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Official Publication of
Indonesian Society of Obstetrics and Gynecology

www.inajog.com

Accredited (2019 - 2024)

by the Directorate General of Higher Education of the Ministry of Education and Culture of the Republic of Indonesia

No. : 14/E/KPT/2019, 10 Mei 2019

Obstetrics Service after Covid-19 Pandemic

Noroyono Wibowo

The coronavirus disease (covid-19) pandemic has worsened maternal and fetal outcomes, as it related to an increase in maternal death, stillbirth, ruptured ectopic pregnancies, and maternal depression. A significant discrepancy of health care services across the globe, between highresource and low-resource settings, might strongly drive their inability to cope with the pandemic.¹

A worsen maternal health is caused by an inappropriate immune response, which could lead to severe inflammation, and thus uncontrolled cell death (panaptosis).² A pathogenic maternal immune response has a pivotal role in fetal development of the central nervous system, as it may result in cerebral palsy, schizophrenia, autism, and allergy in children.³

For this reason, not only health protocol application and vaccination, but cellular health promotion should also be enforced in covid-19 prevention. However, this must be challenging, since based on The Indonesian Basic Health Research (Risikesdas 2018), there was a rise in obstetrical complications rate such as preterm birth, intrauterine growth restriction (IUGR), as well as abnormal maternal fasting blood glucose and glucose tolerance test compared to previous years.⁴ If these issues were not taken seriously by considering all aspects with a comprehensive approach, it would be impossible to achieve the 2045 golden generation with a geographic bonus.

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Research Article

Profile of Pregnant Women who Underwent Cesarean Section and their Perinatal Outcome at a Tertiary Referral Hospital

Profil Ibu Hamil dengan Indikasi Operasi Caesar dan Luaran Perinatal di Rumah Sakit Rujukan Tersier

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Abstract

Objective: To investigate the effectiveness of referral system, in regard to pregnant women with indication of C-section, and to learn the patients' profile and their baby's perinatal outcome.

Methods: The research uses a retrospective descriptive method utilizing patient medical records with history of C-section at RSCM from January 2016 to December 2019. The target population is all pregnant women who were referred and performed cesarean section to at the hospital.

Result: The most indications of C-section were premature membrane ruptures (16.1%), fetal distress (14.5%) and previous C-section (14.1%). There were 1585 cases (41.9%) coming without referral, 779 cases (20.6%) were bookcase, and 806 (21.3%) non-bookcase without referral. The main reasons for referral were absence of NICU facilities (27.31%), premature membranes rupture (20.81%), and eclampsia/preeclampsia/HELLP syndrome (15.40%). Most babies are born with normal weight (2500-3999 grams) as many as 45.1% and 54.9% are groups of babies with abnormal weight. Most babies have an APGAR score 5 minute of 7-10 (83.6%). As many as 47.8% rooming in and infants requiring perinatal care in both SCN and NICU are 52.1%.

Conclusions: The study found that the effectiveness of RSCM tiered referral system still has much room for improvements. The study also found gap between number of referred cases and the cases eventually underwent for C-section with the same indication. The screening can be done better for an indication of the origin of the reference whether it is appropriate to do the reference or not.

Keywords: cesarean section, perinatal outcome, pregnant women, referral system.

Abstrak

Tujuan: Untuk mengetahui efektivitas sistem rujukan pada ibu hamil dengan indikasi seksio sesarea, serta mengetahui profil pasien dan hasil perinatal bayinya.

Metode: Studi ini menggunakan metode deskriptif retrospektif dengan memanfaatkan rekam medis pasien riwayat seksio sesarea di RSCM dari Januari 2016 sampai Desember 2019. Populasi sasaran adalah semua ibu hamil yang dirujuk dan dilakukan seksio sesarea di RSCM.

Hasil: Indikasi seksio sesarea terbanyak adalah ketuban pecah dini (16,1%), gawat janin (14,5%), dan riwayat seksio sesarea sebelumnya (14,1%). Ada 1.585 kasus (41,9%) yang datang tanpa rujukan, 779 (20,6%) bookcase, dan 806 (21,3%) non-bookcase tanpa rujukan. Alasan utama rujukan adalah tidak adanya fasilitas NICU (27,31%), ketuban pecah dini (20,81%), dan eklamsia/preeklamsia/sindrom HELLP (15,40%). Sebagian besar bayi lahir dengan berat badan normal (2500-3999 gram) sebanyak 45,1% dan 54,9% merupakan kelompok bayi dengan berat badan tidak normal. Sebagian besar bayi memiliki skor APGAR 5 menit 7-10 (83,6%). Sebanyak 47,8% rawat inap dan bayi yang membutuhkan perawatan perinatologi baik di SCN maupun NICU sebanyak 52,1%.

Kesimpulan: Studi ini menemukan bahwa efektivitas sistem rujukan berjenjang RSCM masih memiliki banyak ruang untuk perbaikan. Studi ini juga menemukan kesenjangan antara jumlah kasus yang dirujuk dan kasus yang akhirnya menjalani seksio sesarea dengan indikasi yang sama. Penapisan dapat dilakukan lebih baik untuk indikasi asal rujukan apakah layak dilakukan rujukan atau tidak.

Kata kunci: ibu hamil, luaran perinatal, seksio sesarea, sistem rujukan.

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INTRODUCTION

Indonesia's National Health Insurance (JKN) is a part of the National Social Security System (SJSN) organized by the Health Social Security Organizing Agency (BPJS) through a social health insurance mechanism. The implementation of the referral system in Indonesia has been arranged in a tiered form, that is, the first, second and third level health services, where the implementation is highly interconnected. If the primary health service is unable to perform primary-level medical treatment, then it refers the responsibility to the level of service above it, and so on.

Dr. Cipto Mangunkusumo National Center General Hospital is a national referral hospital and the main clinical training center of the Faculty of Medicine, Universitas Indonesia. As a national referral hospital, it provides tertiary services and serves complex cases, which cannot be carried out by lower level hospitals. But in practice, it also helped to serves cases that should be done at lower level hospitals. This situation makes the tiered referral system not running effectively as mandated in the National Social Security System (SJSN) by the Social Security Organizing Agency (BPJS) and Indonesian Healthy Ministry Regulation (Permenkes) Number 1 of 2012.

In this study, the researchers would like to see a whole picture of the profile of pregnant women with an indication of cesarean section in the Dr. Cipto Mangunkusumo tertiary referral hospital. The researchers also want to find out whether the tiered referral system to tertiary hospitals is running well, where cases that could have been done at the primary and secondary service levels were not done at the tertiary service level to improve the efficiency of BPJS standard tariff (INA CBG) rates.

METHODS

The research uses a non-analytic retrospective descriptive method with the main objective of getting a picture or description of a situation retrospectively. It makes use of secondary patients' data derived from patient medical records with history of cesarean section at Dr. Cipto Mangunkusumo Hospital as a tertiary hospital. Cesarean section surgery performed covers both elective and cito. Records were taken from January 2016 to December 2019. The study was conducted at the RSCM as a tertiary referral hospital for obstetric cases with

all the complications that required subspecialist expertise. The target population in this study were all pregnant women who were referred and performed cesarean section to at Dr. Cipto Mangunkusumo General Hospital. The reachable population is mothers who performed cesarean section at Dr. Cipto Mangunkusumo General Hospital between January 2016 and December 2019. The study used consecutive sampling method where the study sample is a reachable population that meets the criteria of acceptance and rejection.

RESULTS

From 2016-2019, there were 3785 cesarean section being performed. In 2016 there were 1070 patients, in 2017 there were 1042 patients, in 2018 there were 817 patients, and in 2019 there were 856 patients. The age distribution of patients has a mean of 30 SD \pm 6.2. Based on obstetric history, gravida has a median of 2, and maternal parity has a median of 1 range 0-10. While abortion has a median of 0 range 0-10.

Based on the patient origin, most of the cases were patients coming with a referral as many as 2200 patients (58.1%). A total of 783 patients (20.7%) were referred from Primary Health Facilities, 473 patients (12.5%) were referred from type B hospitals, 528 patients (13.9%) were referred from type C hospitals, as many as 326 patients (8.6%) were referred from type D hospitals, and 90 patients (2.4%) were referred patients of type A hospitals / internal referrals. There were 1585 cases (41.9%) coming without referral, 779 cases (20.6%) were bookcase, 806 cases (21.3%) non book case without referral.

Table 1. Patient Distribution based on Referral

Referral	Frequency	Percentage (%)
With Referral	2200	58.1
Primary Health Facilities	783	20.7
Hospital Type D	326	8.6
Hospital Type C	528	13.9
Hospital Type B	473	12.5
Hospital Type A/Internal Referral	90	2.4
Without Referral	1585	41.9
Bookcase	779	20.6
Non Book Case	806	21.3
Total	3785	100

Based on gestational age, there is a postterm condition (\geq 42 weeks) in 9 patients (0.2%), term (37– <42 weeks) in 1685 patients (44.5%), preterm (32 - <37 weeks) in 1425 patients (37.6%). very

preterm (28 - <32 weeks) in 487 patients (12.9%) and extreme preterm in 179 patients (4.8%).

From 2016 to 2019, there were 1255 (33.1%) of primigravida patients underwent caesarean section and the remaining multigravida patients formed 2530 (66.9%). Based on cesarean section indications, premature rupture of membranes occupies the highest position with 611(16.1%) followed by fetal distress totaling 547 patients (14.5%). Other indications are Previous C-Section 535 (14.1%), eclampsia / preeclampsia / HELLP syndrome 471 patients (12.4%), Placenta Previa 248 Patients (6.6%). Malpresentation 247 patients (6.5%), Intrauterine Infection 218 patients (5.8%). Failed labor induction 194 patients (5.1%), dystocia / macrosomia / CPD 183 patients (4.8%), maternal medical disease 117 patients (3.1%), pulmonary edema 79 patients (2.1%), congenital abnormalities 61 patients (1.6%), HIV 52 patients (1.4%), solusio / Abruptio placenta 52 patients (1.4%), multiple pregnancy 47 patients (1.2%), placenta accreta spectrum 41 patients (1.1%), premature 21 patients (0.6%), and other indications 61 patients (1.6%).

Table 2. Indication for Caesarean Section Year 2016-2019 (n=3785)

Indication	Frequency	Percentage (%)
Premature rupture of membranes	611	16.1
Fetal distress	547	14.5
Previous C-Section	535	14.1
Eclampsia / Preeclampsia / HELLP syndrome	471	12.4
Placenta previa	248	6.6
Malpresentation	247	6.5
Intrauterine infection	218	5.8
Failed labor induction	194	5.1
Dystocia / macrosomia / CPD	183	4.8
Maternal medical illness	117	3.1
Pulmonary edema	79	2.1
Congenital abnormalities	61	1.6
HIV	52	1.4
Solusio / Abruptio Placenta	52	1.4
Multiple pregnancies	47	1.2
Placenta accreta spectrum	41	1.1
Premature	21	0.6
ETC	61	1.6
Total	3785	100

The absence of NICU is the main reason patients were referred to the RSCM as many as 601 patients (27.31%). The second most common reason is premature rupture of membranes in 458 patients (20.81 %). Other reasons are eclampsia / preeclampsia / HELLP syndrome in 339 patients (15.40%), maternal medical illness

in 163 patients (7.41%), fetal distress in 103 patients (4.68%), previous C-section in 99 patients (4.50%), preterm labor 91 patients (4.14%), placenta spectrum accrete 53 patients (2.41%), congenital abnormalities 52 patients (2.36%), malpresentation 44 patients (2.0%), dystocia / macrosomia / CPD in 30 patients (1.36%), HIV 21 patients (0.95%), to multiple pregnancies 20 patients (0.91%), pulmonary edema 16 patients (0.73%), solusio placenta 12(0.55%), non-availability of obgyn on 5 cases (0.23%), antepartum hemorrhage 4 patients (0.18%), intrauterine infection in 1 patients (0.05%), and other cases 88 patients (4.00%). Out of cases were referred to RSCM as the main reason absence of NICU only 101 (16.8%) really required NICU while 279 cases were treated at SCN.

Table 3. Patient Distribution based on Referral Indication (n=2200)

Indication	Frequency	Percentage (%)
There is no NICU	601	27.31
Premature rupture of membranes	458	20.81
Eclampsia / Preeclampsia / HELLP syndrome	339	15.40
Maternal medical illness	163	7.41
Fetal distress	103	4.68
Previous C-section	99	4.50
Preterm labor	91	4.14
Placenta accreta spectrum	53	2.41
Congenital abnormalities	52	2.36
Malpresentation	44	2.00
Dystocia / macrosomia / CPD	30	1.36
HIV	21	0.95
Multiple pregnancies	20	0.91
Pulmonary edema	16	0.73
Solutio Placenta	12	0.55
Non-availability of obgyn	5	0.23
Antepartum hemorrhage	4	0.18
Intrauterine infection	1	0.05
Others	88	4.00
Total	2200	100

A total of 3436 (90.78%) patients were treated in the ward, 346 (9.14%) patients were treated in the HCU / ICU room, and 3 (0.08%) patients died. Most of the cesarean section took place without complexity namely 3602 (95.2%) and with complexity 183 (4.8%). A total of 80(2.1%) patients had complexity in the form of placenta accreta, 60 (1.6%) uterine atony patients, 6 (0.2%) uterine myoma patients, 4 (0.1%) hematoma patients, and other complexity 33 (0.9%) patients.

There are 3597 single pregnancy, 179 twin pregnancies, and 9 Triplet pregnancies. In total there are 3982 babies, with 3597 single

pregnancy babies, with addition 358 babies from twin pregnancies and 27 babies from triplet pregnancies. Most of the babies were born with normal weight (2500-3999 grams) as many as 1794 (45.1%). There were 1482(37.2%) patients giving birth to babies with low birth weight (1500-2499 grams), 401(10.1%) patients giving birth to babies with very low birth weight (1000-1999 grams), 221 (5.5 %) patients gave birth to infants with extreme low birth weight babies, and there were 84 (2.1%) patients gave birth to infants with birth weight macrosomia (≥ 4000 grams).

Assessment of infant using APGAR scores indicates that most infants born with a normal fifth minute APGAR score (7-10) were as many as 3327 (83.6%). There were 374 (9.4%) babies born with mild APGAR scores in the fifth minute of asphyxia (4-6). There were 167 (4.2%) babies born with a fifth minute APGAR score <4 . A total of 114 (2.9%) babies still birth. There were 63 babies who died after resuscitation before entering the room care.

Most newborns were treated in the rooming in of 1875 (47.8%) and 1595 (40.6) treated at SCN. There were a small number of newborns treated at the NICU of infants 449 (11.5%).

DISCUSSION

The number of cesarean sections performed in RSCM shows a declining trend every year. The decrease in the number of cesarean sections each year may be due to the smaller number of referrals that come with the BPJS system as some patients are managed in the lower health facilities. The rate of cesarean section increases with increasing age of the mother, where nullipara pregnant women aged 35–39 years have a 2-fold risk of doing cesarean section.¹ From this study shows different results indicating cesarean sections that might not only be caused by maternal age and parity, but also due to maternal condition and fetal condition. This study also found that rate of cesarean section in primigravida was 1255 cases (33.1%) smaller than in multigravida. This is similar to other study in that found rate of cesarean section was higher in mutigravida (57%) than 43% in primigravida.²

As a referral hospital, if the referral system runs well and effective, RSCM will only accepts referrals from type B hospitals and type A hospital. However, this study found that most patients were referred from Primary Health Facilities. It also found 806 (21.3%) non bookcase

cases without referral came to RSCM. This shows that the referral system is not working well. In addition, it could also be due to many of Primary Health Facilities are located closer to RSCM than any of type D, type C, or type B hospitals. From previous research it was found that the referral center is a direct referral destination both from regional hospitals, community health centers, and private practice.³ This is in line with research which states that the referral system has not been effective because the majority of patients are referred directly from the primary level to the hospital. This is caused by demographic conditions and indications of maternal referrals.⁴

In this study the absence of NICU is the main reason patients were referred to the RSCM as many as 601 patients (27.31%). The second most common reason is premature rupture of membranes in 458(20.81%). Other reasons are eclampsia / preeclampsia / HELLP syndrome in 339(15.40%). Out of 601 cases were referred to RSCM as the main reason absence of NICU only 101 (16.8%) really required NICU 279 cases were treated at SCN. This finding shows that referral to RSCM with NICU as the main reason might not really requires the facility. However, it might be due to NICU limited capacity at RSCM, pushing the cases to be treated at SCN or Level 2 perinatology, or the condition of baby which does not need any care unit.

The study also found discrepancy between referral indication and the indication of cesarean section. There were 20.81% of cases referred due to premature rupture of membrane but there were 16.1%cases of cesarean section with the same indication. Meanwhile referred cases due to preeclampsia/eclampsia/ HELLP were found on 15.40% of cases. However, there was only 12.4% cases of cesarean section performed with this indication. From this data the screening can be done better for an indication of the origin of the reference whether it is appropriate to do the reference or not.

The study shows that the most common indications for cesarean sections are premature rupture of membranes 16.1%, fetal distress 14.5%, and Previous C-section 535 (14.1%) In another study, indications of fetal distress shown a similiar percentage, which is 12.46%. and, Previous CS (10.25%).⁵ Other studies in developing countries were conducted in Macedonia who stated the rate of cesarean section with indications in premature ruptured of amniotic membrane was 28% of the cases, other

indications are fetal distress, malpresentation, CPD, and failure of induction.⁶ These conditions are in accordance with this study. Other Research at Hasan Sadikin Hospital in 2017 states that the incidence of PROM in Indonesia ranges from 4.5% to 7.6% of all pregnancies, and at Hasan Sadikin Hospital itself, the incidence of PROM is 13.9% of all deliveries.⁷ The most common reason for PROM is ascending infection of the vagina and cervix. While the most frequent vaginal infections are bacterial vaginosis, while cervicitis is mostly caused by *Chlamydia trachomatis*.⁸

The second most common indication is fetal distress in line as the most indicative cesarean section.⁶ In the United States, 1 in 3 women undergoing cesarean delivery in 2011. The most common indication for cesarean sections in the United States is dystocia at 34%, followed by fetal distress 23% and malpresentation 17%. Cesarean sections due to preeclampsia were performed only as much as 3%.⁹ This shows that preeclampsia in developed countries is not much widespread. In contrast to Indonesia where hypertension in pregnancy, including preeclampsia, is one of the most common causes of maternal death.

In this research also found a number of babies with birth weight below normal (<2500 grams) were found to be high as many as (52.8%) This is because the referrals decision the need for perinatal care for the baby to be born. Unlike the birth data in England in 2018 where the most births having a birth weight range of 2500 - 3999 grams with a percentage of 52.1%.¹⁰ This might be due to high number of babies born at less than 37 weeks' gestation at RSCM, which is one of the risk factors for babies born with low body weight.¹¹ The research obtained figures of 55.1% while in the UK only occurred in 7.9% of the population. It could also be due to poorer nutritional status and weight gain patterns in the mother during pregnancy, alcohol use and cigarette smoke exposure which are common in developing countries such as Indonesia.¹¹

In this study, the highest 5-minute APGAR score was obtained in the population, which was 83.6% but it is lower than data obtained from studies in other developing countries, like Brazil, in 2011-2015 which found a rate of 99.56% in hospital births. However, the study in Brazil only included data from low risk births, with gestational times between 37 and 41 weeks, babies weighing 2,500-4,000 grams, maternal ages between 20-40 years, and the absence of congenital anomalies.¹² Similar to our study, in

Ethiopia also obtained a distribution of 88.5% for newborns with an APGAR score of more than 7.¹³ The study also found that 12% of babies must be treated in the NICU room and 40.3% treated in SCN (level 2 perinatology). Different from other studies in California, United States in 2015 which found 12.3% of live births treated at the NICU and the rest were treated in the rooming in.¹⁴

CONCLUSIONS

The study found gap in number of referred cases and the cases eventually underwent for caesarean section with the same indication. The findings confirmed that the effectiveness of tiered referral system to the RSCM has much room for improvements. This data is important for the health facilities as a feedback for improving the referral system.

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Research Article

The Role of Ferritin Levels Serum of Third Trimester Obese Pregnant Women in Neonatal Outcome

Peran Kadar Feritin Serum pada Perempuan Hamil Trimester Tiga dengan Obesitas terhadap Luan Bayi

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Abstract

Objective: To determine relation of obesity to serum ferritin levels in third trimester pregnant women and neonatal outcome at Rumah Sakit Umum Daerah (RSUD) dr. Zainoel Abidin Banda Aceh.

Methods: This was a prospective. The study was conducted in January-November 2019 at RSUD dr. Zainoel Abidin Banda Aceh. Total of 38 patients with 34-40 weeks gestational age with obesity were included in the study. Univariate analysis is presented in the frequency distribution table. Bivariate analysis to test study hypotheses using Spearman's Rank Correlation. P-values > 0.05 were considered significant. The degree of correlation is determined based on the value of the correlation coefficient r .

