher in developing countries, about 40-75% neonatal death.[6,7]

A cross-sectional study in Tertiary Obstetrics and Gynecology Center in Kosovo which total of 200 newborns from pregnant women with PPROM was involved. In this study, there were 13% newborns with early-onset neonatal infection, while 5% of them were neonatal sepsis cases.

## METHODS

This study was a retrospective cohort study conducted at Dr. Cipto Mangunkusumo and Persahabatan Hospital from January 2017 to Augusts 2018. The population in this study was pregnant women with preterm premature of the membrane (PPROM) and their newborn in 28-34 weeks' gestation. The inclusion criteria of subjects were pregnant women with PPROM and born in 28-34 weeks gestation, complete data, mother and her baby data matched, the neonates were hospitalised in NICU minimal 3 days and the exclusion criteria were pregnant women without PPROM, baby birth weight > 2500 gram, born in congenital abnormality, still birth, and referred to other hospitals before one day of age. The samples were collected consecutively.

This study had obtained ethical clearance from the Committee of Medical Research Ethics Dr. Cipto Mangunkusumo and Persahabatan Hospital, Jakarta and all subjects data were confidentially guaranteed before joined this study. The subject data were identified from medical records, including age, education levels, employment status, number of gravidas, gestational age, and baby birth weight. The maternal and umbilical cord vitamin D levels, CRP, IT ratio, and diagnosis of neonatal sepsis was collected by medical records. Data were analyzed by bivariate tests using independent T-test and Mann Whitney test.

## RESULTS

There were 72 patients take part the study. The average age of subjects was 28.50 years in a group with sepsis and 30.74 years in group without sepsis. Majority of subjects in both groups had length of study ≤ 12 years, 17 (77.3%) and 40 (80.0%) subjects, respectively. Most of the subjects were unemployed and became a housewife, there were 18 (82.0%) in group with sepsis and 36 (72.0) in another group. Based on number of gravidas, it was the first pregnancy for a half of subjects. In group with sepsis majority of subjects (11; 50.0%) had gestational age between 30-32 weeks while in group without sepsis majority (28; 56.0%) had gestational age between 32-34 weeks. The average of baby's birth weight was 1609 (1090-2310) grams in group with sepsis and 1824 (1015-2300) grams in group without sepsis. The characteristics of the subjects are presented in table 1.

**Table 1.** Subject's Characteristics

| Demographical and Clinical Characteristics | Suspected Sepsis (n = 22) | Without sepsis (n = 50) |
|---|---|---|
| Age (years) | 28.50 | 30.74 |
| **Education levels (n, %)** | | |
| Length of study ≤ 12 years | 17 (77.3) | 40 (80.0) |
| (elementary school, junior, and senior high school) | 5 (22.7) | 10 (20.0) |
| **Length of study > 12 years (university or academy)** | | |
| **Employment status (n, %)** | | |
| Unemployed | 18 (82.0) | 36 (72.0) |
| Employed | 4 (18.0) | 14 (28.0) |
| **Number of gravida (n, %)** | | |
| 1 | 12 (55.0) | 24 (48.0) |
| 2 | 4 (18.0) | 9 (18.0) |
| 3 | 4 (18.0) | 11 (22.0) |
| 4 | 1 (4.5) | 6 (12.0) |
| 5 | 1 (4.5) | 0 (0.0) |
| **Gestational age (n, %)** | | |
| 28-30 weeks | 7 (31.8) | 7 (14.0) |
| 30-32 weeks | 11 (50.0) | 15 (30.0) |
| 32-34 weeks | 4 (18.2) | 28 (56.0) |
| Baby's birth weight (gram) | 1609 (1090 – 2310) | 1824 (1015 – 2300) |

**Relationship between Vitamin D Levels of Maternal and Umbilical Cord with Early-onset Neonatal Sepsis Suspected**

This study reported that the average of maternal vitamin D levels are 18.88 ng/ml (5.84-55.60 ng/ml) in EONS-suspected group and 28.18 ng/ml (8.25-63.49 ng/ml) in not EONS-suspected group. There were statistically differences between both groups. The relative risk (RR) value in this group were 0.96 (95% CI 0.93-0.99). These results showed that every 1 unit increase of maternal vitamin D level will reduce risk of EONS by 4% (1-7 %).

Based on vitamin D levels of umbilical cord, the average of vitamin D levels were 11.24 ng/ml (6.12-37.29 ng/ml) in EONS-suspected group and 14.81 ng/ml (4.47-53.35 ng/ml) in not EONS-suspected group. There were significant differences between both of groups. The RR value in this group were 0.95 (95% CI 0.89-1.00). These results showed that every 1 unit increase of umbilical cord vitamin D level will reduce risk of EONS by 5% (0-11 %).

**Table 2.** Relationship between Vitamin D Levels of Maternal and Umbilical Cord with Early-onset Neonatal Sepsis

| Vitamin D levels | EONS-suspected (n, %) | Not EONS-suspected (n, %) | *P-value* | RR (95% CI) |
|---|---|---|---|---|
| Maternal vitamin D levels[a] | 18.88 (5.84-55.60) | 28.18 (8.25-63.49) | 0.013[1] | 0.96 (0.93-0,99)[2] |
| Umbilical cord vitamin D levels[a] | 11.24 (6.12-37.29) | 14.81 (4.47-53.35) | 0.024[1] | 0.95 (0.89-1.00)[2] |

*Description: [a]Expressed in the median (min-max); [1] Statistical test using the Mann-Whitney test; [2] RR values based on cox regression*

If vitamin D levels were categorized as normal and low, this study showed that there was a significantly association between maternal vitamin D levels with EONS-suspected. Subjects with low maternal vitamin D levels had risk factor 1.48 times (1.12-1.95) to have baby with EONS higher than subject with normal maternal vitamin D levels. This study also reported that there was no association between umbilical cord vitamin D level with EONS.

**Table 3.** Relationship between Vitamin D Levels of Maternal and Umbilical Cord with Early-Onset Neonatal Sepsis (categorical)

| Vitamin D levels | EONS-suspected n (%) | Not EONS-suspected n (%) | *P-value* | RR (95% CI) |
|---|---|---|---|---|
| Maternal vitamin D levels | | | | Reference |
| Normal | 3 (13.6) | 22 (44.0) | 0.013[1] | 1.48 (1.12 – 1.95) |
| Low | 19 (86.4) | 28 (56.0) | | |
| Umbilical cord vitamin D levels | | | | Reference |
| Normal | 1 (4.5) | 8 (16.0) | 0.259[2] | 1.33 (0.99 – 1.78) |
| Low | 21 (95.5) | 42 (84.0) | | |

*Description: [1]Statistical test using Chi-squaretest, [2]Statistical test using Fisher-exact test*

## DISCUSSION

Neonatal sepsis was systemic infection characterized by clinical manifestation of infection with port entry of microbes. Neonatal sepsis was one of the most common cause of neonatal mortality and morbidity both in developing and developed countries.

A cross-sectional study at the tertiary Obstetrics and Gynecology center in Kosovo. The study involved 200 pregnant women with PROM and newborns. Overall, 13% of newborns had early-onset neonatal infections, and sepsis was evident in 5% of cases.[8]

In this study from total of 72 subjects with preterm premature of membrane (PPROM), there were 22 (31%) early-onset neonatal sepsis (EONS)-suspected newborns while 50 (69%) newborns were not EONS-suspected. These results were higher than in other studies. in Tertiary Obstetrics and Gynecology Center in Kosovo. From total of 200 pregnant women with PPROM, 13% newborns had early-onset neonatal infection and 5% were proved to have neonatal sepsis.[9]

This study showed that maternal vitamin D levels were significant differences between EONS-suspected group and not EONS-suspected group. Every 1 unit increase of maternal vitamin D level will reduce risk of EONS by 4% (1-7 %). If maternal vitamin D levels were classified as normal and less than normal, there was an association between maternal vitamin D levels and EONS. Maternal vitamin D levels less than normal had risk 1.48 times (95% CI 1.12-1.95) to had EONS than maternal with normal vitamin D levels. These results were similar to a study conducted by Muhammad Tariq Nadeem[10]which reported low maternal vitamin D levels is significantly associated with low serum neonatal vitamin D levels and higher risk of EONS. From total of 93 neonates who had neonatal sepsis and 93 neonates born without sepsis as controls, deficiency of vitamin D was found in 88.17% maternal sample and 82.80% neonatal sample who had neonatal sepsis.

Reported 100 neonates in Neonatal Intensive Care Unit in Sultan Suleyman Hospital Turkey in 2012. Total of 50 term babies with clinical signs of infection and 50 term babies without clinical signs of infection were taken for blood collecting to measure 25-hydroxyvitamin D (25-OHD) during first 3 postnatal days. Vitamin D was a prohormone while the main form of vitamin D circulated in blood vessels was 25-OHD. These molecules were specifically bound to plasma carrier proteins which carry vitamin D and calcitriol.[11-13]

Vitamin D deficiency in circulation played role in the pathogenesis of infection. Vitamin D receptors were expressed in all of the ligands cellular immunity subsets by 25-OHD then triggered native immune cells such as monocyte, macrophage, and neutrophil to increased chemotactic, phagocytic, and bactericide activity. This activity caused conversion of 25-OHD3 (calcidiol) to active form 1,25-$OH_3$ (calcitriol). Calcitriol was secosteroid hormone which bind vitamin D receptors to release signals in the tissue and cell so finally induced production of antimicrobe peptide such as cathelicidin, delayed Gram-positive and Gram-negative bacteria colonization. Complex vitamin D receptors directly induced antimicrobe protein expression such as ß-defensin or cathelicidinin the native immune cells.[5,14]Cathelicidinand ß-defensin had wide antimicrobe activity to certain virus and fungi. The role of vitamin D caused increase of cathelicidin 10 times.[15]

In this study, the average vitamin D levels of umbilical cord were significantly difference between EONS-suspected group (11.24 ng/ml) and not EONS-suspected group (14.81 ng/ml). Every 1 unit increase of maternal vitamin D level will reduce risk of EONS by 5% (0-11 %). It was similar from total of 100 preterm neonates with gestational age <37 weeks, 63% had vitamin D deficiency (≤5 ng/ml), 24% had vitamin D insufficiency (5-15 ng/ml), and 13% had lack of vitamin D (>15 ng/ml).[16] Incidence rate of sepsis increased in vitamin D insufficiency group. In this study, we concluded that lack of vitamin D that detected in blood circulation taken by umbilical cord and associated with neonatal sepsis levels in preterm neonates. This result showed that lack of vitamin D was one of risk factors of sepsis in preterm neonates and there was an association between vitamin D levels of the umbilical cord and neonatal sepsis in preterm newborns. However, if vitamin D levels of the umbilical cord was classified as normal and abnormal (insufficiency and deficiency), there was no significant association between vitamin D levels of umbilical cord and EONS.

## CONCLUSION

Maternal and umbilical cord vitamin D levels was significantly associated with EONS in premature newborns.

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**Research Article**

# Effects of Levonorgestrel Implants of One Rod and Two Rod on Lipid Profile, Follicle Stimulating Hormone (FSH), and Estradiol Levels in Acceptors

## *Efek Implan Levonorgestrel Satu Batang dan Dua Batang terhadap Profil Lipid, Kadar Follicle Stimulating Hormone (FSH), dan Estradiol pada Akseptor*

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## Abstract

**Objective:** To find out the comparison of the effect of one-rod and two-rod levonorgestrel implants on FSH, estradiol levels and increase in acceptor lipid profile after a 3-month evaluation in the Mother and Child Hospital of Rika Amelia Palembang.

**Methods:** This study is a phase III clinical trial, "Open" (Open Randomized Clinical Trial), carried out randomization by comparing two types of implant KB, namely levonorgestrel implants, one rod with two rods. This research was conducted at the RSIA Rika Amelia Palembang. Research time is 6 months from November 2018 - April 2019 or until the number of samples is fulfilled.

**Results:** Based on the installation time, the average installation time using one rod LNG was 1.54 ± 0.11 minutes and the LNG for the two rods was 2.49 ± 0.26 minutes. Majority of patients having a normal blood pressure of 89.5% in one rod LNG and 68.4% in two rod LNG. The mean body mass index (BMI) of respondents using LNG implants one rod was 24.19 ± 3.93 kg / $m^2$ and LNG for two rods was 25.09 ± 6.11 kg / $m^2$. Based on the menstrual pattern, it was found that 84.2% of the subjects had regular menstrual patterns in the one-rod LNG group, while there were 63.2 % of subjects who have irregular menstrual patterns. From the statistical test, it was found that there were no differences in cholesterol levels (p = 0.919), HDL (p = 0.793), LDL (p = 0.851) and triglycerides (p = 0.679). There were no differences in FSH levels between respondents using one rod and two rod LNG implants (p = 0.849) and also on estradiol (p = 0.099)

**Conclusions:** There is no difference between the use of one-rod and two-rod levonorgestrel implants against FSH, Estradiol levels and increased lipid profile after 3 months of implant installation. The unpleasant effect in this study was the decline in HDL, but this was accompanied by a decrease in body weight, total cholesterol, LDL, HDL due to a decrease in all aspects.

**Keywords:** estradiol, FSH, implant contraception, levonorgestrel, lipid profile, one-rod, two-rod

## *Abstrak*

***Tujuan:*** *Untuk mengetahui perbandingan efek implan levonorgestrel satu-batang dan dua-batang pada FSH, kadar estradiol dan peningkatan profil lipid akseptor setelah evaluasi 3 bulan di Rumah Sakit Ibu dan Anak Rika Amelia Palembang.*

***Metode:*** *Penelitian ini adalah uji klinis fase III, "Open" (Open Randomized Clinical Trial), yang dilakukan secara acak dengan membandingkan dua jenis KB implan, yaitu levonorgestrel implan, satu batang dengan dua batang. Penelitian ini dilakukan di RSIA Rika Amelia Palembang. Waktu penelitian adalah 6 bulan dari November 2018 - April 2019 atau hingga jumlah sampel terpenuhi.*

***Hasil:*** *Berdasarkan waktu pemasangan didapatkan rerata waktu pemasangan yang menggunakan LNG satubatangadalah 1,54±0,11 menitdanpada LNG dua batang adalah 2,49±0,26 menit. Mayoritas pasien memiliki tekanan darah yang normal 89.5% pada LNG satu batang dan 68.4% pada LNG dua batang. Rerata indeks massa tubuh (IMT) responden yang menggunakan implan LNG satu batang sebesar 24,19 ± 3,93 kg/$m^2$ dan LNG dua batang sebesar 25,09 ± 6,11 kg/$m^2$. Berdasarkan pola haid, didapatkan sebanyak 84,2% subjek yang memiliki pola haid teratur pada kelompok LNG satu batang, sedangkan terdapat sebanyak 63,2% subjek yang memiliki pola haid tidak teratur. Dari uji statistik didapatkan bahwa tidak terdapat perbedaan kadar kolesterol (p = 0,919), HDL (p = 0,793), LDL (p = 0,851) dan trigliserida (p = 0,679). Tidak terdapat perbedaan kadar FSH antara responden yang menggunakan implan LNG satu batang dan dua batang (p = 0,849) dan juga pada estradiol (p=0.099)*

***Kesimpulan:*** *Tidak terdapat perbedaan antara penggunaan implan levonorgestrel satu batang dan dua batang terhadap kadar FSH, Estradiol serta peningkatan profil lipid setelah 3 bulan pemasangan implan. Efek yang tidak menyenangkan dalam penelitian ini adalah terjadinya penurunan HDL, namun hal ini disertai dengan penurunan berat badan, kolesterol total, LDL, HDL dikarenakan terjadi penurunan pada seluruh aspek.*

***Kata kunci:*** *dua batang, estradiol, FSH, kontrasepsi implan, lenovorgestrel, profil lipid, satu batang.*

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## INTRODUCTION

Implant contraception is the most important contraceptive method in various contraceptive methods available today. High efficacy, lack of serious side effects, rapid reversibility, comfort in long-term use make implant method a form of contraception with a high level of acceptance.[1]Implants are hormonal contraceptives that are implanted under the skin (subdermal) and used for a long time. This contraception contains bioactive progestin levonorgestrel (LNG) ingredient, a steroid hormone that is a derivative of 19-nortestosterone. LNG has activities similar to progesterone with weak androgenic activity and has no estrogenic activity.[1,2]With the use of LNG implants, pregnancy is prevented through a combination mechanism as follows.[3-5] The primary mechanism is producing thick cervical mucus that prevents sperm penetration, and inhibits ovulation, at approximately 50% of the menstrual cycle. Secondary mechanisms, which can support the work of the primary mechanism include reducing natural progesterone production by the ovary during the luteal phase even in cycles when ovulation occurs and suppresses endometrial growth (hypoplasia).[1-6]

The most common impact on the use of implants is a change in menstrual bleeding patterns. Other impacts that can arise include headaches, changes in mood, depression, nausea, changes in body weight, changes in reproductive hormone status, changes in carbohydrate metabolism and affect lipid metabolism.[1,6]

The LNG implant is a testosterone derivative that has a mineralocorticoid effect that affects extracellular fluid minerals so that this contraception can also cause an increase in body weight.[1,7-11]Changes in lipid metabolism in the form of elevated triglyceride levels, total cholesterol, LDL and decreased HDL accompanied by an increase in excess body weight are diagnostic criteria for metabolic syndrome which can increase the occurrence of type II diabetes mellitus and cardiovascular disorders. The lipid profile itself is the best predictor of metabolic syndrome. Therefore a study of the effect of Levonorgestrel implant on one rod with two rods on lipid profiles in acceptors is important.[1,6]

