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Editorial

Abnormal Trophoblast Invasion: The Culprit of The Major Obstetrics Problems

Sri Sulistyowati

Pathogenesis of preeclampsia as the consequences of the interaction failure between trophoblast and womb, mainly in the 1st trimester leads to a stress response in the placenta. This may cause poor growth and development of the villous tree, deteriorating transfer of oxygen and nutrients to the fetus.[1] In the simultaneous way huge number of placental debris as the result of necrotic-apoptotic process is released into maternal circulation.[1,2] That of phenomenon related to syncytiotrophoblastic stress is triggering endothelial dysregulation and extreme inflammation process, and so do the clinical respond related, such as: hypertension, proteinuria, edema, convulsion, cerebral edema, acute renal failure, acute liver dysfunction, thrombocytopenia (which are as the maternal complications) and fetal growth restriction, preterm delivery, still birth (which are as the fetal complications).[3]

Fetal growth restriction (FGR) which could be develop solely or as one entity of early-onset preeclampsia is mostly caused by the poor attitude of extravillous trophoblast cells (EVT) in doing its work on maternal spiral artery remodeling process.[4] As we can see clear from the large data of scientific evidence, the only significant modality to prevent FGR until recent is by giving low-dose aspirin before 16 weeks of gestational age in selected pregnancies with high resistance index of uterine artery shown by doppler velocimetry ultrasound.[5] Beyond that, only timely delivery after series of close monitoring that will give better perinatal outcome.[6] This will often end with preterm delivery, which increases the percentage of preterm birth in general.[6]

In the contrary, placenta accreta spectrum (PAS) is a condition where the trophoblast invasion is too aggressive. The development of PAS is a complex multifactorial process related to the combination of decidual-myometrial defect (as the results of previous c-section or other gynecological surgery), absence of the basal plate on decidual layer, and the excessive extravillous trophoblastic invasion.[7] The attitude of trophoblast in PAS is similar to tumor behaviors which are: inducing abnormal angiogenesis, sustained proliferative signaling, resisting cell death, evading immune destruction, and increasing energy metabolism.[8]

Abnormal trophoblast invasion is the lesson of obstetrics and the lesson of life. Too much is against the law of life and will result in negative way. Too shallow, will result on poor placentation: preeclampsia, FGR, preterm delivery, and too deep will result on PAS. So, if we want to avoid the major obstetric problems, is the duty of obstetricians to precede trophoblast to behave normally, including predicting abnormal behavior and preventing it.

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Research Article

Does Lifestyle Affect Dysmenorrhea Intensity? A Cross-Sectional Study

Apakah Gaya Hidup Mempengaruhi Intensitas Dismenore? Sebuah Studi Cross-Sectional

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Abstract

Objective: To determine whether or not there is a relationship between lifestyle and dysmenorrhea intensity in FKIK Atma Jaya students.

Methods: This research is a cross sectional analytic descriptive study with a minimum sample size of 196 students of the FKIK Atma Jaya class 2017-2019. The degree of pain was assessed using the Verbal Multidimensional Scoring System pain scale. Frequency of fast food consumption were assessed with Food Frequency Questionnaire. Frequency of physical activity were assessed with International Physical Activity Questionnaire. The datas were analyzed using the Kolmogorov-Smirnov normality test, the Mann-Whitney U test, and the Kruskal-Wallis test.

Result: The highest percentage of menstrual pain was at grade 1 (painful menstruation; rarely disturbed activity; no systemic symptoms; rarely required analgesics) for the VMSS scale (46.3%). The percentage of fast food consumption in this study was 86.1%. The highest percentage of physical activity in the category of moderate physical activity was 56.2%. The results of this study indicates a significant relationship between consumption of fast food and the intensity of dysmenorrhea with p = 0.017. There were no significant relationship between physical activity and the intensity of dysmenorrhea with p = 0.225.

Conclusion: Consumption of fast food were related to the intensity of dysmenorrhea, whereas physical activity was not related with the intensity of dysmenorrhea.

Keywords: dysmenorrhea, fast food consumption, lifestyle, physical activity.

Abstrak

Tujuan: *Untuk mengetahui ada tidaknya hubungan gaya hidup dengan intensitas dismenore pada mahasiswa FKIK Atma Jaya.*

Metode: *Penelitian ini merupakan penelitian deskriptif analitik cross sectional dengan jumlah sampel minimal 196 mahasiswa FKIK Atma Jaya angkatan 2017-2019. Derajat nyeri dinilai dengan menggunakan skala nyeri Verbal Multidimensional Scoring System. Frekuensi konsumsi makanan cepat saji dinilai dengan Food Frequency Questionnaire. Frekuensi aktivitas fisik dinilai dengan International Physical Activity Questionnaire. Data dianalisis menggunakan uji normalitas Kolmogorov-Smirnov, uji Mann-Whitney U, dan uji Kruskal-Wallis.*

Hasil: *Persentase nyeri haid tertinggi pada derajat 1 (nyeri haid; aktivitas jarang terganggu; tidak ada gejala sistemik; jarang memerlukan analgesik) untuk skala VMSS (46,3%). Persentase konsumsi fast food dalam penelitian ini adalah 86,1%. Persentase aktivitas fisik tertinggi pada kategori aktivitas fisik sedang adalah 56,2%. Hasil penelitian ini menunjukkan adanya hubungan yang signifikan antara konsumsi fast food dengan intensitas dismenore dengan p = 0,017. Tidak ada hubungan yang bermakna antara aktivitas fisik dengan intensitas dismenore dengan p=0,225.*

Kesimpulan: *Konsumsi fast food berhubungan dengan intensitas dismenore, sedangkan aktivitas fisik tidak berhubungan dengan intensitas dismenore.*

Kata kunci: *aktivitas fisik, dismenore, gaya hidup, konsumsi fast food.*

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INTRODUCTION

Dysmenorrhea is a gynecologic complaint found in daily clinical practice. Dysmenorrhea itself is defined as menstrual pain that is common among adolescents and young women.[1] According to the World Health Organization, the global prevalence of dysmenorrhea ranges from 1.7% to 97%, with a higher prevalence in adolescents.[2] The prevalence of dysmenorrhea among adolescents in Indonesia is around 64.25%, consisting of 54.89% primary dysmenorrhea and 9.36% secondary dysmenorrhea.[3] The high incidence of dysmenorrhea can have an impact on daily life and interfere with one's activities. As many as 10-15% of women experience a severe dysmenorrhea intensity every month so that their activities such as work, school, or chores are halt. Several factors affect dysmenorrhea, one of which is lifestyle.[4]

With advances in technology, there are changes in lifestyle one of which is towards the consumption of fast food. A retrospective observational study using data from the Indonesian Family Survey discovered that up to 65% of adults consumed deep-fried food for an average of 4 days and routinely consumed fast food or carbonated drinks.[5] The increased consumption of fast food is because fast food has an affordable price, quick serving and convenient. A research by Ayu et al. found that 42.9% of her samples consumed fast food and experienced dysmenorrhea during their menstruation, this shows that these two are correlated. Fast food has a high composition of trans fat that could increase the level of prostaglandin in the body, therefore causing uterine contraction during menstruation and initiate pain.[6]

Physical activity can become another parameter that reflects one's lifestyle. Several studies have shown that physical activity affects menstruation on many aspects including inducing amenorrhea on athletes and decreasing the pre-menstruation symptoms and dysmenorrhea.[7] A randomized controlled trial of 68 Shiraz University students with dysmenorrhea was conducted to discover the effect of eight-week isometric exercises on dysmenorrhea, the result was a reduced intensity and duration of pain caused by dysmenorrhea, less drug consumption, and a reduced duration of bleeding.[8] There is a positive correlation between the reduced risk from dysmenorrhea with doing regular and healthy physical activity. A hormone called endorphin is produced during a physical activity that can reduce premenstrual symptoms such as pain, depression, and anxiety.[9] Based on the high percentage of dysmenorrhea in adolescents, the high consumption of fast food, and the positive effect of physical activity towards prevention of dysmenorrhea, this research aims to determine whether or not there is a relationship between lifestyle and dysmenorrhea intensity.

METHODS

This research was a cross-sectional analytic descriptive study and was conducted on the faculty of medicine and health sciences of Atma Jaya Catholic University of Indonesia on July - August 2020. The sample for this research was preclinical students class of 2017-2019 and was taken by systematic random sampling.

The inclusion criteria for this research were students of the medicine program at the faculty of medicine and health sciences of Atma Jaya. The exclusion criteria for this research were students who were not willing to participate in this research, students who could not communicate well, and students who did not fill out the questionnaires after being warned three times.

The selected respondents were then given a dysmenorrhea history questionnaire which aims to find respondents who were suspected of having dysmenorrhea. After filling out the history taking questionnaire, the respondents also filled out the Verbal Multidimensional Scoring System questionnaire to assess the intensity of dysmenorrhea, the Food Frequency Questionnaire to assess the frequency of fast food consumption, and the International Physical Activity Questionnaire to assess the physical activity of the respondents. The data were analyzed using the Kolmogorov-Smirnov normality test, the Mann-Whitney U test, and the Kruskal-Wallis test.

RESULTS

Based on the data, a sample of 330 respondents was obtained and after adjusting with the inclusion and exclusion criteria, 201 respondents were chosen. The demographic characteristics of the respondents indicate that the average age was 19.5 years old with a range of 17 - 22 years old, the average menarche age of respondents is 12 years old with a range of 9 - 16 years old, and the average body mass index of the respondents was 21 kg/m^2 with a range of 16 - 34 kg/m^2.

The distribution results of respondents based on the dysmenorrhea intensity using the Verbal Multidimensional Scoring System showed grade 0 or no pain (N=51; 25.4%), grade 1 or mild pain (N=113; 56.2%), grade 2 or moderate pain (N=35; 17.4%), grade 3 or severe pain (N=2; 1.0%).

The distribution results of respondents based on the fast-food consumption using the Food Frequency Questionnaire showed frequent consumption of fast food (N=173; 86.1%) and no consumption of fast food (N=28; 13.9%).The distribution results of respondents based on the level of physical activity using the International Physical Activity Questionnaire showed mild physical activity (N=77; 38.3%), moderate physical activity (N=93 ; 46.3%), vigorous physical activity (N=31; 15.4%).

The result of the normality test using Kolmogorov-Smirnov on dysmenorrhea intensity and consumption of fast food and dysmenorrhea intensity and physical activity showed that the distribution of the data were abnormal ($p=0.000$; $\alpha=0.05$; $p<\alpha$).The results from the Mann-Whitney U test found a significant relationship between dysmenorrhea intensity and consumption of fast food with the value of $p=0{,}017$.The results from the Kruskal-Wallis test found a significant relationship between dysmenorrhea intensity physical activity with the value of $p=0.225$.

DISCUSSIONS

The average of respondents in this research was 19.5 years old with a range of 17 - 22 years old. Respondents aged 20 years old were the most respondent in this research with a total of 63 people (31.3%). This age distribution is similar to a, where the mean age was 20.8 ± 1.8 with a range of 17-23 years old.[10]

The average menarche age of respondents in this research was 12 years old with a range of 9 - 16 years old. Analysis of 2010 basic health research data from the Ministry of Health of the Republic of Indonesia (RISKESDAS) found that the average age of menarche in Indonesia was 12.96 years old, this is interchangeable with the age of menarche in this research.[11] The average age of menarche was 13.8 ± 1.6 with a range of 9 - 19 years old. 4 This data is equivalent to the characteristics of the respondents from this research.

The average of body mass index from this research was 21 kg/mm^2 that indicates the average BMI were within the normal limits. BMI can be classified to underweight (<18.0 kg/mm^2), normal (18.0-24.9 kg/mm^2), overweight/pre obese (25.0-29.9 kg/mm^2), and obese (≥30.0 kg/mm2).[10]

The dysmenorrhea intensity of respondents were assessed using VMSS and the highest data obtained were grade 1 or mild pain as much as 56.2% with physical activity that is seldom inhibited, analgesics are seldom required. In the second place, grade 0 or no pain as much as 25.4% with unaffected daily activity and not required analgesics. Third place, grade 2 or moderate pain as much as 17.4% with affected daily activity, analgesics are required and gave a relief so that absence from school is unusual. Last, grade 3 or severe pain as much as 1.0% with a clearly inhibited activity, poor effect of analgesics, and systemic symptoms such as headache, fatigue, vomiting, diarrhea, constipation.