Result: Spearman test showed no correlation between obesity variables and ferritin reserve status (p : 0.068). Correlation between obesity variable and the infant APGAR value was significant (p : 0.032) and the strength of correlation was weak (r : 0.349). Chi-Square test results showed no correlation between obesity and infant birth weight (p : 0.369). Relationship of serum ferritin levels with APGAR no significant (p > 0.05). Serum ferritin levels with birth weight also did not significant (p > 0.05).

Conclusions: This study shows that obesity in pregnancy has an effect towards the incidence of asphyxia in newborns an increase in serum ferritin or the incidence of macrosomia in newborns.

Keywords: APGAR, birth weight, ferritin, obesity.

Abstrak

Tujuan: Mengetahui hubungan obesitas terhadap kadar feritin serum pada ibu hamil trimester ketiga serta neonatal outcome di Rumah Sakit Umum Daerah (RSUD) dr. Zainoel Abidin Banda Aceh.

Metode: Penelitian analitik observasional menggunakan desain kohort prospective. Penelitian ini dilaksanakan pada Bulan Januari sampai November 2019 di RSUD dr. Zainoel Abidin Banda Aceh. Sebanyak 38 pasien dengan usia kehamilan 34-40 minggu dengan obesitas diikutsertakan dalam penelitian. Analisa univariat disajikan dalam tabel distribusi frekuensi. Analisa bivariat untuk menguji hipotesis penelitian menggunakan Spearman's Rank Correlation. P-value > 0,05 dianggap signifikan. Derajat korelasi ditentukan berdasarkan nilai koefisien korelasi r .

Hasil: Uji hipotesis Spearman menunjukkan korelasi antara variabel obesitas dengan status cadangan ferritin tidak bermakna (p : 0,068). Korelasi antara variabel obesitas dengan nilai APGAR bayi bermakna (p : 0,032) dan kekuatan korelasi lemah (r : 0,349). Hasil uji hipotesis Chi-Square menunjukkan korelasi antara variabel obesitas dengan nilai berat badan lahir bayi tidak bermakna (p : 0,369). Hubungan kadar serum ferritin dengan nilai APGAR menunjukkan hasil tidak bermakna (p > 0,05). Kadar serum ferritin dengan berat badan lahir bayi juga memiliki hubungan yang tidak bermakna (p > 0,05).

Kesimpulan: Penelitian ini menunjukkan bahwa korelasi antara obesitas dengan status cadangan ferritin tidak bermakna. Korelasi antara obesitas dengan nilai APGAR bayi bermakna dan kekuatan korelasi lemah, sedangkan dengan Berat Badan Lahir tidak bermakna. Kadar serum ferritin dengan nilai APGAR dan BBL bayi memiliki hubungan yang tidak bermakna.

Kata kunci: APGAR, berat badan lahir, feritin, obesitas.

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INTRODUCTION

Obesity is excess fat in parts of body that can cause health problems, morbidity, mortality and has become one of the global health problems in the 21st century.¹ Increased prevalence of obesity occurs in many circles, one of which is women in reproductive age, especially during pregnancy.² Prevalence of obesity during pregnancy ranges from 1.8-25.3%.¹ Prevalence of obesity in adult women in Indonesia increases every year to reach 32.9% in 2013.³

Pregnancy and obesity have opposite effects on regulation of iron homeostasis and nutritional status. Increased need for iron in mothers occurs during pregnancy which has implications for anemia during pregnancy. Obesity changes iron homeostasis mediated by inflammatory mediators. Study showed an increase in ferritin serum levels in obese pregnant women,⁴ whereas a different.⁵

Obesity not only affects ferritin levels, but also can have bad implications for fetus. Increased inflammatory mediators in obese mothers during pregnancy can affect intrauterine environment and interfere with fetal development. Mothers who have a BMI ≥ 25 kg/m² during pregnancy are at high risk for giving birth to babies with low APGAR score at minutes 1 and 5.⁶

The study results are in line, also found that obese mothers had a greater risk of giving birth to macrosomia babies which could increase risk of the labor complications such as shoulder dystocia and perineal tears.⁷ Based on results of studies conducted above, we were interested in examining the relationship of obesity to serum ferritin levels in third trimester pregnant women and neonatal outcome at RSUD dr. Zainoel Abidin Banda Aceh.

METHODS

We used prospective study design. This study uses non probability sampling techniques with quota sampling. This study was conducted in January-November 2019 at RSUD dr. Zainoel Abidin Banda Aceh. A total of 38 patients were taken with inclusion criteria 34-40 weeks gestational age with obesity, pregnant women in the latent and active labor phase, single pregnancy, pregnancy control patients and childbirth at RSUDZA, and were willing to participate in the study.

Patients with premature rupture of membranes with signs of intestinal uterine infection, preeclampsia and eclampsia, premature rupture of premature membranes, fetuses with congenital abnormalities, patients with a history of diabetes mellitus and hypertension before pregnancy, and mothers with severe anemia were excluded in this study.

Variables used in this study were Body Mass Index (BMI), serum ferritin levels, and Neonatal Outcomes (birthweight, and APGAR score). Univariate analysis is presented in frequency distribution table. Bivariate analysis to test study hypotheses using Spearman's Rank Correlation. P-values >0.05 were considered significant. Degree of correlation is determined based on the value of the correlation coefficient *r*. (*r* 0.0 - <0.2 (very weak), 0.2 - <0.4 (weak), 0.4 - <0.6 (moderate), 0.6 - <0.8 (strong) , 0.8-1.00 (very strong).

RESULTS

This study was conducted in RSUD dr. Zainoel Abidin Banda Aceh from January-November 2019 and found as many as 38 subjects. Characteristics of redpondents are presented in Table 1.

Table 1. Characteristics of Study Subjects

	Amount (N = 38)	(%)
Age (y.o)		
21-25	2	5.3
26-30	13	34.2
31-35	13	34.2
36-40	9	23.7
41-45	1	2.6
Parity Status		
Primipara	7	18.4
Multipara	31	81.6
Gestational Age (week)		
Preterm (<37)	9	23.7
Early term (37-38)	22	57.9
Full term (39-40)	6	15.8
Late term (41)	1	2.6
Post term (> 42)	0	0
Hemoglobin levels (gr/dL)		
Anemia (<11)	27	71.1
Not Anemia (> 11)	11	28.9
Delivery Method		
Pervaginam	17	44.7
Ferritin Serum $\mu\text{g/L}$		
Low (<12)	5	13.2
Normal (12-150)	30	78.9
High (>150)	3	7.9
Neonatal Outcome		
Apgar Score		
Severely Depressed (0-3)	1	2.6
Moderately depressed (4-6)	13	34.2

Excellent Condition (7-10)	24	63.2
Baby Birth Weight (gr)		
Low (< 2500)	22	57.9
Normal (2500-4000)	11	28.9
More (> 4000)	5	13.2
Stage of Obesity		
Obesitas stg I	11	28.9
Obesitas stg II	22	57.9
Obesitas stg III	5	13.2

Most age groups in this study are 26-30 and 31-35 years. Majority of respondents included in multipara (81.6%). Gestational age at time of delivery in the majority of respondents was 37-38 weeks (57.9%) with the highest number of labor methods (55.3%). Majority of study respondents had anemia (71.1%).

Spearman hypothesis test results showed no correlation between obesity variables and ferritin reserve status (p: 0.068).

Table 2. Results of Correlation Obesity Analysis and Serum Ferritin Levels

Obesitas	Ferritin Serum						Total		P-value
	Low		Normal		High		n	%	
	n	%	n	%	n	%			
Stage I	0	0	10	26.3	1	2.6	11	28.9	0.068
Stage II	3	7.9	17	44.7	2	5.3	22	57.9	
Stage III	2	5.3	3	7.9	0	0	5	13.2	
Total	5	13.2	30	78.9	3	7.9	38	100	

Spearman hypothesis test results showed a correlation between the obesity variable with a significant infant APGAR value (p: 0.032) and weak correlation strength (r: 0.349).

Table 3. Results of Obesity Correlation Analysis and Infant APGAR Value

Obesitas	Apgar Score						Total		R	P-value
	Excellent Condition		Moderately Depressed		Severely Depressed		n	%		
	n	%	n	%	n	%				
Stage I	9	23.6	2	5.3	0	0	11	28.9	0.349	0.032
Stage II	14	36.9	7	18.4	1	2.6	22	57.9		
Stage III	1	2.6	4	10.6	0	0	5	13.2		
Total	24	63.1	13	34.3	1	2.6	38	100		

Results of bivariate analysis of the relationship of serum ferritin levels with infant birth weight showed no significance (p> 0.05). Data analysis results can be seen in full in Table 4.

Table 4. Results of Correlation Analysis of Serum Ferritin Levels and Infant Birth Weight

Ferritin Serum	Birth Weight						Total		P-value
	Low		Normal		High		n	%	
	n	%	n	%	n	%			
Low	4	10.5	2	5.3	0	0	6	15.8	0.673
Normal	17	44.7	7	18.4	4	10.5	28	73.7	
High	2	5.3	2	5.3	0	0	4	10.5	
Total	1	60.5	13	29	24	10.5	38	100	

DISCUSSION

Pregnant women with iron deficiency can experience increased maternal and fetal mortality during prenatal and perinatal periods.⁸ Pregnancy in obese women can have bad implications for their health during pregnancy and even fetuses in the womb.⁹ The results of this study found 38 respondents were trimester pregnant women third who underwent labor in the delivery room and operating room RSUDZA with the category of obesity nutritional status.

The average age of study respondents was 25-35 years with multigravida parity status (81.6%), the results of this study are 6.558 samples, 17% of them were obese and the average age was 30.5 (+5.8).¹⁰ The average gestational age of the study respondents was 37-38 weeks, this result of 4.438 pregnant women respondents with the category of overweight and obese the majority giving birth to babies at 38 weeks gestation.¹¹ Different which shows that 28% of mothers with a BMI >30.0 give birth prematurely on medical indications and 18% spontaneously give birth.¹² According to the American College of Obstetricians and Gynecologist (ACOG) obesity increases the risk during pregnancy one of which is frequent premature birth occur due to an increased incidence of preeclampsia in obesity.¹³

The mean of study respondents had anemia (Hb <11 mg/dl). To assess whether Body Mass Index or BMI in early pregnancy can affect the risk of anemia in respondents in the form of pregnant women from Indonesia and Ghana with prospective cohort study methods, found that in comparison In both of the study groups, a higher weight in early pregnancy affected higher Hb levels so that the risk of anemia was lower. Meanwhile, if the initial weight is low or the BMI under the category of underweight reflects poor nutritional intake, including intake of various important micronutrients that play a role in the haematopoiesis process.¹⁴

Majority of respondents in this study had normal ferritin serum. This can occur due to an increase in the regulation of hepsidin which is induced by IL-6 as one of the inflammatory mediators that is triggered due to excess adipose tissue in obese patients.¹⁵ Hepsidin is a hormone that regulates cellular iron exports, where the expression of hepsidin is feedback regulated by iron concentration, erythropoietic processes, and inflammation. Chronic low-level inflammation associated with obesity can increase the

regulation of hepsidin, and inhibit the absorption of iron in the intestine and release of iron from both the liver and spleen macrophage storage, thereby reducing circulating iron concentration which is characterized by an increase in sTfR and a decrease in serum iron, whereas ferritin can increase or remain in normal concentration.¹⁶

A total of 55.3% of respondents in this study gave birth using the method of Mandarin. This can happen because respondents of this study are pregnant women who have risk factors, namely obesity. The majority of respondents in this study gave birth to babies with excellent condition (63.2%). Yeşilçiçek Çalik study (2018) in Turkey, from 27 study samples with obesity category (BMI > 30) 16 of them (59.3%) gave birth to babies with APGAR score 7-10.^{16,17}

Based on the results of this study, if we look at the correlation of obesity variables and the status of ferritin reserves which were tested using Spearman's Rank showed no significant correlation (p: 0.068 and r: 0.063). Pregnancy and obesity have opposite effect on hepsidin which is a hormone regulator of iron levels in the body and consequently affects regulation on iron homeostasis and nutritional status. Increase in adipose tissue activity of chronic low-level inflammation and involves the removal of cytokines as mediators of information, one of which is interleukin 6 (IL-6) and leptin, thus affecting the effectiveness of the ferroportin membrane which causes internalization and degradation of ferroportin and iron resistance in enterocytes. This causes the absorption and mobilization of iron from the liver and macrophages as storage will decrease.¹⁸

Influence of obesity on Apgar Score in this study has a significant value with weak correlation strength. Obesity in pregnant women can affect the neonatal condition in various ways.¹⁰ Obesity in pregnancy increases the incidence of morbidity in the fetus, thereby affecting the baby's outcome (APGAR and birth weight). Obese female placenta has more lipids that can affect placental pathogenesis through inflammation and oxidative stress.¹⁹ Placental dysfunction disrupts the health condition of the fetus in the womb due to changes in metabolism, inflammation, and endothelial dysregulation in placental tissue which contribute to an increased risk of asphyxia. Pregnancy complicated by obesity can increase the risk of umbilical cord twisting.²⁰

Environmental placental lipotoxicity is influenced by obesity that occurs in mothers

with a metabolic profile that can increase inflammation and oxidative stress, as well as a decrease in angiogenesis regulators. This can cause intrauterine growth restriction (IUGR) or intra uterine fetal growth disturbance.²¹ Mechanisms that can affect neonatal outcome are pathomechanisms of anemia that occur due to increased levels of hepsidin which can reduce the amount of iron available to be released into the circulation, thereby affecting the synthesis of hemoglobin and production of erythrocytes.²² Decreased hemoglobin levels cause a decrease in oxygen transport and treatment of the fetus, thereby supporting the occurrence of hypoxic conditions in the fetus.²³

Direct evidence for the effect of lipotoxicity in pregnancy with obesity on neonatal outcomes is directly lacking, studies are currently only linking lipotoxicity to dysfunction in the placenta. The placenta can cause metabolic abnormalities to the fetus through intra utero, so the consequences can affect the health of children widely. Because of its considerable potential to harm both mother and baby, studies of the level, causes and effects of lipotoxicity in obese pregnancies continue.¹³

Based on an article review study, of about 34 articles that examined the relationship between maternal BMI and infant birth weight, around 15 studies evaluated the relationship between maternal BMI and LBW. The total of subjects included in the study metanalyst review was around 313.569 and using the reference category of mothers with normal BMI, it was found that no relationship was found between the incidence of infants with low birth weight with obese mothers.²⁴

CONCLUSION

This study shows that the correlation between obesity and ferritin reserve status is not significant. The correlation between obesity with a baby's APGAR value is significant and the strength of the correlation is weak, whereas with BBL it is not significant. Serum ferritin levels with APGAR and BBL values of infants have no significant relationship.

SUGGESTION

This study is expected to be continued by looking at other variables such as complications of placental disorders, inflammatory markers and other variables.

ACKNOWLEDGEMENT

The author is very thankful to the Obstetrics and Gynecology and Internal Medicine Department of Faculty of Medicine in Syiah Kuala University, Dr. Zainoel Abidin General Hospital and also to the staff of Prodia Clinic in Banda Aceh for their help and collaboration on this study. This study does not have any conflict of interest.

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Research Article

Role of Maternal Factors in Low Birth Weight**Peran Faktor Ibu dalam Kejadian Berat Bayi Lahir Rendah**Gita S. Candijaya¹, Edihan Mardjuki², Edward Surjono³¹ Faculty of Medicine and Health Science² Department of Obstetrics and Gynecology³ Department of PediatricsFaculty of Medicine and Science Universitas Katolik Atma Jaya
Jakarta**Abstract**

Objective: To determine the correlation between body mass index, age, parity, gestational weight gain and low birth weight at Atma Jaya Hospital in 2016-2019.

Methods: This was a cross-sectional study of 111 sample medical records of pregnant women who gave birth at Atma Jaya Hospital in 2016-2019 and met the inclusion and exclusion criteria. Data management was performed using the Chi-square test and multivariate logistic regression test.

Result: Most of the mothers were in the group with normal BMI (60.4%), the G1 age group (21-29 years old) (45.9%), the low multiparity group (parity 1-3 times) (57.7%). The analysis showed that there was a significant relationship between parity group grand multipara ($p=0.028$; $OR=5.206$; $95\% CI=1.195-22.686$) with the incidence of LBW. There was no significant relationship between BMI group lean ($p=0.303$; $OR=1.646$; $95\% CI=0.638-4.246$), group normal ($p=0.532$), group fat ($p=0.440$; $OR=1.957$; $95\% CI=0.357-10.737$), maternal age group G1 ($p=0.141$), group G2 ($p=0.587$; $OR=1.327$; $95\% CI=0.478-3.687$), group G3 ($p=0.111$; $OR=0.262$; $95\% CI=0.050-1.360$), parity group nulliparity ($p=0.494$; $OR=0.669$; $95\% CI=0.212-2.117$), group low multiparity ($p=0.051$), and gestational weight gain group low ($p=0.955$; $OR=1.028$; $95\% CI=0.396-2.667$), group normal ($p=0.986$), group high ($p=0.897$; $OR=0.917$; $95\% CI=0.245-3.424$) with the incidence of LBW.

Conclusions: There is a significant relationship between parity with the incidence of low birth weight. There is no relationship between body mass index, age, and gestational weight gain with the incidence of low birth weight.

Keywords: age, BMI, gestational weight gain, LBW, parity.

Abstrak

Tujuan: Mengetahui apakah terdapat hubungan antara indeks massa tubuh, usia, paritas, dan penambahan berat badan ibu hamil terhadap kejadian berat bayi rendah di Rumah Sakit Atma Jaya tahun 2016-2019.

Metode: Penelitian ini merupakan penelitian analitik potong lintang dengan menggunakan rekam medis sebanyak 111 sampel ibu hamil yang melangsungkan persalinan di RS Atma Jaya pada tahun 2016-2019 dan memenuhi kriteria inklusi dan eksklusi. Pengelolaan data dilakukan dengan menggunakan uji Chi-square dan uji regresi logistik multivariat.

Hasil: Didapatkan sebagian besar ibu berada pada kelompok dengan indeks massa tubuh normal (60,4%), kelompok usia G1 (21-29 tahun) (45,9%), kelompok paritas low multiparity (paritas 1-3 kali) (57,7%), dan kelompok penambahan berat badan normal (47,7%). Hasil analisis menunjukkan terdapat hubungan antara paritas kelompok grand multipara ($p=0,028$; $OR=5,206$; $95\% CI=1,195-22,686$) terhadap kejadian BBLR. Tidak terdapat hubungan signifikan antara indeks massa tubuh kelompok kurus ($p=0,303$; $OR=1,646$; $95\% CI=0,638-4,246$), kelompok normal ($p=0,532$), kelompok gemuk ($p=0,440$; $OR=1,957$; $95\% CI=0,357-10,737$), usia ibu hamil kelompok G1 ($p=0,141$), kelompok G2 ($p=0,587$; $OR=1,327$; $95\% CI=0,478-3,687$), usia kelompok G3 ($p=0,111$; $OR=0,262$; $95\% CI=0,050-1,360$), paritas kelompok nulliparity ($p=0,494$; $OR=0,669$; $95\% CI=0,212-2,117$), kelompok low multiparity ($p=0,051$), penambahan berat badan ibu hamil kelompok kurang ($p=0,955$; $OR=1,028$; $95\% CI=0,396-2,667$), kelompok sesuai ($p=0,986$), dan kelompok lebih ($p=0,897$; $OR=0,917$; $95\% CI=0,245-3,424$) dengan kejadian BBLR.

Kesimpulan: Terdapat hubungan yang signifikan antara paritas dengan kejadian berat bayi lahir rendah. Tidak terdapat hubungan antara indeks massa tubuh, usia, dan penambahan berat badan ibu hamil dengan kejadian berat bayi lahir rendah.

Kata kunci: BBLR, IMT, paritas, penambahan berat badan, usia.

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INTRODUCTION

Low birth weight (LBW) is one of the big problems, especially in developing countries or countries with low socio-economic conditions, such as Indonesia. LBW are babies born weighing less than 2500 grams, where the normal weight of babies according to the Indonesian Ministry of Health is between 2500 grams - 4000 grams. The level of LBW that occurs in an area can be a benchmark for measuring maternal health, nutrition, and poverty.¹⁻³

LBW can occur due to poor maternal condition, such as extra-uterine infections, chorioamnionitis, trauma, and certain diseases. Conditions that can also occur such as IUGR, infection in the fetus, anomalies, and abnormalities that can occur in the placenta, namely placenta ablatio (placenta separated from the uterus) and placenta previa (the placenta covers part or all of the birth canal). The Indonesian Ministry of Health stated that in DKI Jakarta there were 9.3% of babies born with LBW from all over Indonesia in 2013, and is ranked 24th out of 33 provinces in Indonesia.^{4,5}

The high rate of low birth weight can affect human resources in the future. The government has started efforts to prevent the incidence of LBW, namely by closely maintaining and controlling the risk factors that can cause LBW.⁶

Therefore, the purpose of this study was to determine whether there was a relationship between body mass index, age, parity, and weight gain of pregnant women. on the incidence of low birth weight at Atma Jaya Hospital in 2016-2019.