There was an increase in body weight in the use of levonorgestrel implants for 6 months (1.3 kg) and use of 12 months (2.4 kg). There was an increase in body weight (2.5 kg) during the 5-year use of levonorgestrel implants.[10] Estrogen is cardioprotective (protecting the heart) and anti-atherogenic (anti-fat formation), while progesterone is anti-estrogen. Changes in fat metabolism occur because of the hormonal influence of progesterone which causes a disruption in the balance of lipid profiles in the body. Changes in serum lipid profile (triglyceride, total cholesterol, HDL and LDL) in long-term use of LNG are risk factors for atherosclerosis (accumulation of fat in the arterial wall) and cardiovascular.[1-3,7-11]Two-rod implant contraception, for example Jadena and Norplant 2 rods. Jadena is a type of LNG implant consisting of two flexible rods and inside each of them contains 75 mg of levonorgestrel. The implant rod is wrapped in a thin-walled silicone tube which at the ends is covered with medical-grade adhesive silastic (poly dimethyl-siloxane). His working period is 5 years. Whereas Norplant has 2 soft hollow silasticrods with a length of about 3.4 mm, and a diameter of 2.4 mm, which contains 36 mg of levonogestrel in the form of crystals which are placed in the interior of the capsule and the working period is 3 years.[4,12-14]One-rod implant contraception, for example Implanon is a single implant containing etonogestrel 68 mg wrapped in an ethylene vinyl acetate membrane. His working period is 3 years. On average in the first 6 weeks the hormone is released from 60 to 70 mcg / day, down to 35-45mcg / day at the end of the first year of use. The average hormone is released 30-40 mcg / day in the second year and at the end of the third year the hormone is released to 25-30 mcg / day.[15]

The advantage of a single-rod implant is the lower dose so that the level of levonorgestrel in syrodic circulation is lower, where the dose is expected to have a better effect than two-rod implants such as changes in lipid profile or side effects such as changes in menstrual pattern or blood pressure more beneficial to users but still can prevent the occurrence of pregnancy. This is similar to the effect of levonorgestrel in the vaginal ring and Mirena IUD which only contains 52 mg of levonorgestrel released in small doses (20 µg / day initially and decreases to around 10 µg / day after five years).[14,15]

## METHODS

This study is a phase III clinical trial, "Open" (Open Randomized Clinical Trial), carried out randomization by comparing two types of implant KB, namely levonorgestrel implants, one rod with two rods. This research was conducted at the RSAB Rika Amelia Palembang. Research time is 6 months from November 2018 - April 2019 or until the number of samples is fulfilled. The study sample was women of childbearing age and wanted to postpone or extend their pregnancies up to three years using implant contraception. The inclusion criteria in this study were couples of reproductive age 18-40 years and in good health, not pregnant, getting an explanation and understanding the objectives, risks and benefits of the study, and signing informed consent, subjects willing to return to the clinic, to make a repeat visit according to schedule and willing to only use implants as contraception during the study. The exclusion criteria in this study were a woman who had a history or event such as having experienced contraindications for long-term hormonal contraception including vaginal bleeding with unclear causes, bloody discharge from the nipple, breast cancer or other cancers that are related to hormone dependence, uterine bleeding with unclear causes, thromboembolic disorders or thrombophlebitis or there is a history of both diseases, acute liver disease or liver tumour, possible pregnancy, pregnancy, breastfeeding have a history of idiopathic intracranial hypertension, history of coronary heart disease, cerebral vascular disease, and hypersensitivity to levonorgestrel or other components of the drug. There is a history of hepatitis, diabetes mellitus, depression or other mental disorders and epilepsy.

Blood pressure more than 180/100 mmHg. The study subjects were suspected of being diagnosed as Pelvic Inflammatory Disease (PID). Severe hirsutism. Routine therapy with enzyme-stimulating drugs, such as barbiturates, phenytoin carbamazepine or rifampicin. Women with symptoms of amenorrhea total more than one year while using implants or other hormonal contraceptives. Have not experienced menstruation after giving birth. Have not had menstruation in the past 6 months after using injectable contraception or pills and are currently participating in other studies in the last 3 months.

### Work Procedures

The first step is identification of the patient including name, age, sex, address, diagnosis, education, occupation and income, special history (obstetric and gynecological history (parity, first day of last menstruation), history of previous illness, condition, blood pressure, pulse The patient's next procedure is the determination of nutritional status by measuring the weight and height of the pretreatment and the third month, height and weight measured by researchers assisted by paramedics, standing position and using microtoire. The purpose of the study was briefed and informed to the patients. Patients who agreed to participate in the study were asked to sign the agreement provided for this study.

All patients who were included in this then get a random number, and they would get one of the treatment methods KB (one or two LNG implants) which was in accordance with the list of random numbers. The next step is the assessment of the working effect of one or two LNG implants in the acceptor's lipid profile. This was collected by recording the acceptors' body weight, menstrual patterns, total cholesterol, triglycerides, LDL and HDL after evaluation of blood serum examination from the lab. Finally, acceptors from both treatments were tested on their FSH and estradiol levels in the blood.

## RESULTS

Phase III clinical trials with Open Randomized Clinical Trial to determine the differences in the effects of one-rod and two-rod levonorgestrel implants on FSH and estradiol levels and increase in acceptor lipid profile after 3 months evaluation at RSAB Rika Amelia Palembang from October 2017 to April 2018. 38 people met the inclusion and exclusion criteria, 19 people received one-rod levonorgestrel implants (one rod LNG) and 19 others received two-levonorgestrel implants (two-rod LNG).

### General Characteristics of Research Subjects

The general characteristics of the research subject are shown in table 5. Based on the installation time, the average time of installation using one rod LNG implant was 1.54 ± 0.11 minutes and the two-rod implant was 2.49 ±

0.26 minutes. Based on age, it was found that the average age of respondents using LNG one implant was 31.89 ± 4.97 years with the most age group being 20-35 years (68.4%) while the average age of respondents using two-rod.

LNG implants was 30.79 ± 4.43 years with the most age group being 20-35 years (84.2%). The statistical test showed that there was no difference in age (p = 0.474) or age group (p = 0.447) between respondents who used LNG implants in one rod and two rods. In this study, the majority of parity respondents both using one rod of LNG implants (57.9%) and two rods (68.4%) were ≥ 3. With statistical tests it was found that there was no difference in parity between respondents using one LNG implant and two rods (p = 0.737).

**Table 1.** General Characteristics of Research Subjects

| Variabel | Levonorgestrel | | *P-value* |
|---|---|---|---|
| | **One Rod** | **Two Rod** | |
| **Installation Time** | | | |
| Mean± SD | 1.54 ± 0.11 | 2.49 ± 0.26 | 0.000[d] |
| Median (Min-Max) | 1.52 (1.48 - 2.00) | 2.53 (1.49 - 3.00) | |
| **Age** | | | |
| Mean ± SD | 31.89 ± 4.97 | 30.79 ± 4.43 | 0.474[a] |
| Median (Min-Max) | 31 (23 - 39) | 32 (21-36) | |
| **Age, n(%)** | | | |
| 20-35 | 13 (68.4) | 16 (84.2) | 0.447[b] |
| > 35 | 6 (31.6) | 3 (15.8) | |
| **Parity, n(%)** | | | |
| 0 | 8 (42.1) | 6 (31.6) | 0.737[c] |
| 1-2 | 11 (57.9) | 13 (68.4) | |
| **Education, n(%)** | | | |
| Low | 11 (57.9) | 12 (63.2) | 1.000[c] |
| High | 8 (42.1) | 7 (36.8) | |
| **Blood Pressure** | | | |
| Normal | 17 (89.5) | 13 (68.4) | 0.111[e] |
| Hypertension | 2 (10.5) | 6 (31.6) | |
| **Menstruation Cycle** | | | |
| Regular | 16 (84.2) | 7 (36.8) | 0.007[b] |
| Irregular | 3 (15.8) | 12 (63.2) | |
| **Body Mass Index** | | | |
| Mean ± SD | 24.19 ± 3.93 | 25.09 ± 6.11 | 0.965[d] |
| Median (Min-Max) | 23.2 (19.3 - 35.9) | 23.1 (17.8 – 39.3) | |
| **Body Mass Index, n(%)** | | | |
| Underweight | 0 (0) | 1 (5.3) | 0.595[e] |
| Normoweight | 9 (47.4) | 8 (42.1) | |
| Overweight | 5 (26.3) | 3 (15.8) | |
| Obese | 5 (26.3) | 7 (36.8) | |

*[a]Independent T Test, p = 0.05, [b]Uji Fisher Exact, p = 0.05, [c]Chi Square test, p =0.05, [d]Mann Whitney test, p =0.05, [e]Pearson Chi Square test, p =0.05*

Based on education, it was found that the majority of patients had a low level of education both in the one implant LNG group (57.9%) and two rods (63.2%). Based on statistical tests the results showed no difference in education between respondents using one rod LNG implants and two rods (p = 1.000). Based on blood pressure, the majority of patients had normal blood pressure of 89.5% in one rod LNG and 68.4% in two-rod LNG, with statistical tests showing no relationship between blood pressure and type of implant (p = 0.111). Based on the menstrual pattern, it was found that 84.2% of subjects had regular menstrual patterns and 15.8% had irregular menstrual patterns in one LNG group, whereas 36.8% of subjects had regular menstrual patterns and 63.2 % of subjects who have irregular menstrual patterns. From the statistical test, it was found that there was a correlation between menstrual pattern and implant type (p = 0.007).

The mean Body Mass Index (BMI) of respondents using LNG implants in one rod was 24.19 ± 3.93 kg / m2 with the highest BMI category being normoweight (47.4%) while the BMI average of respondents using two-implant LNG was 25, 09 ± 6.11 kg / m2 with the highest

BMI category normoweight (42.1%). With statistical tests, it was found that there was no difference in BMI (p = 0.965) or BMI category (p = 0.595) among respondents who used one-rod implant and two LNG implants.

## Laboratory Characteristics of Research Subjects

The laboratory characteristics of the research subject can be seen in table 6. Based on statistical tests there were no differences in lipid profiles before treatment of both cholesterol (p = 0.260), HDL (p = 0.989), LDL (p = 0.791) and triglycerides (p = 0.447) between the two group of respondents.

**Table 2.** Laboratory Characteristics of Research Subjects

| Variabel | Levonorgestrel | | *P-value* |
|---|---|---|---|
| | **One Rod** | **Two Rod** | |
| **Total cholesterol** | | | |
| Mean ± SD | 234.4± 30.9 | 246.7 ± 35.00 | 0.260[a] |
| Median (Min-Max) | 235.4 (191.1-308.9) | 240.5 (196.1 – 326.2) | |
| **HDL** | | | |
| Mean ± SD | 66.10 ± 10.63 | 66.05 ± 13.94 | 0.989[a] |
| Median (Min-Max) | 67.3 (44.9 – 88.4) | 65,7 (44.1 – 94.7) | |
| **LDL** | | | |
| Mean ± SD | 103.5 ± 20.88 | 105.28 ± 19.38 | 0.791[a] |
| Median (Min-Max) | 98.9 (68.1 – 150.4) | 101.1 (75.1 – 137.6) | |
| **Triglycerides** | | | |
| Mean ± SD | 31.89 ± 4.97 | 30.79 ± 4.43 | 0.737[b] |
| Median (Min-Max) | 31 (23-39) | 32 (21-36) | |
| **FSH** | | | |
| Mean ± SD | 4.93 ± 2.63 | 5.28 ± 3.45 | 0.673[a] |
| Median (Min-Max) | 5.11 (0.81 – 12.0) | 4.94 (0.87 – 15.1) | |
| **Estradiol** | | | |
| Mean ± SD | 33.52 ± 37.77 | 19.74 ± 9.99 | 0.215[b] |
| Median (Min-Max) | 18.91 (13.42 – 163.9) | 17.7 (10.18–49.84) | |

*[a]Independent T Test, p = 0,05, [b]Mann Whitney test, p =0,05*

Likewise with the levels of FSH and estradiol before treatment, it was found that there were no differences in FSH levels (p = 0.673) or estradiol (p = 0.215) between respondents using one-rod implant and two LNG implants.

## Difference in Effectiveness of Use of One-Rod and Two-LNG LNG Implants on Lipid Profiles

The study found a significant reduction in cholesterol after 3 months both after the use of one rod of LNG (p = 0.000) and two rods (p = 0,000), there was a significant decrease in HDL after 3 months both after the use of one rod LNG (p = 0.000) or two (p = 0.000), there was a significant reduction in LDL after 3 months both after the use of one rod LNG (p = 0.040) and two rods (p = 0.000), and a significant increase in triglycerides after 3 months after the use of one rod LNG (p = 0.687) or two rods (p = 0.543).

**Table 3.** Effectiveness of the Use of One-Rod and Two-LNG LNG Implants on Lipid Profiles

| Variable | One Rod | | | Two Rod | | | |
|---|---|---|---|---|---|---|---|
| | **before** | **after** | ***p-value*** | **before** | **after** | ***p-value*** | ***p-value*** |
| Cholesterol | 234.4 ± 30.9 | 155.9 ± 30.9 | 0.000[a] | 246.7 ± 30.9 | 159.3 ± 32.9 | 0.000[b] | 0.919[c] |
| HDL | 66.1 ± 10.6 | 45.9 ± 8.8 | 0.000[a] | 66.0 ± 13.9 | 47.4 ± 12.5 | 0.000[b] | 0.793[c] |
| LDL | 103.5 ± 20.9 | 92.9 ± 23.7 | 0.040[a] | 105.3 ± 19.4 | 94.2 ± 16.6 | 0.000[a] | 0.851[d] |
| Triglycerides | 94.5 ± 53.9 | 946 ± 34.2 | 0.687[b] | 95.4 ± 45.5 | 99.3 ± 35.9 | 0.543[a] | 0.679[d] |

*[a]Paired T Test, p =0,05, [b]Uji Wilcoxon, p =0.05, [c]Mann Whitney test, p =0.05, [d]Independent T Test, p =0.05*

In addition, it was found that there were no differences in cholesterol levels (p = 0.919), HDL (p = 0.793), LDL (p = 0.851) and triglycerides (p = 0.679) among respondents using one rod implant and two LNG implants.

**The difference in the Effectiveness of Using One-Rod LNG Implants and Two-Rod LNG LNG Implants on FSH and Estradiol**

The results showed that there was no significant decrease in FSH levels before and 3 months after using one rod of LNG (p = 0.063), but it was found that there was no significant decrease in estradiol levels before and 3 months after using one rod of LNG (p = 0.059).

**Table 4.** Effectiveness of the Use of the One-Rod and Two-Rod LNG LNG Implants against FSH and Estradiol

| Variable | LNG One-Rod | | | LNG Two-Rod | | | *p-value* |
|---|---|---|---|---|---|---|---|
| | **before** | **after** | ***p-value*** | **before** | **after** | ***p-value*** | |
| FSH | 4.93 ± 2.63 | 4.15 ± 1.96 | 0.063[a] | 5.28 ± 3.45 | 4.43 ± 2.14 | 0.117[b] | 0.849[c] |
| Estradiol | 33.52 ± 37.77 | 21.86 ± 12.07 | 0.059[b] | 19.74 ± 9.99 | 18.32 ± 10.79 | 0.295[b] | 0.099[c] |

*[a]Paired T Test, p =0.05, [b]Wilcoxon test, p =0.05, [c]Mann Whitney test, p =0.05*

In addition, it was found that there was no significant decrease in FSH levels before and 3 months after using two rods of LNG (p = 0.117), other than that there was a significant decrease in estradiol levels before and 3 months after the use of LNG in two rods (p = 0.295). In this study, it was also found that there were no significant differences in FSH levels between respondents using one-rod and two-rod LNG implants (p = 0.849), respondents who used two-rod LNG had higher FSH levels than respondents using one-rod LNG but not meaningful. In addition, it was found that there were no significant differences in estradiol levels between respondents using one-rod and two-rod LNG implants (p = 0.099), respondents who used two-rod LNG had lower estradiol levels than respondents using one-rod LNG but were not significant.

## DISCUSSION

Contraception is efforts made to prevent pregnancy, both temporary and permanent. Implants are hormonal contraceptives that are implanted under the skin (subdermal) and used for a long time. This contraception contains bioactive progestin levonorgestrel (LNG) ingredient, a steroid hormone that is a derivative of 19-nortestosterone. LNG has activities similar to progesterone with weak androgenic activity and has no estrogenic activity.[1,2]

Levonorgestrel is a progestin hormone which is a derivative of 19-nortetosterone. As an active contraceptive implant substance, levonorgestrel is a steroid hormone with strong progesterone activity and weak androgen activity, the chemical formula of the hormone. There are two types of Levonorgestrel implant contraceptives, one LNG rod and two rods. In this study, several samples were taken at different times. A total of 21 samples were implanted with implants on 15 December 2018 and 17 samples were installed on January 5, 2019. Sampling was carried out at the RSAB Rika Amelia Palembang. There were 21 samples that met the research criteria and were willing to take part in the study from 50 samples. The second sample was taken in a different place and 17 samples that met the study criteria were obtained.

In this study, it was found that the average installation time required for one rod LNG was 1.54 ± 0.11 minutes and for LNG two rods was 2.49 ± 0.26 minutes. From the data above we can see that the installation of one rod of LNG is faster than with two LNG. If viewed from the cost, LNG one rod only requires local anesthetic in the form of one ampoule lidocaine, while LNG for two rods requires two ampoules of lidocaine. There are no other differences either from the use of alcohol cotton, plaster, or syringes between the one rod LNG group and the two rod LNG. From this study it was also found that there was no difference between changes in blood pressure in the LNG group of one rod and LNG in two rod.