This research is parallel to a research on medical students in Egypt who were assessed using VMSS, it was found that grade 1 or mild pain were the largest percentage as much as 27.9%, grade 2 or moderate pain for 23.3%, and grade 3 or severe pain for 14.1%.[12]

Within this research the majority of respondents were reported having dysmenorrhea with mild intensity. Several risk factors of dysmenorrhea are women aged <30 years old, menarche age <12 years old, and nulliparity.[13-18] Those risk factors are consistent with the characteristics of respondents in this research. The high intensity and incidence of dysmenorrhea is associated with young age. A study that has been carried out before confirmed that the intensity of dysmenorrhea will gradually decrease with age. An early menarche age also disrupts the hormonal balance and causing dysmenorrhea.[19] Other risk factors of dysmenorrhea including maternal dysmenorrhea history, smoking history, alcohol consumption history, and caffeine consumption history poses a great risk on increasing the intensity of dysmenorrhea.[20] These other factors mentioned wasn't examined in this study and were only used as a question to diagnose dysmenorrhea.

The majority of the respondents in this research were recorded frequently consuming fast food (86.1%). The type of fast food which frequently consumed are fried chicken (75.1%) and iced coffee (63.2%). The frequent intensity on fast food consumption in this research corresponds with a study from Indonesian Family Life Survey that stated Indonesian people consume fast food every day. Consuming fast food has become a habit, ritual, and comfort for adolescence. Fast food is a form of food that is easy to carry, buy and consume.[21] The high consumption of fast food within the age of 20s can be attributed to the specific qualities desired from this type of food such as food that is quick-serving, convenient, and relatively inexpensive. Other factors that can influence the high consumption of fast food including the delicious taste, easy access, and a greater variety of fast food compared to homemade food.[22]

The classification of physical activity in this research are divided into mild, moderate, and vigorous. Moderate physical activity dominated this research with a percentage of 46.3%, followed by mild physical activity (38.3%), and vigorous (15.4%). Moderate physical activity carried out regularly can provide many health benefits such as reducing the risk of death from cardiovascular disease, improving quality of life, reducing the risk of Alzheimer's disease, obesity, and osteoporosis. Several studies have shown contrasting results between medical students' knowledge of physical activity and its application in everyday life. Medical students have a low level of vigorous physical activity due to high workloads and little free time. The pattern of physical activity in this study is similar to a study conducted on medical students in Poland whereas the category of moderate physical activity dominates by 52%, followed by mild physical activity (26%), and vigorous physical activity (22%).[23]

This research found a significant relationship between consumption of fast food and the intensity of dysmenorrhea. These results were obtained through the Mann-Whitney U non-parametric statistical test with a value of $p = 0.017$ ($\alpha = 0.05$; $p < \alpha$). A group with high fast food consumption had a high incidence of dysmenorrhea significantly. The increase of fast food consumption is considered influenced with the history of skipping breakfast that intensifies the frequency of fast food consumption. The VMSS were used to assess dysmenorrhea intensity and also obtained weekly frequency of fast food consumption.[24] This research also used VMSS as a tool to assess dysmenorrhea intensity, the difference is that food frequency questionnaire were used to obtain specific type and frequency of fast food consumption.

The significant relationship between consumption of fast food and the intensity of dysmenorrhea founded in this research presumably because fast food contains a high saturation of fatty acid and it affects the metabolism of progesterone in menstrual cycle and the response is the increase amount of prostaglandin.[23-25] Phospholipids is one of the components of cell membrane that play a big role in the synthesis of prostaglandin. Prostaglandin helps the uterus to contract and shed the lining of endometrium during the menstrual period. A build-up of prostaglandin were found in women who experience menstrual pain or dysmenorrhea.[6] The resulting prostaglandins cause myometrial hypercontractility resulting in ischemia and hypoxia of the uterine muscles which can cause pain or dysmenorrhea.[26,27] Inadequate micronutrient content in fast food can also become a trigger for dysmenorrhea.[28]

Women with dysmenorrhea have contracted abdominal ligaments and by doing physical activity such as stretching may reduce pain and symptoms of dysmenorrhea.[29] Based on the positive effects of physical activity for dysmenorrhea from various studies and researches, it was hoped that there were a relationship between physical activity and the intensity of dysmenorrhea.

The data analysis showed that there were no significant relationship between physical activity and dysmenorrhea intensity. These results were obtained through the Kruskal-Wallis non-parametric statistical test with a value of $p=0.225$ ($\alpha=0.05$; $p>\alpha$). A similar studies also found that there were no significant relationship between physical activity and dysmenorrhea intensity.[29-31] A research on medical students in Cairo and discovered that there were also no significant relationship between physical activity and dysmenorrhea ($p=0.064$).[32] There are several possibilities that influenced the outcome of this study. The different method used in this research may be one of the possibilities, physical activity obtained in this research were only a weekly physical activity history and were not differentiated between exercise and non-exercise through the International Physical Activity Questionnaire (IPAQ) that might give rise to recall bias. The studies that are significant were more likely to carry out interventions methods or by doing exercise such as stretching exercises. The IPAQ incorporates daily activities such as mopping, washing, walking as physical activities and did not explore aspects of a certain exercise or sports that were routinely carried out. In studies using interventions, the type, duration, and impact of physical activity can be seen first-hand. Respondents in this study were only the students of the Atma Jaya faculty of medicine class of 2017-2019, the lack of sample variation in this study may also be one of the factors that contributes to the outcome possibilities of this research. This research was coincidentally conducted during the COVID-19 pandemic under lockdown conditions which severely limited ones activity outside the home and majorly exposed with activities that are dominated by an online system. This pandemic and system have a high probability of reducing ones physical activity. The absence of the relationship between the level of physical activity and the intensity of dysmenorrhea in this study may not be very representative.

In contrast to the experimental study of abdominal strain on 96 samples which consisted of 48 intervention samples and 48 control samples, it was found that there were a decrease in menstrual pain or dysmenorrhea on the sample given the intervention (p = 0.001).[33] The type of physical activity that has successfully played a role in reducing the intensity of dysmenorrhea is exercise. A routine exercise is fathomed to act as a non-specific analgesic by improving circulation of the pelvic blood vessels and stimulating the release of beta-endorphins which play a role in blocking pain transmission. In addition, prevention and regression of dysmenorrhea can be achieved through stress reducing and mood improvements during exercise.[34]

CONCLUSIONS

The results of this study indicates that consumption of fast food is associated with the intensity of dysmenorrhea (p = 0.017), whereas physical activity is not associated with the intensity of dysmenorrhea (p = 0.225).

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Research Article

The Association betweeen Cesarean Section and Placenta Accreta

Hubungan antara Seksio Sesarea dan Plasenta Akreta

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Abstract

Objective: To determine the relationship between the history of cesarean section and the incidence of placenta accreta in Dr. Zainoel Abidin Hospital Banda Aceh.

Methods: The data collection method used was secondary data collection which was assessed through retrospective medical records. Sampling in this study using total sampling method. The results of the study were processed using the chi square statistical test on 781 research samples that were collected from period April 2019 - April 2020.

Results: The results obtained were 22 respondents (2.8%) experienced placenta accreta where 18 respondents (2.30%) had placenta accreta with a history of CS and 4 respondents (0.51%) placenta accreta without a history of CS. The p value obtained was 0.000 (p value <0.05). In this study, the value of the Risk Estimate (RE) was 6.483 with a Confident Interval (CI) of 95% being (2.21-18.97).

Conclusion: There is a very significant relationship between the history of cesarean section and the incidence of placenta accreta at RSUDZA Banda Aceh and mothers with a history of CS have a 6 times greater risk of experiencing placenta accreta.

Keywords: cesarean section, placenta accrete.

Abstrak

Tujuan: *Untuk mengetahui hubungan riwayat seksio sesarea dengan kejadian plasenta akreta di Rumah Sakit Umum Daerah Dr. Zainoel Abidin Banda Aceh.*

Metode: *Jenis penelitian ini adalah penelitian analitik dengan desain potong lintang. Metode pengambilan data yang digunakan adalah pengambilan data sekunder yang dinilai melalui rekam medik secara retrospektif. Pengambilan sampel pada penelitian ini menggunakan metode total sampling. Hasil penelitian diolah menggunakan uji statistik chi square terhadap 781 sampel penelitian yang telah dikumpulkan dari data periode April 2019 – April 2020.*

Hasil: *Hasil yang didapatkan sebanyak 22 responden (2,8%) mengalami plasenta akreta dimana 18 responden (2,30%) plasenta akreta dengan riwayat SC dan 4 responden (0,51%) plasenta akreta tanpa riwayat SC. Nilai p value yang didapatkan adalah 0.000 (p value <0,05). Pada penelitian ini didapatkan nilai Risk Estimate (RE) 6,483 dengan Confident Interval (CI) 95% berada (2,21- 18,97).*

Kesimpulan: *Hasil ini menunjukkan terdapat hubungan yang sangat signifikan antara riwayat seksio sesarea dengan kejadian plasenta akreta di RSUDZA Banda Aceh dan ibu dengan riwayat SC memiliki risiko 6 kali lebih besar untuk mengalami plasenta akreta.*

Kata kunci: *plasenta akreta, seksio sesarea.*

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INTRODUCTION

Maternal Mortality Rate (MMR) is still quite high in Indonesia until now it is still an annual health problem. According to the data Inter-Census Population Survey (SUPAS) in 2015, the MMR in Indonesia was 305 per 100,000 live births, which tend to decrease compared to the previous year, namely 390 per 100,000 live births, but the number 305 was still high when compared to the SDG's target.[1,2] In Aceh, there were 141 cases of MMR reported in 2018 with the MMR ratio showing a decrease to 139 per 100,000 live births.[3]

Obstetric complications that can lead to mortality and fatal morbidity that increase MMR include placental invasive abnormalities (AIP).The incidence of AIP continues to increase to 1/153 of deliveries in the United States.[4]

Placenta accreta is an abnormal placental disorder in which the placental villi attach to the myometrium.[5,6] The incidence of placenta accreta in America increased 10-15 times from 1: 4017 in 1980 to 1: 272 in 2016.[7] Pathology studies of placenta accreta distribution were found to be 69.5% whereas invasion placenta accreta represents 30.5% of all placenta accreta cases. This incidence has increased in the last two decades.[8] The high incidence of placenta accreta also occurs in the General Hospital (RSUD) Dr. Soetomo with a total of 156 cases with an incidence of 4% of total deliveries.[4] The incidence of placenta accreta has continued to increase in Indonesia since 2016, namely 2% and will continue to increase, this has resulted in an increase in the mortality rate and morbidity of pregnant women in Indonesia.[9]Meanwhile, Aceh Province itself does not have data that is significant enough for the prevalence of placenta accreta. RSUD Dr. Zainoel Abidin obtained initial survey data on the incidence of Placenta accreta as many as 36 cases in 2018 to April 2020.