METHODS

The research design used in this study was analytical using a cross-sectional study with a retrospective approach. The population of this study were pregnant women who gave birth at Atma Jaya Hospital from January 2016 - December 2019. Samples were collected by the patient's medical record. The total population was 96 patients that match the inclusion and exclusion criteria.

The inclusion criteria were pregnant women who gave birth at Atma Jaya Hospital as of January 2016, with a gestation age of 37-42 weeks, and patients with spontaneous labor. The exclusion criteria were if there are complications during pregnancy and childbirth, pregnant women with history of diabetes mellitus and hypertension before and during pregnancy, those

who has a history of infection during pregnancy, patients who smoke, drink alcohol, or consume opioids, cocaine, and immunosuppressive drugs during pregnancy, and the babies are born with congenital abnormalities.

Data collection was carried out using secondary data based on medical records. Data will be retrieved retrospectively from January 2016 to December 2019.

Data were analyzed by Chi Square-test to determine the correlation between body mass index, age, parity, gestational weight gain and low birth weight. Then, using the Logistic Regression test to find out the most dominant variable related to the dependent variable LBW. Data were processed with the help of Statistical Product and Service Solutions (SPSS) for Windows version 22.0.

RESULTS

Table 1. Distribution of BMI Frequency, Age, Parity, Gestational Weight Gain, and Birth Weight

Characteristics	n	%
Body mass index		
Lean	11	9.9
Normal	67	60.4
Fat	33	29.7
Age		
G1*	51	45.9
G2*	36	32.4
G3*	24	21.6
Parity		
Nulliparity	30	27.0
Low multiparity	64	57.7
Grand multipara	17	15.3
Gestational Weight Gain		
Less	42	37.8
Appropriate	53	47.7
Over	16	14.4

*G1 (21-29 years old); G2 (30-34 years old); G3 (≥35 years old).

Table 2. Factors that Most Affecting LBW

Variable	B value	P-value	OR	95% CI	
				lower	upper
Age					
G1		0.141			
G2	0.283	0.587	1.327	0.478	3.687
G3	-1.340	0.111	0.262	0.050	1.360
Parity					
Nulliparity	-0.401	0.494	0.669	0.212	2.117
Low multiparity		0.051			
Grand multiparity	1.650	0.028	5.206	1.195	22.686
Constants	0.925				

Interpretation: parity and age are the most affecting factors.

Table 3. Factors that Most Affecting LBW

Risk factors	Grand multiparity	Nulliparity	Low multiparity	G3	G2	G1	Lean BMI	Less gestational weight gain	Probability %
2	√			√					28
2	√				√				67
2	√					√			60
2		√		√					5
2		√			√				20
2		√				√			16
2			√	√					7
2			√		√				28
2 s			√			√			23
3	√			√			√		29
4	√			√			√	√	36

DISCUSSION

Body mass index (BMI) can be used for screening to determine weight categories that can lead to health problems. Pregnant women with a BMI that is categorized as overweight (>25) will increase the risk of complications, both for pregnant women and for their babies.⁷⁻⁹

The results of this study showed that most mothers were in the normal BMI group (18.5 - 25.0) (60.4%), 11 people (9.9%) thin BMI, and 33 people (29.7%) fat BMI. The average BMI in this study was 23.4. The bivariate test results obtained p value = 0.532 (p > 0.05). This shows that there is no statistically significant relationship between body mass index of pregnant women and the incidence of low birth weight. However, through data analysis, it was found that mothers with body mass index in the thin category showed OR = 1.646 (95% CI 0.638 - 4.246), which means mothers with body mass index underweight category has a 1.6 times greater risk of giving birth to babies with low birth weight compared to mothers with normal body mass index. Mothers with body mass index in the fat category showed OR = 1.957 (95% CI 0.357 - 10.737), which means that mothers with body mass index category fat have a 1.9 times greater risk of giving birth to babies with low birth weight than mothers with normal body mass index.

This study is different from the research at RSUD Wonosari Gunungkidul, which states that there is a significant relationship between body mass index and the incidence of low birth weight babies. The difference in results in this study can be caused by several factors. One of the factors that causes no relationship between the variables in this study is because LBW can be caused by many factors, not only body mass index, but also

maternal age, parity, and maternal weight gain. In addition, it can also be caused by other factors that can influence the occurrence of LBW that cannot be controlled and analyzed by researchers such as the gender of the newborn, socioeconomic status, marital status, and education.¹⁰⁻¹¹

A low BMI can indicate that the mother's nutritional needs have not been fulfilled, so the nutrition for the fetus will be difficult to fulfill.¹⁰

Maternal age at childbirth and pregnancy is very influential on readiness and maturity both physically, emotionally and psychologically.¹² The Ministry of Health of the Republic of Indonesia states that a mother's age of 20-35 years is the safest maternal age to get pregnant, because besides being physically mature, women also feel that they are ready to become mothers.¹³ Based on data from the Japan Society of ObsGyn & WHO, the age of pregnant women is divided into groups G1, G2, and G3.¹⁴ Mothers who are pregnant with more than 35 years of age have a very high risk of complications during pregnancy and childbirth meanwhile, pregnant women less than 20 years old have a pelvis and uterus that are still small and their reproductive organs are still immature.¹²⁻¹⁵

The highest age group for pregnant women was G1 with 51 people (45.9%), G2 with 36 people (32.4%), and G3 with 24 people (21.6%). The average age of pregnant women in this study was 29 years. The bivariate test results obtained p value = 0.428 (p > 0.05), means that there is no significant relationship between the age of pregnant women and low birth weight. Mothers in the G2 age category had an OR = 0.727 (95% CI 0.205 - 2.574), which means that mothers in the G2 age category were 0.7 times less likely to give birth to a baby with low birth weight than mothers in the G1 age category. Mothers in the

G3 age category had an OR = 0.455 (95% CI 0.126 - 1.646), which means that mothers with the G3 age category were 0.4 times less likely to give birth to a baby with low birth weight than mothers with the G1 age category. There is no relationship between these variables may be due to the lack of time available at the time of data collection.

Previous research in Tangerang states that there is no relationship between maternal age and the incidence of LBW (OR = 2.092 95% CI = 0.760-5.759).¹⁶ The results of this study also support the results of previous research in several cities in Japan, the results of their research stated that there was no relationship between maternal age and infant birth weight ($p = 0.397$).¹⁴

The results of the multivariate analysis test found that age is one of the factors that most influences the occurrence of low birth weight when compared to other variables studied. It was said that pregnant women who were in the G2 group had the same relative risk as pregnant women in the G1 group for giving birth to babies with low birth weight (95% CI 0.478 - 3.687). Then for the G3 group the p value was 0.111 where > 0.05 , which means that there was a significant relationship between pregnant women and the G3 group with the incidence of low birth weight. Compared with women in the G3 group who had a 0.26 times lower risk of giving birth to a baby with low birth weight compared to pregnant women in the G1 group (95% CI 0.050 - 1.360).

According to the American College of Obstetricians and Gynecologists, parity is the number of pregnancies that reach gestation more than 20 weeks, and divided into three categories, namely nulliparity, low multiparity (mothers with a total of 1-3 parities), and grand multiparity (mothers with a total of 4-8 parities).¹⁷

The most parity groups were low multiparity with 64 people (57.7%), nulliparity with 30 people (27.0%), and grand multiparity with 17 people (15.3%). The average parity in this study is 1. The bivariate test results showed the value of $p = 0.162$ ($p > 0.05$) which means that it is statistically insignificant between the relationship between parity and low birth weight. Mothers in the nulliparity group had an OR = 2.500 (95% CI 0.805 - 7,764), which means that mothers in the nulliparity group were 2 times more likely to give birth to babies with low birth weight than mothers in the low multiparity group. Mothers in the grand multiparous group had an OR = 3.500 (95% CI 0.897 - 13.663), which means that

mothers in the grand multiparous group were 3 times more likely to deliver babies with low birth weight than mothers in the low multiparity group. The absence of a relationship between variables may occur due to a lack of sample size and there are interactions with other risk factors.

According to previous research which stated that there was no relationship between parity and the incidence of low birth weight ($p = 0.912$). However, clinically, this study shows that the incidence of LBW is increased in women with parity at risk (primiparous and grand multipara) with an OR > 1 .^{10,18}

The researcher then performed a multivariate analysis and the results showed that parity is one of the most influencing factors on the incidence of low birth weight, when compared to other variables that were also studied. In the group of mothers with grand multiparous p value obtained was 0.028 (< 0.05), which means that there is a significant relationship between the grand multiparous group and the incidence of low birth weight. In addition, mothers in the grand multiparity group had a 5 times greater risk of giving birth to babies with low birth weight compared to mothers in the low multiparity group (OR = 5.206; 95% CI 1.195 - 22,686).

Adequate gestational weight gain is very important for fetal development and growth as well as for the storage of maternal fat itself, conversely, if the weight gain is inadequate, the fetus can experience intrauterine growth retardation and also perinatal mortality.^{19,20} The guidelines set by the Institute of Medicine (IOM) in 2009 are in accordance with the BMI before pregnancy and are divided based on the total weight gain of the mother and also the gain per kg / week. Pregnant women who gain more than the recommended weight can increase the risk of having a cesarean section, babies born with macrosomia (babies born larger than 90% of babies of the same age), and can also cause overweight and obesity during the growing period of the child. Meanwhile, pregnant women who gain weight less than recommended can increase the risk of preterm, babies born smaller than 90% of babies of the same age, and mothers who have difficulty in breastfeeding.²¹

The most group of gestational weight gain was normal weight gain, with 53 people (47.7%), pregnant women with less gestational weight gain were 42 people (37.8%), and pregnant women with over in gestational weight gain were 16 people (14.4%). The average gestational weight

gain in this study was 11 kg. Bivariate analysis was carried out on the relationship between maternal weight gain and the incidence of low birth weight, the results obtained were $p = 0.986$ ($p > 0.05$). This shows that there is no significant relationship between the weight gain of pregnant women and the incidence of LBW. Mothers who gained less gestational weight during pregnancy had an OR = 1.028 (95% CI 0.396 - 2.667), which means that mothers with less than normal weight gain during pregnancy had the same relative likelihood of women gaining weight during normal pregnancy for giving birth to babies with low birth weight. Mothers who gain more weight during pregnancy have an OR = 0.917 (95% CI 0.245 - 3.424), which means that mothers who gain more weight during pregnancy are 0.9 times less likely than mothers who gain normal weight during pregnancy.

This study is not in accordance with the previous research where it was stated that there was a significant relationship between maternal weight gain and LBW ($p = 0.000$ OR = 16,724). This study also opposes the results of previous research, where it was found that mothers with less pregnant weight gain based on IOM had a tendency to give birth to low birth weight babies ($p = 0.027$ OR = 2.2).¹⁸⁻²² This difference in results may occur due to the insufficient number of samples studied due to limited research time.

Multivariate Analysis

The results of the multivariate analysis in this study found that the risk factor that most influenced the occurrence of low birth weight was parity. Where mothers in the grand multiparous group got a p value = 0.028 ($p < 0.05$), which means that there is a significant relationship between the grand multiparous group and the incidence of low birth weight, and the OR = 5.206, when compared, mothers with the grand multiparous group have a risk of 5 times greater to deliver babies with low birth weight compared to mothers in the low multiparity group (95% CI 1.195 - 22,686).

The probability value is also obtained from multivariate analysis, the probability of the occurrence of a baby with low birth weight by doing some calculations. It was found that pregnant women who had risk factors at age G3

and also with parity in the grand multiparous group had a 28% chance of delivering babies with low birth weight. Mothers with risk factors were at age G2 and also with parity in the grand multiparous group had a 67% chance of giving birth to a baby with low birth weight. Mothers with risk factors were at age G1 and also with parity in the grand multiparous group had a 60% chance of giving birth to a baby with low birth weight.

Mothers with age risk factors were in the G3 group and the nulliparity group had a 5% chance of giving birth to babies with low birth weight. Mothers with age risk factors were in the G2 group and the nulliparity group had a 20% chance of giving birth to a baby with low birth weight. Mothers with age risk factors were in the G1 group and the nulliparity group had a 16% chance of giving birth to a baby with low birth weight.

Mothers with age risk factors were in the G3 group and the low multiparity group had a 7% chance of giving birth to low birth weight. Mothers with age risk factors were in the G2 group and the low multiparity group had a 28% chance of giving birth to low birth weight. Mothers with age risk factors were in the G1 group and the low multiparity group had a 23% chance of giving birth to a baby with low birth weight.

Researchers calculated the probability of pregnant women having several other risk factors, although the previous analysis did not show a significant relationship. Pregnant women who had age risk factors in the G3 group, the grand multipara group, and classified as having a thin body mass index of 29% gave birth to babies with low birth weight. Then if analyzed further, pregnant women with age risk factors in the G3 group, the grand multipara group, are classified as having a thin body mass index, and with less gestational weight gain during pregnancy, resulting in a 36% probability of giving birth to a low birth weight baby.

CONCLUSIONS

There is a significant relationship between parity with the incidence of low birth weight. There is no significant relationship between body mass index, age, and gestational weight gain with the incidence of low birth weight.

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Research Article

Recombinant FSH versus hMG in Controlled Ovarian Stimulation for IVF***Follicle Stimulating Hormone rekombinan dibandingkan hMG pada stimulasi ovarium terkontrol untuk Fertilisasi in Vitro*****Agus Supriyadi, Achmad K. Harzif, Wael O. Al Jaidy**

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Abstract

Objective: To investigate the relationship between gonadotropins which are used in the process of controlled ovarian stimulation, rFSH and hMG, and the in vitro fertilization outcomes, which are oocyte number, embryo number, and fertilization rate during the period of 2013 to 2019.

Methods: This research was a cross sectional study. Data from medical record of patients who underwent the in vitro fertilization procedure at Melati Clinic, Harapan Kita Child and Mother Hospital were obtained. This research collected the oocyte number, embryo number, and fertilization rate of eligible patients who received rFSH or hMG stimulation.

Result: Four hundred and fifty four patients were eligible for the research, further divided into 309 patients who received rFSH and 145 patients who received hMG. Non-parametric test revealed that patients who belong to the rFSH group had a statistically significant higher oocyte number, embryo number, and fertilization rate compared to hMG group with $p < 0.05$.

Conclusions: Significant difference of oocyte number, embryo number, and fertilization rate exists between rFSH and hMG group ($p < 0.05$) with the mean oocyte number, embryo number, and fertilization rate are consistently observed higher in the rFSH group compared to hMG group.

Keywords: controlled ovarian stimulation, hMG, infertility, in vitro fertilization, rFSH.

Abstrak

Tujuan: Mengetahui hubungan stimulasi ovarium terkontrol yang mendapatkan sediaan gonadotropin berupa rFSH dan hMG dengan luaran FIV berupa jumlah oosit, jumlah embrio, dan tingkat pembuahan pada periode 2013– 2019.

Metode: Penelitian ini menggunakan desain potong lintang menggunakan data rekam medis yang menjalani program FIV di Klinik Melati Harapan Kita tahun 2013 – 2019. Data yang digunakan adalah data pasien yang menjalani program dengan protokol rFSH dan hMG dibandingkan dengan luaran jumlah oosit, tingkat pembuahan, dan jumlah embrio.

Hasil: Dari 454 pasien yang memenuhi kriteria, 309 pasien menggunakan rFSH sebagai obat stimulasi ovarium dan 145 pasien menggunakan hMG sebagai obat stimulasi ovarium. Hasil uji non parametrik lebih tinggi pada kelompok pengguna rFSH dengan ketiga variabel yang diteliti ditemukan bermakna secara signifikan dengan hasil $p < 0,05$.

Kesimpulan: Terdapat perbedaan yang signifikan antara jumlah oosit, fertilization rate, dan jumlah embrio pada kelompok rFSH dan hMG ($P < 0,05$) dengan rata-rata oosit, tingkat pembuahan, dan jumlah embrio kelompok rFSH lebih besar daripada kelompok hMG.

Kata kunci: hMG, infertilitas, fertilisasi in vitro, rFSH, stimulasi ovarium.

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Received: January, 2020

Accepted: September, 2021

Published: October, 2021

INTRODUCTION

World Health Organization (WHO) defined infertility as a disease of the reproductive system characterized by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse.¹ Regular sexual intercourse is defined as having sexual intercourse one or two times a week. In Indonesia, the most prevalent age group who is diagnosed with infertility is on the range of 20 until 24 years old, with a prevalence of 21.3%.²

Infertility is treated by using three main strategies, which are medical therapy, surgical therapy, and assisted reproductive technology.^{2,3} Assisted reproductive technology has become the leading choice of treatment due to its rapid development of knowledge and practice worldwide. One of the assisted reproductive technology is in vitro fertilization (IVF).⁴

IVF procedure consists of many steps, one of the most important among of them is controlled ovarian stimulation. The ovaries are stimulated using gonadotropins, such as recombinant Follicle Stimulating Hormone (rFSH) or human Menopausal Gonadotropin (hMG). As far as the knowledge advances, these groups of the drug are the most common drug used in the IVF procedure.⁴

Many studies have aimed to assess the efficacy of these two groups of drugs. A meta-analysis which was conducted in 2017, showed that there was no significant difference between the two, which were rFSH and hMG group, in terms of the IVF outcomes, which were clinical pregnancy and birth rate.⁵ However, there are three main reasons why research the same question still needs to be conducted. First, although there is evidence of the association between the drugs and IVF outcomes, which are clinical pregnancy and birth rate, evidence of other IVF outcomes such as the number of oocytes, number of embryos, and fertilization rate is yet to be studied. Second, there are only a few researches conducted which aimed to explore the association between the drugs and the IVF outcome in Indonesia. Third, there has never been any research to evaluate the IVF program in Melati Clinic of Harapan Kita Mother and Child Hospital.

Therefore, this research intends to explore the association between IVF outcomes, which are the number of oocyte, number of embryos, and pregnancy rates, and drugs used in IVF stimulation, which are rFSH and hMG, at Melati

Clinic, Harapan Kita Mother and Child Hospital.

METHODS

This study was a cross-sectional study conducted at Melati Clinic, Harapan Kita Mother and Child Hospital. The data was obtained from the medical record of patients who underwent the IVF procedure from January 2013 – July 2019. The inclusion rate of this study was any IVF patient who had either rFSH or hMG stimulation during the determined range of time. The exclusion criteria were patients who failed the stimulation process and patients who decided to freeze their eggs. The total sampling method was done during the process of data collection.

This study had obtained ethical clearance from the Committee of Medical Research Ethics FKUI Jakarta, and all subjects had given informed consent before joined this study. The patient's data was collected from the medical records, including the patient's identity, age, controlled ovarian stimulation protocol, type of gonadotropin stimulation, total dose of gonadotropin stimulation, the number of oocytes, the number of embryos, the number of fertilized embryo. A normality test was carried out to determine whether the data were normally distributed. The data were further analyzed by using univariate and bivariate analysis. Univariate analysis was done to provide the frequency distribution of each variable. On the other hand, bivariate analysis was done to find the association between the groups of drug and IVF outcomes. SPSS 22.0 was used during the process of data analysis.

RESULTS

This study initially obtained data from 557 patients who underwent IVF procedure in Melati Clinic, Harapan Kita Mother and Child Hospital from January 2013 to July 2019. However, only 454 patients who were eligible to be further analyzed. The other 103 patients were excluded from the study due to various reasons, such as incomplete data, cancellation of the procedure, failure of the procedure, and the decision to freeze the eggs.

From these 454 patients, the mean age was 35.2 years old. Most of the patients were more than 35 years old (52.5%), followed by patients ranging from 25 to 35 years old (46%), and the least common was patients with age less than

25 years old (15%). Based on the duration of infertility, the mean duration was 5.5 years. Patients who had been infertile for three until eight years of duration were the most common (36.1%), followed by those who had been infertile less than three years (35.9%), and more than eight years (28%). Based on the indication of IVF, the most common indication was male factor (49.8%), followed by unexplained infertility (24.9%), tubal factor (20.5%), endometrial factor (4.2%), and polycystic ovarian syndrome (0.7%). Patients who underwent the IVF protocol were assigned to different protocols of controlled ovarian stimulation. There were three different protocols, which were long protocol, short protocol, and antagonist protocol. The most common protocol used were the antagonist protocol (86.8%), followed by long protocol (10.1%), and short protocol (3.1%). The patient's characteristic and types of protocol are summarized in Table 1.