Implanted KB acceptors in the study were approximately 31 years old with the majority of the age categories 20-35 years (76.3%). The results of showed the percentage of implant KB acceptors aged 20-35 years was 54.8%. Study in 2017 showed an average age of patients using implants of approximately 34.3 years. The type of contraception used should be adjusted to the stage of reproduction.[16]Age 20-35 years is a period of reproductive life so the choice of contraception used is oral contraception or implant.

The majority of implantable KB acceptors parity ≥ 3 (63.2%) with a mean parity of 3.07

± 1.02. This result is not much different from the research in 2017 where the implant parity acceptor implies a mean of 3.0 ± 2.0. The more often a woman gives birth to a child, the more risks she will have in childbirth. This means that the number of children will greatly influence the choice of mothers to choose contraception.16 In couples with a small number of children (3 children or less) there is a tendency to use low-effectiveness contraceptives, namely pills and condoms, whereas if the child is felt quite a lot, a higher effectiveness contraceptive device will be used such as implants.

Based on blood pressure, the majority of patients had a normal blood pressure of 89.5% in one rod LNG and 68.4% in two rod LNG, with statistical tests showing that there was no correlation between blood pressure and implant type (p = 0.111). Based on the menstrual pattern, it was found that 84.2% of subjects had regular menstrual patterns and 15.8% had irregular menstrual patterns in one LNG group, whereas 36.8% of subjects had regular menstrual patterns and 63.2 % of subjects who have irregular menstrual patterns. From the statistical test, it was found that there was a correlation between menstrual pattern and implant type (p = 0.007).

In this study, it was found that LNG was associated with changes in menstrual patterns, both the use of one rod of LNG and two rods. Descriptively, there were 63.2% of subjects who had irregular menstrual patterns. The possibility of side effects that can occur is irregular menstruation. This is because LNG does not contain estrogen, which causes disruption of the menstrual cycle. Most women can know some variations in menstrual patterns. The use of Jadelle contraception has almost the same side effects as the use of Norplant contraception in the form of irregular menstrual bleeding, prolonged bleeding or spots (longer than a woman usually experiences), heavy bleeding, bleeding or spots between periods, no bleeding at all for several months, or a combination of these patterns. Hypertension can occur in 1.0% - 9.9% of women who use LNG contraception. However, this study did not show a significant relationship between hypertension and use of LNG contraception.[6,17,18]

In the distribution of subjects according to implant type and BMI, there was a mean BMI in one rod of LNG before and after implant placement at 24.16 ± 3.97 kg / m2 and 23.79 ± 4.09 kg / m2. While the mean BMI for LNG in the two rods before and after implant placement was 25.21 ± 6.01 kg / m2 and 26.21 ± 6.60 kg / m2. Descriptively, LNG of two rods showed an increase in body weight of 1 kg / m2 where one rod of LNG decreased BMI by 0.37 kg / m2. This result is different from the results of a study that there was a weight loss of 0.33% in the use of 2 rod LNG. Although there was an increase in BMI on 2-rod LNG, did not find any significant differences. The results of this study on IMT cannot be concluded, because the increase in BMI was influenced by dietary patterns not assessed in this study.[6,19]

In the distribution of subjects according to implant type and cholesterol, there was a mean cholesterol in the type of LNG 1 rod before and after implant placement was 234.42 ± 30.99 mg / dL and 155.86 ± 30.94 mg / dL. While the mean cholesterol in 2 rod LNG before and after implant placement was 246.68 ± 35.01 mg / dL and 159.32 ± 32.85 mg / dL. In this study there was a significant reduction in cholesterol levels in the group that received one rod and two LNG but there was no difference between the two groups. Descriptively, one rod LNG showed a decrease of 78.56 mg / dL, while LNG for two bars showed a decrease of 87.36 mg / dL. Two more LNG trunks show a larger decrease compared to one rod LNG. Research in 2017 showed an increase in total cholesterol levels after 6 and 12 months of implant placement, but decreased after 24 months. The difference obtained is probably because in this study the follow-up was carried out for 3 months. There was a decrease in cholesterol after LNG use after 3 months with a p value of <0.05 and a mean cholesterol value of 141.17 ± 14.67 mg / dL.[18,20]

In the distribution of subjects according to implant type and HDL in the blood, there was a mean HDL in LNG rods before and after implant placement was 66.10 ± 10.62 mg / dL and 45.94 ± 8.79 mg / dL. While the mean HDL in 2-rod LNG before and after implant placement was 66.05 ± 13.95 mg / dL and 47.40 ± 12.53 mg/dL. Descriptively, one rod of LNG showed a decrease in HDL of 20.16 mg / dL, while LNG of two rods showed a decrease in HDL of 18.65 mg / dL. One rod LNG showed more levels of HDL decrease. In the distribution of subjects according to implant

type and LDL in the blood, there was a mean LDL in implant type 1 rod before and after implant placement was 103.54 ± 20.88 mg / dL and 92.92 ± 23.68 mg / dL. While the mean LDL in the 2-rod implant type before and after implant placement was 105.28 ± 19.38 mg / dL and 94.18 ± 16.56 mg / dL. Descriptively LNG one rod showed a decrease of 10.62 mg / dL, while LNG for two rods showed a decrease of 11.1 mg / dL. Two more LNG LNG showed a decrease in LDL compared to one rod LNG.

There was a significant reduction in HDL and LDL in the group that received one rod and two LNG LNG but there was no difference between the two groups. In 2017 LDL reduction was found after 6, 12 and 24 months but there was an increase in HDL levels, this is different from the results of this study. Dash's research found that there was a significant decrease in HDL after the installation of 2-rod LNG within 3 months with a value of p = 0.02 and an average HDL level of 40.00 ± 8.65 and a significant decrease in LDL after installation of 2-rod LNG within 3 months with p = 0.05 and the mean LDL level was 92.33 ± 11.60.[18,20]

In the distribution of subjects according to implant and triglyceride types, there were mean triglycerides in LNG 1 rod before and after implant placement were 94.46 ± 53.87 mg / dL and 94.58 ± 34.23 mg / dL. While the mean of triglycerides in 2 rod LNG before and after implant placement was 95.38 ± 45.48 mg / dL and 99.33 ± 35.93 mg / dL. Descriptively, one rod LNG showed an increase of 0.12 mg / dL, while LNG for two bars showed an increase of 3.95 mg / dL. LNG of two rods showed an increase in triglycerides compared to one rod LNG. In this study there was an increase in triglyceride levels both in the group that received one rod and two LNG LNG but the increase that occurred was not statistically significant. The increase in the LNG group of two rods was greater than that in the one-rod LNG group but was not significant. These results are in line. Study in which triglyceride levels increased after administration of implants for 6, 12 and 24 months. There was a significant decrease in triglycerides after the installation of 2-rod LNG within 3 months with a p value of <0.01 and the average triglyceride level was 76.65 ± 19.95.[18,20]

Changes in fat metabolism in hormonal contraceptive use are caused by estrogen and progesterone, each of which has a different effect. Estrogen is cardioprotective (protecting the heart) and antiatherogenic (anti-fat formation), while progesterone is anti-estrogen. The use of a single estrogen will reduce the activity of the lipoprotein lipase enzyme, increase HDL cholesterol levels and reduce LDL cholesterol levels. The effect of progesterone is precisely inversely proportional to the effect of estrogen, and this effect depends on the potential of the androgen. The stronger the androgen potential, the greater the adverse effect on fat metabolism.[3,7-9,11]

The mineral corticoid effects of LNG implants can cause weight gain. Weight gain is one of the causes of an increase in triglyceride levels and a decrease in HDL levels that occurred in this study, but it is different with decreasing total cholesterol and LDL levels.

Some of the results of this study are different from previous studies. Research in Ghana shows that hormonal contraception can increase BMI, diastolic blood pressure, total cholesterol levels, LDL cholesterol levels and reduce HDL cholesterol levels in the blood. Where this change is a potential risk factor for developing cardiovascular disease.[8]Research at the Benin Teaching Hospital, Nigeria showed that Implanon had an effect on lipid metabolism, there was a significant decrease in HDL and an increase in LDL levels in the 6th and 12th months.[10]The differences that occur in this study are likely because the patient's follow-up time is too short.

In the distribution of subjects according to implant type and FSH, there was a mean FSH for implant types 1 rod before and after implant placement was 4.93 ± 2.63 and 4.15 ± 1.96. While the mean FSH for 2-rod implant types before and after implant placement was 5.29 ± 3.46 and 4.44 ± 2.14. Descriptively, one rod LNG showed a decrease in FSH of 0.78, while LNG of two rods showed a decrease in FSH of 0.85. Two more LNG LNG showed a decrease in FSH compared to one rod LNG. From the results of the analysis, it was found that there was a significant decrease in FSH levels after the installation of one rod LNG implant or two rods for 3 months. In the distribution of subjects according to implant and estradiol types, there were Estradiol meanings on the type of implant 1 rod before and after implant

placement 33.52 ± 37.77 and 21.86 ± 12.07. While the Estradiol mean on the 2-rod implant type before and after implant placement was 19.74 ± 9.99 and 18.32 ± 10.79. Descriptively, one rod LNG showed a reduction in Estradiol of 11.66 while the LNG of two rods showed a decrease in Estradiol of 1.42. There is a greater decrease in one-rod LNG with Estradiol levels. From the results of the analysis it was also found that there was no significant decrease in estradiol levels after the installation of one rod LNG implant or two rods for 3 months.

In two-rod implants that are effective for 5 years, levonorgestrel will be released as much as 50-80 µg / day for the first year of installation and release the following year until the 5th year of use is 30-35 µg / day.[4,5]Whereas on one rod implant the average in the first 6 weeks of the hormone is released from 60 to 70 mcg / day, down to 35-45mcg / day at the end of the first year of use. The main working mechanism of LNG is to inhibit ovulation in about 50% of the menstrual cycle. A small amount of LNG released from the implant continuously will work in the hypothalamus and anterior pituitary gland. Furthermore, there is a decrease in FSH secretion (follicle stimulating hormone) and LH (lutenizing hormone). LNG will inhibit or reduce LH surge in the middle of the cycle. The anterior pituitary sex hormone, Follicle Stimulating Hormone (FSH) is secreted in response to hypothalamic hormones. FSH functions to stimulate the ovaries to produce steroids. Steroid hormones have a large effect on the menstrual cycle, where estrogen is produced in the follicular and progesterone phases during the luteal phase of the ovary. Estrogen has a strong effect on inhibiting LH and FSH production. The effect of inhibiting estrogen will increase if there is progesterone, although the progesterone itself has only a small effect.[16-18,20,21]

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## CONCLUSION

There is no difference between the use of one-stem and two-stem levonorgestrel implants against FSH, Estradiol levels and increased lipid profile after 3 months of implant installation with a value of p = 0.673, p = 0.215, p = 0.260, p = 0.989, p = 0.791. The unpleasant effect in this study was the decline in HDL, but this was accompanied by a decrease in body weight, total cholesterol, LDL, HDL due to a decrease in all aspects.

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**Research Article**

# Cortisol Levels in Chronic Primary Dysmenorrhoea Patients and Non-Dysmenorrhoea : A Cross- Sectional Study

## *Kadar Kortisol antara Pasien Dismenorea Primer Kronis: Sebuah Studi Potong Lintang*

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## Abstract

**Objective:** To investigate whether chronic primary dysmenorrhoea will significantly increase cortisol levels in the body. This study can provide an overview of the importance of handling primary dysmenorrhoea so that it does not continue to become menstrual disorders.

**Methods:** This study used a cross-sectional comparative study method with a total sample of 26 subjects with 13 subjects included in the dysmenorrhea group and 13 other subjects belonging to the non-dysmenorrhea group. The study was conducted at Department of Obstetrics and Gynecology Faculty of Medicine Universitas Andalas network primary healthcare and Dr. M. Djamil Padang Central General Hospital. Data were analyzed using computational calculation of SPSS program with bivariate test using X2 test or chi-square test with a significance degree of 0.05.

**Results:** Twenty six subjects (13 each group) have been sampled in this study, the mean age of the dysmenorrhea group was 26.23 ± 3.92 while the mean age of the non-dysmenorrhea group was 28.62 ± 7.10. The age difference between groups was not statistically significant with a value of p = 0.30 (p> 0.05). In the comparison of cortisol levels between the two groups, it was found that the dysmenorrhea group had a higher cortisol level of 72.3077 (7.2 µg / dL) compared to the non-dysmenorrhoea group of 60.3846 (6 µg / dL). Based on the results of the bivariate analysis using the chi-square test, the value of p = 0.148 (P> 0.05) showed that there was no significant difference between the cortisol levels of the group with chronic primary dysmenorrhea compared with the non-dysmenorrhea group.

**Conclusions:** Chronic primary dysmenorrhea can not significantly increase cortisol levels in the body.

**Keywords:** comparative study, chronic primary dysmenorrhea, cortisol levels, non-dysmenorrhea, menstrual disorders

## *Abstrak*

***Tujuan:*** *Mengetahui apakah dismenorea primer kronis akan meningkatkan kadar kortisol dalam tubuh secara signifikan. Penelitian ini dapat memberikan gambaran pentingnya penanganan dismenorea primer agar tidak berlanjut menjadi gangguan menstruasi.*

***Metode:*** *Penelitian ini merupakan penelitian dengan desain potong lintang studi banding dengan jumlah total sampel sebanyak 26 subjek dengan rincian 13 subjek termasuk ke dalam kelompok dismenore dan 13 subjek lainnya termasuk ke dalam kelompok non-dismenore. Penelitian dilakukan di Puskesmas jejaring PPDS Obgyn FK Unand dan RSUP Dr. M. Djamil Padang. Data dianalisis menggunakan perhitungan komputasi program SPSS dengan uji bivariat menggunakan ujiX2 atau uji chi-square dengan derajat kemaknaan 0,05.*

***Hasil:*** *Dari 26 subjek (masing-masing 13 subjek) yang dijadikan sampel dalam penelitian ini, didapatkan usia rerata kelompok dismenore ialah 26,23 ± 3,92 sedangkan usia rerata kelompok non-dismenore ialah 28,62 ± 7,10. Perbedaan rerata usia antar kelompok ini tidak signifikan secara statistik dengan nilai p = 0,30 (p > 0,05). Pada perbandingan kadar kortisol antar kedua kelompok, didapatkan kelompok dismenore memiliki kadar kortisol yang lebih tinggi yaitu 72,3077 (7.2 µg/dL) dibandingkan dengan kelompok non-dismenorea yaitu 60,3846 (6 µg/ dL). Berdasarkan hasil analisis bivariat menggunakan uji chi-square, didapatkan nilai p = 0,148 (P > 0,05) yang menunjukkan tidak adanya perbedaan yang signifikan antara kadar kortisol kelompok dengan dismenore primer kronis dibandingkan dengan kelompok non-dismenore.*

***Kesimpulan:*** *Dismenore primer kronis dapat meningkatkan kadar kortisol dalam tubuh secara signifikan.*

***Kata kunci:*** *dismenore primer, gangguan menstruasi, kadar kortisol, kronis, tidak dismenore, studi perbandingan.*

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## INTRODUCTION

Dysmenorrhea is spasmodic pain in the hypogastric and lumbar regions between, before and during menstruation. Dysmenorrhea is generally classified as primary or secondary. Primary dysmenorrhoea is associated with the ovulation cycle and resulted from myometrial contraction, in the absence of proven disease. Secondary dysmenorrhea refers to pain during menstruation that is associated with pelvic pathologies, such as endometriosis, adenomyosis, or uterine myoma.[1-3]

Dysmenorrhea is one of the most common gynecological problems in women of reproductive age. Primary dysmenorrhea usually begins during adolescence, but only after ovulation occurs; 20–45% of adolescent girls ovulate 2 years after menarche, and 80% at 4-5 years. 20-90% of young women experience dysmenorrhea, 15% experience severe dysmenorrhoea. Overall prevalence of primary dysmenorrhoea in adolescent girls is between 60% and 90% and decreases with age. However, only about 15% of teenage girls seek medical treatment for painful menstrual complaints.[1]

Cortisol is synthesized from cholesterol in the adrenal gland (suprarenal). It is controlled through the Hypothalamus-Pituitary-Adrenal (HPA) axis, while secretions will increase if exposed to Stress.[4-6] The levels of cortisol in the blood vary, the highest levels are found in the morning (08.00 WIB) 20 g / dL and decrease at night 5 g / dL.[7,8] High cortisol level will enter the circulation suppressing the growth of the body's immune cells and affect the release of adrenaline neurotransmitters which results in blockage of Gn-RH secretion resulting in impaired FSH and LH production which results in menstrual disorders. Until now, the "gold standard" biomarkers and values for chronic stress examination were debated because of the complex etiology and diverse manifestations.[7]

## METHODS

This study used a cross-sectional comparative study design. Samples were taken from women diagnosed with chronic primary dysmenorrhea with VAS> 7 in the Network puskesmas and RSUP Dr. M. Djamil Padang. Informed consent was carried out by providing a detailed explanation of the purpose, objectives, procedures and benefits of the study and the signing of a statement form willing to join the study without any coercion from any party.

Subjects that met the inclusion and exclusion criteria were continued for clinical and supportive examinations (USG). Blood samples for examination of serum cortisol levels are taken on the first or second day of menstruation at 8:00 am by qualified health workers. All collected data is then processed statistically. This Study has been qualified and approved by the Research Ethics Committee of the Medical Faculty of Universitas Andalas, Padang.

## RESULTS

The twenty-six groups have been sampled in this study, the mean age of dysmenorrhea group was 26.23 ± 3.92 while the mean age of non-dysmenorrhea group was 28.62 ± 7.10 (Table 1). The difference between groups is not statistically significant with a value of p = 0.30 (p> 0.05).