Method of delivery in mothers giving birth is thought to be a risk factor for the incidence of placenta accreta. Mothers with a history of previous cesarean section have a greater risk of experiencing placenta accreta compared to mothers who deliver vaginal delivery. An increase in the number of prior history of cesarean section increased the risk of placenta accreta by an eightfold increase after two or more histories of cesarean section.[10]

The incidence of cesarean section in the United States and Australia, has increased by 30%, which is quite a high number, while WHO recommends limiting the percentage of cesarean section for a country to a maximum of only 10% to 15% and not allowed to pass this limit. [11]Asia is the 6th highest cesarean section in the world. The increase in cesarean section over the past few decades has generated global concern, including from the scientific community as well as public health and medical groups.[12]

The latest RISKESDAS results in 2018 the incidence of cesarean section increased to 17.6%.[13] According to the RISKESDAS results, the delivery rate for cesarean section in Lampung Province in 2013 was around 4.5%.[14] In Dr. Zainoel Abidin, the cesarean section rate also continued to increase to 54.35% at the end of December 2016 which was previously only 13.29% in 2011-2013.[15]

Cesarean section has short term and long-term risks. The short-term risks for mothers with a history of cesarean section include peri- and postoperative complications such as: bleeding requiring transfusion or hysterectomy, bowel injury, bladder injury or ureteral injury, thromboembolic disease, and maternal death. Long-term risks of cesarean section include ectopic pregnancy, miscarriage, abnormal invasive placenta (AIP), and uterine rupture. The study reported that women who had Placenta Praevia and a history of previous cesarean section increased the incidence of placenta accreta by 3%, 11%, 40%, 61% and 67% for cesarean section 1 time, 2 times, 3 times, 4 times and respectively. 5 times.[7,16] Based on these data, the researcher was interested in conducting research on the relationship between the history of cesarean section and the incidence of placenta accreta at RSUDZA Banda Aceh.

METHODS

This type of research is an observational analytic study with a cross sectional design, which is a study between 2 variables carried out simultaneously. This study is called analytic because it wants to analyze the relationship between the history of cesarean section as a risk factor for placenta accreta. Retrieval of data through secondary data in the form of patient medical records retrospectively. The research was conducted at General Hospital Dr. Zainoel Abidin Banda Aceh. Data collection was carried out from 12 August to 21 September 2020.

The population in this study were all women who gave birth using the method of cesarean section at the General Hospital Dr. Zainoel Abidin Banda Aceh for the last 1 year, namely April 2019 to April 2020, namely 854 people. Samples were taken using a non-probability sampling method using total sampling type and the sample in question was all women who gave birth using the cesarean section method for the last 1 year, namely April 2019 to April 2020 who met the inclusion and exclusion criteria of 781 samples.

The research instrument used maternal medical record data with cesarean section in General Hospital Dr. Zainoel Abidin Banda Aceh for the past 1 year from April 2019 to April 2020. Collecting data in this study by taking patient data in the registration booklet in the delivery room and Arafah 2 room then tracing the medical records of cesarean section patients to find out whether there was a history of cesarean section or not.

RESULTS

Table 1. Subject Characteristics

Characteristics	Frequency (N)	(%)
Mother's Age		
<20	10	1.3
20 - 35	609	78.0
>35	162	20.7
Gravida		
Primigravida	209	26.8
Multigravida	572	73.2
Parity		
Nullipara	245	31.4
Primipara	208	26.6
Multiparous	328	42.0
Abortion		
Yes	126	16.1
No	655	83.9

Table 2. Distribution of the Frequency of Placenta Accreta Occurrences in Maternal CS at RSUDZA Banda Aceh April 2019 - April 2020

	Frequency (N)	(%)
Placenta accreta	22	2.8
No Placenta accreta	759	97.2
Total	781	100

Tabel 3. The Relationship between Cesarean Section History and the Incidence of Placenta accreta at RSUDZA Banda Aceh April 2019 - April 2020

History of Cesarean Section	Placenta Accreta				Total		*P-value*	Risk Estimated
	Yes		No					
	N	%	N	%	N	%		
Yes	18	2.30	302	38.68	320	40.98	0.000	6.483
None/Primary SC	4	0.51	457	58.51	461	59.02		
Total	22	2.81	759	97.19	781	100		

Table 4. Characteristics of placenta accreta patients with a history of cesarean section at RSUDZA April 2019 - April 2020

Characteristics	Frequency (18)	(%)
Mother's Age (years)		
20 - 35	14	77.8
> 35	4	22.2
Gravida		
Multigravida	18	100
Parity		
Primipara	5	27.8
Multiparous	13	72.2
Abortion		
Yes	4	22.2
No	14	77.8
History of the Cesarean Section		
1X	7	38.8
2X	9	50.0
3X	2	11.1
Placenta Position		
Fundal Placenta	1	5.6
Low laying Placenta	1	5.6
PPT	10	55.6
PPT Anterior	6	33.3
Probability of Invasion PAS (%)		
33	5	27.8
51	4	22.2
69	8	44.4
19	1	5.6
Anatomical Pathology Results		
Not Placenta accreta	2	11.1
Placenta accreta	7	38.9
Placenta Increta	1	5.6
Placenta Percreta	2	11.1
PA results are unknown	6	33.3
Education		
Diploma IV	7	38.9
Diploma III	2	11.1
High school	8	44.4
Junior High School	1	5.6
Profession		
Honorary	2	18.2
Housewife	11	61.1
Civil servants	2	11.1
Private	2	11.1
Nurse	1	5.6
Outcome mother		
Life	17	94.4
Death	1	5.6
Outcome Baby		
Life	18	100

DISCUSSION

The majority of samples in this study were aged 20-35 years with a percentage of 78.0%. This is in line with the analysis of the 2017 IDHS data in 2019 that the method of cesarean section delivery in Indonesia is mostly for mothers aged 20–35 years.[13] This is also in accordance with research in 2019 at Pringsewu Hospital Lampung that the majority of mothers at the age of 20-35 years experienced cesarean section which may be caused by several factors such as maternal health conditions that do not allow vaginal delivery, one of which is heavy bleeding during pregnancy or physical stress. as well as mental and can be caused by other pregnancy complications so it should use the method of cesarean section.[17] The majority of respondents in this study were multigravida status at 73.2%. Based on parity status, respondents with multiparous status were 42.0%. The multiparous parity status was higher when compared to nulliparous and primiparous. While the majority of women who gave birth with cesarean section who experienced abortion, only 16.1% and 655 other mothers did not experience abortion (83.9%).

In this Study shows that women with CS with a history of CS 2.30% had Placenta accreta while women who gave birth with a cesarean section who did not have a history of CS 0.51% had Placenta accreta.[18] Chi-square test with Confident Interval (CI) 95% resulted in a p value of 0.000 which means that there is a significant relationship between the history of cesarean section and the incidence of placenta accreta. A retrospective cohort study in 2019 in China also supported the results of this study that there was statistical significance on history of CS, the amount of vaginal bleeding, medications during pregnancy, and placenta previa which were independent risk factors for placenta accreta with a p value of 0.04 for history of CS.[19]

Our study also shows the Risk Estimate which aims to estimate the risk of women in cesarean section with a history of CS experiencing placenta accreta. The result of the Risk estimate obtained was 6.483 with a Confident Interval (CI) of 95% (2.21-18.97), which means that mothers with a history of CS have a 6 times greater risk of experiencing placenta accreta. The results of this study are supported by a study entitled Analysis of pregnancy in women with a history of previous cesarean section and it was found that this study showed an association between abnormal placenta in women with a history of previous CS. Cesarean section was associated with an increased risk of abnormal placenta including 2.6 times higher placenta accreta and placenta previa 1, 8 times higher than that of mothers who did not have a previous CS. A cohort study conducted in the UK reported that the incidence of abnormal placenta was the reason that 40% of women had to have hysterectomy.[20]

Characteristics of Placenta Accreta Patients with a History of Cesarean Section

Mother's Age

The characteristics of placenta accreta patients with a history of CS in RSUDZA are presented in table 4 where the age of mothers who experienced placenta accreta with a history of CS was 77.8% experienced by mothers aged 20-35 years as many as 14 people. This occurs because almost part of the sample in the study were mothers of productive age for the pregnancy process, although at the age of 20-35 the uterus was still quite strong, but it did not rule out placenta accreta due to other factors. This result is different from the research at RSUP Dr. M. Djamil Padang in 2017 who found that the mother who experienced placenta accreta was more at age> 35 years.[21]One of the risk factors that can affect the condition of the mother is age. At the age of> 35 years the uterus is associated with decreased vascularity which can lead to tissue hypoxia.

Gravida

The results of this study indicate that mothers who have 100% placenta accreta are multigravidas, meaning that placenta accreta predominantly occurs in women who have been pregnant more than once. Placenta accreta in multigravida mothers is associated with previous gestational measures be it previous methods of delivery such as CS, condition of the mother's uterus and other supportive factors.

Parity

Parity is one of the characteristics of placenta accreta in this study, Table 4 shows that placenta accreta occurs mostly in multiparous women as much as 72.2%. This is consistent with a study conducted in 2018 entitled The relationship between placenta accreta index scores and the incidence of placenta accreta at RSUP M. Djamil Padang where the results showed that cases of placenta accreta were more prevalent in multiparous women with a percentage of 57.7%.[22]

Abortion

Patients with placenta accreta with a history of CS who experienced a slight abortion, namely 22.2%. This means that the characteristics of placenta accreta patients in RSUDZA majority do not experience abortion.

History of Cesarean Section

The results of this study indicate a significant relationship between history of CS and the incidence of placenta accreta. The results of the characteristics obtained in table 4 show that the number of CS was twice, more experienced with placenta accreta with a percentage of 50.0%, while the number of CS three times was only 11.1%.

Placenta Position

The characteristics of placenta accreta based on the position of the placenta when seen from Table 4, the majority are placenta previa totalis. The most frequent distribution of placenta positions in placenta accreta patients is placenta previa totalis, namely 55.6%. The results of this study are also in line with the results of research at Hasan Sadikin General Hospital Bandung in 2017 that the most common type of placenta previa found in invasive placenta including placenta accreta is placenta previa totalis anterior where the significance of the p value was 0.001 for anterior PPT.

Probability invasion of PAS

Probability of invasion of placenta accreta based on table 4, the largest proportion was 69% with a percentage of 44.4%. This means that the mean placenta accreta index scoring is 5, with an invasion probability of 69%, a sensitivity of 52% and a specification of 92%.

Type of Placenta Accreta Spectrum

The type of placenta accreta spectrum based on ultrasound results with laboratory confirmation of anatomic pathology in table 4 was mostly placenta accreta with a percentage of 38.9% and 6 of the 18 placenta accreta patients with a history of CS had no anatomic pathology results.

Education and Work

Education and work are demographic characteristics that accompany placenta accreta patients, in table 4 it shows that most mothers with placenta accreta have Diploma IV and high school education, while work for mothers with placenta accreta is housewives with a percentage of 61.1%. These results indicate that the majority of placenta accreta patients are educated and know the actions and health problems they experience.

Outcome Mothers and Infants

Outcome mothers and infants in patients with placenta accreta can describe the mortality and morbidity rates of placenta accreta itself. Table 4 shows that the maternal outcome for placenta accreta was 94.4% alive. Meanwhile, the mortality rate in mothers with placenta accreta was 5.6%, this shows a high enough number when viewed from the number of patients. The number 1 in 18 mothers with placenta accreta who experience death is quite alarming. This is also supported by a study conducted in 2019 in a survey analysis of the world health organization that the greatest effect between maternal outcomes and CS results is severe maternal outcomes reaching 6.5 per 1000 live births and maternal mortality 5.5 per 1000 live birth. The infant outcome in placenta accreta patients was 100% alive.

CONCLUSSION

Based on the results of the study, it can be concluded that there is a significant relations between history of cesarean section and the incidence of placenta accreta at the General Hospital Dr. Zainoel Abidin Banda Aceh.

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Research Article

The Characteristics Urinary Tract Infection and Antimicrobial Sensitivity Patterns in Pregnant Women

Karakteristik Infeksi Saluran Kemih dan Pola Sensitivitas Antimikroba pada Ibu Hamil

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Abstract

Objective: To determine the comparison of uropathogenic patterns and antimicrobial sensitivity tests in pregnant women in Manado.

Methods: This study was a cross-sectional study on 28 pregnant women with UTI who presented to Prof. Dr. R. D. Kandou General Central Hospital, Pancaran Kasih Hospital, and Manado City Bhayangkara Hospital in Manado from February 2021 to April 2021. The data were analyzed using Microsoft Excel software.