Table 1. Subject's Characteristics

Characteristic	Value, n=454 (100) %
Age (y.o)	35.2 ± 4.9
25	7 (1.5)
25-35	209 (46)
>35	238 (52.5)
Duration of Infertility	5.5 ± 3.8
3	163 (35.9)
3-8	164 (36.1)
>8	127 (28)
IVF Indication	
Male factor	226 (49.8)
Unexplained	113 (24.9)
Tubal factor	93 (20.5)
Endometrial factor	19 (4.2)
PCOS	3 (0.7)
Controlled Ovarian Stimulation Protocol	
Antagonist	394 (86.8)
Long	46 (10.1)
Short	14 (3.1)

Patients who underwent the process of controlled ovarian stimulation were stimulated using gonadotropins to stimulate the growth and release of oocytes from the ovaries. This study only included rFSH and hMG type of gonadotropins. Table 2 summarizes the distribution of patients who had either rFSH or hMG for the controlled ovarian stimulation and mean total dose value in each protocol. Most of the patients were stimulated using rFSH (68.1%). In contrast, only 31.9% of patients were stimulated using hMG. The mean total dose of rFSH was 2451.2 IU, whereas the mean total dose of hMG was 2494.7.

Table 2. Gonadotropin used in Controlled Ovarian Stimulation

Gonadotropin used in Controlled Ovarian Stimulation	Value n = (%)	Mean Total Dose Value (IU)
rFSH	309 (68.1)	2451.2
hMG	145 (31.9)	2494.7

This study analyzed the relationship between the type of gonadotropin used with the IVF outcomes, which were the number of oocyte, the number of embryo, and fertilization rate. The result of the analysis is presented on the Table 3.

Table 3. Relationship between Type of Gonadotropin Used with the IVF Outcomes

	rFSH (Mean ± SD; Median)	hMG (Mean ± SD; Median)	P-value ^a
Oocyte number	9.1 ± 6.9; 7	6.8 ± 5.1; 6	0.002
Fertilization rate	50% ± 23%; 50%	40% ± 27%; 40%	0.016
Embryo number	2.6 ± 1.6; 3	2.1 ± 1.4; 2	0.002

^aNon-parametric analysis, Mann-Whitney test, was used

DISCUSSION

In this study, most of the patients were given rFSH (68.1%) compared to hMG (31.9%) as the drug of choice in controlled ovarian stimulation.

Based on demographic data, this study showed that the average age of patients who underwent the IVF procedure was 35.2 years old. Further analysis compared the IVF outcomes of both intervention groups regarding the patient's age. The result reported that there was no significant association between IVF outcomes on both intervention groups in regard of the patient's age. However, the IVF outcomes on both intervention groups have a declining trend as the age increases, indicating a subtle effect of age on IVF outcomes. Many other studies have concluded that the risk of IVF failure increased as the age progressed. Starting from the age of 35 and beyond, the risk of IVF failure was increased progressively.^{6,7} The finding in this study indicates that the age of IVF patients at Melati Clinic reaches the upper limit before the risk of failure starting to increase gradually. Therefore, special concerns must be given to the patient's age to optimize the IVF outcome.

In this study, the mean duration of infertility was 5.5 years. Further analysis compared the IVF outcomes of both intervention groups regarding the patient's infertility duration. The result reported that there was a significant difference

in oocyte number and embryo number on the patients who had been infertile for less than three years and somewhere between three and eight years. These two findings were found higher on the rFSH group compared to the hMG group. Other findings noted that the fertilization rate was found to be significantly higher in the rFSH group on the duration of infertility between three and eight years. However, the IVF outcomes on both intervention groups have a declining trend as the duration of infertility increases, indicating a subtle effect on IVF outcomes. The length of infertility has been linked with IVF outcomes, one study reported.⁸ The duration of infertility of more than 13 years had a significant association with the risk of failure of pregnancy on IVF procedure.⁸ Less than 13 years, the research showed that the duration of infertility had no significant impact on IVF outcomes.

Most of the patients in this study were enrolled in the IVF procedure with an indication of the male factor, followed by unexplained infertility, tubal factor, endometrial factor, and polycystic ovarian syndrome subsequently. In general, further analysis showed that there was no significant association between IVF outcomes on both intervention groups regarding the IVF indication. The research which supported this finding was carried out, which found that there was no association between IVF indication with the IVF outcomes.⁸

In this study, three different protocols of ovarian stimulation were used. Many studies have explored the association between ovarian stimulation protocol with the IVF outcomes.^{9,10} Unfortunately, many of which were not the main interest of IVF outcomes studied on this research.^{9,10} Those studies found conflicting evidence of the association between protocols and IVF outcomes, such as clinical pregnancy and live birth rate.^{9,10} Nevertheless, there was only one study that examined the association between ovarian stimulation protocol with the number of the oocyte.¹¹ This study concluded that agonist protocol resulted in a significantly higher number of the oocyte compared to antagonist protocol.¹¹ In contrast, the result of this study showed that the most common protocol used at Melati Clinic was agonist protocol. This finding contradicted the previous study result. Therefore, further evaluation is needed to assess the efficacy of the ovarian stimulation protocol at Melati Clinic.

The mean total dose of the gonadotropin stimulation was also obtained in this study.

Based on the previous meta-analysis, there was no significant association between mean total dose with the IVF outcomes, such as clinical pregnancy or live birth.¹² Another retrospective study also reported that there was no significant association between clinical pregnancy with the differences among the mean total dose given to the patients.¹³ This study showed that rFSH had a higher mean doses, but had no significance to IVF outcomes.

The results of this study showed that there was a significant difference in the oocyte number, embryo number, and fertilization rate on both groups of intervention. All the findings reported that the rFSH group had a higher number of oocytes, a higher number of embryos, and a higher rate of fertilization compared to the hMG group.

Oocyte number was also observed significantly higher in the rFSH group compared to the hMG group on a meta-analysis conducted.⁵ Another study also showed the same result.¹⁴ These findings support the notion that oocyte development is directly under the influence of gonadotropin hormones, which are FSH and LH. Exogenous gonadotropin can stimulate multiple ovulation, thereby increasing the number of oocytes ovulated at the same time.⁵ The process of multi ovulation is crucial in IVF. Multiple oocytes will enhance the success rate of fertilization, therefore increasing the chance of implantation, pregnancy, and live birth.⁵ In this study, a significant difference between the oocyte number on rFSH and hMG group was observed.

This phenomenon can be explained from the physiological perspective of the hormones used, FSH and LH. rFSH contains only FSH, whereas hMG contains a combination of FSH and LH with a ratio of 1:1. In several studies, LH was found to induce apoptosis of follicular cells.⁵ Furthermore, it will decrease the number of oocytes.⁵ However, LH was also found to increase the quality of the ovum due to its role in inducing gene expression during the development process of follicle.⁵ This physiological basis will be useful for explaining the result found in the next section.

Conflicting evidence found on a meta-analysis of 11 studies.⁵ They discovered that there was no significant difference between fertilization rate in the rFSH group compared to the hMG group.¹⁴ This result can be attributed to the physiological basis of LH in hMG, which increased the quality of the ovum. As the quality of the ovum increased, the chance of the oocytes getting fertilized is also

increased. On another hand, in the rFSH group, they initially had a higher number of oocytes. Although FSH does not improve ovum quality, the higher ovum quantity can contribute to the higher likelihood of fertilization. Therefore, no significant difference is found on both groups. In this study, a significant difference was noted. The fertilization rate was higher on the rFSH group compared to the hMG group. The variance of the result that was found in this study can be attributed to the disparity of the sample size in both groups and the study design that allowed many factors can not be controlled.

Another conflicting evidence found on a meta-analysis of 16 studies.⁵ They found there was a significant difference between the amount of embryo in the rFSH compared to the hMG. However, the hMG group had a higher number of embryos compared to the rFSH group. On the other hand, this study found that the number of embryos was higher in the rFSH group compared to the hMG group. The result of the meta-analysis by Santi et al. was consistent with the physiological basis of LH. Because LH increase the quality of the ovum, the survival rate of the embryo will also be noted higher in the LH group compared to FSH group.⁵

This study had several limitations which significantly influenced the result of the research, including the study design, incomplete patient characteristics data, and disparity of the sample size in both groups. The best study design to assess the efficacy of an intervention is a randomized controlled trial. However, due to limited time and resources, we decided to perform a cross-sectional study. This study could not give us a clear causal relationship between variables that were being studied. Second, the patient's characteristics data was not comprehensive enough to provide us with a holistic condition of the patients. Data such as the duration of stimulation, initial FSH and LH level, size of the follicles, ovarium volume are also crucial for the research. Third, a disparity was noted in the sample size on the rFSH and hMG group. In the future, a proper ratio of both group is needed to draw an appropriate conclusion of the study.

CONCLUSION

The proportion of patients who had the rFSH was 68.1%, whereas the hMG was 31.9%. The patients had a mean age of 35.2, a mean duration of infertility of 5.5 years, and most of the patients

indicated of IVF due to male factor. A significant difference of oocyte number, embryo number, and fertilization rate existed between rFSH and hMG group ($p < 0.05$) with the mean oocyte number, embryo number, and fertilization rate are consistently observed higher in the rFSH group compared to hMG group.

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Research Article

Vaginal Microorganism Pattern in Premature Rupture of Membrane

Pola Mikroorganisme Vagina pada Ketuban Pecah Dini

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Abstract

Objective: To determine the pattern of vaginal microorganisms in pregnant women and risk factors for premature rupture of membranes (PROM) in Manado.

Methods: This is a case-control study. Samples was 40, divided into 20 pregnant with PROM and 20 control samples. Samples were taken from Kandou Manado Hospital and network hospitals within the inclusion criteria. Samples were taken from vaginal swab for microorganism culture.

Result: The highest age distribution in the case of PROM was in the reproductive age group of 20-35 years, 19 people (95%, $p = 1,000$). Primiparas were dominant in the PROM were 11 people (55%, $p = 0,204$). The distribution of BMI mostly from the overweight and obesity groups of 11 people (55%, $p = 0,527$). In the PROM, 19 people (95%, $p = 0,605$) did not smoke. *Escherichia coli* was the most microorganisms in swab vaginal of PROM: 7 people (29.17%).

Conclusions: The most microorganisms found in PROM are *Escherichia coli*, *Enterobacter cloacae* and *Staphylococcus aureus* and in non-PROM are *Klebsiella oxytoca*, *Staphylococcus epidermidis*, *Staphylococcus saprophyticus* and *Pseudomonas fluorescens*. There was no relationship between BMI, age, parity, smoking, and gestational age with the incidence of PROM in this study.

Keywords: PROM, vaginal microorganisms pattern, vaginal swab.

Abstrak

Tujuan: Untuk mengetahui pola mikroorganisme vagina pada kultur vaginal swab wanita hamil dan faktor risiko pada KPD di Kota Manado.

Metode: Studi ini bersifat case control. Total sampling 40 sampel dibagi menjadi 20 sampel hamil dengan KPD dan 20 kontrol. Sampel diambil dari RSUP Kandou Manado dan RS jejaring yang memenuhi kriteria inklusi. Semua pasien dilakukan pengambilan sampel swab vagina untuk dilakukan kultur mikroorganisme.

Hasil: Hasil sebaran usia pada KPD paling banyak pada usia reproduksi 20-35 tahun yaitu 19 orang (95%, $p = 1,000$). Primipara dominan pada KPD yaitu 11 orang (55%, $p = 0,204$). Hasil sebaran IMT paling banyak kelompok overweight dan obesitas yaitu 11 orang (55%, $p = 0,527$). Pada KPD sebanyak 19 orang (95%, $p = 0,605$) tidak merokok. Mikroorganisme terbanyak pada swab vagina KPD adalah *Escherichia coli* sebanyak 7 orang (29,17%).

Kesimpulan: Mikroorganisme terbanyak pada KPD adalah *Escherichia coli*, *Enterobacter cloacae* dan *Staphylococcus aureus* dan pada non KPD adalah *Klebsiella oxytoca*, *Staphylococcus epidermidis*, *Staphylococcus saprophyticus* dan *Pseudomonas fluorescens*. Tidak ada hubungan antara IMT, usia, paritas, merokok, dan usia kehamilan dengan kejadian KPD pada penelitian ini.

Kata kunci: hMG, infertilitas, fertilisasi in vitro, rFSH, stimulasi ovarium.

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Received: April, 2020

Accepted: September, 2021

Published: October, 2021

INTRODUCTION

Maternal Mortality Rate in 2012 is 359 per 100,000 live births.¹ The causes of maternal death are bleeding 60-70%, pre-eclampsia and eclampsia 10-20%, and infections 10-20%. 23% infection in pregnancy can be caused by premature rupture of membranes.² Premature rupture of membranes (PROM) can cause maternal complications such as chorioamnionitis, sepsis, placental abruption and endometritis. Genital infection of mother can occur in the event of PROM due to rupture of the membranes will make it easy for bacteria to enter the uterus and multiplied.³

The cause of PROM is multifactorial. Risk factors include depending on the socioeconomic, previous history of PROM, smoking and infection.⁴ Intrauterine infection is the most common cause of complications in pregnancy, such as PROM. Microorganisms can enter the amniotic fluid or the fetus through several channels, such as ascending from the vagina and cervix, through hematogenous from the placenta (transplacental infection), retrograde from the abdominal cavity through the fallopian tube and from invasive procedures such as amniocentesis.⁵

This study aimed to determine the pattern of vaginal microorganisms in pregnant women and risk factors for PROM in Manado.

METHODS

This is a case-control study conducted in the Obstetrics and Gynecology Department, Faculty of Medicine, Sam Ratulangi University/Prof. Dr. R.D. Kandou General Hospital, Manado. The study was conducted from June 2019 to September 2019.

The study population was pregnant women who came to the Obstetric clinic for ANC or Emergency room Prof. Dr. R.D. Kandou General Hospital, Manado and Pancaran Kasih Hospital Manado. The study sample was pregnant women who came to the emergency room at the Department of Obstetrics and Gynecology, Prof. dr. R. D. Kandou Manado and Pancaran Kasih Hospital Manado within the inclusion criteria and sign the informed consent.

The inclusion criteria were all pregnant women with main complain there was amniotic discharge from the birth canal <24 hours with evidenced by a positive nitrazin test, and women without amniotic discharge from the birth canal as a

control who is willing to participate in the study and signed the informed consent.

The exclusion criteria were pregnant women with obstetric complications, such as antepartum bleeding, decreased consciousness, pregnant women with medical complications, such as heart disease, diabetes mellitus, HIV, malignancy, in treatment using antimicrobials, immunosuppressants, using vaginal wash fluids in the past 2 weeks, have sex in the past 24 hours and who were not willing to participate in the study.

The patient was taken for a vaginal swab sample. Culture was carried out with agar media, continue with identification test. Samples were carried out at Prodia Manado Laboratory. The results called positive if after bacterial breeding the growth of microorganism colonies is found. Data is collected and processed using the statistical data processing software program SPSS version 23.0.

RESULTS

In this study, the most age distribution results were in the reproductive age group of 20-35 years, which were 19 people (95%) in the case of PROM and 19 people (95%) in the case of non- PROM. Chi-square test (χ^2) shows that $\chi^2 = 0,000$ with $p = 1,000$ which means there is no relationship between maternal age and the incidence of PROM. The results of the distribution of marital status found that the average patient was married with 18 people (90%) in the PROM group and 19 people (95%) in the non-PROM.

Table 1. Characteristics of Subject

Characteristic	PROM		Non PROM		P-value
	N	%	N	%	
Age (years)					1.000
High risk (< 20 and > 35)	1	5	1	5	
Normal (20-35)	19	95	19	95	
Marital status					1.000
Marry	18	90	19	95	
Single	2	10	1	5	
Parity					0.204
Primipara	11	55	7	35	
Multipara	9	45	13	65	
Level of education					0.661
Primary school	0	0	1	5	
Secondary school	2	10	7	35	
High school	14	70	10	50	
University	4	20	2	10	
Occupation					0.288
Housewife	13	65	16	80	
Working	7	35	4	20	

Gestational age (weeks)					0.752
< 37	9	45	10	50	
≥ 37	11	55	10	50	
Body Mass Index					0.527
Normoweight	9	45	11	55	
Overweight/Obesity	11	55	9	45	
Smoking history					0.605
Yes	1	5	3	15	
No	19	95	17	85	
UTI history					1.000
Yes	3	15	2	10	
No	17	85	18	90	
Duration of rupture of membranes (hours)					
≤ 12	12	60	0	0	
>12	8	40	0	0	

Fisher's Exact test shows $p = 1,000$ which means there is no relationship between marital status and the incidence of PROM.

The results of the distribution of parity in which primipara is more dominant in the PROM are 11 people (55%) and multipara in 13 people (65%). Chi-square test (χ^2) shows that $\chi^2 = 1.616$ with $p = 0.204$ which means there is no relationship between parity and the incidence of PROM. The most education distribution results were in the high school group. In the PROM group was 14 people (70%) and in the non-PROM group was 10 people (50%). Fisher's Exact test shows $p = 0.661$ which means there is no relationship between education status with the incidence of PROM.

The most occupation distribution both groups of PROM and non-PROM are mostly on the housewife group. Chi-square test (χ^2) shows that $\chi^2 = 1.129$ with $p = 0.288$ which means there is no relationship between occupation and the incidence of PROM. Education, socioeconomic and poor hygiene, cultural factors, limited health facilities, unhealthy eating habits affect the increased prevalence of infections in the vagina that cause PROM.⁶

The most common distribution of gestational age is in the gestational group ≥ 37 weeks. Chi-square test (χ^2) shows that $\chi^2 = 0.100$ with $p = 0.752$ which means there is no relationship between gestational age and the incidence of PROM. The results of the distribution of body mass index in PROM group mostly came from the overweight / obesity group of 11 people (55%). In the non-PROM group, most came from the normoweight group, with 11 people (55%). Chi-square test (χ^2) shows that $\chi^2 = 0.400$ with $p = 0.527$ which means there is no relationship between BMI and the incidence of PROM.

Most samples does not have a history of smoking. 19 people (95%) did not smoke in

PROM group and 17 people (85%) did not smoke in non PROM. Fisher's Exact test showed $p = 0.605$ which means there is no relationship between smoking status and the incidence of PROM. There is 17 people (85%) in PROM group and 18 people (90%) in non-PROM do not have a history of urinary tract infections. Fisher's Exact test shows $p = 1.000$ which means there is no relationship between the history of UTI with the incidence of PROM.

Table 2. Characteristics of Culture Results Found in Vaginal Swabs

Microorganism	PROM		Non PROM	
	N	%	N	%
Escherichia coli	7	29.17		
Enterobacter cloacae	4	16.67		
Staphylococcus epidermidis	4	16.67	3	21.43
Klebsiella pneumoniae	2	8.33	1	7.14
Staphylococcus aureus	2	8.33	1	7.14
Staphylococcus saprophyticus	1	4.17	2	14.29
Raoultella ornithinolytica	1	4.17		
Enterobacter aerogenes	1	4.17		
Serratia odorifera	1	4.17		
Sternotrophomonas maltophilia	1	4.17		
Klebsiella oxytoca			3	21.43
Pseudomonas fluorescens			2	14.29
Pseudomonas oryzihabitans			1	7.14
Kluyvera spp			1	7.14
Total	24	100	14	100

In Table 2, 14 variants of microorganisms were found in vaginal swabs of pregnant patients with PROM and non-PROM from a total of 40 patients, namely gram-positive bacteria (Staphylococcus sarophyticus, Staphylococcus aureus, and Staphylococcus epidermidis), gram-negative bacteria (Enterobacter cloacae, Enterobacter aerogenes, Raoultella ausus, Raoultella ausus ornithinolytica, Klebsiella pneumoniae, Klebsiella oxytoca, Escherichia coli, Serratia odorifera, Kluyvera spp, Pseudomonas fluorescens, Pseudomonas oryzihabitans and Sternotrophomonas maltophilia). Most microorganisms found in vaginal swabs of pregnant patients with PROM were Escherichia coli (29.17%), as much 7 patients.

Table 3. Comparison of the Microorganisms with Duration of Rupture of Membranes

Microorganism	Duration of Rupture of Membranes			
	≤ 12 hours	%	>12 hours	%
Escherichia coli	6	40.00	1	11.11
Enterobacter cloacae	2	13.33	2	22.22
Staphylococcus aureus	2	13.33		
Raoultella ornithinolytica	1	6.67		
Staphylococcus epidermidis	1	6.67	3	33.33
Staphylococcus saprophyticus	1	6.67		
Enterobacter aerogenes	1	6.67		
Sternotrophomonas maltophilia	1	6.67		
Klebsiella pneumoniae			2	22.22
Serratia odorifera			1	11.11
Total	15	100	9	100

In table 3 we found that results comparison of the distribution of types of microorganisms in the PROM group based on the duration of rupture of membranes is divided into ≤12 hours and > 12 hours. The highest distribution in ≤12 hours came from *Escherichia coli*, 6 people (40%) followed by *Enterobacter cloacae* as many as 2 people (33.33%) and *Staphylococcus aureus* as many as 2 people (33.33%). While the distribution of microorganisms in PROM > 12 hours at most, namely *Staphylococcus epidermidis* 3 people (33.33%), *Enterobacter cloacae* 2 people (22.22%) and *Klebsiella pneumoniae* 2 people (22.22%).