**Table 1.** Characteristics of Respondents by Age

| Group | Age (year) Mean ± SD | *P-value* |
|---|---|---|
| Non-dysmenorrhea | 28.62 ± 7.10 | 0.30 |
| Dysmenorrhea | 26.23 ± 3.92 | |

Before the bivariate analysis test is carried out, the data normality test is conducted first. The normality test of the data using the Shapiro-Wilk test (Table 2) showed a value of P> 0.05 (the P-value of the dysmenorrhoea group = 0.774 and the P-value of the non-dysmenorrhoea group = 0.987), indicating that the subject data from this study were normal.

In the comparison between the two groups (Table 3), it was found that the dysmenorrhea group had a higher cortisol level of 72.3077 (7.2 µg / dL) compared to the non-dysmenorrhoea group of 60.3846 (6 µg / dL). However, there are still in the normal reference range of 2.9 - 17.3 µg / dL. The test of the value of p = 0.148 (P> 0.05) showed that there was no significant difference in the cortisol levels of the group with chronic primary dysmenorrhea compared with the non-dysmenorrhea group.

**Table 2.** Test of Normality

| Diagnosis | | Kolmosgorov - Smirnov | | | Shapiro - Wilk | | |
|---|---|---|---|---|---|---|---|
| | | Statistic | df | Sig | Statistic | df | Sif |
| Cortisol level | Dysmenorrhea | 0.138 | 13 | 0.200* | 0.961 | 13 | 0.774 |
| | Non-Dysmenorrhea | 0.098 | 13 | 0.200* | 0.982 | 13 | 0.987 |

* this is a lower bound of the true significance, a.Lilie fors significance correction.

**Table 3.** Differences in Cortisol Levels between Non-Dysmenorrhea and Dysmenorrhea

| Group | Mean Cortisol Levels±SD | *P-value* |
|---|---|---|
| Non-dysmenorrhea | 60.3846 | 0.148 |
| Dysmenorrhea | 72.3077 | |

## DISCUSSION

Increased cortisol levels in the group with a history of dysmenorrhoea was believed to be the result of the mechanism of anxiety inherent in individuals experiencing chronic pain. Psychological factors play an important role in the occurrence of primary dysmenorrhea. Factors such as social support, anxiety, depression, stress, neurosis, comfortness, and personality have an influence on the onset of menstrual pain.[9,10] This dysmenorrhea itself will also cause anxiety to the subject and can change the perception of pain. A person who experiences dysmenorrhea every month feels a negative impact on her life. A study showed a positive relationship between psychological stress and dysmenorrhea (p = 0.001).[11]

Stressors such as chronic pain can trigger the hypothalamus to secrete corticotropin-releasing Hormones (CRH aka CRF, Corticotropin Releasing Factor) and Arginine Vasopressin (AVP), thus triggering the production of Adrenocorticotropin hormone (ACTH) from the posterior pituitary and its activation.[12] ACTH pushes the adrenal cortex to produce cortisol, which increases cortisol levels. The glucocorticoid (cortisol) and their receptors bonds in the limbic system will activate the pathway of the hypothalamus-pituitary-adrenal axis so that the cycle will repeat itself. The limbic system will also affect the sympathetic nerves which will increase heart rate (palpitations), sweating, and increased intestinal peristalsis. High levels of cortisol will enter the body's circulation to suppress the growth of the body's immune cells. This hormone will also affect the release of adrenaline neurotransmitters which will result in inhibition of Gn-RH secretion resulting in impaired FSH and LH production and result in menstrual disorders.[9,12,13]

Stress can directly change the regulation of the pituitary-hypothalamus from a person's reaction. Stress activates the hypothalamic-pituitary axis that affects menstrual function, causing menstrual disorders such as dysmenorrhoea and irregular menstrual patterns.[13] Prove that in groups with inherent anxiety, cortisol production increases and CD3 + T cells, CD45 + T cells, CD3 + CD4 + helper T cells, and CD3 + CD8 + cytotoxic T cells are fewer, so this can affect someone's immunity and health. This is in accordance with the results of this study, which shows higher cortisol levels in the group of subjects with chronic primary dysmenorrhea than in the group without a history of dysmenorrhoea.[14]

The results of this study indicates that chronic primary dysmenorrhoea has an influence on increasing blood cortisol levels. Cortisol levels in the group of women with chronic primary dysmenorrhoea showed slightly higher levels when compared to the group of subjects who did not experience primary dysmenorrhoea. It was found from the results obtained that there were indeed differences in mean cortisol levels in the two groups of subjects, namely the dysmenorrhoea group and the non-dysmenorrhoea group. In the dysmenorrhoea group, the mean cortisol level was indeed higher at 72.3077 (7.2 µg / dL), compared to the non-dysmenorrhoea group of 60.3846 (6 µg / dL). The incidence of chronic primary dysmenorrhoea can increase blood cortisol levels. But further need to be underlined that in the statistical calculation using bivariate analysis, the ratio of cortisol levels between the two groups had a P value of 0.148 (P > 0.05), which meant that the difference in cortisol levels in the dysmenorrhoea group and those without statistics. This statistical meaninglessness can be caused by differences in stress coping between subjects with one another.

In the data of the study conducted by the author, there is an interesting thing to note, that the oldest subject age was 47 years in the non-dysmenorrhoea group, the cortisol level was the least among the other subjects, which was 2.7 µg / dL. This needs to be further analyzed by regression analysis whether the older the age, the less the cortisol hormone level, of course with data or a larger number of subjects.

Higher levels of cortisol in the group with dysmenorrhea in this study were still in the range of normal reference values (2.9 - 17.3 µg / dL) with the highest levels of 11 µg / dL in subjects aged 22 years. It should be noted that different sampling times can affect the results of cortisol levels. Cortisol production is usually higher in the morning and in the day or afternoon, the production is getting lower. The time for taking samples in this study is uniformly carried out on the morning of 08.00 on the first or second day of menstruation so that minor biases that can occur due to differences in sampling time can be avoided. The best and most informative sample collection is the morning when cortisol is at one's optimal level.[12,15]

The strength of this study is the focus in objective data collection, blood cortisol levels. Taking blood samples from each subject conducted by qualified health workers can minimize the study bias that can occur. Determination of diagnosis Chronic primary dysmenorrhoea is also carried out by clinicians (doctors) so that the determination of the subject group is more adequate based on the objective clinical judgment conducted by experts. Measurement of body weight or body mass index and physical activity were not included in this study because it was not the main focus of the study, both of these factors were believed to not affect the onset of menstrual pain.[16,17]

The weakness of this study is that it has not excluded non-organic risk factors from dysmenorrhea such as early menarche, BMI < 20 kg/m2, smokers, heavy menstrual bleeding, nulliparity, strict diets, anti-social life, anxiety and depression. These factors were not included in the exclusion criteria because there were too many and if included, it would be difficult to find the subject of the study and reduce the sample.[1,16]

## CONCLUSION

In this study, the average cortisol level in the group with chronic primary dysmenorrhoea was higher, namely 72,3077 (7.2 g / dL) compared to the non-dysmenorrhoea group with 60,3846 (6 g / dL) but the values of both were still within normal limits. From the results of bivariate analysis, the value of p = 0.148 (p> 0.05). So we can conclude that there is no statistically significant difference between serum cortisol levels of patients with chronic primary dysmenorrhoea and non-dysmenorrhoea.

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**Research Article**

# Serum Vascular Endothelial Growth Factor Levels and Uterine Fibroid Volume

## *Hubungan Kadar Serum Vascular Endothelial Growth Factor dengan Volume Mioma Uteri*

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## Abstract

**Objective:** To investigate the correlation of serum Vascular Endothelial Growth Factor (VEGF) levels and uterine fibroid volume.

**Methods:** Observational analytic study was carried out on 80 patients with uterine fibroids indicated myomectomy. Each sample was examined for VEGF levels and volume of myoma tissue post myomectomy was measured by using Archimedes' law. Correlation test using the Spearman test.

**Results:** A total of 80 samples of patients were examined for VEGF levels and uterine fibroids volume. The median VEGF is 360 pg/mL, the median uterine fibroids volume is 325 ml. The Spearman'stest shows p values (<0.01) and r (0.999).

**Conclusions:** There is a significant correlation between VEGF levels and uterine fibroids volume. The higher the VEGF level, the greater the volume of uterine fibroids.

**Keywords:** archimedes law, uterine fibroids volume, VEGF.

## *Abstrak*

***Tujuan:*** *Untuk mencari adanya korelasi antara kadar VEGF terhadap volume mioma uteri.*

***Metode:*** *Penelitian ini berupa analitik observasional. Sampel yaitu pasien dengan mioma uteri yang diindikasikan tindakan miomektomi. Setiap sampel diperiksa kadar VEGF dan pascamiomektomi dilakukan pengukuran volume terhadap jaringan mioma dengan menggunakan hukum Archimedes. Uji korelasi menggunakan Spearman test.*

***Hasil:*** *Sebanyak 80 sampel penderita mioma uteri diperiksa kadar VEGF kemudian dilakukan tindakan miomektomi. Median VEGF adalah 360 pg/mL, median volume uteri adalah 325 ml, uji korelasi Spearman didapatkan nilai p (<0,01) dan r (0,999).*

***Kesimpulan:*** *Terdapat korelasi antara kadar VEGF dengan volume mioma uteri, semakin tinggi kadar VEGF maka semakin besar volume mioma uteri.*

***Kata kunci:*** *hukum Archimedes, VEGF, volume mioma uteri.*

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## INTRODUCTION

The knowledge of the mechanisms of growth of uterine fibroids has increased dramatically in recent years. Today, there are numerous potential directions for both the clinician and researcher to proceed when trying to attack these tumours medically.[1] Each tumour appeared to have its own intrinsic growth rate. Tumour size has been related to variation in molecular markers, and it has been assumed that the molecular differences reflect differences in tumour growth rates.[2]

In recent years tumour volume investigations have become a subject of increasing interest.[3] Estimating the size change of an organ is research and clinical assessment that is used to relate symptom development to organ growth, to identify treatment needs, and to evaluate treatment effectiveness.[4]

Vascular Endothelial Growth Factor (VEGF) is the trigger of angiogenesis. VEGF, also known as vascular permeability factor (VPF), is a multifunctional cytokine that increases microvascular permeability and directly stimulates endothelial cell growth and angiogenesis. Vascular endothelial growth factor (VEGF) is synthesized and secreted by various cultured tumour cells and tumours in humans.[5] These observations suggest that VEGF and other proangiogenic factors might be involved in the

development of uterine fibroids.[6]

Measurement of the uterine volume is very important in the follow-up of the treatment response. [7] A range of measurement techniques has been described which may be used to calculate uterine fibroid volume. [8] Archimedes principle can be used as a direct measurement of uterine fibroid volume.[9] Archimedes' principle is one of the most essential laws of physics and fluid mechanics. One of the applications of Archimedes' principle is in the measurement of the density of an irregularly shaped object.[10]

Further experimental studies are required in order to gain a better understanding of the growth factors that are involved in normal and pathological myometrial angiogenesis and to assess the potential of anti-angiogenic treatment strategies for uterine fibroids.[11] Therefore, based on the theories that have been outlined, researchers want to see the correlation of serum levels of Vascular Endothelial Growth Factor (VEGF) with tumorigenesis of uterine myoma which is assessed through the volume of uterine myoma.

## METHODS

This is an analytic study with a cross-sectional approach. This study aims to determine the correlation between serum Vascular Endothelial Growth Factor (VEGF) levels and the volume of uterine fibroids. This research was conducted in Obstetrics Gynecology Wards and the Operating Room of the General Hospital Dr. Zainoel Abidin (RSUZA) Banda Aceh from April 2019 to September 2019. Laboratory tests for serum vascular endothelial growth factor (VEGF) levels were conducted at the Prodia Laboratory in Banda Aceh. Measurement of uterine fibroids volume was conducted in the Operating Room.

Inclusion criteria include a diagnosis of uterine fibroids which was proven based on the results of anatomic pathology and patients underwent total myomectomy surgery. Exclusion criteria include tumour metastasis or suffering from other malignancies, pregnancy, menopause, adenomyosis, and being on analogue Gn-RH therapy.

Blood specimens for the examination of VEGF levels were taken from median cubital vein. About 3 ml was inserted into a serum separator tube and sent to the Banda Aceh Prodia Laboratory. The volume of uterine fibroids specimens from myomectomy was measured according to Archimedes' law. A 1000 ml measuring cup is filled with 0.9% NaCl liquid as much as 600 ml (recorded as V1). Cleaned uterine fibroid tissue is dipped into a measuring cup until the entire surface of the uterine fibroids is in the liquid. The increasing volume in the measuring cup is recorded as V2 in ml. Uterine fibroids volume is calculated by the formula V2-V1. Data analysis was performed using the Spearman test. Every numerical data will be tested for normality test.

## RESULTS

There were 120 patient with a diagnosis of uterine fibroids in the period of April 2019 to September 2019. A total of 29 were menopause, 2 patients were accompanied by adenomyosis and the remaining 9 were pregnant so were excluded from this study. A total of 80 samples that fit the criteria were conducted anamnesis, physical examination and additional examinations for analysis. All samples were given information and explanations regarding their participation in this study. Ethical eligibility was approved by the Health Research Ethics Committee at the Faculty of Medicine Universitas Syiah Kuala.

General characteristics assessed in this study were age, parity, location of uterine fibroids and patient complaints (Table 1). The independent variable is VEGF levels and the dependent variable is the volume of uterine fibroids.

Ages are grouped based on intervals per 10 years ie 20-29 years, 30-39 years and 40-49 years. Most of the patients in this study were 40-49 years as 67 (83.3%) patients. The mean age in this study was 41.73 ± 4.3 years with a minimum of 26 years to a maximum of 49 years.

The multipara group is the highest frequency in this study as 62 (77.5%) samples. The mean parity in this study was 2.64 ± 1.15.

The most of location uterine fibroids in this study was intramural as 71 (88.8%) samples. The most symptoms that are complained is prolonged menstrual phase (only) as many as 52 (65.0%) samples.

**Table 1.** General Characteristic

| Categoric | Frequency (N=80) | (%) |
|---|---|---|
| **Age (years)** | | |
| 20-29 | 2 | 2.5 |
| 30-39 | 11 | 13.8 |
| 40-49 | 67 | 83.3 |
| **Parity** | | |
| Nullipara | 2 | 2.5 |
| Primipara | 16 | 20.0 |
| Multipara | 62 | 77.5 |
| **Fibroid uterine location** | | |
| Intramural | 71 | 88.8 |
| Subserosum | 3 | 3.8 |
| Submucosal | 6 | 7.5 |
| **Symptoms** | | |
| Prolonged uterine bleeding | 52 | 65.0 |
| Uterus enlargement | 2 | 2.5 |
| Prolonged uterine bleeding and Uterus enlargement | 15 | 18.8 |
| Prolonged uterine bleeding and abdominal pain | 11 | 13.8 |

The normality test on the VEGF variable shows an abnormal distribution with p-value 0.000 (normally distributed if p> 0.05). After transforming the data using the Log10 function, the p-value obtained still shows that the data are not normally distributed (p = 0.002).

Normality test on variable of uterine fibroid volume shows an abnormal distribution with p-value < 0.001. After transforming the data using the Log10 function, the p-value obtained still shows that the data are not normally distributed (p = 0.002).

The central values and the spread values of the variable VEGF levels and uterine fibroids volume are presented in table 2. The table shows that the median VEGF levels in this study were 360 pg/ mL and the median uterine fibroids volume was 325 ml.

**Table 2.** Median, Minimum and Maximum of VEGF Level and Uterine Fibroids Volume

| Parameter | Median | Minimum | Maximum |
|---|---|---|---|
| VEGF | 360 | 82 | 1528 |
| Uterine fibroids volume | 325 | 70 | 1390 |

Because the data distribution of the two variables is not normal, the statistical analysis that can be used to analyze the hypothesis is the Spearman test. The results are presented in Table 3 below.

**Table 3.** Analysis Results of Spearman's Correlation Test

| | Uterine fibroids volume |
|---|---|
| VEGF level | r = 0.999<br>p <0.001<br>n = 80 |

*Spearman's correlation test*

The Spearman test showed that there was a significant correlation between VEGF levels and uterine fibroid volume with p values <0.001. The r-value of 0.999 shows a positive and strong correlation between the two variables.

## DISCUSSION

The prevalence varies, one of them based on the parity, age. Pathologically, the incidence of diagnosed fibroids amplifies gradually with age. At 25-30 years the incidence is only 0.3 per 1000 women-years, but by age 45-50 yearsold, the incidence has raised 20 fold. 9 The frequency of uterine fibroid cases in this study based on age, 20-29 years was 2 (2.5%) samples, 30-39 years was 11 (13.8%) samples and peaked in the 40-49 years was 67 (83.3% ) sample. These data indicate that uterine fibroids incidence is increasing by age. The increase in the age of group 40-49 years in this study reached 33-fold compared to the age group 20-29 years.

Most studies conclude that parity is associated with the incidence of uterine fibroids. A woman who has given birth has a lower risk of developing uterine fibroids compared to nulliparous women.[12] Parity was associated with a reduced risk of developing uterine fibroids. In a single-centre study in Japan, the risk of uterine fibroids in women who had given birth three or more times was less than one-fifth that of nulliparous women[13] Although a direct protective effect of pregnancy has been demonstrated, little is known of the mechanism. There have been some suggestions that during postpartum uterine remodelling, there could be selective apoptosis of small lesions. Ischemia during parturition has also been proposed as a mechanism. Thus, it may be implied that fibroid tissue could be highly susceptible to ischemia during both parturition and remodelling.[14]

The highest incidence frequency of uterine fibroids in this study based on parity is the multipara. The increasing incidence of uterine fibroids in the multipara compared to nulliparous

and primiparous was 8-fold and 31-fold, respectively. This result is different from previous studies. The researcher assumes that the sample in this study does not reflect the population in our area so that there are possible differences in results with existing theories.