Results: Most pregnant women with UTI were within the age range of 20-35 years, namely 16 subjects (57.14%). Most had parity status of multipara, namely 15 subjects (53.57%). For the history of UTI, most subjects had no history of UTI, namely 16 subjects (57.14%), and had no history of contraception uses, namely 20 subjects (71.43%). Most subjects also had no history of vaginal discharge, namely 18 subjects (64.29%). Of 28 pregnant women with UTI, 23 (82.14%) were asymptomatic, while 5 (17.86%) were symptomatic. E.coli was the most commonly found pathogen and was still sensitive to most antibiotics.

Conclusion: The description of pregnant women with UTI in Prof. Dr. R. D. Kandou General Central Hospital, Pancaran Kasih Hospital, and Bhayangkara Hospital in Manado City was pregnant women aged 17-34 years, multigravida, in the 3rd trimester, had an education level of Elementary-High school, unemployed, under the minimum wage, had no history of UTI or contraception uses and had a history of vaginal discharge. Most pregnant women with UTI were asymptomatic. The most common bacterial growth was in E.coli, and it was still sensitive to most antibiotics.

Keywords: antimicrobial, microorganism, pregnancy, UTI.

Abstrak

Tujuan: *Untuk mengetahui perbandingan pola uropatogen dan uji kepekaan antimikroba pada perempuan hamil di kota Manado.*

Metode: *Penelitian ini merupakan penelitian yang menggunakan pendekatan potong lintang terhadap 28 perempuan hamil dengan ISK yang datang memeriksakan diri di RSUP Prof dr. R. D. Kandou Manado, RS Pancaran Kasih, dan RS Bhayangkara kota Manado dari Februari 2021 hingga April 2021. Analisis data dilakukan menggunakan program Microsoft Excel.*

Hasil: *Kelompok usia terbanyak dengan ISK pada ibu hamil adalah 20-35 tahun sebanyak 16 orang (57,14%). Karakteristik graviditas paling banyak adalah pada kelompok multipara yaitu sebanyak 15 orang (53,57%). Hasil karakteristik kelompok tanpa riwayat ISK merupakan yang paling banyak yaitu sebanyak 16 orang (57,14%). Mayoritas peserta penelitian tidak mempunyai riwayat pemakaian KB yaitu sebanyak 20 orang (71,43%). Mayoritas peserta penelitian mempunyai riwayat flour albus yaitu sebanyak 18 orang (64,29%). Hasil sebaran distribusi ibu hamil dengan ISK, didapatkan dari 28 subyek, terdapat 23 orang (82,14%) yang tidak memiliki gejala, sedangkan 5 orang (17,86%) memiliki gejala. Hasil sebaran jenis mikroorganisme yang tumbuh pada kultur paling banyak adalah E. coli dan mikroorganisme ini masih sensitif terhadap mayoritas antibiotik.*

Kesimpulan: *Gambaran sebaran perempuan hamil dengan ISK di RSUP Prof. Dr. R. D. Kandou, RS pancaran Kasih, dan RS Bhayangkara di kota Manado adalah pada perempuan hamil dengan usia 17-34 tahun, multigravida, hamil trimester 3, berpendidikan SD-SMA, tidak bekerja, memiliki penghasilan di bawah UMR, tidak memiliki riwayat ISK, tidak memiliki riwayat KB, dan memiliki riwayat fluor albus. Mayoritas perempuan hamil dengan ISK tidak memiliki gejala Pertumbuhan bakteri terbanyak adalah E.coli dan mikroorganisme tersebut masih sensitif terhadap mayoritas antibiotik.*

Kata kunci: *antimikroba, ISK, kehamilan, mikroorganisme.*

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INTRODUCTION

Pregnant women are a group that is of concern in healthcare services. Urinary tract infection is an issue in pregnant women. Urinary tract infection (UTI) is the most commonly found bacterial infection in pregnancy, with a mean prevalence of 2-10%.[1,2] Data has shown that approximately 150 million people suffer from UTI annually.[3] In Indonesia, the prevalence of asymptomatic bacteriuria is 7.3%.[5]

Physiological changes in the urinary tract during pregnancy increase the risk of UTI. Progesterone hormone and obstruction from the uterus cause pelvicalyceal system and ureter dilatation and increased vesicoureteral reflux. The pressure generated by the fetus head also obstructs blood and lymph drainage from the vesica, therefore causing edema and susceptibility to trauma.[6] UTI is the leading cause of poor pregnancy outcomes. It is associated with poor outcomes such as premature labor, intrauterine growth retardation, chorioamnionitis, and stillbirth, which increases neonatal mortality.[2]

According to SDKI in Indonesia, Infant Mortality Rate (IMR) has dropped from 35/1000 live birth (LB) in 2004 to 34/1000 live birth in 2007.[7] This complication is not only caused by symptomatic UTI but also asymptomatic bacteriuria.[8] Urinary tract infection is a condition that cannot be ignored since the prevalence of asymptomatic bacteriuria in pregnancy is still 7.3%. The incidence in adult women is higher than men or children.[9] Studies have shown that approximately 7% of pregnant women have a bacterial count in the urine of >100.000 cfu (colony forming unit)/ml. In nonpregnant women, the frequency ranges from 2.8%-22%. True infection occurs between gestational age 26 to 36 weeks, with the peak incidence in gestational age 30-32 weeks.[7] A study reported that 24% of pregnant women with urinary tract infection had preterm labor, and with the appropriate treatment, the premature labor could be reduced to 10%.[10,11]

Antimicrobial drugs as a pillar in modern medicine play a critical role in prophylaxis and treatment for infectious diseases. Large quantities and inappropriate uses are the leading cause of such a high number of resistant pathogenic microorganisms and commensal bacteria globally, which increases the demand for new antimicrobial drugs. Reducing the number of inappropriate antimicrobial drugs is the best approach to control bacterial resistance to antimicrobial drugs.[12,15] For this reason, the authors aimed to conduct a study to determine the comparison of uropathogenic patterns and antimicrobial sensitivity tests in pregnant women in Manado.

METHODS

This study was a cross-sectional study to evaluate the microorganism pattern of UTI in pregnant women. The study population was pregnant women who presented to Prof. Dr. R. D. Kandou General Central Hospital, Pancaran Kasih Hospital, and Manado City Bhayangkara Hospital in Manado from February 2021 to April 2021. The subjects in this study were selected by consecutive sampling who met the inclusion criteria and had signed informed consent. The total sample size was 28 women. The Hospital Ethics Committees and Institutional Review Board Approval approved this study.

The inclusion criteria for the subjects of this study were pregnant women with UTI who presented for antenatal care in the Department of Obstetrics and Gynecology, Prof. Dr. R. D. Kandou General Central hospital and Pancaran Kasih Hospital, and Manado City Bhayangkara Hospital in Manado; and willing to participate in the study and signing the Informed Consent. The exclusion criteria of this study were ongoing antimicrobial treatment, ongoing immunosuppressive treatment, history of urinary catheter use, history of sexual intercourse in the last 24 hours, and not willing to participate in the study. The sample was examined for urinalysis and culture tests.

The variables in this study were age, parity, gestational age, educations, occupations, socioeconomic background, history of UTI, history of contraception uses, history of vaginal discharge, UTI symptoms, types of microorganism, and antimicrobial sensitivity pattern. The data were analyzed using Microsoft Excel software.

RESULTS

The study population were pregnant women with UTI who presented to Prof. Dr. R. D. Kandou General Central Hospital, Pancaran Kasih Hospital, and Bhayangkara Hospital in Manado from February 2021 to April 2021 (Table 1).

Table 1. Characteristics of the Subjects

Characteristics	**Total**	
	N	**%**
Age range (years)		
<20	2	7.14
20-35	16	57.14
>35	10	35.72
Parity		
Primipara	13	46.43
Multipara	15	53.57
Gestational Age (trimester)		
1^{st}	4	14.2
2^{nd}	5	17.9
3^{rd}	19	67.90
Education Level		
Elementary-High school	20	71.43
University/higher degree	8	28.57
Occupation		
Unemployed	21	75.00
Employed	7	25.00
Socioeconomic Status (wage)		
< Minimum	19	67.86
> Minimum	9	32.14
History of UTI		
Yes	12	32.14
No	16	42.86
History of contraception		
Yes	8	28.57
No	20	71.43
History of vaginal discharge		
Yes	18	64.29
No	10	35.71
UTI symptoms		
Yes	5	17.86
No	23	82.14

Most pregnant women with UTI were within the age range of 20-35 years, namely 16 subjects (57.14%). Most had parity status of multipara, namely 15 subjects (53.57%). For the history of UTI, most subjects had no history of UTI, namely 16 subjects (57.14%), and had no history of contraception uses, namely 20 subjects (71.43%). Most subjects also had no history of vaginal discharge, namely 18 subjects (64.29%). Of 28 pregnant women with UTI, 23 (82.14%) were asymptomatic, while 5 (17.86%) were symptomatic.

Table 2. Microorganism Growth

Microorganism Type (n=28)	**Total N**	**%**
E. coli	11	39.30
Enterobacter sp	3	10.71
Staphylococcus sp	4	14.29
Klebsiella sp	2	7.14
Streptoccocus sp	2	7.14
Stenotrophomonas sp	2	7.14
Others	2	7.14
Negative / No growth	2	7.14
Total	28	100

Table 2 showed that *E.coli* was the most commonly found pathogen in our study (11 subjects or 39.30%), followed by *Staphylococcus sp.* (4 subjects or 14.29%), *Enterobacter sp.* (3 subjects or 10.71%), *Klebsiella sp.* (2 subjects or 7.14%), *Streptococcus sp.* (2 subjects or 7.14%), *Stenotrophomonas sp.* (2 subjects or 7.14%), and other microorganisms (2 subjects or 7.14%). Other microorganisms included *Acinetobacter baumannii* (1 subject) dan *Trichosporon asahii* (1 subject). 2 subjects (7.14%) had no growth in their urinary bacterial culture test.

Table 3. Microorganism Sensitivity Test Result Found in UTI in Pregnancy

Antibiotics	E.coli			Enterobac-ter sp.			Staphylococ-cus sp.			Klebsiella sp.			Streptococcus sp.			Stenotroph-omonas sp.		
	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R
Amikacin	9	1	1	3	0	0	3	0	1	2	0	0	1	0	1	2	0	0
Azithromycin	8	1	2	1	1	1	2	1	1	2	0	0	2	0	0	1	0	1
Ampicillin	9	0	2	2	0	1	3	1	0	1	0	1	2	0	0	1	1	0
Amoxiclav	8	2	1	3	0	0	3	0	1	2	0	0	1	1	0	2	0	0
Cefotaxime	7	3	1	1	1	1	3	1	0	1	0	1	1	1	0	2	0	0
Cefazolin	9	2	0	3	0	0	4	0	0	2	0	0	1	0	1	2	0	0
Ampicillin/ Sulbactam	10	1	0	3	0	0	3	1	0	1	1	0	1	0	1	1	0	1
Cefixime	9	1	1	1	2	0	3	0	1	2	0	0	1	1	0	2	0	0
Cefuroxime	8	1	2	2	1	0	2	1	1	2	0	0	2	0	0	2	0	0
Ceftriaxone	7	3	1	2	0	1	2	0	2	1	0	1	1	1	0	1	1	0
Chloramphenicol	7	2	2	2	0	1	3	0	1	1	1	0	1	0	1	2	0	0
Ceftazidine	8	1	2	3	0	0	4	0	0	2	0	0	2	0	0	1	0	1
Clindamycin	9	1	1	2	1	0	3	0	1	1	0	1	2	0	0	2	0	0
Ciprofloxacin	8	1	2	1	2	0	2	0	2	2	0	0	1	1	0	2	0	0
Doxycyclin	7	3	1	3	0	0	3	0	1	1	1	0	2	0	0	2	0	0
Fosfomycin	9	0	2	2	1	0	2	0	2	1	0	1	2	0	0	2	0	0
Levofloxacin	8	1	2	2	1	0	3	0	1	1	1	0	1	0	1	2	0	0
Linezolid	8	2	1	3	0	0	3	1	0	2	0	0	1	1	0	1	1	0
Meropenem	8	1	2	3	0	0	4	0	0	1	0	1	1	0	1	2	0	0
Moxifloxacin	9	1	1	2	0	1	3	1	0	2	0	0	2	0	0	1	0	1
Mincocycline	7	1	3	3	0	0	3	0	1	2	0	0	1	1	0	2	0	0
Ofloxacin	9	2	0	3	0	0	2	1	1	2	0	0	2	0	0	1	1	0
Pipemidic Acid	7	1	3	2	1	0	3	0	1	1	1	0	1	0	1	2	0	0
Sulbactam/ Cefoperzone	10	1	0	2	1	0	2	1	1	1	1	0	2	0	0	2	0	0
Sulfametoxazole/ trimethoprim	9	1	1	1	1	1	2	1	1	1	0	1	1	1	0	1	0	1
Ticarcillin/ Clavulanic acid	10	0	1	2	1	0	3	0	1	2	0	0	2	0	0	2	0	0
Vancomycin	9	2	0	2	0	1	2	2	0	1	1	0	2	0	0	2	0	0
Tetracycline	9	0	2	2	0	1	3	0	1	1	0	1	1	0	1	2	0	0
Ticarcillyn	8	3	0	2	0	1	2	2	0	1	0	1	2	0	0	1	1	0
Trimetoprim	9	0	2	1	1	1	3	0	1	2	0	0	2	0	0	2	0	0
Novobiovim	8	3	0	2	1	0	3	1	0	2	0	0	2	0	0	2	0	0