The most number of *Escherichia coli* microorganisms were in PROM ≤ 12 hours as much as 6 cases (50%). Chi-square test (χ^2) shows that $\chi^2 = 2.967$ with $p = 0.849$ which means there is no relationship between the type of germ and rupture of membranes.⁷

Gram-negative bacteria (*Escherichia coli* and *Enterobacteriaceae*) are the most frequent organisms in the recto-vaginal area of the mother. Two studies conducted in the United States showed that *Escherichia coli* was associated with premature birth, especially giving birth before 34 weeks' gestation. Urinary tract infections by *Escherichia coli* have also been linked to preterm birth.⁸

DISCUSSION

In this study, the most common age distribution results were in the reproductive age group of 20-35 years. According to Surekha S. Mohan et al (2017), in a study of 358 pregnant women with PROM in India, young adults aged 20-30 years (50.1%) experienced the most PROM in pregnancy.⁴ This is consistent with the

results of the study this. Similarly, in Iran of 200 pregnant women with PROM, found infections occur on average at age 27.6 ± 2.3 years, 3 and in Uganda of 87 pregnant women with PROM, was found most at the age of 20-34.99 years (84%).⁹ Distribution of parity showed that primipara was more dominant in the PROM, this is in accordance in India of 120 pregnant women with PROM, the highest number was found in primigravida in 86 cases (71.16%).¹⁰

The results of the distribution of education in general are mostly in the middle school group. This is in accordance with research in India in 50 pregnant women with PROM obtained the most recent education on the matric which is a high school level of 20 people (40%). This is because Indonesia and India have the same socioeconomic level.¹¹

Education, socioeconomic and lack of hygiene, cultural factors, limited health facilities, unhealthy eating habits also play a role for the increased prevalence of infections in the vagina that can cause PROM.⁶

The distribution of gestational age at the time of rupture of membranes occur mostly from the pregnancy group ≥ 37 weeks. Research conducted in China comparing 577 (80.8%) women with term PROM and 137 (19.2%) women with preterm PROM stated that there were significant differences in intrauterine infection. Intrauterine infection is a mechanism that often causes premature birth. The mechanism by which intrauterine infection causes preterm labor is related to the activation of the immune system, which reflects four main pathogenogenic processes, activation of the hypothalamic-pituitary-adrenal axis in the mother and fetus, decidualechorioamniotic or systemic inflammation, decidual bleeding, and pathological distension of the uterus.¹²

In obesity hormonal imbalance can occur, so that it can cause a shift in the balance of the normal vaginal flora to pathogenic flora. Also in obesity there is an increase in vaginal moisture so that pathogenic bacteria that cause infections easily develop so that it facilitates spontaneous rupture of membranes. Six hundred and thirty three obese pregnant women with PROM found to experience chorioamnitis more frequently than non-obese patients ($p < 0.01$).¹³

The results of the distribution of smoking history of patients - the average patient does not have a history of smoking. This is consistent with the multicenter study conducted by Robert L. Andres et al (2014) in Utah, United States of

America saying that there is no relationship between smoking and the incidence rate of PROM.¹⁴

In this study, it was found that the most microorganisms found in vaginal swabs of pregnant patients with PROM were *Escherichia coli*. Research in Nigeria on vaginal swabs of pregnant women with PROM found that most bacteria were *Klebsiella* (32.1%) followed by *Escherichia coli* (19.6%).¹⁵ Research in Iran found the most bacteria in endocervical swab culture were *Escherichia coli* (24.2%), *Staphylococcus coagulase negative* (27.2%), *Enterococcus* and *Candida* (11.7%)³ and research in India, found the most bacteria were *E. E. coli* followed by *Staphylococcus aureus* and 1 (2%) growing *Candida* species.¹¹

Hormonal changes are a trigger for an increase in pH due to changes in the amount and thickness of vaginal secretions during pregnancy. Rapid pH changes, causing the vaginal acid-base balance to be disrupted and the rapid growth of normal and anaerobic microorganisms, resulting in an increase in phagocytic processes and the results of metabolism of microorganisms that can change vaginal albus fluorine found to be alkaline and trigger normal vaginal flora into parasites for cervical mucosa and vagina. This situation will change the quality of fluor albus and can be categorized as pathological fluor albus. Genital tract infection is one of the causes of PROM. One possible mechanism is ascending infection and replicating in the placenta, decidua and membrane.⁷ Of the vaginal swabs conducted in this study were found to be entirely normal vaginal flora. Most microorganisms found were *Escherichia coli*, *Enterobacter cloacae* and *Staphylococcus epidermidis*. Where *Escherichia coli* is a gram-negative microorganism that is non-pathogenic that is commonly found in the human intestine as well as *Enterobacter cloacae*. According to research in Iran that gram-negative bacteria (*Escherichia coli* and *Enterobacteriaceae*) are the most frequent organisms in the recto-vaginal area of the mother. Two studies conducted in the United States showed that *Escherichia coli* was associated with premature birth, especially giving birth before 34 weeks' gestation. Urinary tract infections by *Escherichia coli* have also been linked to preterm birth.¹⁶

CONCLUSION

Most microorganisms found in PROM are *Escherichia coli*, *Enterobacter cloacae* and *Staphylococcus aureus*. Most microorganisms found in non-PROM are *Klebsiella oxytoca*, *Staphylococcus epidermidis*, *Staphylococcus saprophyticus* and *Pseudomonas fluorescens*. There is no relationship between BMI, age, parity, smoking, and gestational age with the incidence of PROM in pregnancy in this study.

RECOMMENDATION

This study is to determine the pattern of microorganisms that exist in the vagina in pregnancy with PROM in Manado. Further research is needed with a larger sample size so that it can provide results that are closes to accurate in determining the pattern of microorganisms in the vagina in pregnancy with a PROM in Manado. This study found that most microorganisms in pregnancy with PROM, namely *Escherichia coli* where the transmission is often in contaminated food or unclean hands. Appeals are given to every pregnant woman to wash their hands before eating and maintain their personal hygiene in the genital area.

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Research Article

Interaction of Physical Activity and Body Mass Index with Age at Menarche

Interaksi Aktivitas Fisik dan Indeks Massa Tubuh dengan Usia Menarche

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Abstract

Objective: To investigate the interaction of physical activity and body mass index with age at menarche in Babun Najah Junior High School.

Methods: This was a cross sectional study. The sampling technique in this study is non-probability sampling by a total sampling.

Result: The results of the study were processed using the Chi-Square statistical test on 142 samples, obtained p-value = 0.748 ($p > 0.05$) for the relationship between physical activity and age at menarche, p-value = 0.048 ($p < 0.05$) for relationship between body mass index with age at menarche, and p-value > 0.05 for the interaction of physical activity and body mass index with age at menarche.

Conclusions: There is no interaction of physical activity and body mass index with age at menarche in Babun Najah Junior High School.

Keywords: body mass index, interaction, menarche age, physical activity.

Abstrak

Tujuan: Mengetahui interaksi aktivitas fisik dan indeks massa tubuh dengan usia menarche di Madrasah Tsanawiyah Swasta Babun Najah.

Metode: Jenis penelitian ini adalah observasional analitik dengan desain penelitian potong lintang. Teknik pengambilan sampel dalam penelitian ini adalah pengambilan sampel non probabilitas dengan metode total sampling.

Hasil: Terdapat hubungan antara indeks massa tubuh dengan usia menarche (p -value = 0,048), tidak terdapat hubungan antara aktivitas fisik dengan usia menarche (p -value = 0,784) serta tidak terdapat interaksi antara aktivitas fisik dan indeks massa tubuh dengan usia menarche (p -value $> 0,05$).

Kesimpulan: Tidak terdapat interaksi aktivitas fisik dan indeks massa tubuh dengan usia menarche di Madrasah Tsanawiyah Swasta Babun Najah.

Kata kunci: aktivitas fisik, indeks massa tubuh, , interaksi, usia menarche.

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Received:

Accepted:

Published:

INTRODUCTION

According to the World Health Organization, adolescence is a period of human growth and development that occurs after childhood and before adult with an age range of 10 to 19 years¹ The United Nations International Children's Emergency Fund (UNICEF) defines adolescents as those who have an age range of 10 to 14 years (young adolescents) who are experiencing a transition period from childhood to adulthood and need attention and protection² Based on The Ministry of Health of Republic Indonesian in 2009, adolescents classification becomes early

adolescence (12- 16 years) and late adolescence (17-25 years).¹ Physical activity of teenagers majority decreases every year along with the times, from playing outside the home a lot has shifted to being indoors such as playing games on smartphones, watching television, using computers instead of cycling, walking or exercising.³

Mild physical activity makes low energy expenditure resulting in an imbalance between incoming and outgoing energy. As a result, the remaining energy will be stored as fat and influence body mass index (BMI).^{3,4} Assessment of adolescent nutritional status is BMI according

to age, but before entering adolescence, a person experiences a puberty period first.^{2,5} Puberty is the growth and development that occurs gradually from secondary sex characteristics and the ability to reproduce.⁶ This puberty period will be an acceleration of growth and physical development from childhood to adulthood.⁵ This is characterized by the maturity of the reproductive organs such as psychological changes, rapid physical growth and secondary sex characteristics.⁵ In a girl, a sign of reproductive organ maturity is menarche.

Menarche is menstruation that occurs for the first time in a woman and is a sign of a young woman growing up and ready to become a complete woman, meaning that all of the woman's intimate organs are ready to reproduce.^{7,8} The age of menarche in each individual varies, where the age range of 11-15 years is the normal range.⁵

In the mid-19 century, the age of menarche was 16-17 years and decreased by 4-5 years in the middle of the 20th century in the age range < 13 years.^{9,10} The average age of menarche in Portugal, Italy, Spain, Venezuela, and England for women born in 1880-1890 was 15 years, but adolescents born in 1970-1980 are 12,03 years.⁷ Studies in this decade have suggested a remarkable decrease in age at menarche.¹¹ Studies in Europe reported a significant decrease from the mean age of menarche, from 13,66 years to 13,05 over 50 years.¹¹ In the United States, early menarche (< 11 years) increased from 4% to 11,8% in 50 years, while in Indonesia in 2010, the average age of menarche among girl was 12,96 years.^{9,11}

Age of menarche describes several health aspects of a population, and can also represent a potential health risk if it deviates from the normal value of menarche it self.⁷ Recent studies reported that the age of menarche can affect the risk of some diseases as adults, such as an increased risk of cardiovascular disease, gestational, cancer, and psychological disorder.¹¹⁻¹³

Many factors influence the age of menarche, such as genetics, geography, eating habits, physical activity, socio-economic status, environmental conditions, body mass index (BMI), and even climate.^{8,11} BMI was statistically inversely related to age at menarche.¹¹ The results of a study found that there was a very significant relationship between BMI and age of menarche, the girl with overweight menstruated earlier than women who had normal and underweight BMI.^{14,15}

Physical activity also affects the onset of puberty and the age delay of menarche in women who are exposed to intense physical exercise during childhood and adolescence.¹¹ A study stated that there was a significant relationship between physical activity and age of menarche, namely a meta-analysis of 12 athletes / non-athletes showing that female athletes experienced menarche 1.13 years later than non-athletes.¹⁶ Although physical activity and BMI are separately associated with menarche age, the interaction between physical activity and BMI with menarche age is still less to be discussed. Reported that there was an interaction between physical activity and BMI with the age of menarche.¹¹ It is against this background that researchers are interested in researching the Interaction of Physical Activity and Body Mass Index with Menarche Age in Babun Najah Private Madrasah (MTsS), where junior high school students have an age range of 12 to 15 years.

METHODS

This study used an observational analytic research method with a cross-sectional approach to determine the interaction between physical activity and body mass index with the age of menarche at Madrasah Tsanawiyah Swasta Babun Najah. This research was conducted from October to November 2020. Data were collected from 26 October to 10 November 2020. The sampling of this study used non-probability sampling with a total sampling method in which the research sample was obtained based on inclusion and exclusion criteria, which was 142 students. The instrument used in this study was the International Physical Activity Questionnaire short form (IPAQ) questionnaire specifically for adolescents and measuring body weight and height to assess body mass index.

Data analysis was using univariate and bivariate methods. The characteristics of respondents based on age, class, socioeconomic, physical activity, body mass index, and age of menarche were using the univariate test. The chi-square used bivariate test to determine the relationship between physical activity and age at menarche, the relationship between body mass index and age at menarche, and the interaction between physical activity and body mass index and age at menarche at MTsS Babun Najah.

RESULTS**Table 1.** Characteristics of the sample among Babun Najah Junior High School

Response Characteristics	Total	%
Age (years)		
11	3	2.1
12	36	25.4
13	54	38.0
14	47	33.1
15	2	1.4
Grade		
7	40	28.2
8	51	35.9
9	51	35.9
Socio-economics		
Low	26	18.3
Moderate	88	62.0
High	28	19.7
Physical Activity		
IPA	20	14.1
SMPA	37	26.1
SVPA	85	59.9
Body Mass Index		
Very thin	1	0.7
Thin	3	2.1
Normal	90	63.4
Overweight	33	23.2
Obese	15	10.6
Age at menarche		
Have not	22	15.5
Early	18	12.7
Normal	102	71.8

SVPA = sufficient vigorous physical activity; SMPA = Sufficient moderate physical activity; IPA= insufficient physical activity.

Table 3. Interaction of Physical Activity and Body Mass Index with Age at Menarche

BMI	Physical Activity	Age at Menarche				Total		Total
		< 11 years		≥ 11 years		n	%	
Normal	IPA	n	%	n	%	n	%	0.320
	SMPA	0	0	10	100	10	100	
	SVPA	4	15.4	22	84.6	26	100	
Over-weight	IPA	3	7.7	36	92.3	39	100	0.448
	SMPA	3	42.9	4	57.1	7	100	
	SVPA	2	25	6	75	8	100	
		6	20	24	80	30	100	

SVPA = sufficient vigorous physical activity; SMPA = Sufficient moderate physical activity; IPA= insufficient physical activity.

DISCUSSION

Bivariate analysis using Chi-square test showed $p = 0.784$ ($p > 0.05$). The results explain that physical activity does not affect the age of menarche in young women. The results are not in line with several previous studies, a cross-sectional and multistage sampling study conducted in 2013 on 660 adolescents found that low menarche age was independently associated with high calorie and protein consumption and low daily physical

Table 2. Relationship between Physical Activity and Age of Menarche

IPAQ*	Age at Menarche						P-value
	< 11 years		≥ 11 years		Total		
	n	%	n	%	n	%	
IPA	3	17.6	14	82.4	17	100	0.784
SMPA	6	17.6	28	82.4	34	100	
SVPA	9	13	60	87	69	100	

SVPA = sufficient vigorous physical activity; SMPA = Sufficient moderate physical activity; IPA= insufficient physical activity.

activity.¹⁷ As well as research on overweight and physical activity on menarche age in 2014 on 62 young women, it was reported that there was a significant relationship between physical activity and age of menarche, in which young women with high physical activity experienced menarche longer than girls with low physical activity.¹⁸ This study was supported by research conducted in 2018 on 124 female students who stated that there was no significant relationship between physical activity and age of menarche.¹⁹

Research in Iran in 2017 also reported that there was no relationship between physical activity and menarche.²⁰

Physical activity does not directly affect the age of menarche, but physical activity has a secondary effect on the hypothalamus-pituitary axis through its effect on changes in body mass index.²¹ Heavy physical activity, intense and makes mental stress can slow down the age of menarche, but daily physical activity does not affect the age of menarche.²² Research on 65 female students in Jambi City had a significant relationship between physical activity and age of menarche, this is presumably because the majority of physical activities carried out by respondents were daily physical activities, not physical activities such as sports, but rather activities, extracurricular activities, where the effect of regular and intense exercise is more significantly related to slowing the age of menarche than daily physical activities.²³

Bivariate analysis using Chi-square test showed $p = 0.048$ ($p \leq 0.05$). The Odds ratio value obtained is 2.619 (1.094 - 6.268), then the $OR > 1$ is obtained. The Odds Ratio is 2.619 means that students with a BMI of overweight and obesity tend to experience early menarche by 2.619 or 2 times greater than students who have a normal, underweight BMI. These results are in line with a 2014 study of 15,005 adolescent girls with an age range of 12-18 years, that BMI had a significant relationship with the age of menarche where someone who had an overweight BMI tended to early menarche.²¹ A 2020 study of 5,863 young women reported that the age of early menarche was related to the BMI value of adolescents who were classified as overweight BMI.²⁴ The majority of studies regarding the association of BMI with menarche age have a significant correlation, this related study in 2017 on 2000 adolescents with an age range of 9 to 18 years had significant results between BMI and age of menarche.²⁵ Research in 2018 on adiposity markers and their relationship with age at menarche with 400 respondents found that women with a high BMI, high waist-to-hip ratio, and high waist ratio are at risk of experiencing early menarche.²⁶ A study in 2018 on the mediation analysis and randomization of Mendel regarding birth weight, time-varying adiposity, and early menstruation in women found that levels of the protein hormone derived from adipocyte leptin were higher in individuals with high BMI.²⁷

Interaction of physical activity and body mass index with age at menarche in female students of MTsS Babun Najah, using the Chi-Square statistics obtained p value > 0.05 . So it can be concluded that there is no interaction between physical activity and body mass index with the age of menarche to students at MTsS Babun Najah. The result of this study is not in line with the research which was carried out in 2017 which is the first study examining the combined effects of physical activity and BMI with the age of menarche in China, it is reported that there is significant results regarding the interactions of physical activity and BMI with the age of menarche, this is because BMI has a negative correlation with age at menarche which can be modified with the physical activity done by teenagers, it means when the adolescents' physical activity is classified as insufficient, it will affect the value of the BMI tend to be overweight so it gives impact on adolescent menarche age.¹¹

However, daily physical activity is not has a great influence in modifying BMI values, based on research conducted in 2018 for respondents aged 13-15 years who noted overweight on BMI have vigorous physical activity seen from their extracurricular activities in their school. Meanwhile, students who are having a thin BMI tend to have insufficient physical activity, seen from one who noted overweight on BMI has insufficient physical activity. On the other hand, not everyone with a thin BMI has vigorous physical activity. So that the term insufficient physical activity is not always associated with the value of an overweight BMI or obese.²⁸

Research found that vigorous physical activity, continuously, and mentally stressful activity can slow down the age of menarche, however, daily physical activity is not affecting the age of menarche.²² Thus, when there is an interaction between vigorous physical activity, continuously, and mentally stressful activity with the adolescents' body mass index, it affects the age of menarche. This is because BMI has a negative correlation to the age of menarche, while vigorous physical activity, continuously, and mentally stressful activity have a correlation which is directly proportional to the age of menarche.^{22,24}

CONCLUSION

Based on the results of this study, it can be concluded that the average menarche age of students at MTsS Babun Najah is 11.5 years old (which is classified as normal) with majority of students' physical activity is classified as vigorous physical activity and there is no relationship between physical activity and the age of menarche in MTsS Babun Najah. Most of students' Body Mass Index were at normal BMI (63.4%) and there is a relationship between body mass index with the age of menarche to students at MTsS Babun Najah. There is no interaction between physical activities and body mass index with the age of menarche to students at MTsS Babun Najah.

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Research Article

Risk Factors of Postpartum Urinary Retention

Faktor Risiko Retensio Urine Pascasalin

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Abstract

Objective: To determine the correlation between risk factors and the incidence of postpartum urinary retention (PUR) at RSUP Dr. Mohammad Hoesin Palembang.

Methods: Analytical observational study with cross sectional design to find out the correlation between risk factors and incidence of PUR at emergency room, delivery room and ward at dr. Mohammad Hoesin General Hospital Palembang since October 2018 to April 2019. There were 82 samples that met inclusion criteria. The correlation between risk factors and the incidence of urinary retention was analyzed using Chi Square test/ Fisher Exact test, and the most important risk factor was determined using the Logistic Regression test. Data analysis used SPSS version 22.0.

Result: In this study, it was found that there was a significant relationship between prolonged second stage of labor (PR=40.75, $p=0.000$), type of labor (PR=9.028 CI 95% 2.114–38.558; $p=0.004$) and perineal laceration (PR=12.938 CI95% 1.872–89.414; $p=0.016$) with PUR. However, there was no significant relationship between age, parity, neonatal birth weight, episiotomy, vulvar edema and urinary retention ($p>0.05$). It was concluded that instrumental delivery had a significant effect on the incidence of urinary retention (PR=13,541 CI95% 2.381–77.018, p value=0.003) by using logistic regression test.

Conclusions: The most important risk factor of urinary retention was instrumental delivery.

Keywords: instrumental delivery, perineal laceration, postpartum urinary retention, type of labor.

Abstrak

Tujuan: Untuk mengetahui hubungan antara faktor risiko dan kejadian retensio urin pascasalin di RSUP Dr. Mohammad Hoesin Palembang.