Uterine myomas have been classified according to their general uterine position: submucous, intramural, and subserosal.[15] Intramural myomas are the most prevalent of all the leiomyomas. Two-dimensional transvaginal sonography detected a 58%–79% occurrence of intramural myomas among study populations with observable myomas.[16] In a multicenter retrospective study involving two-dimensional transvaginal sonography, MRI, and LUS, intramural myomas comprised 58% of all myomas imaged, regardless of the imaging method used.[15] Most of the locations of uterine fibroids in this study are intramurally followed by submucosal and subserosal.

Presenting symptoms play an important role in deciding the appropriate form of treatment for the affected woman. Management strategies are usually individualized based on the severity of the symptoms, the size and location of the fibroid, the patient's age and their chronological proximity to menopause, and the patient's desire for future fertility[12]

The majority of women with uterine fibroids are asymptomatic, and consequently get less clinical attention; fibroid tumours often remain undiagnosed. The most common presenting factor that symptomatic women typically complain about is abnormal uterine bleeding, specifically in terms of heavy and prolonged bleeding.[12] The main complaint in this study is similar to existing epidemiological data. Prolonged menstrual phase complaints are the most common complaints in cases of uterine fibroids.

**Correlation of VEGF Levels to Uterine Fibroids Volume**

Theoretically, fibroid tumours generally grow slowly. In addition, the rate of growth of uterine fibroid in a patient also varies and some tumours will even spontaneously regress during growth. Therefore, it will be very difficult to predict the growth of uterine myomas or the onset of symptoms.[2]

Fibroid volume is one of important parameter for choosing the management options from no need any intervention as in small asymptomatic myomas, to surgical intervention in symptomatic one or cases of the large uterus with myomas comparable to or in surplus of 12-14 week pregnancy. Uterine fibroid volume is also necessary in follow up of cases under medical treatment (e.g Gn-RH analogues) to assess its success, while in cases of rapid growth planned for surgical intervention, myoma volume helps us to decide the incision type, site and length to diminish the surgical complications.[9]

Growth factors are involved in the pathogenesis of uterine fibroid by regulation of angiogenesis, which is necessary for the growth of uterine fibroid. Angiogenesis is a system that is controlled by proangiogenic and antiangiogenic factors.[6, 17]One of the important factor in angiogenesis is vascular endothelial growth factor (VEGF).[18] Several authors report that VEGF plays an important role in stimulating tumour growth.[19] VEGF has a mitogenic effect on endothelial cells that cause cell proliferation. VEGF also influences endothelial cell survival by inhibiting apoptosis.[2]

Spearman's correlation analysis in this study shows that there is a correlation between VEGF levels and the volume of uterine fibroids. The correlation between these two variables is very strong (r=0.999) with the direction of a positive correlation which means that the higher the level of VEGF, the greater the volume of myoma fibroids regardless of other factors that make biased.

VEGF is a potent proangiogenic factor and is an essential growth factor for vascular endothelial cells. The development of leiomyoma is associated with exposure to ovarian sex steroids and an increased requirement for vascular supply for their growth. These observations suggest that VEGF and other proangiogenic factors might be involved in the development of leiomyomas.[6]

The contribution of VEGF to tumour angiogenesis is well understood. VEGF is up-regulated in many tumours and VEGF protein was detected in the culture media from a range of tumour cell lines. VEGF mRNA was also detected in numerous tumours and metastases, with immune reactivity for VEGF localized on tumour cells and in the stromal matrix. VEGF might be released

into the surrounding stromal matrix, which might contribute to tumour growth and metastasis in a paracrine manner through angiogenesis and increased vascular permeability. These findings suggested VEGF may promote tumour growth by direct pro-survival effects in tumour cells.[6]

## CONCLUSION

The median VEGF and median volume of uterine fibroids in this study were 360 pg/mL and 325 ml, respectively. There is a significant correlation between VEGF levels and uterine fibroids volume. The higher the VEGF level, the greater the volume of uterine fibroids.

## SUGGESTION

Hopefully, this research can be continued to find a VEGF cut off point to detect a beginning of progressive growth rate of uterine fibroids in a larger sample.

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**Research Article**

# Correlation of Normal Labor and Vacuum Extraction with Postlabor Stress Urinary Incontinence

## *Hubungan Cara Persalinan Normal dan Vakum Ekstraksi dengan Stres Inkontinensia Urin Pascasalimdi*

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## Abstract

**Objective:** To determine the correlation between normal delivery methods and vacuum extraction with postpartum stress urinary incontinence in West Sumatra.

**Methods:** This study used *cross-sectional study design* in the Obstetrics and Gynecology Department of the RSUP Dr. M. Djamil Padang, network hospital and Puskesmas in Padang City from October 2018-February 2019. The sampling technique was consecutive sampling. Urinary stress incontinence were assessed using a Questionnaire for Urinary Incontinence Diagnosis (QUID).

**Results:** There was a correlation between normal delivery and vacuum extraction with stress urinary incontinence after delivery in the province of West Sumatra ($p < 0.05$).

**Conclusions:** There is a correlation between normal labour and vacuum extraction with stress urinary incontinence after delivery in the province of West Sumatra.

**Keywords:** normal labour, stress urinary incontinence, vacuum extraction.

## *Abstrak*

***Tujuan:*** *Mengetahui hubungan cara persalinan normal dan vakum ekstraksi dengan stress inkontinensia urin pascasalin di Provinsi Sumatera Barat.*

***Metode:*** *Penelitian ini menggunakan desain potong lintang di Poliklinik Bagian Obstetri dan Ginekologi RSUP Dr. M Djamil Padang, RS jejaring dan Puskesmas di Kota Padang sejak bulan Oktober 2018-Februari 2019, Teknik pengambilan sampel dengan consecutive sampling. Penilaian stress inkontinensia urin dengan menggunakan Questionnaire for Urinary Incontinence Diagnosis (QUID).*

***Hasil:*** *Terdapat hubungan cara persalinan normal dan vakum ekstraksi dengan stress inkontinensia urin pascasalin di provinsi Sumatera Barat ($p<0,05$).*

***Kesimpulan:*** *Penelitian menyimpulkan terdapat hubungan cara persalinan normal dan vakum ekstraksi dengan stres inkontinensia urin pascasalin di provinsi Sumatera Barat.*

***Kata kunci:*** *persalinan normal, stres inkontinensia urin, vakum ekstraksi.*

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## INTRODUCTION

Urinary Incontinence (UI) is a condition where the released urin cannot be controlled. Based on the type of UI, there are acute urinary incontinence and chronic urinary incontinence which consists of four types, namely Stress Urinary Incontinence (SUI), urge urinary incontinence/ sudden incontinence, *overflow* urinary incontinence type, and mixed type urinary incontinence[1-3]. SUI is an inability to control urine discharge. This condition can occur if intravesical pressure is excessive compared to the pressure of the urethral closure and is associated with several conditions such as laughing, coughing and other physical activities but not related with contractions in the bladder[4-6]. Results of the overall prevalence of UI in nulliparous women based on a review of 15 studies. The prevalence of UI ranges from 1% to 42.2% (Median: 20.1%). The prevalence of UI in the form of stress urinary incontinence (SUI) varies from 12.5% to 79% (Median: 49.4%)[7]. Among women with SUI, 77.5% reported the reported troublesome symptoms , and 28.8% reported their symptoms to be quite disturbing; the level of interference is associated with the severity of SUI[8,9].

Risk factors that play a role in the occurrence of SUI are age, obesity, history of labour, vacuum

extraction or forceps, history of SUI during pregnancy, episiotomy, spontaneous perineal rupture, phase II time, multiparity, estrogen deficiency, smoking, collagen disease and history of hysterectomy[10-12]. The use of vacuum extraction increases the risk of SUI in the next five years. This is explained through its relation to laceration of the birth canal. But, when compared with forceps, the risk of vacuum extraction is lower for SUI. The use of forceps and vacuum extraction in labour lasting more than 60 minutes significantly increases the risk of SUI after the first delivery[13].

Clinical findings with history and physical examination can predict the diagnosis of SUI with rational accuracy. Women who have symptoms of SUI with complaints alone have a diagnostic accuracy of 64% -90% when compared with the urodynamic test as the gold standard. Of these patients, 10% - 30% are found to have symptoms of detrusor instability (alone or together with SUI). Rare events that can cause SUI symptoms are urethral diverticulum, genitourinary fistula, ectopic ureter, and urethral instability[14]. Clinics must recognize occured clinical situations that diagnoses SUI based solely on clinical symptoms still have a range of uncertainties. A urodynamic test is performed when the diagnosis is doubtful, for diagnostic confirmation, and the patient will undergo a surgical therapy process. This is justification because of research shows low morbidity and cost reasons[14].

When counselling needs to be traced, it begins with complaints of a history of urination due to activity. In the history of uncontrolled urine output, information that must be extracted must include symptoms of storage and voiding, the impact of SUI on the quality of daily life, the extent of SUI, and post-treatment improvement[15]. Some supporting examinations are needed, among others[16,17]. Urinalysis for infection, evaluation must also include urinalysis and culture. Urinary tract infections can cause urinary incontinence, although urge incontinence is more frequent than stress incontinence, cystometry is a bladder filling test and its storage function and urodynamic multichannel to examine urethral function, bladder capacity and stability, and urinary function are not indicated before the initiation of treatment of the bladder and its storage function and multichannel urodynamic to check urethral function, capacity and stability of the bladder, and the function of urinary incontinence is not indicated before the initiation of treatment in stress urinary incontinence.

However, urodynamic examinations are often recommended before surgical interventions to support the diagnosis of stress leaks without bladder contractions for documentation of micturial function. Assessment of post-saline urinary stress can be assessed using a Questionnaire for Urinary Incontinence Diagnosis (QUID) developed in 2010. QUID is a questionnaire consisting of 6 questions to distinguish urinary stress incontinence. This questionnaire was created through a series of processes of literature review, clinical review, expert opinion and screening in patients. QUID is a valid questionnaire in establishing the diagnosis of urinary incontinence. QUID is proven to be consistent, valid, and can assess the progress of therapy. QUID includes the presence and frequency of IU symptoms of stress type and urgency type[16,17].

Scores > 4 on examination of urinary incontinence stress index indicate a diagnosis of urinary incontinence by 80%, while values > 6 on urge incontinence index indicate the same degree of diagnostic accuracy[18]. Previous research states that the proportion of SUIs has decreased in normal labour, but has increased in labour with vacuum extraction[19]. The risk of SUI is significantly higher after vaginal delivery using vacuum extraction compared to spontaneous labor[20]. The incidence of SUI in vacuum extraction labour was greater (32.2%) than in normal vaginal delivery (11.9%). This illustrates that the incidence of SUI is higher in vaginal labour with vacuum extraction than in normal labor[19].

There is no significant difference in the incidence of urinary incontinence in normal labour and vacuum extraction ($p > 0.05$)[21]. There was no significant difference in the incidence of stress urinary incontinence in normal labour, vacuum extraction and forceps ($p > 0.05$)[22,23]. Based on previous research that has been described, there is still a controversial relationship between the occurrence of stress urinary incontinence in normal labour and vacuum extraction.

## METHODS

This study used a cross sectional comparative study design. The research was carried out in the Obstetrics and Gynecology Department of the General Hospital Dr. M. Djamil, network hospital (M. Zein Painan Hospital, Prof. Hanafiah Batusangkar Hospital, Solok District Hospital, Padang Panjang Hospital and Achmad Muchtar Bukittinggi Hospital) and Public health center in Padang City (Padang Pasir, Seberang Padang, Lubuk Buaya, Ikur Koto, Air Dingin, Bungus, Pauh and Nanggalo).

The study was conducted from October 2018 to March 2019. The population of this study were all postpartum women with normal deliveries and vacuum extraction who were treated at RSUP Dr. M. Djamil Padang and networks hospital. The sampling technique in this study was Consecutive Sampling, which is a postpartum woman with normal delivery and vacuum extraction treated and met the inclusion criteria, with a total sample of 31 people. Data analysis was performed univariately and bivariate using Pearson correlation tests. If a p-value <0.05 was found to be statistically significant. Data were analyzed using the SPSS 21.0

## RESULTS

### Subject Characteristics

**Table 1.** Frequency Distribution of Incidence of Stress Urinary Incontinence Postpartum in Normal and Vacuum Extraction

| Method of Normal Delivery | Stress Urinary Incontinence (SUI) | |
|---|---|---|
| | SUI (n = 60) (f /%) | Normal (n = 44) (f /%) |
| Vacuum Extraction | 50 (83.3) | 8 (18.2) |
| Normal | 10 (16.7) | 36 (81.8) |
| Total | 60 (100.0) | 44 (100.0) |

*Most urine incontinence in subjects with vacuum extraction is 83.3% compared to 16.7% normal labor. The results of the SUI assessment are based on The Questionnaire for female Urinary Incontinence Diagnosis (QUID) in extraction vacuum.*

**Table 2.** Stress Urinary Incontinence Assessed according to the Questionnaire for Female Urinary Incontinence Diagnosis(QUID) on Vacuum Extraction

| | No | Rarely | Once a day | Frequently | Always | Every time |
|---|---|---|---|---|---|---|
| Urinating (even small droplets), which wet pads or underwear in | | | | | | |
| Sneezing or coughing | 10 (17.2) | 25 (43.1) | 15 (25. 9) | 8 (13.8) | 0 | 0 |
| Bending or lifting something | 24 (41.4) | 16 (27.6) | 10 (17.2) | 8 (13.8) | 0 | 0 |
| Exercising, brisk walking and jogging | 25 (43. 1) | 21 (36.2) | 7 (12.1) | 5 (8.6) | 0 | 0 |
| Using the toilet and taking off your pants | 24 (41.4) | 20 (34.5) | 10 (17.2) | 4 (6.9) | 0 | 0 |
| Having a strong and uncomfortable urge to urinate (even small drops) which results in wet underwear before reaching the toilet | 2 (3.4) | 23 (39.7) | 20 (34.5) | 13 (22.4) | 0 | 0 |
| Rush to the toilet because of a strong desire to urinate | 1 (1.7) | 21 (36.2) | 24 (41.4) | 12 (20.7) | 0 | 0 |

*Interpretation: in wet underwear before reaching the toilet ie 22.4%, rushed to the toilet because of a strong desire to urinate that is 20.7%, issued urine even small drops when coughing or sneezing and bending or lifting something each 13.8%, when walking fast, jogging or exercising is 8.6% and when using the toilet and removing pants is 6.9%.*

**Table 3.** Stress Incontinence Urine Assessed According to the Questionnaire for Female Urinary Incontinence Diagnosis (QUID) in Normal Delivery

| | No | Rarely | Once a day | Frequently | Always | Every time |
|---|---|---|---|---|---|---|
| Urinating (even small drops), which wet pads or underwear in | | | | | | |
| Sneezing or coughing | 26 (56.5) | 20 (43.5) | 0 | 0 | 0 | 0 |
| Bending or lifting something | 26 (56.5) | 20 ( 43.5) | 0 | 0 | 0 | 0 |
| Exercising, brisk walking and jogging | 45 (97.8) | 1 (2.2) | 0 | 0 | 0 | 0 |
| Using the toilet and taking off your pants | 35 (76.1) | 11 (23.9) | 0 | 0 | 0 | 0 |
| Have a strong and uncomfortable urge to urinate (even small drops) which results in wet underwear before reaching the toilet | 15 (32.6) | 27 (58.7) | 4 (8.7) | 0 | 0 | 0 |
| Hurried to the toilet because of a strong desire to urinate | 7 (15.2) | 26 (56.5) | 13 (28.3) | 0 | 0 | 0 |

*Interpretation: most gravidity status of subjects are multiple.*

**Table 4.** Relationship of Normal Labor and Vacuum Extraction Methods with Stress Urinary Incontinence Postpartum

| Type of labour | Urinary Stress Incontinence (SUI) | | POR (95% CI) | *P-value* |
|---|---|---|---|---|
| | SUI (n = 60) (f /%) | Normal (n = 44) (f /%) | | |
| Vacuum Extraction | 50 (83.3) | 8 (18.2) | | |
| Normal | 10 (16.7) | 36 (81.8) | 22.5 (8.1-62.6) | <0.001 |
| Total | 60 (100.0) | 44 (100.0) | | |

*Interpretation: the results of statistical tests with chi-square there is a significant relationship between the way of normal delivery and vacuum extraction with stress urinary incontinence after delivery*

## DISCUSSION

The results of the study found that the incidence of stress urinary incontinence was more in the study subjects with vacuum extraction which was 83.3% compared to 16.7% of normal labour. Previous research states that the proportion of SUIs has decreased in normal deliveries, but increased in labour with vacuum extraction[19]. The risk of SUI is significantly higher after vaginal delivery using vacuum extraction compared to spontaneous labor[19]. The incidence of SUI in vacuum extraction labour is greater (32.2%) than in normal vaginal delivery (11.9%). This illustrates that the incidence of SUI is higher in vaginal labour with vacuum extraction than in normal labour. The risk of vaginal delivery with vacuum extraction compared to normal delivery for SUI is 2.71, meaning that patients with vacuum extraction have a 2.71 times chance of experiencing SUI compared to normal labor[20].