Notes : S = Sensitive, I = Intermediate, R = Resistant

DISCUSSION

Of 28 subjects who met the inclusion and exclusion criteria, we obtained 26 (92.86%) subjects with positive urinary culture (detected bacterial growth) and 2 subjects (7.14%) with negative urinary culture (no bacterial growth detected). Most pregnant women with UTI were in the age range of 20-35 years, compared to <20 years and >35 years (57.14% vs. 7.14% vs. 35.72%, respectively). Most subjects were in multigravida, namely 15 subjects, compared to primigravida, 13 subjects (46.43% vs. 53.73%, respectively). As for the gestational age, most subjects were in their 3rd trimester, namely 19 subjects (67.9%). Most subjects had a low educational level, namely 20 subjects, compared to a higher degree (71.43% vs. 28.57%). Most subjects were also unemployed/ housewives, namely 21 subjects (75% vs. 25%). A higher number of subjects with UTI was found in the reproductive age, multipara, and the 3rd trimester. This result is in line with other studies, which suggested that women in these categories are sexually active.[16]

Most patients had no history of UTI (57.14% vs. 42.86%), no history of contraception uses (71.43% vs. 28.57%), had a history of vaginal discharge (64.29% vs. 35.71%), and were asymptomatic (82.14% vs. 17.86%). For the microorganism type distribution in the urinary culture, we found that the most common cause of UTI in pregnant women in Manado City was *E.coli,* namely 11 subjects (39.30%), followed by *Staphylococcus sp.* (14,29%), *Enterobacter sp.* (10,71%), Klebsiella sp. (7,14%), Streptococcus sp. (7,14%), *Stenotrophomonas sp.* (7,14%), and other microorganisms (7,14%) including *Acinetobacter baumannii* (1 subject) and *Trichosporon asahii* (1 subject).

E.coli is a commensal flora in the perineum region; thus, it can easily invade the urinary tract. The orifice of the urethra near the anus and a significantly shorter urethral length than men are the cause of such susceptibility to urinary tract infection. The incidence of asymptomatic bacteriuria of 15% and caused mainly by E.coli.[17]Ethiopia found that the most common microorganism that causes UTI is E.coli (45.7%).[18,19] E.coli as the most microorganism (34.6%).[20] Studies in Hongkong, Pakistan, India, and Poland also found E.coli as the most common organism causing UTI.[14,21]

Half of *Staphylococcus sp* is normal flora on the skin, respiratory tract, and gastrointestinal tract in humans; however, there is also a primary pathogen in humans. Urinary tract infection caused by *Staphylococcus sp.* Typically occurs secondary to blood-borne infection. In this study, contamination was prevented by rinsing the genital with water and soap and drying it according to the standard protocol to obtain a midstream urinary sample. The time interval between taking the urine sample to examination was under 1 hour; therefore, contamination bacteria did not grow over 100.000 cfu (colony forming unit)/ml. The urine sample was midstream urine during the subject's ANC visit.

In this study, we found that *E. coli* microorganism was still sensitive to most antibiotics, such as amikacin, azithromycin, ampicillin, amoxiclav, cefotaxime, cefazolin, ampicillin/sulbactam, cefixime, cefuroxime, ceftriaxone, chloramphenicol, ceftazidime, clindamycin, ciprofloxacin, doxycycline, levofloxacin, meropenem, moxifloxacin, ofloxacin, sulfamethoxazole / trimethoprim, vancomycin, tetracycline, and novobiovim. *Staphylococcus sp.* was still sensitive to amikacin, azithromycin, ampicillin, amoxiclav, cefotaxime, cefazolin, ampicillin/sulbactam, cefixime, cefuroxime, ceftriaxone, chloramphenicol, ceftazidime, clindamycin, ciprofloxacin, doxycycline, levofloxacin, meropenem, moxifloxacin, ofloxacin, sulfamethoxazole / trimethoprim, ticarcillin / clavulanic acid, vancomycin, tetracycline, and novobiovim. *Enterobacter sp.* was still sensitive to amikacin, azithromycin, ampicillin, amoxiclav, cefotaxime, cefazolin, ampicillin / sulbactam, cefixime, cefuroxime, ceftriaxone, chloramphenicol, ceftazidime, clindamycin, ciprofloxacin, doxycycline, levofloxacin, meropenem, moxifloxacin, minocycline, ofloxacin, sulfamethoxazole/trimethoprim, sulbactam / cefoperazone, vancomycin, and tetracyclin

CONCLUSION

The description of pregnant women with UTI in Prof. Dr. R. D. Kandou General Central Hospital, Pancaran Kasih Hospital, and Bhayangkara Hospital in Manado City was pregnant women aged 17-34 years, multigravida, in the 3rd trimester, had an education level of Elementary-High school, unemployed, under the minimum wage, had no history of UTI or contraception uses and had a history of vaginal discharge. Most pregnant women with UTI were asymptomatic. The most common bacterial growth was in *E.coli,* followed by *Staphylococcus sp.,* and *Enterobacter sp.*The microorganisms in the urinary culture were still sensitive to most antibiotics. *E. coli* was sensitive to ampicillin/sulbactam, sulbactam/cefoperazone, *clavulanic acid*, amikacin, ampicillin, cefazolin, cefixime, clindamycin, Fosfomycin, and moxifloxacin.

DECLARATIONS

ACKNOWLEDGMENT
None to declare

FINANCIAL DISCLOSURE or FUNDING
None to declare

CONFLICT of INTEREST
There is no conflict of interests.

INFORMED CONSENT
Obtained

INSTITUTIONAL REVIEW BOARD APPROVAL
Approved

ETHICAL COMPLIANCE with HUMAN

This study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration. The Hospital Ethics Committees approved this study.

DATA AVAILABILITY

The authors declare that data supporting the findings of this study are available within the article.

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Research Article

C-Reactive Protein and Matrix Metalloproteinase-7 in Preterm Premature Rupture of Membranes (PPROM) and Premature Rupture of Membranes (PROM)

C-Reactive Protein dan Matrix Metalloproteinase-7 pada Ketuban Pecah Dini Kehamilan Preterm dan Aterm

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Abstract

Objective: To determine the difference in qualitative serum CRP and MMP-7 levels between PROM and PPROM.

Methods: Research with a case-control design with premature rupture of membranes in term pregnancy as a control group and preterm pregnancy as a case group conducted in the delivery room of the Regional General Hospital dr. Zainoel Abidin Banda Aceh starting from January 2020. Total number of each group as many as 30 samples that met the inclusion and exclusion criteria by taking venous blood samples to check the levels of qualitative CRP serum and levels of the Metalloproteinase-7 Matrix (MMP-7). Statistical tests for categorical - numerical data groups were tested using *independent sample t-test* and categorical - categorical data groups were tested using Chi-Square test.

Results: A total of 60 samples with 30 PPROM and 30 PROM mothers. There was no statistically significant difference in the qualitative CRP serum result in PROM patients with term and preterm pregnancies. On MMP-7 examination, the mean MMP-7 level of preterm PROM mothers was higher than at term PROM, which was 5.28 mg / L and there was a significant relationship between MMP-7 and qualitative CRP in PROM patients with term pregnancy ($p < 0.05$).

Conclusion: There is no significant difference in the value of qualitative CRP and MMP-7 between PPROM and PROM. However, there was a significant association between qualitative serum CRP and plasma MMP-7 in PROM.

Keywords: c-reactive protein, matrix metalloproteinase 7, rupture of membranes.

Abstrak

Tujuan: *Untuk mengetahui perbedaan gambaran serum CRP kualitatif dan kadar MMP-7 antara kehamilan preterm dan aterm dengan ketuban pecah dini di RSUD Dr. Zainoel Abidin Banda Aceh.*

Metode: *Penelitian dengan desain kasus kontrol dengan ketuban pecah dini kehamilan aterm sebagai kelompok kontrol dan kehamilan preterm sebagai kelompok kasus. yang dilakukan di Kamar Bersalin Rumah Sakit Umum Daerah dr. Zainoel Abidin Banda Aceh pada Januari 2020. Dengan jumlah masing-masing kelompok sebanyak 30 sampel yang memenuhi kriteria inklusi dan eklusi dengan pengambilan sampel darah vena untuk dilakukan pemeriksaan kadar serum CRP kualitatif dan kadar Matrix Metalloproteinase-7 (MMP-7). Uji statistik untuk kelompok data yang bersifat kategorik - numerik diuji menggunakan uji T tidak berpasangan dan pasangan kelompok data yang bersifat kategorik - katergorik akan diuji menggunakan uji Chi-Square.*

Hasil: *Sebanyak 60 penderita KPD dengan 30 Ibu KPD Preterm dan 30 KPD aterm. Tidak dijumpai perbedaan yang bermakna secara statistik gambaran serum CRP kualitatif pada penderita KPD dengan kehamilan aterm dan preterm. Pada pemeriksaan MMP-7 rerata kadar MMP-7 ibu KPD preterm lebih tinggi dibandingkan KPD aterm yakni senilai 5,28 mg/L dan terdapat hubungan bermakna antara MMP-7 dan CRP kualitatif pada penderita KPD dengan kehamilan aterm ($p < 0,05$).*

Kesimpulan: *Tidak terdapat perbedaan gambaran signifikan nilai CRP kualitatif dan MMP-7 antara KPD preterm dan aterm. Namun, terdapat hubungan yang signifikan antara serum CRP kualitatif dan MMP-7 plasma pada penderita ketuban pecah dini dengan kehamilan aterm.*

Kata kunci: *c-reactive protein, matrix metalloproteinase-7, ketuban pecah dini.*

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INTRODUCTION

Preterm premature rupture of membranes (PPROM) is defined as rupture of the membranes that occur before labour signs under 37 weeks of gestation while Premature rupture of membranes (PROM) takes place at 37 weeks of gestation or later.[1-3] The incidence of PROM is a global obstetric problem with the incidence rate varying between 5-10% of all births. In term pregnancy, as many as 70% and 30% of PROM cases cause preterm birth. The incidence of PROM also plays a role in causing chorioamnionitis infection which can lead to sepsis, therefore increasing maternal and perinatal morbidity and mortality due to ascending infection and cord compression.[4-6]

Various risk factors are suspected to be the basis for the occurrence of PROM. The incidence of PROM in preterm pregnancy can also be caused by infection or inflammation of the choriodecidua and a decrease in the amount of collagen from the amniotic membrane is thought to be a predisposing factor for preterm PROM.[7] Early identification of infection due to PROM is important to prevent complications. However, the results of the parameters for the examination of infection in the basic laboratory such as blood leukocyte count, sedimentation rate, and specificity are difficult to rely on because of their low sensitivity and specificity due to physiological and hematologic changes in pregnant women.[8]

One of the parameters for establishing an early diagnosis or a useful marker of an infection and inflammation process is C-Reactive Protein (CRP) which is an acute-phase protein that can be an early and reliable indicator of clinical histopathology and chorioamnionitis.[8,9] Several studies have shown that the mechanical strength of fetal membranes and reduced tension resistance in PROM due to increased collagen degradation and matrix metalloproteinase (MMP) are the main mediators of collagen degradation from the amniotic membrane.[10,11] Multiple MMPs participate in the degradation of the extracellular matrix of the fetal membrane at preterm or in labor. Metalloproteinase-7 (MMP-7) or matrilysin is classified as collagenase which can cause degradation of the amniotic membrane and can decrease various components of the matrix including collagen type IV, fibronectin, elastin, and laminin.[10,12]

Several studies have assessed the increase in both CRP and MMP in premature rupture of membranes. However, differences in their value between preterm and term pregnancies is not yet known. The authors of this study wanted to know the differences in serum levels of CRP and MMP-7 associated with PPROM and PROM cases at the Regional General Hospital Dr. Zainoel Abidin Banda Aceh.