Metode: Penelitian observasional analitik dengan desain potong lintang untuk mengetahui hubungan antara faktor risiko dan kejadian retensio urin pascasalin di IGD, kamar bersalin dan bangsal perawatan RSUP Dr. Mohammad Hoesin Palembang sejak Oktober 2018 sampai April 2019. Didapatkan 82 sampel yang memenuhi kriteria inklusi. Hubungan antara faktor risiko dan kejadian retensio urine dianalisis menggunakan uji Chi Square/Fisher Exact, sedangkan untuk mengetahui faktor risiko yang paling berperan menggunakan uji regresi logistik. Analisis data menggunakan SPSS versi 22.0.

Hasil: Pada penelitian ini, didapatkan hubungan yang signifikan antara lama kala II (PR=40,75, $p=0,000$), jenis persalinan (PR=9,028 IK95% 2,114–38,558; $p=0,004$), laserasi perineum (PR=12,938 CI95% 1,872–89,414; $p=0,016$), dan retensio urine pascasalin. Namun, didapatkan hubungan yang tidak signifikan antara usia, paritas, BBL bayi, episiotomi, edema vulva, dan kejadian retensio urin ($p>0,05$). Dengan uji regresi logistik, didapatkan kesimpulan bahwa jenis persalinan dengan instrumen berpengaruh secara signifikan terhadap kejadian retensio urin (PR = 13,541 IK95% 2,381–77,018, p value = 0,003).

Kesimpulan: Faktor risiko yang paling berperan terhadap kejadian retensio urin pascasalin adalah persalinan dengan instrumen.

Kata kunci: jenis persalinan, instrumen, laserasi perineum, retensio urin pascasalin.

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INTRODUCTION

Postpartum urinary retention (PUR) is a common condition that is often complained by postpartum women during fourth stage of labor.¹ It is the inability of the bladder to empty urine spontaneously within 6 hours postpartum or 6 hours after the release of the bladder catheter after cesarean section.² The prevalence of PUR varies depending on the risk factors that might cause urinary retention, including instrumentation used during the delivery process, duration of labor, epidural analgesia agent, episiotomy, neonatal birth weight and nulliparity. The pathophysiology of PUR is due to the influence of elasticity of the entire urinary tract seems to increase during pregnancy, especially the hormonal effects that can reduce detrusor muscle tone.³

The prevalence of PUR varied, ranging from 1.5–45% of postpartum mothers.⁴ Approximately 3.38–24.1% of them are mothers who were in labor.⁵ The rate of urinary retention after the cesarean section at RSMH Palembang in 2012 was 3.6% with the length of comparison more than 24 hours and primiparity was an influential risk factor.⁶ At RSCM, the prevalence of PUR was as much as 14.8% and the incidence of PUR was 26.7%. The incidence of PUR in Ulin Hospital Banjarmasin in 2002–2003 by 0.38% in which 11 PUR cases from 2850 labors such as 737 cesarean sections (25.85%), 1,891 spontaneous deliveries (66.35%) and 222 vacuum extractions (7.78%).⁷⁻⁹

Chronic PUR was a serious condition that required integrated management to prevent maternal morbidity such as urosepsis. Because catheter placement persisted in postpartum mothers could increase the risk of urinary tract infection, it was necessary to identify the factors that affected urinary retention. It was useful to help pregnant women get normal urination postpartum by early intervention and appropriate postpartum management.¹⁰

Postpartum urinary retention was often diagnosed late and was found 3–5 days postpartum. This happened because birth attendants, both doctors and midwives, did not know about PUR even though there were risk factors for these patients. Therefore, early detection of PUR was needed to prevent complications and delayed in handling.

This study aims to determine the parameters of PUR risk factors in pregnant women who underwent vaginal delivery at Dr. RSUP. Mohammad Hoesin Palembang. Besides that,

there was information about the risk factors of PUR in vaginal delivery and appropriate management that can reduce the number of deaths and complications. Moreover, this research had not been performed before at our hospital.

METHODS

The observational analytical study with a cross sectional design was conducted to determine the relationship between the risk factors and postpartum urinary retention at emergency room, delivery room and ward at Dr. Mohammad Hoesin General Hospital Palembang since October 2018 to April 2019. There were 82 samples that met the inclusion criteria. The relationship between risk factors and the incidence of urinary retention was analyzed using Chi Square test / Fisher Exact. Besides that, we used Logistic Regression test to determine the most important risk factors. Data analysis used SPSS version 22.0.

RESULTS

There were 11 patients with urinary retention (13.4%) and 71 patients without urinary retention (86.6%). The mean age of respondents with urinary retention was 29.36 ± 4.05 years, while the average age of respondents without urinary retention was 28.69 ± 6.31 years. The statistical test showed that there was no difference in age ($p=0.737$) between respondents with and without urinary retention.

Most patients were multigravid in both groups. Moreover, there was no difference in the number of pregnancies between respondents with and without urinary retention ($p=0.736$). In this study, there was no patient with urinary tract infection during pregnancy in either urinary retention group or without urinary retention.

The average score of respondents with urinary retention was 37.36 ± 8.36 while the mean score respondents without urinary retention was 13.09 ± 13.58 . By using statistical tests, there were differences in age ($p=0.000$) between both groups. The score of respondents with urinary retention was greater than the score of respondents without urinary retention.

Based on scoring, patients with a possibility of urinary retention were 72.7% in the urinary retention group and only 22.5% in the group without urinary retention. From the Fisher Exact test, it was concluded that there was a significant correlation between the possibility of urinary

retention based on scoring and the incidence of urinary retention. Mother with the possibility of urinary retention was 9.167 times more prone to have significant PUR (OR = 9.167 CI95% 2.174–38.649; p=0.000).

In this study, there were 18,2% patients with age ≥ 35 years in the urinary retention group and 16.9% in the group without urinary retention. From the Fisher Exact test, it was concluded that there was no significant correlation between age and PUR, mothers with age ≥ 35 years were 1.093 times more prone to have urinary retention but it was not significant (OR = 1.093 CI95% 0.209–5.707; p=1.000).

Besides that, multiparity was 45.5% in the urinary retention and 31% in the group without urinary retention. By using Chi Square test, there was no significant correlation between parity and PUR. Multiparity was 1.856 times more prone to experience urinary retention but it was not significant (OR=1.856 CI95% 0.511–6.736; p=0.545).

There were 9% of patients with macrosomia infants in the PUR group and 1.4% in the group without urinary retention. Moreover, there was no significant correlation between neonatal birth weight and PUR. Women with macrosomia babies were 7 times more risky towards PUR but it was not significant (OR=7.000 CI95% 0.405–121.003; p=0.252).

Patients with prolonged second stage of labor were 36.4% in the urinary retention group and were not found in the group without urinary retention. By using Fisher Exact test, there was a significant correlation between the length of the second stage and PUR. Mothers with prolonged second stage were 40.57 times experiencing PUR (OR=40.57; p=0.000).

In addition, patients with episiotomy were 63.6% in the urinary retention group and 49.3% in the group without urinary retention. There was no significant correlation between episiotomy and PUR, mothers with episiotomy were 1.8 times more prone to urinary retention but it was not significant (OR=1.800 CI95% 0.484–6,695; p=0.520). In this study, the instrumental labors were as much as 45.5% in urinary retention group and 8.5% in the group without urinary retention. There was a significant correlation between the type of labor and PUR, the instrumental labors contributed nine times experiencing urinary retention (OR=9.028 CI95% 2.114–38,558; p=0.004) (Table 1).

Table 1. The Correlation between Type of Labor and PUR

Characteristics	Urinary Retention		Total	PR * (95% CI)	P-value*
	Yes	No			
Type of Labor					
Instrumental	5	6	11	9.028	0.004 (2.114–38.558)
Spontaneous	6	65	71		
Total	11	71	82		

* Chi Square test, p = 0.05

In this study, there were 9.1% of patients with vulvar oedema in the urinary retention group and were not found in the group without urinary retention. By using Fisher Exact test, there was no significant relationship between vulvar oedema and PUR. Women with vulvar oedema were 7.1 times more risky towards urinary retention but it was not significant (OR=7.100; p=0.134). There were 27.3% patients with perineal lacerations in the urinary retention group and 2.8% in the group without urinary retention.

Table 2. The Correlation between Perineal Lacerations and PUR

Characteristics	Urinary Retention		Total	PR * (95% CI)	P-value*
	Yes	No			
Perineal lacerations					
Yes	3	2	5	12.938	0.016 (1.872–89.414)
Not	8	69	77		
Total	11	71	82		

* Fisher Exact Test, p = 0.05

It was concluded that there was a significant relationship between perineal lacerations and PUR, women with perineal lacerations were 12.9 times more significantly risky towards urinary retention (OR = 12.938 CI95% 1.872–89.414; p=0.016) (Table 2).

From table 3, type of labor had a significant effect on the incidence of urinary retention. Labor using instrument affected women more prone to urinary retention 13.541 times compared with spontaneous labor significantly (PR=13.541 CI95% 2.381–77.018, p value=0.003).

Table 3. Bivariate and Multivariate Analysis of Urinary Retention Risk

Variable	Bivariate *		Multivariate *	
	PR	P-value	PR	P-value
Types of labor	9.028	0.004	13.541	0.003
Perineal laceration	12.938	0.016	4.089	0.361
Duration of second stage of labor	40.57	0.000	1.465	0.999
Vulvar oedema	7.100	0.134	0.632	1.000

* Logistic Regression Test

DISCUSSION

Postpartum urinary retention is defined as the inability of the bladder to void spontaneously within 6 hours after vaginal delivery or 6 hours after the release of the bladder catheter after cesarean section.² The prevalence of PUR varied, ranging from 1.5–45% postpartum mothers.⁴ In this study, the prevalence of PUR in postpartum mothers were 13.4%. The results of this study was similar with the research at RSCM where the prevalence of PUR was 14.8%.⁷ However, this result was greater than the research at RSMH Palembang which was 3.6%.⁶ Meanwhile, the rate of PUR was greater than this study which was 26.7%.⁸ In this study, the mean age of patients with PUR was 29.36 ± 4.05 years of age. This result was similar, which found that the average age of PUR patients was 27.79 ± 7.18 years of age. In addition, we found that the average age of patients with PUR was 27.90 ± 6.69 years of age.

Increasing age caused the decreased ability and function of the muscles of the urinary system due to degeneration followed by decreased renal function. Structural or functional abnormalities due to aging can block bladder emptying and the increased risk of urinary tract infection. In this study, the average age of respondents ranged from 20–35 years of age. In this age, the urinary muscles are still well-functioned. Even though labor trauma occurs, the mass and strength can return to normal immediately with exercise. Trauma in labor will reduce bladder muscle strength, but muscle tone will soon be restored in healthy young women. However, those in the group without urinary retention are at the same mean age. By using bivariate analysis, it showed that no association between age and of urinary retention in this study.

In this study, most patients with PUR were nulliparity (54.5%). This result is slightly different, where most of parity in patients with PUR were multiparity (59.7%). We found that most patients with PUR were multiparity 56.9%. During labor, there was trauma to the urethra and bladder due to suppression of the fetal head. Not only the bladder wall, but also urethra, and external meatus were also hyperemia and edema. Trauma in urinary muscles causes interference with reflexes and urge urination. In this study, although the percentage of PUR in nulliparity was higher, from bivariate analysis, there was no relationship between parity and PUR. In the non-PUR group,

we also found a greater percentage of nulliparity (69.0%).

In the PUR group, there was 9.1% macrosomia infants (birth weight ≥ 4000 g), while in the group without PUR, we obtained 1.4% macrosomia infant. The statistical analysis showed that patients with macrosomia infants were 7 times more likely to undergo PUR compared with mothers with non-macrosomia infants (birth weight $< 4,000$ g). This result was in line, which found that patients with macrosomia infants were 13.99 times more likely to undergo PUR compared with mothers with non-macrosomia infants ($p < 0.001$). The larger the infant's birth weight was, the greater the urinary tract and urethral pressure were when the head went down. This would cause bladder trauma which increased the risk of urinary retention. Excessive stretching of the bladder or prolonged fetal head pressure could cause a reduction in bladder stimulation because the nerves and motor impulses could be disrupted.

The pressure of the fetal lower part at the pelvic floor could affect the nerve plexus in the pelvic soft tissue. This caused tissue edema or detrusor muscle dysfunction due to neuropraxia, resulting in PUR.¹¹ Prolonged labor was considered to have a significant relationship with the incidence of PUR. This was caused by the suppression of the fetal head on the pelvic floor, especially during labor with prolonged second stage of labor.¹² In this study, patients with prolonged second stage (> 2 hours) risked 40 times to undergo PUR compared with labor less than 2 hours. This result is in line where patients with prolonged second stage of labor were found to be 16 times more likely to undergo PUR.

The results of this study showed that patients with episiotomy had a risk of 1.8 times having PUR compared with patients without episiotomy, but these results were not statistically significant. In addition, patients with episiotomy were 2.468 times more likely to have PUR compared with patients without episiotomy, but the difference in the Emilia study was statistically significant ($p = 0.013$). The results of patients with an episiotomy was 5.250 times more likely to have PUR compared with patients without episiotomy ($p = 0.022$). Episiotomy suturing was associated with pain which caused disruption of bladder sensitivity and central inhibition of bladder function.¹³

Labor with instruments was a significant risk factor of PUR (PR=3.44). It could affect the ability of the urethral sphincter and surrounding

areas for relaxation, so the detrusor contraction strength could increase to exceed the urethral lumen pressure. In addition, labor with the instrument caused perineal oedema or vesical trauma.¹⁴ Patients with instrumental labor were 9 times more likely to have PUR compared with patients undergoing spontaneous labor without instruments. Labor with instrument was a risk factor for overt type of PUR which was statistically significant (PR=4.5).¹⁴

In this study, women with vulvar oedema were 7.1 times more risky towards having urinary retention but it was not statistically significant. Moreover, vulvar edema was 1.015 times more likely to undergo urinary retention but it was not statistically significant ($p=0.943$). Urethral and perineal edema can increase the risk of PUR due to increased urinary flow resistance due to obstruction and damage to the pudendal nerve. Vaginal delivery can directly cause damage to the pudendal nerve and / or cause changes in the connective tissue around the nerve. The pudendal nerve supplies the external urethral sphincter. Axon regeneration can improve nerve conduction, so that injuries occurred are not permanent.

In vaginal delivery, there is direct trauma to the pelvic floor muscles and nerve innervation found in the birth canal resulting in a decreased bladder sensibility. In further cases, peri-urethral and vulvar oedema occur causing obstruction-type PUR. Another hypothesis is that hormonal changes could also change bladder function during pregnancy and puerperium. In patients with PUR, there was an increase in progesterone level. The progesterone hormone has an inhibitory effect on the smooth muscle of the bladder. This results in shortening of the interval between contraction of the bladder muscle cells, decreased emptying of the average volume and increasing residual volume. In the vaginal delivery, there was a decrease in bladder muscle sensation and smooth tone that can increase the risk of PUR. After vaginal delivery, bladder becomes less sensitive towards the effect that becomes increasingly distended bladder.¹⁵

There are several risk factors of PUR including perineal lacerations, prolonged second stage of labor, instrumental labor, and the use of narcotic analgetics.¹⁶ Urethral and perineal edema can increase the risk of PUR due to increased urine flow resistance due to obstruction and damage

to the pudendal nerve. Vaginal labor can directly cause damage to the pudendal nerve and/or cause changes in the connective tissue around the nerve. The pudendal nerve supplied the external urethral sphincter. Axon regeneration can improve nerve conduction, so that injuries were not permanent.

In this study, mothers with perineal lacerations were 12.9 times more likely to urinary retention than mothers without perineal lacerations. These results are in line which showed that patients with perineal lacerations had a risk of 3,766 PUR compared with patients without perineal lacerations ($p = 0,007$). It was found that patients with perineal lacerations had 12.8 times risk of PUR compared with patients without perineal lacerations ($p<0.001$).¹³ The PUR prediction scoring system can reduce morbidity and mortality due to urinary retention and reduce the risk of postpartum bleeding. In this study, there were differences in scores between patients with PUR and patients without PUR. The scoring system of patients with urinary retention was greater than patients without urinary retention, and the possibility of urinary retention based on predictive urinary retention scores associated with urinary retention. Based on scoring, patients with possible urinary retention is 9 times the risk of having PUR, so this scoring system can predict the occurrence of PUR.

With multivariate analysis, the most important risk factors of PUR were the type of labor, the instrumental labor patients was 13.5 times more risky to have PUR significantly compared with patients undergoing spontaneous labor without instruments ($p=0.033$). In addition, the results of perineal lacerations and length of second stage of labor more than 2 hours were found to be at risk of PUR but it was not statistically significant ($p>0.05$).

CONCLUSION

The incidence of PUR were 13.4 %. There are several risk factors of PUR, namely instrumental labor, severe perineal laceration, and length of second stage of labor more than 2 hours. Based on scoring, patients with possible urinary retention are 9 times more likely to have PUR, so this scoring system can predict the occurrence of urinary retention.

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Case Report

Diagnosis and Management of Severe Peripartum Cardiomyopathy

Diagnosis dan Manajemen Kardiomiopati Peripartum Berat

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Abstract

Objective: To describe the diagnosis and management of severe peripartum cardiomyopathy.

Methods: A case report.

Case: A 35-year-old woman presented with dyspnea and leg edema. The patient gave birth 3 months ago. The hemodynamic was unstable and the physical examination showed a mild rhonchi in the basal of the lung and pansystolic murmur in the apex. Echocardiography showed a dilated heart chamber and reduced ejection fraction (30%). The patient was diagnosed as severe PPCM. The initial management was to stabilize the patient using furosemide, catecholamine, and vasopressor administration. After the patient's condition was stable, ramipril, bisoprolol, and bromocriptine were given as heart failure therapy.

Conclusions: Patient with suspicion of PPCM should be managed thoroughly from detailed history taking to proper diagnostic testing such as echocardiography. Prompt treatment of severe PPCM according to the guideline will improve the cardiac function.

Keywords: catecholamines, echocardiography, peripartum cardiomyopathy, pregnancy, vasopressor.

Abstrak

Tujuan: Untuk mendeskripsikan mengenai diagnosis dan manajemen pasien pada kasus kardiomiopati peripartum yang berat.

Metode: Laporan kasus.

Kasus: Seorang Perempuan 35 tahun datang dengan dispnea dan edema tungkai. Pasien melahirkan 3 bulan lalu. Hemodinamik tidak stabil dan pemeriksaan fisik menunjukkan ronki ringan di basal paru dan murmur pansistolik di apeks. Ekokardiografi menunjukkan dilatasi ruang jantung dan fraksi ejeksi berkurang (30%). Pasien didiagnosis dengan PPCM berat. Penatalaksanaan awal adalah menstabilkan pasien dengan pemberian furosemid, katekolamin, dan vasopresor. Setelah kondisi pasien stabil, diberikan ramipril, bisoprolol, dan bromokriptin sebagai terapi gagal jantung.

Kesimpulan: Pasien dengan kecurigaan PPCM harus dikelola secara menyeluruh mulai dari anamnesa yang rinci hingga uji diagnostik yang tepat seperti ekokardiografi. Pengobatan segera untuk PPCM derajat berat yang sesuai dengan pedoman akan meningkatkan fungsi jantung.

Kata kunci: ekokardiografi, kardiomiopati peripartum, katekolamin, kehamilan, vasopresor.

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Received: October 28, 2020

Accepted:

Published:

INTRODUCTION

Peripartum cardiomyopathy (PPCM) is a rare condition that could be life-threatening. It is characterized by a disruption in systolic phase and the presence of sign and symptoms of heart failure at the end of pregnancy and first 5 months after the delivery process, with left ventricular ejection fraction (LVEF) <45%.¹ PPCM is different from other heart failure. Diagnosis of PPCM is made after excluding any other possible causes

of heart failure (pregnancy-related myocardial infarction and pre-existing heart disease).²

The incidence of PPCM differs in numerous countries. In USA, the overall incidence from 2004 to 2011 was about 1 in 968 live births.³ Nigeria and Haiti reported a higher incidence; 1 in 100 pregnancies and 1 in 300 pregnancies respectively.⁴ The study about PPCM incidence in Asia is lacking. However, a study showed that the incidence of PPCM was about 1 in 3.790 live births.⁵ Heart dysfunction in PPCM may cause

complications that range from mild (shortness of breath and swelling of the leg) to severe (cardiogenic shock and death). The mortality rates of PPCM was reported to be as high as 30% worldwide.⁴ Risk factors for PPCM may vary from hypertensive disorders, older age during pregnancy, and also African population.¹

Although the definition and diagnostic criteria of PPCM is already available, PPCM may present a challenge for physician in clinical settings because of the nonspecific signs and symptoms that could be similar to the physiologic changes in pregnancy. Therefore, it is important to evaluate pregnant/post-partum woman with heart failure symptoms.⁴ The purpose of this case report is to share the knowledge about how to diagnose and treat patients with severe PPCM based on our experience in managing 35-years-old woman with PPCM.