In the study results it is known that the percentage of SUI is higher in labour with vacuum extraction (83.3%) compared to normal labour (16.7%). Based on the results of statistical tests with *chi-square* there is a significant relationship between the way of normal delivery and vacuum extraction with stress urinary incontinence after delivery with p = <0.001 (p <0.05), *prevalence odds ratio* (POR), 22.5, meaning that subjects with vacuum extraction have a 22.5 times chance of experiencing SUI compared to normal labour. If seen the risk factors that play a role in the occurrence of SUI related to demographics are gestational age where the older the woman's gestational age the higher the risk of SUI. Data from West Sumatra Province shows that the average age of a woman's pregnancy in West Sumatra is 24.6 years with the lowest gestational age range is 16 years and the highest is 44 years, in theory, the age group> 35 years will experience SUI with a proportion of 10.25%. Another factor of SUI is maternal obesity, based on provinces in Indonesia the prevalence of obesity in women in West Sumatra Province in 2013 was 13.46%, this could illustrate the risk of SUI will increase through the amount of obesity in mothers in West Sumatra. This demographic factor can be a supporter of SUI caused by the mode of delivery.

Some studies show a higher prevalence of SUI in women younger than 60 years and urge type urinary incontinence in older women, suggesting

that the type of incontinence can vary with age. Reports that between 17% and 55% of elderly women have experienced urinary incontinence, compared with younger women 12-42%. The incidence of SUI is strongly associated with increasing age especially it was confirmed only in young and middle-aged women[24,25]. Women over 40 years had a ratio of 2.18 times having SUI compared to women less than 40 years of age 40.

## CONCLUSION

Research concludes there is a relationship between normal labour and vacuum extraction with stress urinary incontinence after delivery in the province of West Sumatra.

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**Research Article**

# Prevalence of Appendical Metastasis in Primary Surgery of Ovarian Epithelial Cancer

## *Prevalensi Metastasis Apendiks Pada Bedah Primer Kanker Epitel Ovarium*

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## Abstract

**Objective:** To determine the prevalence of metastasis to appendix from primary surgery of ovarian epithelial cancer at National General Hospital Dr. Cipto Mangunkusumo (RSCM), Indonesia.

**Methods:** A cross sectional study was done using ovarian epithelial cancer patient medical record whose primary ovarian cancer and appendectomy surgery were conducted on July to December 2019 at RSCM. Patients without appendix histopatology result and previous chemotherapy were excluded in this study. Consecutive method and random sampling were used in this study.

**Results:** A total of 80 subjects were included in this study. Subjects have average age of 48 years old. Out of all samples, 43 samples (53.8%) were defined as stage I patient, 7 subjects (8.8%) as stage II, 30 subjects (37.5%) as stage III, and none as stage IV. Appendectomy were done and eight subjects (10%) experienced metastasis to appendix. A total of 19 subjects (23.8%) had chronic appendicitis and 53 subjects (66.3%) did not have metastasis to the appendix. Among eight subjects having appendix involvement, 4 had mucinous histology, 2 serous, and 2 endometrioid. Six out of eight were diagnosed at clinical stage III and two were diagnosed at stage I.

**Conclusions:** The prevalence of appendix metastases from primary surgery in ovarian epithelial cancer at RSCM was 10%. Based on this research, appendectomy can be considered on ovarian cancer surgery.

**Keywords:** appendix, metastasis, ovarian cancer.

## *Abstrak*

***Tujuan:*** *Mengetahui prevalensi metastasis kanker epitelial ovarium ke apendiks pada pembedahan primer kanker epitelial ovarium di Rumah Sakit Umum Pusat Nasional Dr. Cipto Mangunkusumo (RSCM), Indonesia.*

***Metode:*** *Penelitian ini merupakan studi potong lintang menggunakan data rekam medis pasien kanker ovarium epitelial yang menjalani pembedahan primer dan apendiktomi pada bulan Juli hingga Desember 2019 di RSCM Pasien tanpa histopatologi apendiks atau pernah dilakukan kemoterapi sebelumnya dieksklusi dari penelitian. Digunakan metode pengambilan sampel secara acak.*

***Hasil:*** *Didapatkan 80 subjek penelitian yang diikutsertakan dalam penelitian. Dari 80 subjek penelitian, didapatkan rerata usia 48 tahun. Sebanyak 43 subjek (53,8%) didiagnosis dengan stadium I, 7 subjek (8,8%) sebagai stadium II, 30 subjek (37,5%) stadium III. Dari 80 subjek yang menjalani apendiktomi, didapatkan 8 subjek (10%) anak sebar ke apendiks, 19 subjek (23,8 %) apendisitis kronis, 53 subjek (66,3%) tidak terdapat anak sebar. Dari 8 subjek yang terdapat anak sebar ke apendiks dengan temuan histologi 4 musinosum, 2 serosum, 2 endometroid. Sebanyak enam dari delapan subjek terdiagnosis pada stadium klinis stadium III dan dua lainnya pada stadium klinis satu.*

***Kesimpulan:*** *Prevalensi metastasis apendiks pada operasi primer kanker ovarium epitelial di RSCM adalah sebesar 10%. Berdasarkan hasil penelitian ini, apendektomi dapat dipertimbangkan dilakukan pada pembedahan baik stadium awal maupun stadium lanjut.*

***Kata kunci:*** *apendiks , kanker ovarium, metastatis.*

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## INTRODUCTION

Ovarian cancer is one of the leading causes of morbidity and mortality of women in the world. It is the 7th most prevalent cancer in women and the 9th most prevalent of all cancer.[1] Incidence of ovarian cancer is predicted to be 3.4% per year with 4.3% mortality rate.[1] Over 90% of all malignant ovarian cancer is epithelial ovarian cancer. Epithelial ovarian cancer consists of various subtypes, such as serous, endometrioid, clear cell, mucinous, transitional cell, undifferentiated, and not classified. Federation of Gynecology and Obstetrics (FIGO) in its guideline recommends surgical staging on ovarian cancer through finding during exploration.[2] Optimally performed surgical staging is the key to treatment after surgery which supports accurate prognosis, better chemotherapy outcome, and higher survival rate by removing all tumour and its metastasis.

Appendix is an intraperitoneal organ prone to be a site of metastasis of epithelial ovarian cancer due to its anatomical site near paracloica space where ascites could build-up, especially in right ovarian cancer.[3] Appendectomy is routinely done in patients with epithelial ovarian cancer subtype mucinous in order to exclude appendix carcinoma. There were some controversies regarding the decision of routine appendectomy in other subtypes of cancer, although previous study has shown that appendix pathologic examination would promote better staging and optimal cytoreduction.[4] There was no previous research on metastasis to the appendix on epithelial ovarian cancer in our institution. Therefore, this study aims to determine the prevalence and characteristic of appendical metastasis of ovarian cancer undergoing primary surgery.

## METHODS

A descriptive research with cross-sectional method with was done in National General Hospital Dr. Cipto Mangunkusumo Jakarta on July to December 2019. The study population were all ovarian cancer patients undergoing primary surgery with concurrent appendectomy. Patients without appendix histopathology and previous chemotherapy were excluded from this study. Total sampling method was done in regards to small prevalence in the population. Patients were then divided into metastasis and non-metastasis group. Baseline characteristics were analyzed and compared. Ethical clearance was issued from the ethical committee of Faculty of Medicine, Universitas Indonesia with letter number KET-636/UN2.F1/ETIK/PPM.00.02/2019.

## RESULTS

During the course of the study, there were 80 ovarian cancer patients undergoing primary surgery with appendectomy with the average age of 48.6 years. The proportion of metastasis to the appendix was 10% (8 subjects). Among 53 (66.3%) patients who did not have metastasis to the appendix, 19 (23.8%) patients were found to have chronic appendicitis. Baseline characteristics of subjects can be found in Table 1.

**Table 1.** Baseline Characteristics of Subjects

| Variables | N = 80 |
|---|---|
| Age | 48.6 (25 – 72) |
| **Clinical Stage** | |
| I | 43 (53.8 |
| II | 7 (8.8) |
| III | 30 (37.5) |
| IV | 0 (0.0) |
| **Subtype** | |
| Brenner | 1 (1.3) |
| Mucinous | 22 (27.5) |
| Serous | 12 (15) |
| Endometrioid | 17 (21.3) |
| Clear Cell | 26 (32.5) |
| Mixed | 2 (2.5) |
| **Metastasis to the Appendix** | |
| Positive | 8 (10.0) |
| Negative | 72 (90.0) |

Subjects of this study were then categorized into two groups, namely positive metastasis to the appendix group {metastatis (+) group} and negative metastasis to the appendix group {metastatis (-) group}. Characteristics of subjects in each group can be found in Table 2.

**Table 2.** Characteristics of Subjects

| Variables | Study Groups | |
|---|---|---|
| | Metastasis (+) | Metastasis (-) |
| **Age (years)** | | |
| < 50 | 3 (3.75) | 40 (50) |
| > 50 | 5 (6.25) | 32 (40) |
| **Clinical Stage** | | |
| I | 2 (2.5) | 41 (51.3) |
| II | 0 | 7 (8.8) |
| III | 6 (7.5) | 24 (30) |
| IV | 0 | 0 |

Among 8 patients having metastasis to the appendix, some subjects were having more than one subtype of cell. Subtypes of cancer cell having metastasis to the appendix can be found in table 3.

**Table 3.** Subtype Distribution of Metastasis Ovarium Cancer to Appendix Metastasis

| Subtype of Histopathology | Stage I | Stage II | Stage III |
|---|---|---|---|
| Mucinous | 2 | 0 | 2 |
| Serous | 0 | 0 | 2 |
| Endometrioid | 0 | 0 | 2 |

## DISCUSSION

In this study, it was found that the average age of subjects in this study was 48.6 years, lower than the average age of various studies showing that ovarian cancer patients having primary surgery would have an average age of 50 to 70 years old due to the lack of symptoms and compliance of older patients, probably delaying the treatment necessary.[5,6] It was also found that the most prevalent subtypes in ovarian cancer in this study was clear cell subtype with proportion of 32.5%, followed by mucinous (27.5%), endometrioid (21,3%), serous (15%), and mixed type (1.3%). Cell subtypes is one of prognostic factors in epithelial ovarian cancer, with clear cell subtypes having worse progrnosis due to lower chemotherapy response.[7] In earlier stage, clear cell subtype would have similar prognosis and even higher survival rate than serous type. However, it was not until advanced stage that clear cell subtype would give worse outcome to the patient.[7]

Epithelial ovarian cancer is mainly divided into five subtypes according to its prevalence, namely high-grade serous carcinoma (HGSC), endometrioid carcinoma (EC), clear cell carcinoma (CCC), mucinous carcinoma (MC), and low-grade serous carcinoma (LGSC). Usually, HGSC would be diagnosed much later than other subtypes, in accordance to the finding this study and previous studies.[8,9] In this study, 50% of serous subtype were founded in advanced tumour stage, much higher than mucinous (31%), clear cell (37,5%), endometrioid (3.5%), and Brenner (0%).

Ovarian cancer spreads primarily in the abdominal and pelvic cavity. Although patients with early clinical stages usually do not have involvement with the appendix, evaluation of the appendix is needed during surgery because the involvement of the appendix will make cancer grading increase and require adjuvant treatment.4,9,10 Appendectomy should also be done in ovarian cancer patients due to its anatomical site, where ascites could build-up especially in right ovarian cancer and further increase the rate of metastasis.[10]

It was discovered that 10 per cent of the subjects of this study experienced involvement from the appendix. This percentage is still lower than other studies which stated that appendix involvement was 15% or even 29%.4,1 Ovarian epithelial cancer has a very poor prognosis at an advanced stage regardless of the subtype of cancer. In our study, the spread to the appendix was more severe at stage 3-4 (advanced stage) with a proportion of 20% compared to stage 1-2 (early stage) with a percentage of 4 %. Higher percentage of metastasis in this study is related to higher stadium at the time of diagnosis.

Limitation of this study is the method used which is retrospective cohort to determine the prevalence of appendical metastasis in ovarian cancer. Further studies should be done prospectively to have higher degree of causality.

## CONCLUSIONS

The prevalence of metastasis to the appendix in ovarian cancer patients having primary surgery and concurrent appendectomy in this study is 10%. Ovarian cancers with appendix metastasis were made of various subtypes and clinical stages.

## DECLARATIONS

This study was acknowledged by Ethical Committee for Medical Research of Faculty of Medicine, University of Indonesia. The authors declare that they have no competing interests.

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**Case Report**

# Contraceptive Choices for Women with Intellectual Disability

## *Pemilihan Kontrasepsi untuk Perempuan dengan Disabilitas Intelektual*

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## Abstract

**Objective:** To describe the case of contraceptive choices for women with intellectual disability.

**Methods:** A case report.

**Results:** In the case of intellectual disability, we need to perform a holistic approach to the patient.

**Conclusions:** Contraceptive method selection needs much consideration such as medical, ethical, law, and social aspect, therefore it's recommended to start giving an informed choice since antenatal care. The downside of this case is that medical practitioners often overlook the patient's degree of intellectual disability, hence, the patients' judgement, compliance, and self-treatment of complications. The result of counselling with the patient's family, they have chosen LARC method for this patient. Sterilization for eugenic reasons cannot be done because it violates law and ethics of medical practice in Indonesia.

**Keywords:** contraceptive, eugenics, intellectual disability, sterilization.

## *Abstrak*

***Tujuan:*** *Untuk menjelaskan tentang kasus pemilihan alat kontrasepsi untuk perempuan dengan disabilitas intelektual.*

***Metode:*** *Laporan kasus.*

***Hasil*** *: Dalam kasus disabilitas intelektual, kita perlu melakukan pendekatan holistik kepada pasien.*

***Kesimpulan:*** *Pemilihan alat kontrasepsi memerlukan pertimbangan berberapa aspek seperti faktor medis, etika, hukum, dan sosial. Maka itu, edukasi tentang informed choice alat kontrasepsi perlu diberikan sejak mulai antenatal care. Kekurangan pada kasus ini yaitu tenaga medis tidak menilai derajat keparahan disabilitas intelektual pasien. Oleh karena itu, tenaga medis tidak dapat menilai tingkat kemampuan dalam pertimbangan, kepatuhan, dan perawatan diri sendiri terhadap komplikasi penyakit. Hasil dari konseling dengan keluarga pasien, mereka memilih metode LARC untuk pasien. Tindakan sterlisasi untuk alasan eugenik tidak dapat dilakukan, karena tindakan tersebut melanggar etika dan hokum praktik medis yang berlaku di Indonesia.*

***Kata kunci:*** *disabilitas intelektual, eugenik, kontrasepsi, sterilisasi.*

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## INTRODUCTION

At this moment, there is a change of terminology from Mental Retardation into Intellectual Disability. Based on World Health Organization (WHO) International Classification of Disease (ICD) advance, the change of terminology is to help the patient obtain health care that they deserve. Intellectual Disability (ID) is characterized by a marked impairment of core cognitive functions necessary for the development of knowledge, reasoning, and symbolic representation of the level expected of one's age peers, cultural, and community environment. The severity of this condition can be classified by mild (IQ 50 – 70), moderate (IQ 30 – 50), severe (IQ 20 – 30), and profound (IQ < 20).[1,2]Intellectual disability can be found in every community, and geographical area, the prevalence as well as incidence roughly can be found in all over the world. Women with intellectual disability can experience many problems in their daily life, especially in reproductive health. They have the risk to experience bad menstrual hygiene, sexual harassment or abuse, early age pregnancy, premature birth, and increase the incidence of caesarean section. Besides that, they have the risk to experience many complications during pregnancy. Women with intellectual disability do not have a good mind set about birth or take care of a baby. Therefore, contraceptive has a huge role in protecting women with intellectual disability reproductive health. Contraceptive methods that available for women with intellectual disability are

similar with women without intellectual disability. Although, many health care provider have some trouble in choosing appropriate contraceptive for women with intellectual disability because of their capability in considering the pros and cons of each contraceptive method, compliance level, ability in reporting sexual abuse and overcome problems come from using contraceptive.[3-7]

There are few cases of women with intellectual disability are advised to do sterilization that was one-sided decision for the purpose eugenic. However, the action is no longer advised because it violates the medical ethics and informed consent law that applied in Indonesia.[8]If sterilization is not the method of choice; it is necessary to give cognitive behavioural therapy as an adjunctive treatment to prevent contraceptive complications. If the women with intellectual disability do not have any capacity in choosing an appropriate contraceptive, so the medical team need to do a holistic approach which is appropriate for the patient.[3,8-10]

## CASE

A twenty-year-old woman with intellectual disability (gravida 1, parity 0, abortus 0). The patient was a victim of rape. The patient has undergone antenatal care since 18 weeks of pregnancy and has made informed choice for choosing appropriate contraceptive after birth at Siloam General Hospital. The patient was hospitalized because of premature contraction at 36 weeks of pregnancy and consulted to a psychiatrist to assess her disability and to discuss some option for baby delivery and contraceptive method. The psychiatrist advised to do a cesarean section, and for contraceptive methods such as tubectomy or hysterectomy need to be considered the patient and family wishes of getting married and have children again. The patient was conducted cesarean section at 36 – 37 weeks of pregnancy at Siloam General.

Hospital, and a healthy baby was delivered. The patient is living with her parents and sister. Patient daily activities are taken care of by her mother. The rape incident was occurred near the patient's home. Other patient history was unremarkable. After discharge from hospital, the patient doesn't return for follow-up after delivery.