METHODS

This was an unpaired numerical comparative analytic study with a case-control design conducted in the Maternity Room of the Regional General Hospital dr. Zainoel Abidin Banda Aceh starting from January 2020 until the amount of sample is fulfilled. The sample of this study is population that meets the research criteria in the form of inclusion criteria, namely PPROM pregnant women, PROM pregnant women, single fetuses living intrauterine, and those who are willing to participate by signing informed consent form. Exclusion criteria includes pregnancy with inflammatory diseases and systemic infectious diseases such as pneumonia, typhoid, malaria, hepatitis, pre-eclampsia, eclampsia, antepartum hemorrhage, prior antibiotic treatment, cervical incompetence, polyhydramnios, history of trauma during pregnancy, mothers with smoking habits, multiple pregnancies, and fetuses with congenital abnormalities.

The results of the sample calculation for preterm and term group were 30 respondents. The research procedure was carried out by examining all pregnant women with PROM who came to the delivery room of the Regional General Hospital dr. Zainoel Abidin Banda Aceh, who was included in the inclusion criteria. For each patient, history taking was done followed by ultrasound examination to rule out the exclusion criteria. Examination of the amniotic fluid either by direct observation, examination with inspeculo or with nitrazine paper then informed consent was then carried out. 6 cc of blood samples were taken from 6 thecubital veins to check qualitative CRP serum and MMP-7 levels, then the samples were centrifuged at a speed of 40,000 rpm for 10 minutes until the serum was divided into 10 small serum tubes of 0.3 cc each and stored in a refrigerator with a temperature of -40° C and was sent to Prodia Laboratory for further examination.

The data obtained from the research will be analyzed in univariate and bivariate methods. Categorical and numerical group pairs were tested using the independent sample t-test and samples that did not meet the requirements of the normal distribution based on the Kolmogorov Smirnov test were tested using the Mann Whitney U test. Pairs of categorical and categorical data groups were tested using the Chi-Square test with the significance level used was α = 0.05 with 95% Confidence Interval.

RESULTS

After the data was collected, there were 60 patients with rupture of the membranes with 30 mothers with gestation <37 weeks classified as preterm pregnancy (case group) and 30 mothers with gestation ≥ 37 weeks classified as term pregnancy (control group).

Based on the characteristics of our research subjects including age and obstetric status, the age of PROM patients were relatively younger than PPROM patients. However, there is no significant difference in the mean age between the two groups ($p > 0.05$). From their obstetrical status, both groups of PROM patients with term and preterm pregnancies showed the same distribution, namely Gravida 2. From their obstetric status, we did not find any significant difference between the two groups with a significance value of > 0.05.

Analysis of differences in qualitative CRP serum images in PROM patients with term and preterm pregnancies is presented in Table 1.

Table 1. Analysis of Differences in Qualitative Serum CRP Features in PROM and PPROM

	Rupture of membranes		*P-value**
	Preterm	Aterm	
CRP (+)	7	6	0.754
CRP (-)	23	24	

** Chi-Squared test*

According to the Chi-squared test in Table 1. there were 7 PROM mothers with preterm pregnancy who showed positive CRP values. Statistically, the qualitative CRP serum appearance on PROM and PPROM did not show any significant difference.

Analysis of differences in levels of MMP-7 in PROM and PPROM patients is presented in Table 2.

Table 2. Analysis of Differences in Levels of MMP-7 in PROM and PPROM

Rupture of membranes Group	Median	Min - Max	*P-value**
Preterm pregnancy, n = 30	5.28	1.95 – 11.7	0.109
Aterm pregnancy, n = 30	4.34	2.7 – 10.37	

** Mann- Whitney U test*

Table 2. analyzes the differences in levels of MMP-7 in PROM and PPROM. The average MMP-7 level of PROM women with preterm pregnancy was higher than that of term pregnancy, which was 5.28 mg / L. Based on statistical tests using the Mann-Whitney U test, it is known that there is no significant difference in levels of MMP-7 in PROM and PPROM patients.

Analysis of the relationship between plasma MMP-7 levels and qualitative CRP in PROM patients is presented in Table 3.

Table 3. Analysis of the Relationship between Plasma MMP-7 Levels and Qualitative CRP in PROM

CRP	Median	Min - Max	*P-value**
Positive, n = 6	3.4	2.76 – 4.36	0.015
Negative n = 24	4.6	2.7 – 10.37	

** Mann- Whitney U test*

Table 3. analyzes the relationship between plasma MMP-7 levels and qualitative CRP at PROM and PPROM. Patients with a negative qualitative CRP value had higher plasma MMP-7 levels than positive CRP, with a mean level of 4.6 mg / L. Statistically, based on the Mann-Whitney U test, it was found that there was a significant relationship between MMP-7 and qualitative CRP in PROM patients ($p < 0.05$).

Table 4. Analysis of the Relationship between Plasma MMP-7 Levels and Qualitative CRP in PPROM

CRP	Mean ± SD	*P-value*
Positive, n = 7	4.58 ± 1.65	0.130
Negative, n = 23	6.03 ± 2.26	

** Independent sample t-test*

Analysis of the relationship between plasma MMP-7 levels and qualitative CRP in PPROM patients is presented in table 4. Patients with negative qualitative CRP values had higher levels of MMP-7 than positive CRP with a mean difference of 1.45 mg / L. Statistically, based on the Independent sample t-test, it is known that there is no significant relationship between MMP-7 and qualitative CRP in PPROM patients (p> 0.05).

DISCUSSION

In theory, an infection can cause PROM through several mechanisms. Macrophages and other cells also produce and release various cytokines such as IL-1 which is an endogenous pyrogen, TNF-α, and IL-6 when infection occurs. These three cytokines stimulate the liver to synthesize and release several plasma proteins such as acute-phase proteins, including CRP which can increase rapidly.[13] The synthesis of CRP in the liver takes place very rapidly with serum concentrations increasing above 5mg / L for 6-8 hours and reaching optimum levels in around 24-48 hours. CRP levels will drop dramatically when the inflammatory process or tissue damage subsides and within about 24-48 hours it reaches normal values again. CRP levels will be stable in plasma and are not influenced by diurnal variations.[13,14]

In this study, statistically, the analysis of differences in the qualitative features of CRP serum in PROM and PPROM patients using the Chi-squared test did not show any significant differences. Several previous studies compared CRP values between PROM and normal pregnancy, some analyzed CRP quantitatively and obtained similar results, namely that there were significant differences between the control group and the case group, thus showing that CRP was very well used as an early predictor of subclinical chorioamnionitis. In contrast to this study, when one examines a conclusion that the CRP value will indeed increase significantly in cases of PPROM and PROM.[9,13,15] However, if the description of the CRP value between the two groups is compared, it is also not a qualitatively significant difference.

Research has shown that collagen degradation can also occur in an intracellular pathway. Most have focused on the role of MMP-2 and MMP-9 in the rupture of the amniotic membrane, and only a few are concerned about other members of the MMP group (such as MMP-7) which have high degradative activity properties and are capable of triggering the cascade activation of other members of the MMP group.[16,17] Nishihara et al. found increased expression and activity of MMP-7 in amnion in PROM cases. These data suggest that MMP-7 may play an important role in rupture of the membrane and precipitate preterm birth.[18]

MMP-7 levels in PPROM patients in this study ranged from 1.95 - 11.7 mg / L. While the levels of MMP-7 in PROM mothers ranged from 2.7 - 10.37 mg / L. The mean plasma MMP-7 levels of PROM women with preterm pregnancy were higher than those of term pregnancies, namely 5.28 mg / L. This is different from that described by Wang et al., That the amniotic fluid concentration of MMP-7 increased significantly with increasing gestational age (Spearman ρ, r = 0.8; P <.001).(17) A previous study concluded that intra-amniotic infection is associated with a significant increase in Matrilysin (MMP-7) in the amniotic fluid in preterm labor and patients with PPROM without microbial invasion of the amniotic cavity.The MMP-7 values of both groups were increased, microbial invasion of the amniotic cavity was associated with a significant increase in the amniotic fluid MMP-7 concentration between the two groups.[19,20]

The results of this study did not find any significant differences in the features of qualitative serum CRP and serum MMP-7 between preterm and term pregnancies with premature rupture of membranes at the Regional General Hospital Dr. Zainoel Abidin Banda Aceh. Nonetheless, CRP and MMP-7 examinations can be used as markers of potential predisposing factors for PROM and PPROM cases.

Referring to the analysis of the relationship between plasma MMP-7 levels and qualitative CRP in PROM patients with term pregnancy, based on the Mann-Whitney U test, it was found that there was a significant relationship between plasma MMP-7 and qualitative CRP in PROM patients (p <0.05). However, statistically based on the Independent sample t-test, it was found that there was no significant relationship between plasma MMP-7 and qualitative CRP in PPROM patients (p> 0.05). From these two analyzes, in either PROM or PPROM, it is clear that plasma MMP-7 levels were more elevated in the CRP-negative group although in the CRP-positive group there was also an increase in MMP-7.

Physiologically, there is an increase in the concentration of MMP-7 with increasing gestational age. However, this is precisely the opposite of the results of this study in PROM conditions, MMP-7 levels were higher in preterm pregnancy (much younger gestational age) than in term pregnancy (6.03 vs 4.6 mg / L). This interpretation is consistent with the observation that microbial invasion of the amniotic cavity at term is not associated with a significant increase in MMP-7 nor CRP. Proinflammatory cytokine concentrations were significantly lower among patients with microbial invasion of the amniotic cavity in term pregnancy than in preterm patients with premature rupture of membranes.[19]

CONCLUSION

In this study, there was no significant difference in the qualitative serum CRP and MMP-7 values between preterm and term pregnancies with premature rupture of membranes. In terms of the relationship between CRP and MMP-7, it was found that there was a significant relationship between serum qualitative CRP and MMP-7 in patients with PPROM. However, it did not have a significant relationship in patients with premature rupture of membranes with term pregnancy.

SUGGESTIONS

It is hoped that there will be further studies with a larger number of research subjects as well as further multivariate studies to evaluate how strong the correlation between CRP, MMP-7, and other parameters related to examining the presence of microbial invasion as a marker of infection has occurred. It is hoped that CRP examination can be performed as a standard examination during antenatal care to predict the occurrence of PROM in patients with a high risk of infection.

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CONFLICT of INTERESTS

None to declare

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Research Article

Response of External Radiotherapy Alone in Stage IIB – IIIC Cervical Cancer Patients

Respon Radioterapi Eksterna Pasien Kanker Serviks Stadium IIB – IIIC

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Abstract

Objective: To investigate the therapeutic response and toxicity in cervical cancer patients with stage IIB-IIIC who undergo external radiation.

Methods: This was a retrospective study using the medical records of the Obstetric Oncology and Radiotherapy Department at Prof. Dr. R. D. Kandou Hospital Manado. The research subjects were stage IIB-IIIC cervical cancer patients who underwent external radiation from September 2016 to December 2020. External radiation was administrated using ^{60}Cobalt. The statistical analysis assessments in this study was carried out using descriptive analysis, while the analysis of the relationship was carried out using the Chi-Square method. The toxicity assessments were carried out from first day started external radiation up until 1 month after the therapy was deemed completed.