CASE

A 35-year-old woman came to the emergency room, with shortness of breath and leg edema in the last 3 months after given birth to her first baby. She reported that the shortness of breath was exacerbated by activity. She did not check herself to the doctor earlier because she thought that this was normal in pregnancy. There was no similar symptom and no history of hypertension during the pregnancy. The patient looked ill with GCS E4V5M6. The initial examination for vital signs were notable with blood pressure of 86/50 mmHg, heart rate of 110 beats/minute, respirations of 28x/minute, and oxygen saturation of 95% on room air. The patient did not have fever.

As an initial management, we gave oxygen to the patient 3 liter/minute with nasal canule. Through the physical examination, we found a grade 4 pansystolic murmur at the apex. We also found mild rhonchi at the basal of the lung. We conducted an electrocardiography on the patient. The result showed a sinus tachycardia with heart rate of 125 beats/minute with right axis deviation. There was also an inverted T wave at III, V5, V6, and aVF. The ECG also showed a right atrial dysfunction, left atrial enlargement, and incomplete left bundle branch block (LBBB). Ventricular extrasystole was also found at lead I and III (figure 1). Blood test was done and the result showed a shift-to-the right leukocyte count. The electrolyte evaluation showed a mild hyponatremia (131 mmol/L), hyperchloride (109

mmol/L), and hypocalcemia. The urinalysis was negative for proteins.

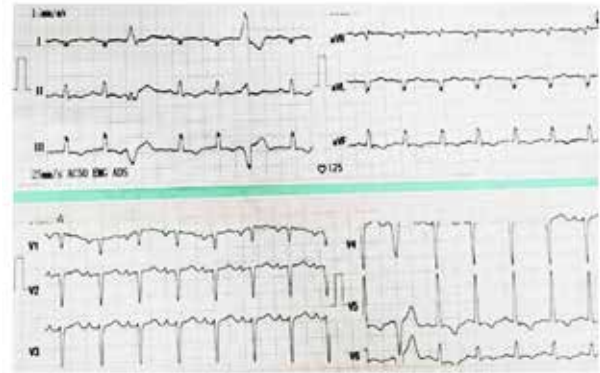


Figure 1. ECG of the patient showed T-wave inversion at III, V5, V6, and aVF right atrial dysfunction, left atrial enlargement, and incomplete left bundle branch block (LBBB), and ventricular extrasystole at I and III

We decided to perform echocardiography to evaluate the heart of the patient. The left ventricular internal diameter end diastole (LVIDd) was 5.71cm and the left ventricular internal diameter end systole (LVIDs) was 4.53cm, suggestive of an increased diameter of the left ventricle (figure 2). The mitral valve showed a moderate to severe regurgitation and the tricuspid was mild to moderate regurgitation, supported by Doppler examination. The patient had a reduced LVEF (30%). Echocardiography prior to pregnancy, the LVEF was normal (61%) with mild mitral regurgitation due to mitral valve prolapse. From the result of thorough examination, the diagnosis of severe peripartum cardiomyopathy was made.

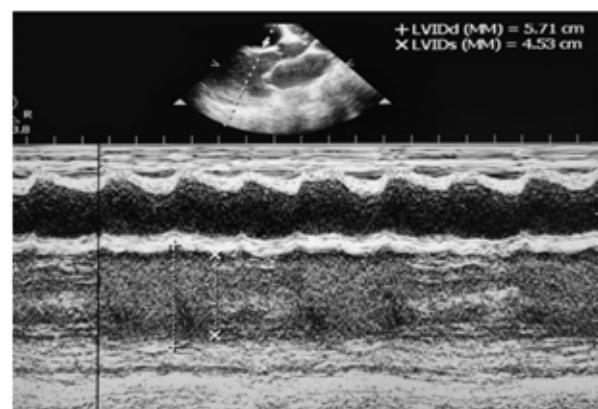


Figure 2. Echocardiography showed a dilated left ventricle.

After diagnosing the patient with severe PPCM because of the hemodynamic instability, we initiated the treatment with furosemide IV drip, followed by the administration of dobutamine. We also corrected the hypocalcemia

with calcium gluconate IV. However, no improvement can be seen in the patient, so that we added norepinephrine. The administration of norepinephrine improved the hemodynamic of the patient. The patient was monitored closely and her condition kept on improving until declared stable. The patient was prescribed with oral bromocriptine, ramipril, and bisoprolol. She was then discharged from the hospital after three days of treatment and was being monitored in outpatient clinic.

DISCUSSION

The diagnosis of PPCM is a diagnosis of exclusion. The physician needs to exclude other etiologies of heart failure in the patient. Initial history taking is essential to collect the data of any pre-existing cardiac dysfunction, whether during or before the pregnancy. Patients with PPCM may present with dyspnea, orthopnea, edema, palpitation, and impairment of activity.⁶ To establish the diagnosis, the physician should conduct an echocardiography examination. ECG can also be performed at the beginning.

ECG is an easily accessible and safe tool to evaluate the patients. Several patterns could appear such as inversion of T-wave and bundle branch block. T-wave inversion is more common than the other pattern and is negatively correlated with the systolic function ($p= 0.03$). T-wave inversion pattern at the baseline is also associated with a persistent systolic dysfunction until six months after the first diagnosis.⁷ The ECG of our patient also showed a pattern of LBBB, which is a sign of cardiomyopathy.⁸ Echocardiography is important in examining the left ventricular ejection fraction (LVEF). In PPCM cases, we would find the LVEF to be $< 45\%$. Echocardiography is able to find a dilatation of the chamber and M-mode fractional shortening $<30\%$.^{9,10} Mitral regurgitation may appear in PPCM due to left ventricular dilation.¹¹ Echocardiography is also capable to exclude other diagnosis. Patients who present with diastolic dysfunction but with good systolic function should be suspected to have preeclampsia.¹²

Furthermore, these several criteria can be used in making the diagnosis of PPCM. The criteria include the presence of left ventricular systolic dysfunction from echocardiography examination in the peripartum period, the onset of the symptoms during the last month of pregnancy and 5 months post-partum, no other etiologies

of heart failure, and no evidence of heart disease before the last month of pregnancy.⁹

Diuretic should always be prepared to be administered to PPCM patients especially in emergency settings. Two types of diuretic, loop and thiazide, were recommended as the initial treatment for moderate and severe PPCM patient.¹³ Both are considered to be safe during pregnancy but there is a very limited data on furosemide usage during lactation.¹⁴ We initiated furosemide IV drip in this patient because the patient did not breastfeed.

Norepinephrine is recommended to be the first-line treatment for patient with classic wet and cold presentation while dobutamine is added when the patient stabilizes.¹⁵ However, the recommendation can be considered to oversimplify the management of cardiogenic shock in clinical practice because the treatment should not only be focused on improving blood pressure. A review conducted recommended that there are three aspects that should be assessed in treating patient with cardiogenic shock which are metabolic optimization, pump function optimization, and tissue perfusion optimization.¹⁶ The main problem within the patient was the inadequate left ventricle contractility so that we administered dobutamine to optimize the pump function. However, since the administration of maximum dose dobutamine did not improve the blood pressure, we added norepinephrine. Currently, there is no study that directly compared the efficacy and safety of dobutamine and norepinephrine combination to dobutamine in heart failure patient, let alone in PPCM patient. A study conducted by Levy B et al concluded that epinephrine was as effective as the combination of norepinephrine and dobutamine in improving global hemodynamic effect of cardiogenic shock patients, but the combination was more reliable and safer.¹⁷

The existing guideline in the management of PPCM by ESC based on multiple trials suggested that bromocriptine should be given in PPCM patients with any severity. The treatment is differentiated into two groups: the uncomplicated patients (1 week treatment, 2.5 mg once daily) and complicated patients with EF $<25\%$, right ventricular involvement, intensive care treatment, and/or cardiogenic shock (2.5 mg twice daily for two weeks and 2.5 mg once daily for 6 weeks).¹⁵ Therefore, we prescribed the patient with bromocriptine for 8 weeks. In addition to bromocriptine, we added ramipril and

bisoprolol as regular oral HF drugs. ACE-inhibitor is suggested to be given to patient that did not breastfeed and contraindicated to be given in pregnant patient, while beta-blockers should be prescribed to all PPCM patients (pregnant or after delivery).¹⁵

CONCLUSION

Peripartum cardiomyopathy is a rare condition in daily practice, yet causes a high mortality rate. It may not be easy to diagnose because the symptoms are not specific and may present in normal pregnancy. Good history taking and diagnostic testing may help to make the diagnosis. Echocardiography is an important tool to evaluate the cardiac function and rule out the other cause of cardiomyopathy. Proper management can improve the clinical symptoms and improve the cardiac function.

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Case Report

Rectovaginal Fistulae in Post Repair Chronic Perineal Rupture***Fistula Rektovagina pada Pascarepair Ruptur Total Perienum Lama*****Budi I. Santoso¹, Shirley Anggraini², Yulia Margaretta Sari¹**

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Abstract

Objective: To report and discuss the causes and management of rectovaginal fistula in post repair chronic total perineal rupture.

Methods: A case report, a 29-year-old female patient who came to Fatmawati General Hospital with complaints of anal incontinence 9 days after repair chronic total perineal rupture. Rectovaginal examination revealed a rectovaginal fistula 2 mm in diameter at 1.5 cm proximal to the hymenal ring.

Discussion: Rectovaginal fistula is one of the complications after repair of chronic total perineal rupture which disturbs the quality of life of women. The patient was diagnosed with a rectovaginal fistula in post repair chronic total perineal rupture. Conservative management with wound care and administration of honey to the patient showed improved postoperative outcome.

Conclusions: Anatomical identification of the anal sphincter complex, surgical technique and postoperative care are important in preventing complications following repair of chronic total perineal rupture repair.

Keywords: obstetrics sphincter anal injury, postrepair chronic, rectovaginal fistulae.

Abstrak

Tujuan: Untuk melaporkan dan mendiskusikan penyebab dan tatalaksana kasus fistula rektovagina pasca repair ruptur perineum total lama.

Metode: Sebuah laporan kasus, pasien perempuan 29 tahun yang datang ke RSUP Fatmawati dengan keluhan inkontinensia anal 9 hari pascarepair ruptur perineum total lama. Pemeriksaan rectovaginal menunjukkan fistula rektovagina diameter 2 mm pada 1,5 cm proksimal hymenal ring.

Diskusi: Fistula rektovagina merupakan salah satu komplikasi pascarepair ruptur perineum total yang mengganggu kualitas hidup perempuan. Pasien didiagnos fistula rektovagina pascarepair ruptur perineum total lama. Manajemen konservatif dengan perawatan luka dan pemberian madu pada pasien menunjukkan perbaikan luaran paska operasi.

Kesimpulan: Identifikasi anatomis kompleks sfingter ani, teknik operasi dan perawatan pascaoperasi penting dalam mencegah komplikasi pascarepair ruptur perineum total lama.

Kata kunci: cedera sfingter ani obstetri, fistula rektovagina, repair ruptur perineum total lama.

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Received: May,2021

Accepted: September,2021

Published: October,2021

INTRODUCTION

Perineal trauma is the most common obstetric complication of childbirth, occurring in 55%-85% of vaginal births. Complications of perineal trauma include pain, infection, and wound breakdown.¹ Perineal trauma occurs either spontaneously with vaginal delivery or secondarily as an extension to an episiotomy. Severe perineal trauma can involve damage to the anal sphincters and anal mucosa. Obstetric anal sphincter injuries include third and fourth degree perineal tears.² Obstetric Anal Sphincter Injuries (OASIs) remain an important complication of vaginal delivery and its incidence appears to be rising. While many women suffer no consequences, others develop varying degrees of flatus and faecal incontinence, which correlates to the degree of tear sustained.³

Complications following obstetric anal sphincter injuries (OASIS) during vaginal delivery are relatively rare events, with an incidence of approximately 5-13%.⁴ One of the most devastating complications is perineal wound breakdown, occurring with an incidence of 0.1-4.6%. Although uncommon, perineal wound complications can lead to significant morbidity, including chronic pain, incontinence, embarrassment, rectovaginal fistula, and loss of sexual function.⁴

CASE

A 29-year-old primipara woman was consulted to Fatmawati Hospital with chief complain of stool leakage through vagina 5 days after underwent repair of chronic total perineal rupture. Patient always experience flatal and solid stool incontinence, never experience liquid stool incontinence and rarely wearing pad. Patient was gave birth her first child three month ago with birth weight was 2900 grams. Her spontaneous delivery was assisted by midwife without instrumental delivery. Patient was experienced obstetric sphincter anal injury (OASIS) and first repair of OASIS was performed immediately by midwife. A week after delivery, she complained anal incontinence and she was reffered to Fatmawati Hospital. Repair of OASIS in this patient was performed 3 month after tha last repair. The procedure was under regional anesthesia. Anal mucosa was sutured with simple interrupted with 3-0 Vycril. Internal anal spincter was sutured with mattress suture using 3-0 Vycril. External anal sphincter was sutured with overlapping

technique using 2-0 Vycril. Perineal musculature and vaginal mucosa was sutured with running closure using 2-0 Vycril, and perineal skin was sutured with subcuticular suture using 2-0 Vycril. Post-operative management were administration of combination oral Cephalosporin and Metronidazol for 7 days, administration of stool softners (dependent on patient stool consistency), and urinary catheter was maintained for 12 hours. Patient was hospitalized for 2 days until she have defecation.

Physical examination revealed that vital sign were within normal limit and BMI was 24 kg/m². Gynecological examination showed defect in posterior vaginal mucosa, 1,5 cm proximal hymenal ring, approximately 2 mm in diameter and connected to anal mucosa.

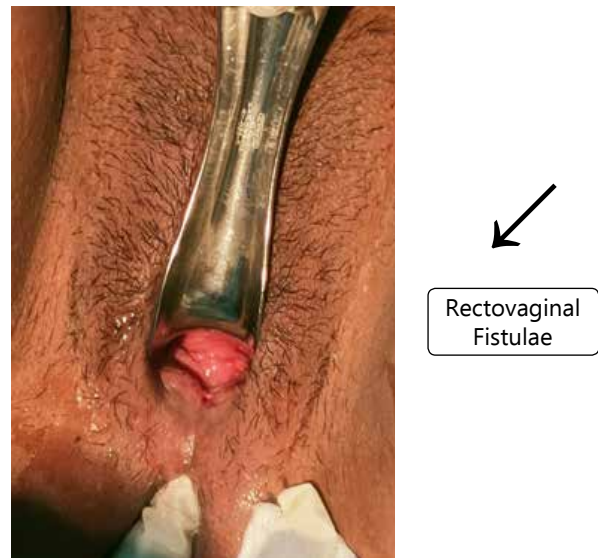


Figure 1. Physical Examination

The patient was diagnosed with rectovaginal fistulae in post repair chronic perineal rupture. Patient was managed with conservative therapy which are wound toilet, high protein diet, and honey application in fistula.

DISCUSSION

Obstetric anal sphincter injuries (OASIS) are serious complications of vaginal birth with a reported incidence globally from 1 % to 10 %. OASIS is one of the most significant risk factors for anal incontinence in young women, longterm dyspareunia and perineal pain. Despite optimal primary repair, approximately 39 % of women who sustain an OASIS will suffer from anal incontinence.⁵

Many risk factors for third and fourth degree perineal lacerations have been identified, including race, operative vaginal delivery, episiotomy, perineal length, nulliparity, length of second stage, and birth weight. However, there has been relatively little research to identify factors associated with these perineal wound complications.⁴

This patient had wound dehiscence which leads to rectovaginal fistula. Several factors were associated with wound complication in this patient. From patient characteristic, we found that patient was overweight, history of fourth degree perineal tear, and underwent spontaneous delivery. Factors associated with wound complications are race, body mass index (BMI), and smoking. Women who were colonized with GBS were more likely to have a wound complication as compared to those who were not colonized. Women with a fourth-degree laceration (compared to third-degree), those who sustained a blood loss of more than 500 mL, and those receiving antibiotics in the postpartum period were also more likely to have wound complications. The use of intrapartum antibiotics was found to be associated with a reduced risk of wound complications. Method of vaginal delivery was a significant predictor of wound complications. More specifically, wound complications occurred in 9.5% vs 7.8% vs 3.9% of forceps, vacuum, and spontaneous deliveries, respectively.⁴

Primary repair failed in 31.7% of the tears. These included more tears repaired by less experienced personnel and more repairs performed during on-call hours than in the successful primary repair group. Significantly more pain medication was used in the failed group, and the use of antibiotics and laxatives after the repair was more common in the successful group. Sphincter injuries were repaired using the overlapping suture technique in 95.1% of the repairs in the successful group compared with 47.4% in the failed group. The mean (SD) Wexner score was significantly higher in the failed group.⁶

The patient underwent full bowel preparation and administration of intravenous Cephalosporin preoperatively. Intraoperatively, anal mucosa was sutured with simple interrupted with 3-0 Vicryl. Internal anal sphincter was sutured with mattress suture using 3-0 Vicryl. External anal sphincter was sutured with overlapping technique using 2-0 Vicryl. Perineal musculature and vaginal mucosa was sutured with running closure using

2-0 Vicryl, and perineal skin was sutured with subcuticular suture using 2-0 Vicryl.

Following a fourth degree perineal tear, the anal mucosa can be approximated by a number of techniques. The mucosal repair can be carried out with an interrupted 3-0 Vicryl suture with the knots tied in the anal lumen or external to the anal canal. Alternatively the anal mucosa can be approximated with a 3-0 PDS suture with a submucosal continuous suture. There are currently no studies that suggest a benefit from any of these repair techniques for the anal mucosa with respect to outcomes including anovaginal and rectovaginal fistulas.²

Obstetric anal sphincter tear repair is performed with an end-to-end surgical technique. However, such a procedure does not restore normal anatomy or function. Sultan *et al.* found EAS defects in 82% of women after primary repair of an anal sphincter tear by endoanal ultrasonography. Due to unsatisfactory of outcomes, overlapping repair was introduced to correct sphincter defect and the rate of flatus and fecal incontinence reduced significantly. Nevertheless, one randomized control trial conducted by Farrell *et al.* found that there was no long-term benefit associated with the overlapping technique over the end-to-end repair after 3 years' follow-up. Repairing both the IAS and EAS muscles separately in cases of combined tears during primary repair reportedly reduces the risk of developing fecal incontinence. Thus, careful rectovaginal examination after vaginal birth is the crucial factor in reducing anal incontinence.⁷

Regarding suture material, there are no differences between polyglactin (Vicryl) and polydioxanone (PDS) for repairing the anal sphincter. Additionally, well-trained clinicians are associated with successful repair.⁷ The suture ends should be cut short and the knots covered by the overlying superficial perineal muscles in order to minimize any discomfort from suture ends and knots. Monofilament sutures maybe beneficial as they are less likely to harbour organisms and predispose to infection.²

A randomized trial (n = 112), compared OASIS repairs with polyglactin (Vicryl) and polydioxanone (PDS). At 6 weeks, there was no significant difference in suture-related morbidity. There may be benefit to delayed absorbable suture with respect to longer term functional outcomes but this has yet to be evaluated in clinical trials. Many of the more recently published studies have used delayed absorbable sutures but have not been

undertaken to compare suture material.²

Surgical technique might also associated with wound dehiscence that lead to rectovaginal fistulae in this patient. Surgical wound dehiscence may occur because of technical issues with the closure of the incision. Surgical incisions are closed to bring together the sides of the wound to facilitate healing and minimise scar formation. The most appropriate closure material and technique for a surgical incision depends on a wide variety of factors including the number of tissue layers to be closed, the anatomical location of the incision, the condition of the patient, and surgeon experience/preference.⁸

Wound dehiscence may occur if the method of incisional closure fails or is not strong enough to hold the edges and sides of the incision together. It may occur if suture knots slip or unravel, or sutures break, stretch, or cut through tissue because they have been placed too close to the edge of the incision, too far apart and/or put under too much tension. A retrospective study of 363 patients with surgical wound dehiscence following laparotomy attributed 8% of surgical wound dehiscence to broken sutures and 4% to loose knots.⁸

Another intraoperative risk factor for wound dehiscence is tissue trauma or large area of dissection and/ or undermining and failure to obliterate dead space. In addition to being caused by disrupted healing and mechanical stress, wound dehiscence can result from failure of the material used to close the incision, including stretching, slippage or breakage. Mechanical stress placed on a closed surgical incision can cause wound dehiscence by disrupting the material used for closure and/or rupturing the healing tissues. Mechanical stress can result from excessive forced tension during wound closure or swelling of the tissues around the incision due to oedema. The latter may occur as part of the inflammatory phase of the healing process or in response to infection, Mechanical stress may also be due to a haematoma, seroma or abscess below the surface of the incision.⁸

Excellent technique include gentle handling of tissues, meticulous control of bleeding, maintenance of blood supply, prevention of tissue drying, removal of devitalised or contaminated tissues, avoidance of dead space, and the use of an appropriate closure technique. The wound closure technique selected for primary closure should be appropriate for the site of the incision and surgical procedure, and should ensure

that the tissue layers are accurately apposed and tension across the incision is minimised. Minimising tension may require suturing of individual tissue layers and careful consideration of the spacing and length of the sutures.⁸

The postoperative management comprised a fluid diet for 5 days and antibiotics for 5 days (metronidazole, cefixime). Avoidance of constipation was also important. It is important to avoid disruption of the sutured mucosa due to faecal impaction caused by constipation. Accordingly, laxatives were given in most cases. After an OASIS repair, laxatives are given post-operatively to reduce straining and faecal impaction. The use of laxatives is recommended because the passage of the faeces may cause wound dehiscence.^{9,10}

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Systematic Review**Maternal and Perinatal Outcomes of COVID-19 in Pregnant Women*****Luaran Maternal dan Perinatal pada Ibu Hamil dengan COVID-19*****Putu H. I. Pramana¹, Gede B. S. Wirawan², Made Y. D. Astiti³, Kaspan¹**

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Abstract

Objective: To describe and identify risk factors of maternal and perinatal outcome of COVID-19 in pregnant women.