## DISCUSSION

Women with intellectual disability have low intellectual level and marked impairment of core cognitive functions necessary for the development of knowledge, reasoning, and symbolic representation of the level expected of one's age peers, cultural and community environment. Majority women with an intellectual disability need a caretaker to help his/her daily activities and maintaining their health. Besides that, every caretaker have the same concerns about menstrual hygiene, sexual abuse, pregnancy, and their offspring.[1-5] These problems occurred because women with an intellectual disability need more time to adapt the changes that occurred when puberty such as the development of secondary sex organs, hair growth, menstruation, and reproductive health than women without intellectual disability.[5]Incidence of sexual abuse can happen on every woman with or without intellectual disability. However, the incidence rate of sexual abuse found higher in women with intellectual disability population than women without intellectual disability because they have difficulty in recognizing any sexual activities, and reporting it. Besides that, women with intellectual disability experience difficulty in forming intimate relationships and are highly vulnerable to abuse in their relationships.[6]Women with intellectual disabilities have the tendency to be pregnant in young age, so it increases the risk of complication during pregnancy. Complication such as preterm birth and preeclampsia. This complication occurred because women intellectual disability can't recognize the signs. The incidence of cesarean section found higher in women with intellectual disabilities population than without intellectual disabilities because they can't recognize the early sign of giving birth.[5,6]

Clinicians offer family planning can be beneficial to women with intellectual disability. Contraceptive methods that available for women with intellectual disability aren't different than women without intellectual disability, such as abstinence, natural methods, barrier methods, vasectomy, combination oral contraceptive, contraceptive progesterone only, intrauterine device, and operation methods. However, in choosing appropriate contraception methods for women with intellectual disabilities need to consider many aspect such as medical, ethical,

law, and social aspect.[3-7]Many consideration need to be asses in choosing an appropriate contraceptive.

**Medical Aspect**

There are a few medical aspects that need to be reviewed, including the severity of an intellectual disability, ability in maintaining reproductive health, ability in considering the pros and cons of each contraceptive method, compliance level, and side effects of contraceptive, awareness of sexual activities, and ability in reporting sexual abuse incident. If women with intellectual disability don't have any abilities that mention above, so medical team whose response to the patient needs to discuss holistic management that appropriates for the patient.[1-5]

In this case, the medical team do poorly in assessing the severity of intellectual disabilities. As a result, patient ability in maintaining reproductive health, ability in considering the pros and cons of each contraceptive method, compliance level, cope with contraceptive side effects, identify and reporting sexual activities can't be assessed.

**Ethical Aspect**

The medical team have an obligation to do good, beneficial, and do not cause harm to the patient. Besides that, the medical team needs to respect human dignity, where each need to be treated as they have the right to choose their faith. Therefore, sterilization decided unilaterally is a violation of medical ethics. If the medical team or family worried about patient menstrual hygiene, the foremost action to take first is less invasive contraceptive methods such as combination oral contraceptive, medroxyprogesterone injection, intrauterine device, and endometrial ablation[3,6,8,9]

The medical team responsible for the patient wellbeing have differents opinion in managing this case. Obstetricians-gynecologist (ob-gyn) suggested doing sterilization as a form of precaution to prevent this incident reoccurs. However, the psychiatrist doesn't agree with ob-gyn and appreciate patient and family choice, which they chose a patient to get married and form a family. Medical team whose handle this case are doing a great job in discussing with patient and family in choosing appropriate contraceptive method for the patient. In the end, they have reached an agreement to use long term contraceptive.

**Law Aspect**

To perform a medical treatment is a need for medical approval or informed consent. Informed consent that can be done by patient him/herself or their representation. This is supported by PERMENKES no 290/MENKES/PER/III/2018 about medical approval. Clause 1, subsection (1) medical approval is approval given by the patient or closest family after getting a full explanation about medical or dentists procedure that will be done to the patient. Subsection (2) closest families are husband or wife, biological father or mother, biological children, biological relative. Subsection (3) medical or dentistry hereinafter referred to as medical procedure for preventive, diagnostic, therapeutic or rehabilitation that performed by doctors or dentists on patients. Subsection (7) competent patient who is an adult or not child based on legislation or already/ever married, no impairment of physical awareness, able to communicate naturally, not experiencing mental retardation and not experiencing other mental health so capable make decisions freely. Clause (2), subsection (1) every medical procedure requires medical approval. Subsection (2), approval as referred to in subsection (1) can be given in writing or verbally. If an adult suffers from a mental health disorder, the approval can be given by parents/guardian/curator. Civil code article clause 434, each blood member needs to be family curator because of mental health disorder.[10-12]

In this case, the medical team had educated patient and family in choosing an appropriate contraceptive method since the first visit of antenatal care at Siloam General Hospital, which the patient's pregnancy age is 18 weeks. Ob-gyn suggested patient do sterilization after giving birth. Based on the law issued by the ministry of health Indonesian republic number 290/MENKES/PER/III/2008, the patient is not component in giving medical approval. Therefore, the patient family have the right to give medical approval for the patient. On the day of birth of the patient's child, the patient family did not give informed consent to do sterilization. Therefore, the medical

team didn't do sterilization. Legally, the medical team whose responsible for the patient did not break the law about the patient's informed consent.

### Social Aspect

The medical team need to assess caretaker ability in protecting the patient, neighbourhood. Caretaker for women with intellectual disability must be able to protect the patient, which they don't get sexual abuse and prevent for unwanted pregnancy. Patient's neighbourhood needs to be safe from sexual abuse incident. The patient's partner must be able to take care of and protect her.[6] In this case, the patient's social condition is considered to be unideal as the caretaker and the neighbourhood can't ensure patient safety and health. Patient needs full support from both of her parent to live. Patient's family come from a low social-economic background, with only her mother takes care of her.

Based on much clinical consideration, contraceptive methods that appropriate for the patient is LARC method. This contraceptive has effectiveness in pregnancy prevention up to 99%, with a long period, affordable, no change in sexual function and the patient can plan for the next pregnancy. Sterilization for eugenic purpose can't be done because of the law and medical ethics that applied in Indonesia.

## CONCLUSION

Contraceptive method selection needs much consideration such as medical, ethical, law, and social aspect, therefore it's recommended to start giving an informed choice since antenatal care. The downside of this case is that medical practitioners often overlook the patient's degree of intellectual disability; hence, the patients' judgement, compliance, and self-treatment of complications. The result of counselling with the patient's family, they have chosen the LARC method for this patient. Sterilization for eugenic reasons cannot be done because it violates law and ethics of medical practice in Indonesia.

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**Case Report**

# Management of Aplastic Anemia in Pregnancy

## *Manajemen Anemia Aplastic pada Kehamilan*

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## Abstract

**Objective:** To illustrate the management of anemia aplastic in pregnancy.

**Methods:** Case report.

**Case:** A 29 years old women came to Dr. Cipto Mangunkusumo due to aplastic anemia in 24 weeks of gestational age. Laboratory result showed anemia normocytic normochromic and thrombocytopenia. During the next visit, the patient had hypertension with controlled blood pressure and IUGR. Therefore, the pregnancy should be terminated and the mode of delivery was a cesarean section.

**Results:** The baby was asymmetric IUGR indicating hypoxic environment due to anemia in pregnancy.

**Conclusions:** Anemia aplastic was a rare case during pregnancy and close monitoring was imperative to detect early complication such as intrauterine growth retardation.

**Keywords:** aplastic anemia, pancytopenia, pregnancy

## *Abstrak*

***Tujuan:*** *Untuk menggambarkan manajemen anemia aplastik pada kehamilan.*

***Metode:*** *Laporan kasus.*

***Kasus:*** *Seorang perempuan 29 tahun datang ke RSCM karena kehamilan 24 minggu. Hasil laboratorium menunjukan anemia normositik normokrom dan trombositopenia. Pada kunjungan berikutnya pasien memiliki tekanan darah tinggi terkontrol, dan PJT. Maka dari itu, kehamilan harus diakhiri dan cara persalinan adalah seksio sesarea.*

***Hasil:*** *Bayi PJT asimetris menandakan keadaan hipoksia karena anemia selama kehamilan.*

***Kesimpulan:*** *Anemia aplastik pada kehamilan adalah kasus yang jarang dan pengawasan ketat penting dalam mendeteksi komplikasi seperti PJT.*

***Kata kunci:*** *anemia aplastik, kehamilan, pansitopenia*

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## INTRODUCTION

Acquired aplastic anemia is an uncommon disorder characterized by progressive pancytopenia caused by altered bone-marrow function.[1] Incidence is estimated to be one to two cases per million per year.[1] Given the complexity of anemia aplastic and the limited experience by most providers, new guidelines by the British Society for Standards in Hamatology on the diagnosis and management of adult aplastic anemia were recently published.[2] Pathogenic mechanisms underlying this disease are likely to be immune-mediated and include the overproduction of bone marrow inhibiting cytokines elicited by abnormal T-cell response in a genetically predisposed individual.[3] Pregnancy in association with aplastic anemia is a rare but serious condition that poses serious maternal and fetal risks. Unfortunately, most of the current literature has been limited to case reports, with few studies exploring risk factors and perinatal complications.[4]

Pathophysiological mechanisms underlying the association between aplastic anemia and pregnancy have not been clearly elucidated.[4] It is known that estrogens increase plasma volume in pregnancy more than red-blood-cell production, resulting in anemia of pregnancy. It has been postulated that hormonal influences may contribute to worsening of blood counts in pregnant patients with aplastic anemia, but the exact mechanism and causes are still unclear.[5] Animal models have provided some insight into mechanisms for altered maturation and

proliferation of blood cells in pregnancy. In a murine model, injection of 17-estradiol inhibits the development of developing thymocytes.[6] Demonstrated enhanced proliferative activity of erythroid precursors in bone marrow that was increased by concomitant administration of iron.[7] According to one theory, a population of primitive CD34 progenitors responsible for cellular proliferation and regeneration is produced in maternal bone marrow in response to interaction with umbilical cord blood cells via immunologic signals.[8] Pregnancy is also sometimes accompanied by gestational thrombocytopenia and relative leukocytosis. The factors responsible for the observed thrombocytopenia in pregnant patients with aplastic anemia are yet to be definitively elucidated.[9]

## CASE

A 29 years old woman, G1 24 weeks of gestational age was referred due to bicytopenia which was anemia and thrombocytopenia to Dr. Cipto Mangunkusumo Hospital. There was negative sign for fatigue, headaches, weakness, and pale. Her LMP and ultrasound in second trimester equivalent to 24 weeks. Her blood count (table 1) revealed anemia macrocytic hyperchromic (Hemoglobin level 9 g/dl, MCV 101.9 fl and MCH 34.1 pg), neutrophil (3,096 /µL) and thrombocytopenia (53,000/µL). The result of Bone Marrow Punction 5 years ago at Abdul Moeloek Hospital, Lampung was hypocellular suggesting aplastic anemia. She was assessed as G1 24 weeks gestational age with anemia aplastic and treated with methylprednisolone orally.

During 3rd visit, her blood pressure was 150/100 mmHg, on Nifedipine 10 mg with proteinuria +1 (qualitatively) and 1 gram/24 hours (quantitatively). General status was normal. Complete blood count showed haemoglobin, leukocyte and thrombocyte were 9.2 g/dl, 5,450/µl, 14,000/µl, respectively. Other tests including liver function, renal function, and total bilirubin/direct/indirect revealed normal value. Immunology test such as ANA and Anti DS-DNA tests gave negative results. Ferritin was high 706.444 ng/mL. Coombs test was not performed due to antibody tests were negative. Ultrasound examination revealed an estimated fetal weight of 1500 g in 31 weeks gestation. She was assessed as G1 31 weeks gestational age with anemia aplastic, hypertension in pregnancy, IUGR.

A multidisciplinary team consisting of obstetricians, anesthesiologists, hematologists, and neonatologists planned on cesarean section under general anaesthesia. Cesarean section was performed at 33 weeks of gestation born baby boy of 1,600 g with Apgar scores of 7 and 8, at 1 and 5 min, respectively. The head circumference, abdominal circumference, and ratio Head to Abdominal circumference were 30 cm, 24 cm, and 1.25 equivalent to asymmetric IUGR.

**Table 1.** Laboratory Examination

| Parameter | 2nd Visit | 3rd Visit |
|---|---|---|
| Hb/Ht/Leukocyte/Thrombocyte | 9/26.9/5.470/53.000/ | 9.2/27.1/5.450/14.000/ |
| MCV/MCH/MCHC | 101.9/34.1/33.5 | 92.2/31.3/33.9 |
| Basophil/Eosinophil/Neutrophil/ Lymphocyte/Monocyte (%) | 0.4/0.2/56.6/34.9/7.9 | 0.2/0.2/49.4/44.2/7 |
| Reticulocyte Absolute (/µl) | 96600 | |
| RET-HE | 36.2 | |

**Table 2.** Ultrasound Examination

| Parameter | 24 weeks | 26 weeks | 31 weeks |
|---|---|---|---|
| BPD/HC/AC/FL (mm) | 58/218/190/38 | 64/234/203/44 | 80/285/247/58 |
| EFW (g) | 569g | 750g | 1500g |
| AFI/SDAU | 12/4.9 | 15.5/5.5 | 12.8/3.8 |

## DISCUSSION

Finding Hemoglobin level, MCV, MCH was 9 g/dl, 101 fl and MCH 34.1 pg equivalent to anemia macrocytic hypochromic. The differential diagnosis for it was deficiency B12 and aplastic anemia. The diagnosis of anemia aplastic was established by finding 2 out 3 of anemia, neutropenia, and thrombocytopenia In this patient anemia (Hemoglobin level 9 g/dl) and thrombocytopenia (53,000/µL) occurred.

The cause of anemia aplastic remained unknown. However, it was related to the pharmacologic agent, infection (particularly hepatitis), or hereditary forms with late-onset manifestation (telomeropathies). The severity of the disease was based on the level of neutrophils, platelets and reticulocyte. The level of neutrophil, platelets, and reticulocytes were 3.096 /µL, 24,000/µl, 96600/µl. Therefore, the classification was non-severe.[4,5]

Pregnancy in association with aplastic anemia was a rare but serious condition that poses serious maternal and fetal risks. Unfortunately, most of the current literature had been limited to case reports, with few studies exploring risk factors and perinatal complications.[6,7]

Aplastic anemia was known to increase antenatal complications. The risk of preterm birth was 12.1 %, intrauterine fetal death was 16.7 %, stillbirth was 15.1 %, and spontaneous miscarriage was 16.7 % among pregnant women with the diagnosis of aplastic anemia. Although previously cited complications are commonly encountered in cases of aplastic anemia, no such complications accompanied our case. Hemorrhage at the time of delivery/abortion is another danger. Postpartum hemorrhage is an important complication among patients with the diagnosis of aplastic anemia due to decreased platelet count. However, we've been managed this possibility by given platelets pre-operatively. Intrauterine growth retardation complicated as one of our cases.[4,9-11]

Fetal growth surveillance should be performed by 28 weeks of gestation, and antenatal testing should also be offered by 30-32 weeks, due to the high prevalence of growth restriction. In this case, growth restriction was identified after close monitoring and established by abdominal circumference and estimated fetal weight in 31 weeks gestational age correspond to 1500 g. The asymmetrical IUGR finding from the ratio head and abdominal circumference (>1.2) indicated new-onset hypoxia. This was caused by maternal factors which was aplastic anemia.[10,11]

Cesarean in our case was indicated due to fetal IUGR although in cases of aplastic anemia, vaginal birth is preferred. As recommended to this patient we make sure that the platelet count was >20x103/µL which acceptable for vaginal delivery and 50x103/µL for cesarean delivery.[10,11]

## CONCLUSION

Aplastic anemia is a complex disorder that warrants a comprehensive multidisciplinary-team approach, in order to devise an obstetric, hematological, anesthetic, and neonatal plan and anticipate complications during the peripartum period. Conservative transfusion strategies are necessary to avoid complications related to alloimmunization. Anesthetic management has to be individualized and should include considerations related to the degree of blood cell line compromise, as well as possible complications that have an impact on the anesthetic technique. An absolute number of circulating platelet count necessary to perform a safe neuraxial block cannot be recommended at this time, and the choice of the anesthetic technique depends largely on thorough clinical evaluation leading to a judicious balance of risks and benefits on a case-by-case basis. Despite good supportive care, we had a case of fetal growth restriction, but the fetal outcome was good.

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**Literature Review**

# Purse String Double Layer Closure in Cesarean Section (Turan Technique) : A Novel Approach to Reduce Cesarean Scar Defect

## *Teknik Turan (Penjahitan Dua Lapis Purse String): Pendekatan Terkini untuk Menurunkan Defek Jaringan Parut Bekas Seksio Sesarea*

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## Abstract

**Objective:** To compare cesarean scar defect incidence and other parameters between Turan technique and Conventional technique.

**Methods:** Literature Review

**Results:** The Turan technique uses a purse-string double-layer closure method, which can shorten the incision length and reduce the incidence of postpartum cesarean scar defect that can be detected by ultrasound. Uterine incisional defects are etiologic factors of postoperative pelvic adhesion, placenta previa and accreta, uterine rupture, abnormal uterine bleeding and dysmenorrhea. This means that a decrease in the incidence of uterine incisional defects is essential to prevent cesarean-related complications. In 51 patients in the study group (closure the uterine incision with Turan technique) and 65 patients in the control group collected within six weeks postoperative for transvaginal ultrasound, the length of the uterine incision closure in the study group shorter than the control group (p= 0.0001, 95% IK = 2,854-6,876). Significantly, the number of patients with cesarean scar defect was 12 (23.5%) in the study group and 39 in the control group (76.5%) with P = 0.0001.

**Conclusions:** Turan technique is new uterine closure method technique on CS. This technique can reduce the incidence of cesarean scar defect.