Results: As many as 413 cervical cancer patients underwent external radiation during the study. However, only 192 cervical cancer patients with stage IIB-IIIC met the inclusion criteria in this study. The complete response to the therapy based on the findings was 65.6%, the partial response was 31.8%, the stable response was 1.6%, and the progressive response was 1%. In statistical analysis there was a significant association between cervical cancer stage and Overall Treatment Time with response to external radiotherapy. However, no significant association between tumor size and histopathological type with response to external radiotherapy. There were hematological toxicity (45.8%), skin toxicity (45.3%), gastrointestinal toxicity (6.3%) and urinary tract toxicity (2.6%).

Conclusion: External radiotherapy response was a complete response where there was an association between cervical cancer stage and Overall Treatment Time with response to external radiotherapy, whereas there is no significant association found between the tumor size and histopathological type based on this research's findings. Most toxicity were hematology with complaints of anemia and thrombocytopenia.

Keywords: cervical cancer, external radiation response, toxicity.

Abstrak

Tujuan: *Untuk mengetahui respon terapi dan efek samping pasien kanker serviks stadium IIB-IIIC yang menjalani radioterapi eksterna.*

Metode: *Penelitian ini adalah penelitian deskriptif rektrospektif dengan menggunakan rekam medis Poli Onkologi Kandungan dan Instalasi Radioterapi RSUP Prof. Dr. R. D. Kandou Manado. Subyek penelitian adalah pasien kanker serviks stadium IIB-IIIC yang menjalani radiasi eksterna mulai September 2016 sampai Desember 2020. Radiasi eksterna dilakukan dengan sinar 60Cobalt. Penilaian analisis statistika pada penelitian ini menggunakan analisis deskriptif dan analisis hubungan menggunakan metode Chi Square. Penilaian efek samping dilakukan sejak hari pertama pasien memulai radiasi eksterna sampai 1 bulan setelah dinyatakan selesai menjalani radioterapi eksterna.*

Hasil: *Selama periode penelitian didapatkan 413 pasien kanker serviks yang menjalani radiasi eksterna namun hanya 192 pasien kanker serviks stadium IIB-IIIC yang memenuhi kriteria inklusi pada penelitian ini. Respon terapi komplit sebesar 65,6%, respon terapi parsial sebesar 31,8%, respon terapi tidak berubah sebesar 1,6%, dan respon terapi progresif sebesar 1%. Pada analisis statistik terdapat hubungan bermakna stadium kanker serviks dan Overall Treatment Time dengan respon radioterapi eksterna, dan tidak terdapat hubungan bermakna ukuran tumor dan jenis histopatologi dengan respon radioterapi eksterna. Didapatkan efek samping hematologi (45,8%), efek samping kulit (45,3%), efek samping gastrointestinal (6,3%) dan efek samping traktus urinarius (2,6%).*

Kesimpulan: *Respon radioterapi eksterna berupa complete response dimana terdapat hubungan bermakna antara stadium kanker serviks dan Overall Treatment Time dengan respon radioterapi eksterna. Tidak terdapat hubungan bermakna antara ukuran tumor dan jenis histopatologi. Efek samping terbanyak yaitu hematologi dengan keluhan berupa anemia dan trombositopenia.*

Kata kunci: *efek samping, kanker serviks, respon radiasi eksterna.*

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INTRODUCTION

Cervical cancer is one of the deadliest cancers in the world that occurs in women. Global Cancer project data (GLOBOCAN) from the International Agency for Research on Cancer WHO revealed that there have been 570,000 cases and 311,000 deaths worldwide caused by cervical cancer. It was found that 32,469 or 17.2% new cases of female cancer in Indonesia were cervical cancer. Referring to these data, cervical cancer ranks fourth as malignant disease and the main cause of death in women due to cancer.[1,2] More than 40% of malignancies in Indonesian women are gynecological cancers.[3]

The incidence rate of cervical cancer in Southeast Asia reached 15.8 per 100,000 population in 2011. This number increased slightly compared to 2008.[4-6] It was reported that 20,928 new cases of cervical cancer with 9,498 cervical cancer-related deaths in 2012 in Indonesia. North Sulawesi Province has a cervical cancer prevalence of 1.4 0/00 and 1,615 new cases have been reported.[4] In Southeast Asia, most cases of cervical cancer are advanced stage (IIB-IVB). In Indonesia, 70% of cervical cancer patients come at an advanced stage (above stage IIB) which has a low survival rate.[6] Detecting cancer at an early stage is quite an effective way, considering that 85% of it can reduce the death rate and the incidence rate caused by cervical cancer.[7]

It was stated that the primary management of cervical cancer is surgery or radiation therapy with chemotherapy as a valuable adjunct.[8-11] In the field of gynecological cancer, radiation therapy is widely used as a therapeutic modality for cervical cancer, vulvar/vaginal cancer, and endometrial cancer.[3] Radiotherapy is one of the main treatment options in cancer management where about 50% to 60% of patients require radiation therapy at some stage of the disease.[8] Along with other modalities such as surgery and chemotherapy, radiotherapy plays an important role in the treatment of the majority of patients who are cured of their cancer. Radiotherapy is also an effective treatment option to relieve and control symptoms in advanced or recurrent local cancer cases.[8]

Several research reports have been published regarding therapeutic response in cervical cancer patients who only undergo external radiation. the overall results of patients who do not receive brachytherapy are unsatisfactory. There is a need to reduce the Overall Treatment Time (OTT) and consideration of chemo-radiation action along with cisplatin to reduce this deficiency.[10] Patients who do not receive brachytherapy therapy can still reach the loco-regional level if given at high radiation doses (> 65 Gy).[9] The prognosis of patients who get only external radiation therapy will get much worse results than patients who get a combination of external radiation and brachytherapy. Brachytherapy should be used whenever technically possible and its co-administration with chemotherapy should be considered.[12]

Prof. Dr. R. D. Kandou Hospital Manado is a Type A/tertiary hospital as it is the center of a referral hospital in North Sulawesi Province. This hospital has been currently equipped with Radiotherapy services. This service has been running since September 2016 where most of the gynecological cancer patients who undergo radiotherapy are cervical cancer patients. Radiotherapy at Prof. R. D. Kandou Hospital Manado is external radiation that uses Cobalt and is not equipped with internal radiation/brachytherapy.

METHODS

This is a retrospective study. We evaluated the medical records of the Gynecologist and Radiotherapy Clinic, Prof. Dr. R. D. Kandou Hospital Manado. These data are intended to determine the therapeutic response of stage IIB-IIIC cervical cancer patients undergoing external radiation. External radiation was administrated using Cobalt.

The population in this study were cervical cancer patients registered from September 2016 to December 2020 who underwent radiotherapy at the Radiotherapy department of Prof. Dr. R. D. Kandou Hospital Manado. The sample in this study were cervical cancer patients who underwent radiotherapy to completion. Evaluation of the response to therapy 1 month after receiving the total dose in a sample of patients who met the inclusion criteria was performed. The evaluation was carried out using RECIS criteria.

The inclusion criteria in this study were stage IIB-IIIC cervical cancer patients who underwent radiotherapy to completion from September 2016 to December 2020. The exclusion criteria for this study were women with stage I, IIA, and IV cervical cancer; women with cervical cancer who undergo chemoradiation; women who have residing cervical cancer; women with cervical cancer who underwent radiotherapy but did not complete. Cervical cancer staging was carried out by gynecological oncologists and radiation oncologists regarding FIGO criteria. The staging of the research subjects in 2016-2018 in this case was determined based on the 2009 FIGO criteria, while the stage determination of the research subjects in 2019-2020 was done based on the 2018 FIGO criteria.

The independent variables in this study consisted of patient characteristics, risk factors, and prognosis which included age, number of marriages, parity, occupation, smoking, stage, tumor size, histopathology, overall treatment time. The dependent variable was a response to external radiotherapy.

The steps were taken after data collection were descriptive studies and statistical analysis using the SPSS (Statistical Product and Service Solutions) program. The toxicity assessments were carried out from first day started external radiation up until 1 month after the therapy was deemed completed.

RESULTS

The collection of medical record data was carried out at the Gynecologist and Radiotherapy Clinic Prof. Dr. R. D. Kandou in January - March 2021 where the data are taken were those that met the inclusion criteria. The number of cervical cancer patients who underwent external radiotherapy from September 2016 to December 2020 was 413 patients, of which 221 patients were excluded from this study. Thus, 192 patients met the inclusion criteria in this study. Demographic characteristics in this study are presented in table 1 below.

Table 1. Demographic Characteristics of Research Subjects

Characteristics	Amount (n)	%
Age (years)		
< 40	26	13.5
40-59	125	65.1
≥ 60	41	21.4
Married		
Once	173	90.1
More than once	19	9.9
Parity		
0	9	4.7
1	17	8.9
2	66	34.4
> 2	100	52.1
Occupation		
Housewife	143	74.5
Civil Servant	20	10.4
Retired	10	5.2
Others	19	9.9
Smoker		
Yes	25	13.0
No	167	87.0

Clinical characteristics were obtained based on the results of general physical examination, internal examination, and anatomical pathology. The clinical characteristics of this study are presented in Table 2.

Table 2. Clinical Characteristics of Study Subjects

Characteristics	Amount (n)	%
FIGO Stadium		
II B	93	48.4
III A	36	18.8
III B	49	25.5
II C	14	7.3
Tumor size (cm)		
≤ 4	108	56,3
> 4	84	43,8
Histopathology		
Squamous cell carcinoma	163	84.9
Adenocarcinoma	17	8.9
Adenosquamous carcinoma	8	4.2
Another type	4	2.1
Overall Treatment Time (days)		
≤ 56	107	55.7
> 56	85	44.3
Therapeutic Response		
Complete response	126	65.6
Partial response	61	31.8
Stable disease	3	1.6
Progresive disease	2	1.0

A bivariate analysis was performed to know the response to external radiotherapy based on clinical characteristics in cervical cancer patients using a statistical test that is the X^2 test (Chi-square).

Table 3. Response Analysis to External Radiotherapy Based on Clinical Characteristics

Characteristics	Diagnosis/Cases								
	Complete		Partial		Stable		Progressive		*P-value*
	n	%	n	%	n	%	n	%	
Stadium									0.028
II B	70	75.3	21	22.6	1	1.1	1	1.1	
III A	26	72.2	9	25.0	0	0	1	2.8	
III B	24	49.0	23	46.9	2	4.1	0	0	
III C	6	42.9	8	57.1	0	0	0	0	
Tumor size (cm)									0.06
≤ 4	78	72.2	27	25.0	1	0.9	2	1.9	
> 4	48	57.1	34	40.5	2	2.4	0	0	
Histopathology									0.171
Squamous cell carcinoma	112	68.7	47	28.8	2	1,2	2	1,2	
Adenocarcinoma	8	47.1	9	52.9	0	0	0	0	
Adenosquamous carcinoma	3	37.5	4	50.0	1	12.5	0	0	
Another type	3	75.0	1	25.0	0	0	0	0	
Overall Treatment Time (days)									0.001
≤ 56	82	76.6	25	23.4	0	0	0	0	
> 56	44	51.8	36	42.4	3	3.5	2	2.4	

The toxicity assessments were carried out from first day started external radiation up until 1 month after the therapy was deemed completed.