Methods: Literature search was conducted on MEDLINE and Google Scholar databases for articles published in December 2020 to January 2021. Keywords used includes 'COVID-19', 'pregnant women', 'maternal outcome' and 'fetal outcome.' Critical appraisal and selection were conducted to identify articles that fulfill inclusion criteria. The selected articles were analyzed thematically to answer the research questions.

Results: Literature search yielded 124 articles with 11 included in final analysis. The results showed low to moderate risk of maternal and perinatal adverse outcomes, including low risks for maternal and perinatal mortality coupled with moderate risk for maternal ICU admission and preterm birth with NICU admission for the newborn. Higher risk was observed for pregnant women with symptomatic COVID-19 infection, which points to the necessity for awareness of the risk and targeted early detection efforts.

Conclusions: There are low risk for adverse maternal and perinatal outcomes, including mortality and ICU/NICU admission, associated with COVID-19 infection in pregnant women. Risk factors for adverse outcomes included pregnant women with symptomatic COVID-19 infection.

Keywords: COVID-19, ICU, maternal mortality, NICU, perinatal mortality, preterm birth.

Abstrak

Tujuan: Mendeskripsikan dan mengidentifikasi faktor risiko luaran maternal dan perinatal COVID-19 pada ibu hamil.

Metode: Penelusuran literatur dilakukan di database MEDLINE dan Google Scholar untuk artikel yang diterbitkan pada Desember 2020 hingga Januari 2021. Kata kunci yang digunakan meliputi 'COVID-19', 'wanita hamil', 'keluaran ibu' dan 'hasil janin'. Penilaian dan seleksi kritis dilakukan untuk mengidentifikasi artikel yang memenuhi kriteria inklusi. Artikel yang dipilih dianalisis secara tematis untuk menjawab pertanyaan penelitian.

Hasil: Penelusuran literatur menghasilkan 124 artikel dengan 11 termasuk dalam analisis akhir. Hasil penelitian menunjukkan risiko rendah hingga sedang untuk luaran buruk maternal dan perinatal, termasuk risiko rendah untuk kematian maternal dan perinatal ditambah dengan risiko sedang untuk masuk ICU ibu dan kelahiran prematur dengan masuk NICU untuk bayi baru lahir. Risiko yang lebih tinggi diamati untuk wanita hamil dengan infeksi COVID-19 bergejala, yang menunjukkan perlunya kesadaran akan risiko dan upaya deteksi dini yang ditargetkan.

Kesimpulan: Terdapat risiko rendah untuk luaran buruk maternal dan perinatal, termasuk kematian dan rawat inap di ICU/NICU, terkait dengan infeksi COVID-19 pada wanita hamil. Faktor risiko untuk luaran buruk adalah wanita hamil dengan gejala infeksi COVID-19.

Kata kunci: COVID-19, ICU, kelahiran preterm, mortalitas maternal, mortalitas perinatal, NICU.

Correspondence author.

Received:

Accepted:

Published:

INTRODUCTION

COVID-19 has infected over 100 million people worldwide, causing over 2 million deaths. In many countries, its spread is uncontrolled with most nations in the world reporting community transmissions.¹ In such countries, every members of community are considered at risk population, regardless of known contact to an infected person, including pregnant women.²

There has been no definitive data on the extent pregnant women make up COVID-19 confirmed cases worldwide. An early screening study in New York, United States, found 13.5% asymptomatic infections and 1.9% symptomatic infections from 215 screened obstetric patients presenting for delivery.³ However, an epidemiological update by Pan-American Health Organization (PAHO) in September 2020 presented much lower rate with 60,458 cases in pregnant women from over 6 million cumulative cases, a much lower proportion.⁴

Nevertheless, infection of a novel virus to pregnant women population opens up various unknown risks. The most immediate being to the pregnancy, maternal, and perinatal outcomes. Reviews on early reports of COVID-19 impacts on pregnancy showed differing results. One review reported over 90% pregnant women with COVID-19 required caesarean sections with 10.7% fetal distress and 21.3% preterm birth.⁵ Another reported much bleaker situation with over 60% fetal distress.⁶

These early reviews relied much on case reports and case series, each reporting few cases. As demonstrated by aforementioned PAHO report, COVID-19 cases in pregnant women were quite rare. As situation developed, more reports emerged which included larger sample size and more accurately described the outcome of COVID-19 infection among pregnant women.

In accordance to these new emerging evidences, we aimed to review it to make a more cohesive picture. Our primary objective in this review is to describe maternal and perinatal outcome of COVID-19 infection in pregnancy. Meanwhile, our secondary objective is to describe risk factors for adverse outcomes for pregnant women with COVID-19 infection.

METHODS

We conducted a review on open-access literatures on COVID-19 infection in pregnant

women. Literature search was conducted on MEDLINE and Google Scholar databases from December 2020 to January 2021 using keywords that included 'COVID-19', 'pregnant women', 'maternal outcome' and 'fetal outcome.' Results was limited to those published after May 1st 2020.

For analysis, we included descriptive and analytic studies describing maternal and fetal outcome of confirmed COVID-19 infection during pregnancy. We excluded case reports, case series, and studies with sample size less than 50 to give more accurate picture of the situation. We also excluded studies which conflated the statistics of confirmed and suspected COVID-19 cases among pregnant women.

Variables of interest for maternal outcome included ICU admission and maternal mortality rate. Meanwhile, variables of interest pregnancy and perinatal outcomes included percentage of live birth, preterm birth, NICU admission, and mortality. Included studies do not have to report on all these variables. Report one at least one variable was sufficient for inclusion.

Studies were appraised for quality before inclusion and analysis. Quality appraisal was conducted using CASP (Critical Appraisal Skills Programme) Checklist for appropriate study design reported. The checklist included questions on research questions, methodology, and analysis technique employed to assess validity of results.

Data extraction was conducted with pre-piloted forms by both authors independently of each other. Extracted data included date of publication, study design, sample size, and description of variables of interest. The results were compared between the two authors and duplicates were reconciled. Inclusion or exclusion was discussed and agreed upon by all authors before effected.

RESULTS

As visible in Figure 1, literature search identified 124 studies, of which 77 was immediately excluded due to having 'review', 'case report', or 'case series' on the title and/or abstract. We reviewed the abstract for the remaining 47 studies and excluded 19 more for describing case report or case series results. From 28 studies with underwent data extraction, another 17 studies were excluded for having sample size less than 50 or results that conflate confirmed and suspected COVID-19 cases. The remaining 11 studies was

included for analysis.

There are variations between included studies, based on design and inclusion criteria. By design, there were 4 cohorts, either prospective or retrospective, 5 retrospective studies, either analytic or descriptive, and 2 case-control designs.

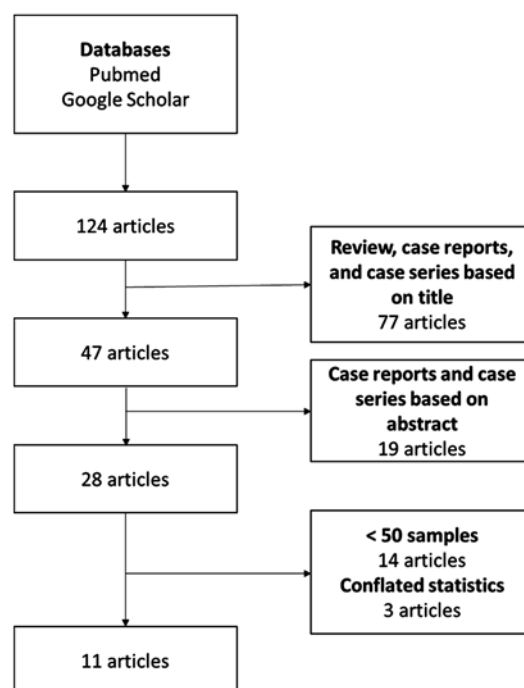


Figure 1. Literature search and selection diagram.

Inclusion criteria varies, even between studies with similar design. Some analytic studies included both confirmed, suspected, and/or non-COVID-19 cases,⁷⁻⁹ as well as pregnant and non-pregnant COVID-19 cases.¹⁰ For these studies, we only extracted data for pregnant women with confirmed COVID-19 cohort or group.

Table 1. Characteristics of included studies

Author	Title	Design	Sample Size	Ref.
Di Mascio <i>et al.</i>	Risk factors associated with adverse fetal outcomes in pregnancies affected by Coronavirus disease 2019 (COVID-19): a secondary analysis of the WAPM study on COVID-19	Prospective cohort	388 pregnant women with confirmed COVID-19, 266 of which completed their pregnancy	11
Gabriel <i>et al.</i>	Maternal, Perinatal and Neonatal Outcomes With COVID-19: A Multicenter Study of 242 Pregnancies and Their 248 Infant Newborns During Their First Month of Life	Retrospective cohort	242 women who gave live birth while having confirmed COVID-19	12
London <i>et al.</i>	The Relationship between Status at Presentation and Outcomes among Pregnant Women with COVID-19	Retrospective cohort	68 pregnant women with confirmed COVID-19, 56 of which completed their pregnancy	13
Adhikari <i>et al.</i>	Pregnancy Outcomes Among Women With and Without Severe Acute Respiratory Syndrome Coronavirus 2 Infection	Prospective cohort	252 pregnant women with confirmed COVID-19 who completed their pregnancy	7
Ayed <i>et al.</i>	Maternal and perinatal characteristics and outcomes of pregnancies complicated with COVID-19 in Kuwait	Retrospective analytic	185 pregnant women with confirmed COVID-19, 169 of which completed their pregnancy	14

Delahoy <i>et al.</i>	Characteristics and Maternal and Birth Outcomes of Hospitalized Pregnant Women with Laboratory-Confirmed COVID-19 — COVID-NET, 13 States, March 1–August 22, 2020	Retrospective analytic	598 pregnant women with confirmed COVID-19, 458 of which completed their pregnancy	15
Woodworth <i>et al.</i>	Birth and Infant Outcomes Following Laboratory-Confirmed SARS-CoV-2 Infection in Pregnancy — SET-NET, 16 Jurisdictions, March 29–October 14, 2020	Retrospective analytic	4,442 completed pregnancy with confirmed COVID-19	16
Nayak <i>et al.</i>	Impact of the Coronavirus Infection in Pregnancy: A Preliminary Study of 141 Patients	Retrospective analytic	141 completed pregnancy with confirmed COVID-19	9
Yen <i>et al.</i>	Coronavirus disease 2019 in pregnant women: a report based on 116 cases	Retrospective descriptive	65 pregnant women with confirmed COVID-19, 50 of which gave live birth	8
Badr <i>et al.</i>	Are clinical outcomes worse for pregnant women at < 20 weeks' gestation infected with coronavirus disease 2019? A multicenter case-control study with propensity score matching	Case control	83 pregnant women with confirmed COVID-19	10
Yang <i>et al.</i>	Pregnant women with COVID-19 and risk of adverse birth outcomes and maternal-fetal vertical transmission: a population-based cohort study in Wuhan, China	Case control	65 pregnant women who gave live birth with confirmed COVID-19	17

Due to different in design and inclusion criteria, there were also difference in outcome of observation reported between included studies. Most studies included pregnant women with COVID-19 regardless of pregnancy completion.^{11,13–16} Some studies included only women who give live birth with concurrent COVID-19 infection, thus did not report incidences of adverse pregnancy outcomes such as miscarriage or stillbirths.^{10,12,17}

As much as 7 studies reported both variables of interest on maternal outcome, namely ICU admission and mortality, while 2 studies reported only maternal mortality rate. There are wide variation in reported ICU admission rate for pregnant women with confirmed COVID-19, ranging from 1.1%¹⁴ to 17.6%.¹³

Accounting for sample size variation, however, the reports indicate there was a cumulative of 125 ICU admission from 1,629 observed pregnant women in the seven studies that reported this variable.^{8,10–15} This translates to an ICU admission rate of 7.67%.

Table 2. ICU Admission and Maternal Mortality Rate Reported in Included

Authors	ICU admission (%)	Maternal mortality rate (%)	Ref.
Di Mascio <i>et al.</i>	11.1	0.8	11
Gabriel <i>et al.</i>	2.9	0.4	12
London <i>et al.</i>	17.6	0	13
Adhikari <i>et al.</i>	-	0	7
Ayed <i>et al.</i>	1.1	0	14
Delahoy <i>et al.</i>	7.4	0.3	15
Nayak <i>et al.</i>	-	2.12	9
Yen <i>et al.</i>	9.2	0	8
Badr <i>et al.</i>	13.34	0	10

Meanwhile, from 9 studies which reported maternal mortality rate, 6 reported no deaths.^{7,8,10,13,14} The others reported very low mortality rate, ranging from 0.3%¹⁵ to 2.12%.⁹ Overall, there was only 9 mortality events from 2,022 observed pregnant women observed by studies that reported this variable.^{7–15} This translates to maternal mortality rate of 0.5%.

Almost all included studies reported one or both of rate of live and preterm births from observed pregnant women with COVID-19. Most reported high live birth rate, in excess of 95%.

The lowest reported live birth rate was 94.4%¹¹ while the highest was 99.3%.¹⁶

Table 3. Pregnancy outcomes reported in included studies

Authors	Live births (%)	Preterm births (%)	Ref.
Di Mascio et al.	94.4	27.9	11
Gabriel et al.	-	14.5	12
London et al.	98.2	16.4	13
Adhikari et al.	97	11	7
Ayed et al.	97.6	26.7	14
Delahoy et al.	97.8	12.5	15
Woodworth et al.	99.3	12.9	16
Nayak et al.	92.9	-	9
Yen et al.	-	32	8
Yang et al.	-	14	17

Some of these studies included multiple pregnancies, which leads to the number of live births to exceed the number of observed mothers. A significant proportion of these births was preterm, however, with preterm births making up around 20% of live births. The lowest reported proportion of preterm births was 11%⁷ and the highest was 32%.⁸ From 5,439 observed live births with known gestational age, there was 773 preterm infants, translating to preterm birth rate of 14.2%.

Meanwhile, there was 8 studies who followed up on the newborn and reported either one or both of NICU admission and perinatal mortality. Similar to ICU admission for pregnant women, there was wide variation of NICU admission rate among newborn of these women. The lowest reported NICU admission rate was 3%¹⁴ while the highest was ten-times that at 34%.⁸ Mortality was low, however, with most studies reported zero death and the highest reported 2% perinatal mortality rate.^{8,11}

Table 4. Perinatal Outcomes Reported in Included Studies

Authors	NICU admission (%)	Perinatal mortality (%)	Ref.
Di Mascio et al.	27.5	2.0	11
Gabriel et al.	11.3	0	12
Adhikari et al.	3.3	0	7
Ayed et al.	3.0	0	14
Delahoy et al.	-	0.4	15
Woodworth et al.	9.3	0.2	16
Nayak et al.	17.9	-	9
Yen et al.	34.0	2	8

Several included studies reported comparison between pregnant women with Some included studies reported comparison between pregnant women with confirmed COVID-19 with outside

groups, which may include pregnant women with suspected, but not confirmed, COVID-19⁸ or pregnant women without COVID-19.^{7,9,10,17} Others reported comparison between two subgroups of symptomatic and asymptomatic pregnant women with COVID-19.^{13,15,16}

Comparison of maternal outcomes between confirmed and suspected groups showed no difference in mortality rate. However, pregnant women with confirmed COVID-19 were more likely to be admitted to ICU compared to suspected group (9.2% vs 3.9%). However, no statistical tests were conducted to see the significance of this difference.⁸

Nayak *et al.* reported higher risk of maternal mortality in COVID-19 confirmed pregnant women (2.12% vs 0.95%) although the difference was not statistically significant ($p > 0.05$).⁹ However, Badr *et al.* reported higher risk of ICU admission for pregnant women with confirmed COVID-19.¹⁰ Meanwhile, conflicting evidence was presented on risk of preterm birth between the two groups, with one study reporting no statistically significant difference⁷ while another reporting significant increased risk of preterm birth in confirmed group with OR of 3.71 (95% CI 1.70 – 8.03).¹⁷

Results on comparison between symptomatic and asymptomatic confirmed COVID-19 pregnant women painted a more cohesive picture. Women with symptomatic confirmed COVID-19 was more at risk for ICU admission necessitating ventilation support (26.1% vs 0%)¹³ and mortality (0.7% vs 0%).¹⁵ Women with symptomatic COVID-19 was also less likely to give live birth compared to their asymptomatic counterparts (95% vs 99.1%).¹⁵ Meanwhile, conflicting evidence was reported on risk of preterm birth with Delahoy *et al.* reporting increased risk among symptomatic group while Woodworth *et al.* reporting no difference.^{15,16}

DISCUSSION

Our review result showed relatively low risk of adverse outcomes for pregnant women with concurrent COVID-19 infection. While there was moderate risk of ICU admission, there was relatively low risk of maternal mortality. Similarly, there was high chance of successful pregnancy with live birth although it was accompanied with moderate risk of preterm pregnancy and NICU admission. Perinatal mortality rate, however, was low.

This result was not much different from early

reviews, although early reviews tend to report higher proportion of mortality or other adverse events. One early review reported preterm birth rate of 63.8% and NICU admission rate of 76.92%.⁶ Another review reported 2 maternal mortality out of 20 pregnant women reviewed from case reports, a mortality rate of 10%.¹⁸ Another early review, however, reported similar results to ours with 21.3% preterm birth rate and 1.2% perinatal mortality.⁵

The similarity of these early reviews, however, was the low number of cases included in the review. As report by PAHO showed, pregnant women with COVID-19 was not that frequent.⁴ Thus these early reviews reported results based on under 100 cases based mostly on case reports and case series.^{5,6,18} Some of these reviews also included suspected but not confirmed COVID-19 cases in the review.⁶

Later reviews and meta-analyses involving more observed reported much lower rate of adverse event however, similar to our results. Two large reviews published in the latter half of 2020 found maternal mortality rate of 1.7% and 0.6%, similar to our findings.^{19,20} Similar lower rate for other maternal and perinatal outcomes was also reported by other later reviews.

The reasoning was that earlier case reports and case series was made in the period when many things was unknown about COVID-19, such as lack of understanding of the prevalence of asymptomatic cases. This cause many reviews to include disproportionately more symptomatic cases, increasing risk of adverse events in their cohort.²¹

Our results also imply the highest risk of adverse event was among pregnant women with symptomatic COVID-19 infection. This point to the probability that the viral infection itself was not the cause of adverse event, unlike some other viral infection.²² Instead, inflammation, its associated symptoms, and potential exacerbation was the cause for the majority of adverse outcomes such as necessity for induction or caesarean section, preterm delivery, and perinatal complications.²¹

The clinical implication from our findings was the necessity to be aware of the risk of adverse outcomes when facing cases of pregnant women with concurrent COVID-19 infection. The risk would be higher in cases of symptomatic cases. As such, due preparation should be made, such as close monitoring of maternal and fetal conditions, as well as preparation for ICU and NICU admission.

Meanwhile, our result also points to a possible public health intervention in the form of targeted screening for symptomatic women during antenatal care in places where community transmission was common. Awareness for this necessary action should be emphasized in outpatient antenatal care facility which may not have in-house laboratory. Earlier detection would allow for closer monitoring and better preparation, hopefully improving outcomes. However, more study should be conducted on the cost-effectiveness of the measure.

While this study may provide updated picture of COVID-19 infection during pregnancy, it comes with its own shortcomings. Our literature search which relied on open-access databases may causes less than comprehensive results. As such, there may be some studies fulfilling inclusion criteria that was not included in this study.

CONCLUSION

Our results showed relatively low occurrences of adverse maternal and perinatal outcomes for pregnant women with concurrent COVID-19 infection. Increased risk was observed in symptomatic infections compared to asymptomatic ones. Awareness of the potential risk should be coupled with attempts for targeted early detection during antenatal care.

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