**Keywords:** cesarean section, turan technique, uterine incision.

## *Abstrak*

***Tujuan:*** *Untuk membandingkan angka kejadian defek jaringan parut uterus dan parameter lain antara teknik Turan dan teknik konvensional.*

***Metode:*** *Kajian Pustaka*

***Hasil:*** *Teknik Turan menggunakan metode penutupan purse-string double layer, di mana dapat memperpendek insisi dan mengurangi insidensi defek jaringan parut uterus postpartum yang dapat dideteksi dengan ultrasonografi. Defek insisional uterus merupakan faktor etiologi dari adhesi pelvis paska operasi, plasenta previa dan akreta, ruptur uteri, kehamilan ektopik pada parut uterus, perdarahan uterus abnormal dan dismenore. Ini berarti penurunan kejadian defek insisional uterus sangat penting untuk mencegah terjadinya komplikasi terkait seksio sesarea. Pada 51 pasien kelompok studi (teknik Turan) dan 65 pasien pada kelompok kontrol yang dilakukan pemeriksaan ultrasonografi transvaginal 6 minggu pascaoperasi didapatkan data bahwa panjang insisi uterus lebih pendek pada kelompok studi (p = 0.0001, 95% IK = 2.854–6.876). Secara signifikan, jumlah pasien dengan defek parut bekas operasi (Cesarean Scar Defect) adalah 12 orang (23.5%) pada kelompok studi dan 39 orang pada kelompok kontrol (76.5%) dengan nilai p = 0.0001.*

***Kesimpulan:*** *Teknik Turan adalah teknik baru mengenai metode penjahitan pada insisi operasi SC. Secara signifikan tehnik ini mampu menurunkan insidensi defek parut bekas operasi.*

***Kata kunci:*** *insisi uterus, seksio sesarea, teknik turan.*

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## INTRODUCTION

Almost all women in the world will experience pregnancy and delivery. Labour is physiological process on human life. One mode of delivery is cesarean section (CS). To date, there are no data that provide the best operating CS techniques.[1] Some CS techniques have been done routinely, for example, one-layer, two-layer and uterine closure techniques with different stitches and incisions.[2,3] These techniques have been associated with long-term risks such as postoperative pelvic adhesion, uterine rupture and placental complications such as placenta previa and placenta accreta.[4,5]. Consideration should be given to techniques for the closure of the uterine incision that are capable provide benefit and minimalize risk of uterine damage. Currently, purse strings double-layer uterine closure technique (Turan technique) has been considered as technique of CS incision closure that can reduce level of uterine tissue damage. The length of the uterine incision closure becomes shorter, less of bleeding and minimal cesarean scar defect.[5] Expected no short-term and long-term complications that can occur in patients. Turan technique with purse-string double-layer closure principle, which can shorten incision closure length and reduce the rate of occurrence of cesarean scar defect detectable by transvaginal ultrasound. A significant decrease of uterine incisional defects in patients undergoing cesarean section by Turan technique compared to the double layer uterine closure technique.

## RESULTS

Cesarean scar defect is dehiscence followed by a discontinuity in the location of the previous myometrium scar. CS procedure may be associated with many clinical problems such as ectopic pregnancy at the CS scar, uterine rupture in subsequent pregnancies, dysmenorrhea and abnormal uterine bleeding. It tends to be associated with poor uterine wound healing after CS.[6] Methods regarding the closure of the uterine incision should be noted with benefits and potential hazards in order to provide the best surgical procedure for women undergoing CS. Closure technique and mechanical pull is the most important thing affecting the surgical wound. Therefore, a new method designed, the purse-string double-layer uterine closure (Turan technique) compared with conventional techniques, and then compare the incidence of postoperative scar defect as a short-term result and long term complications. Turan technique shows a different technique than classical double-layer uterine closure, where there is a decreased incidence of cesarean scar defect and the mechanical stress in the area around the uterine incision. High mechanical pressure on lower uterine segment will interfere with perfusion and oxygenation, where oxygen is an essential factor for a wound healing process.[5]

### Turan Technique Procedure

Turan technique in Turkish research begins with Pfannenstiel abdominal incision and Kerr technique for uterine incision. Uterine closure begins from one corner of the incision and then the uterine incision wound is closure using Poliglactin 910 number 1 thread 1. The first layer transversely passes the inner line of the myometrium and the second layer transversely passes the outline of the myometrium- visceral peritoneum, which then followed by the purse string method. Next, the Poliglactin back to the beginning and tied with a knot. By using a purse-string double-layer closure, the aperture in the centre of the uterine incision will be added with a single figure of eight stitches. Uterine exteriorization and peritonealization as well as rectus muscle and subdermal spaces are also performed on this technique. Each patient received a 1-gram intravenous Cefazolin prophylactic antibiotic, and the patient was able to return home three days after surgery.[6]

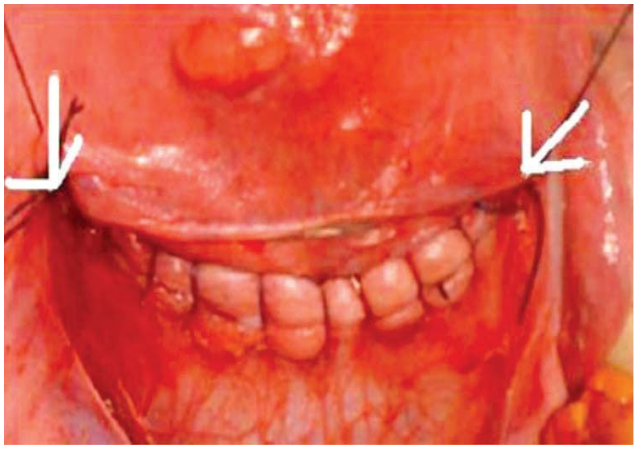

**Figure 1.** Conventional technique
(arrow shows edge of the uterine incision)[6]

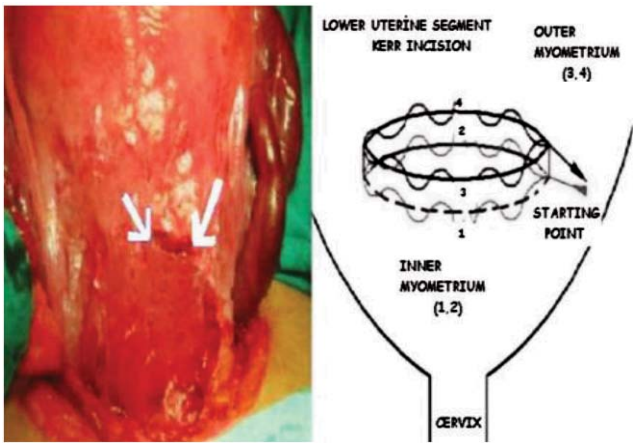


**Figure 2.** Turan technique
(arrow shows edge of uterine incision)[6]

In order to evaluate cesarean scar defect with Turan technique can be performed using transvaginal ultrasonography at six weeks post-cesarean delivery with high transducer frequency (5-6 Mhz). The uterine dimension as well as the occurrence of intracavity, parametrial, and subvesical hematoma are assessed. The length of the incision is measured by a transversal axis. The integrity of the incision closure is assessed with transverse and longitudinal axis. The wedge shaped anatomical distortion in scar tissue of the uterine incision definite as uterine scar defect. Evaluation is also performed on the length of the defect.[6]

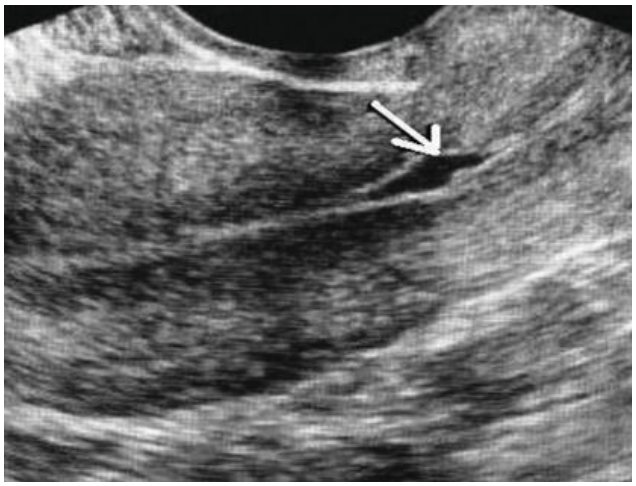

**Figure 3.** Cesarean scar defect
by transvaginal ultrasonography
(arrow shows uterine scar defect)[7]

## Research Evidence related Turan Technique

Based on research Turan technique can be an alternative closure method of the uterine incision. The mechanical tension at lower uterine segmen will decrease and then provide minimal incision defect. The length of the incision closure also becomes shorter when compared to conventional techniques. Turan technique is able to dramatically decrease cesarean scar defect.[6] The potential benefits of shorter scars of the Turan closure technique have not been widely studied. This is a natural consequence of the purse-string double-layer closure method. This method can change the anatomy of the lower segment for two reasons. First, segments can become narrower. The length of the incision before the closure is about 12 cm and then to 8.5 cm and 3.7 cm after the usual closing technique and Turan closure technique. Second, the Turan method pulls the tissue around uterine incision closure, which can change the structure of local anatomy. The combination of these two points explains the reduction of incidence postpartum uterine scar defect in the short term[6,7]

**Table 1.** Turan Technique Compare with Conventional Technique[6]

| | Study group ($n$ = 51) | Control group ($n$ = 65) | *P-value* |
|---|---|---|---|
| Operation time (min) | 28.5 ± 10.6 | 27.9 ± 4.8 | 0.177§ |
| Length of uterine incision before suturing (cm) | 12.0 ± 1.9 | 12.3 ± 2.3 | 0.361‡ |
| Length of uterine incision after suturing (cm) | 3.7 ± 0.9 | 8.5 ± 1.7 | <0.001‡ |
| No. of patientscwho needed additional sutures | 14 (27.5%) | 28 (43.1%) | 0.02† |
| Duration of hospital stay (days) | 2.5 ± 0.6 | 2.5 ± 0.5 | 0.919‡ |
| Preoperative hemoglobin value (g/dL) | 11.6 ± 1.1 | 11.5 ± 1.4 | 0.854‡ |
| Postoperative 1st day hemoglobin value (g/dL) | 11.3 ± 1.2 | 11.3 ± 1.5 | 0.825‡ |
| Postoperative 6th week hemoglobin value (g/dL) | 10.4 ± 1.3 | 10.3 ± 1.5 | 0.817‡ |

Bolding indicates statical significance. †$x^2$-Test, independent samples Student's $t$-test, §Mann-Whitney $U$-test.

Similar with study showed better results associated with bleeding control, Turan technique was able to reduce blood loss during CS procedures without having to use additional sutures compared to conventional techniques (27.5% vs 47.1%). This shows the superiority of this technique in terms of hemostasis.[8] For long-term results, more research is still needed. The results are promising because of the 10 patients who followed none of whom had complications.[6] Reported a significantly lower incidence of cesarean scar defect in patients undergoing cesarean section with Turan technique (23.5%) than the double layer uterine closure technique (60%). Uterine incisional defects or cesarean scar defect are an etiologic factor of postoperative pelvic adhesion, placenta previa and accreta, uterine rupture, ectopic pregnancy of the uterine scar, abnormal uterine bleeding and dysmenorrhea. This means that a decrease incidence of uterine incisional defects is critical thing to prevent cesarean-related complications.[6]

**Table 2.** Comparison of Ultrasound Evaluation at 6 weeks Postoperation[6]

| | Study group ($n$=51) | Control group ($n$=51) | $t$ | d.f. | $P$ | 95% CI | |
|---|---|---|---|---|---|---|---|
| | | | | | | Lower | Upper |
| Uterine incision length (mm) | 21.41 ± 4.38 | 26.28 ±6.11 | 4.793 | 114 | 0.0001 | 2.854 | 6.876 |
| Height of uterine incision defect (mm) | 3.62 ± 1.19 | 4.06 ± 1.43 | 1.053 | 21.678 | 0.304 | -0.424 | 1.297 |
| No. of patients with uterine incision defect | 12 | 39 | | | 0.0001 ($x^2$ = 15.429, d.f. = 1) | | |

Bolding indicates statical significance. CI, confidence interval; d.f., degrees of freedom.

In 51 patients in the study group (suturing the uterine incision with Turan technique) and 65 patients in the control group were collected 6 weeks postoperative for transvaginal ultrasound examination, it was found that the length uterine incision closure was shorter in the study group (p = 0.0001, 95% IK = 2,854-6,876). Significantly, the number of patients with cesarean scar Defect was 12 (23.5%) in the study group and 39 in the control group (76.5%) with p = 0.0001.6. CSSH (Contrast Saline Sonohysterography) is a technique in which the saline fluid inserted into the uterine cavity using a hysteroinjector. CSSH combined with three dimensional ultrasonography provides several advantages over conventional sonography and can be used to detect cesarean scar defect. However, there was no clinical trials compare these two methods. Due to its simple, non-invasive and low-cost tool, transvaginal sonography remains the tool of choice for cesarean scar defect assessment.

In a recent study, a transvaginal ultrasound is a cesarean scar defect evaluation method that has a 100% sensitivity and very specific.[9] Another way to use CSSH is the Gel Instillation Sonohysterography (GIS) technique, which has the advantage of making the cervical filling more stable and reducing the discomfort for the patient while performing the procedure. Both CSSH and GIS can provide better imaging the edge of scar and the injury appears larger.[10] Research on cesarean scar defect has increased over the past few years and has been widely published. A variety of ways to detect and measure it has been widely described. Until now, there has been no consensus or standardization for detecting and measuring cesarean scar defect. Besides, there is an interest in the relationship between CSD and other gynecological symptoms, as well as the mechanisms behind the development of these symptoms. [11]

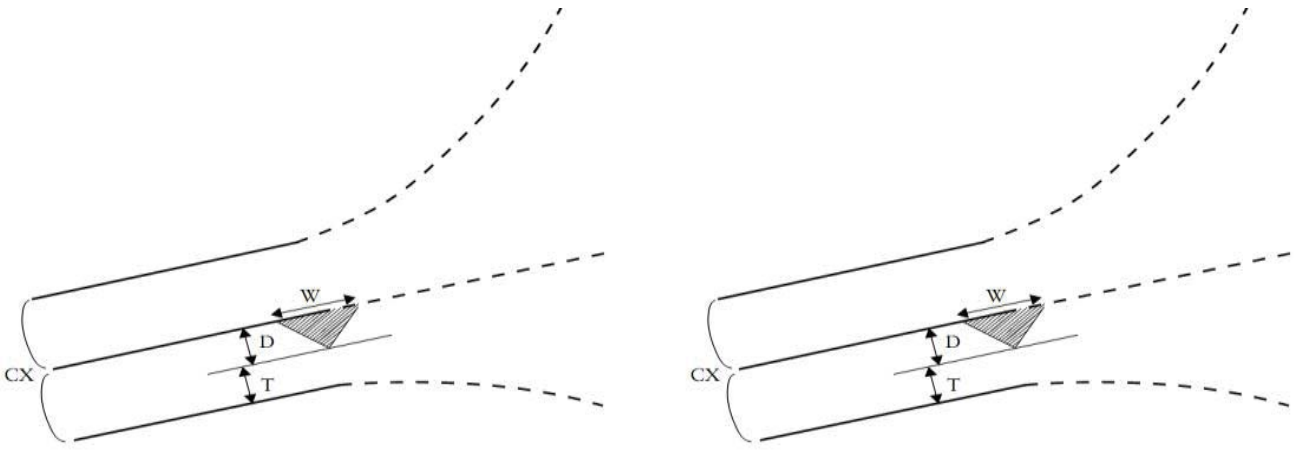


**Figure 4.** Cesarean scar defect measurement[12]

Cesarean scar defect is hypoechogenic area of lower uterine segment previous CS incision wound with a minimum depth of 1 mm. The measurement technique using TVS with the following measurement criteria.

**Table 3.** Cesarean Scar Defect Measurement Criteria

| Size measurement criteria | |
|---|---|
| Scar defect width : | >5 mm |
| Scar defect depth: | >1 mm |
| Residual myometrial thickness : | >3 mm |
| Total thickness | 2+4 |
| Ratio depth/total thickness : | >50 % |

Cesarean scar defect involves myometrial discontinuous at the site of a previous CS. These anatomical defects resulting from previous CS have been reported with clinical symptoms. Transvaginal ultrasound is highly accurate in detecting such defects.[10]

**Table 4.** Parameter Obtained by Multiple Logistic Regression Analyses of Uterine Position, History of Multiple CS and Scar Defect in Prediction on Clinical Symptom[10]

| | *β (SE)* | *Wald $x^2$* | *P-value* | *OR (95%CI)* |
|---|---|---|---|---|
| Postmenstrual bleeding | | | | |
| Anteflexed or retroflexed uterus | -0.35 (0.44) | 0.62 | 0.43 | 0.70 (0.30-1.68) |
| History of multiple CS | 0.003 (0.34) | 0 | 0.99 | 1.00 (0.51-1.97) |
| Defect width | 0.23 (0.06) | 15.65 | <0.05 | 1.26 (1.12-1.41) |
| Dysmenorrhea | | | | |
| Anteflexed or retroflexed uterus | -0.63 (0.43) | 2.08 | 0.15 | 0.54 (0.23-1.25) |
| History of multiple CS | 0.78 (0.34) | 5.27 | <0.05 | 2.18 (1.12-4.25) |
| Defect width | 0.19 (0.05) | 14.07 | <0.05 | 1.21 (1.10-1.34) |
| Chronic pelvic pain | | | | |
| Anteflexed or retroflexed uterus | -0.17 (0.45) | 0.15 | 0.70 | 0.84 (0.35-2.01) |
| History of multiple CS | 0.46 (0.37) | 1.52 | 0.22 | 1.58 (0.76-3.28) |
| Defect width | 0.25 (0.05) | 22.47 | <0.05 | 1.29 (1.16-1.43) |

Multiple cesarean section and retroflexed uteri are risk factors for larger cesarean scar defects. The size of cesarean scar defect is associated with postmenstrual spotting, dysmenorrhea and chronic pelvic pain[10-12]

## CONCLUSION

Turan technique is a new suturing technique method on CS. This technique can be alternative because provide to reduce the incision closure length, better to control bleeding and reduce the incidence of the uterine scar tissue defect. Turan technique uses a purse-string double-layer closure method associated with low cesarean scar defect incidence at six weeks postoperative using transvaginal ultrasonography.

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