Table 4. Distribution of External Radiotherapy Side Effects

Toxicity	Amount	%
Skin	87	45.3
Gastrointestinal	12	6.3
Urinary tract	5	2.6
Hematology	88	45.8

DISCUSSION

There were 13.5% of 192 cervical cancer patients diagnosed before 40 years old, while the highest proportion was 65.1% who were diagnosed at the age of 40-59 years. The median age, in this case, was 50.0 years with a range of 28-86 years. The older a person is, then the risk of having a cervix also increases. This is due to increased exposure time to carcinogens and a weaker immune system because of age. This happens since the latent period from pre-invasive to invasive is about 10 years, so that most cervical cancer cases are only known after old age.[3,6]

The number of sexual partners, in this case, is associated with the number of marriages experienced by the patient. The highest frequency of cervical cancer in this study was in the group who was married once with a percentage of 90.1%, while the frequency of those who were married more than once was 9.9%. This finding is not the same as that obtained by Suhatno et al, who found that women with 2 sexual partners will have a 2 times higher risk of developing cancer, while women with 6 or more sexual partners will have 3 times higher risk compared to women with 1 sexual partner.[11] This increased risk is generally due to an increased risk of HPV infection. However, there is some other factor contributing to the increased risk of cervical cancer in patients with multiple sexual partners, such as the age at first sexual intercourse.[12] These data indicate a low correlation between the number of sexual partners (how many times the patients get married) and the risk of cervical cancer in this study, so further findings may point to a role for male sexual behavior.[13,14]

The patient parity range in this study was 0-10 and the median was 3.0 with a standard deviation of 1.532. Most patients had parity > 2 (52.1%), followed by subjects with parity 2 (34.4%), parity 1 (8.9%) and parity 0 (4.7%). Multiparity is known to increase the risk of cervical cancer by maintaining the transformation zone in the ectocervix. In the immature development phase, metaplastic cells are most susceptible to HPV infection which will then develop into cervical cancer. The metaplastic transformation zone in the ectocervix of a woman, in this case, will be repeatedly exposed to carcinogenetic agents.[14]

Most of the cervical cancer patients in this study were housewives (74.5%) followed by civil servants / PNS (10.4%), other occupations (9.9%), and retirees (5.2%). Al-amro et al stated that women who do not work are more at risk of developing cervical cancer. This is related to the low awareness of cervical cancer screening.[15] It is also thought that exposure to certain substances from a job (dust, metal, chemicals, tar, or engine oil) can be a risk factor for cervical cancer.[16-18]

The characteristics of the smoking habit in this study were divided into 2 groups, namely the group with a smoking habit of 13.0% and the non-smoking group of 87.0%. The data in this research was secondary data where the researcher did not study further whether the subjects were active or passive smokers. Women who smoke are twice as likely to have cervical cancer as those who do not smoke. Researchers believe that smoking can damage cervical cell DNA and can contribute to the development of cervical cancer. Smoking also makes the immune system less effective at fighting HPV infection. Smoking may be a cofactor affecting the development of high-grade cervical dysplasia in women with chronic HPV infection and a higher risk of developing cervical dysplasia and invasive carcinoma.[12]

Assessment of response to external radiotherapy was carried out by evaluating tumor size before and after external radiation with a total dose of 50 Gy followed by booster radiation replacement for intracavitary radiation (box system) for a total dose of 20 Gy. External radiotherapy response was assessed by gynecological oncologists and radiation oncologists. In this study, the findings related to the results of the complete response were 65.6% followed by a partial response by 31.8%, then the stable disease by 1.6%, and progressive disease by 1.0%.

Bivariate statistical analysis using the Chi-Square method was carried out to see the association between clinical characteristics and response to external radiotherapy.

The staging group statistically based on this study was associated with response to external radiotherapy with a value of $p = 0.028$ (p-value < 0.05). Thus it is concluded that stage of cancer has association with response to external radiotherapy. The stage of cancer is one of the main factors affecting cancer survival. Cancer cells in patients with advanced cervical cancer show a high rate of DNA synthesis and rapid cell proliferation. Radiotherapy is very effective for cancer cells as long as DNA synthesis and proliferation are active. Thus, the stage of cancer has a significant therapeutic response after radiation.[19]

In the Overall Treatment Time group, the p-value obtained concerning the radiotherapy response was 0.001 (p-value < 0.05). The conclusion was that the Overall Treatment Time was statistically related to the response to external radiotherapy. The prolongation of the Overall Treatment Time results in decreased pelvic survival and control by 1% per day. In theory, the Overall Treatment Time may affect the availability of more time for tumor cells to pass their doubling time. In patients who cannot complete the complete radiation within the due time limit, a recalculation of the radiation fraction should be carried out to compensate for the dose deemed insufficient to compensate for the radiation dose. However, this will cause the Overall Treatment Time to be longer.[20,21]

Group tumor size and histopathology type did not have a significant relationship with radiotherapy response where the p-value of each group was > 0.05. This indicates that the group was not statistically associated with response to external radiotherapy. Tumor size in cervical cancer is an important factor concerning radiation response. The availability of oxygen is very important for the radiosensitivity of a cell. Oxygen is important for enhancing the ability of ionizing rays to have direct radiation effects. Tumors > 200 μm have a central necrotic portion with limited diffusion from oxygen. This becomes very important in radiation administration because tumor cells in a hypoxic state become radioresistant. The type of histopathology also has a role in determining the prognostic condition of cervical cancer. Yokio et al reported that 9.6% of patients with advanced cervical stage had significantly worse adenocarcinoma histology or adenosquamous histology than patients with squamous histopathology.[17,20] Radiotherapy response can also be caused by other factors, including Hb level when diagnosed with cervical cancer, type of treatment (radiation or chemoradiation), and the degree of differentiation of histopathological types.[18,22,23]

Acute toxicity are related to technique, total dose, volume, duration of radiation therapy, hygiene, and patient nutrition, including socioeconomic conditions. In this study, the most toxicity of external radiotherapy were hematological toxiciy (45.8%) followed by skin toxiciy (45.3%), gastrointestinal toxicity (6.3%) and urinary tract toxicity (2,6 %). The toxicity in this study are acute and the pathophysiology of the acute reaction is injury and cell loss in tissues that have a rapid turn-over rate, which is generally repairable and self-limiting.[24]

CONCLUSION

The number of cervical cancer patients with stage IIB-IIIC who underwent external radiotherapy during 2016-2020 based on the findings of this study was 192 patients. Knowing the response to external radiotherapy, it was found a complete response of 65.6%; partial response 31.8%; stable disease 1,6%; progressive disease 1.0%. The study findings also revealed a significant association between cervical cancer stage and Overall Treatment Time on response to external radiotherapy. Most toxicity were hematology with complaints of anemia and thrombocytopenia.

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Research Article

Germ Patterns and Antibiotic Susceptibility in Pregnancy and Labor with Risk of Infections

Pola Kuman dan Sensitivitas Antibiotik pada Kehamilan dan Persalinan dengan Faktor Risiko Infeksi

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Abstract

Objective: To determine the pattern of germs and antibiotic susceptibility tests in pregnant women related to risk factors for infection in preterm PROM cases, the threat of preterm labor, pathological fluor albus, and prolonged labor in Manado city.

Methods: This study is a cross-sectional descriptive study. A total of 21 samples were obtained, consisting of six preterm PROM cases, five premature contraction cases, five pathological fluor albus cases, and five prolonged labor cases. The study was conducted in Kandou General Hospital and Affiliated Hospitals, Manado. All patients were informed about the study and signed informed consent. Germ pattern and antibiotics susceptibility data were analyzed.

Results: Of 21 samples, the detected microorganisms included *Staphylococcus aureus* (12), *Coagulase-negative staphylococcus* (2), mixed microorganisms (*Staphylococcus aureus + Candida sp, Coagulase-negative staphylococcus + Candida sp*), *Bacillus sp* and *Candida sp*. The susceptible and safe antibiotics for pregnancy were Ampicillin / Sulbactam and Meropenem. The resistant antibiotics were Ceftriaxone, Tetracycline, and Neomycin.

Conclusion: The most common type of bacteria found in pregnant women and women in labor was *Staphylococcus aureus*. Susceptible and safe antibiotics for pregnancy were Ampicillin / Sulbactam and Meropenem.

Keywords: antibiotic sensitivity test, germ pattern, pregnancy and labor infection.

Abstrak

Tujuan: *Mengetahui pola kuman dan uji sensitivitas antibiotik pada perempuan hamil terkait faktor risiko infeksi pada kasus KPD preterm, ancaman partus prematurus, fluor albus patologis dan partus lama di kota Manado.*

Metode: *Studi ini merupakan studi deskriptif potong lintang. Jumlah sampel yang didapatkan sebesar 21 sampel di mana terbagi pada masing-masing kasus KPD preterm 6 sampel, ancaman partus prematurus 5 sampel, fluor albus patologis 5 sampel dan partus lama 5 sampel. Sampel diambil dari RSUP Prof. Dr. R. D. Kandou Manado dan Rumah Sakit Jejaring di kota Manado yang memenuhi kriteria inklusi dan eksklusi. Semua pasien dijelaskan mengenai prosedur penelitian dan penandatanganan inform consent baru dilakukan pengambilan sampel. Data dianalisis dengan cara deskriptif tentang pola kuman dan uji sensitivitas antibiotik pada kehamilan dan persalinan dengan faktor risiko infeksi.*

Hasil: *Dari 21 sampel, sebaran jenis mikroorganisme diantaranya Staphylococcus areus (12), Staphylococcus non koagulase (2), mikroorganisme campuran (Staphylococcus aureus + Candida sp, Staphylococcus non koagulase + Candida sp), Bacilus sp dan Candida sp. Hasil uji sensitivitas antibiotik yang sensitif dan aman untuk kehamilan di antaranya Ampicillin/Sulbactam dan Meropenem. Hasil uji sensitivitas antibiotik yang resisten adalah Ceftriaxone, Tetracycline dan Neomycin.*

Kesimpulan: *Jenis mikroorganisme paling banyak adalah Staphylococcus aureus. Hasil uji sensitivitas antibiotik yang sensitif dan aman untuk kehamilan di antaranya Ampicillin/ Sulbactam dan Meropenem.*

Kata kunci: *infeksi kehamilan dan persalinan, pola kuman, uji Sensitivitas antibiotik.*

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INTRODUCTION

Infectious disease is a global issue that occurs in both developing and developed countries. The infection can be caused by bacteria, viruses, fungi, and parasites, while the transmission may occur intrauterine, during labor, or after birth. Infection is one of the leading causes of death in the world. In Indonesia, the most common causes of maternal death are bleeding (8%), eclampsia (24%), infection (11%), prolonged or obstructed labor (5%), and others (11%). In North Sulawesi, maternal death caused by infection was 8%.[1-3]

Risk factors for infections in pregnancy and childbirth include premature rupture of membranes (PROMs), urinary tract infections (UTIs), and vaginal discharge. In India in 2019, the most common bacteria found in pregnancy infections were *Escherichia coli, Candida albicans, Klebsiella,* and *Staphylococcus aureus*. In Manado, the most common infections found in the obstetric case was Staphylococcus epidermis.[4,5]

Genital infections during pregnancy and childbirth are a relatively common cause of morbidity, occurring in one-third of pregnant women. It may lead to restricted intrauterine growth, preterm labor, and premature rupture of membranes, even in asymptomatic women. On the other hand, infections increase the risk of morbidity in infants. Pregnant women are at high risk of infection, especially in the second and third trimesters.[4]

Antibiotics are natural or synthetic compounds that suppress or cease the biochemical processes in organisms, especially in the infection process by microbes. For global purposes, the availability, selection, and use of antibiotics should be conducted appropriately. Therefore, it is necessary to identify pathogenic bacteria and select antibiotics that are effective against these microorganisms. Improper use of antibiotics has resulted in multiple drug resistance against antibiotics. Untreated infections can cause complications in pregnancy and childbirth. In order to prevent these complications, knowledge of the prevalence of various infections in pregnancy is essential for effective treatment and to improve perinatal outcomes.

METHODS

This was a cross-sectional study. The study was conducted at Prof. Dr. R. D. Kandou hospital and affiliated hospitals in Manado from January 2021 to March 2021.

The population of this study was pregnant women with risk factors for infections who visited the obstetric clinic for Antenatal Care (ANC) or emergency room in the Obstetrics and Gynecology Department.

The inclusion criteria were all pregnant women with risk factors for infections in preterm PROM cases, premature contraction, pathological fluor albus, and prolonged labor, and willing to participate in the study. Exclusion criteria were pregnancy with medical complications, such as heart disease, diabetes mellitus, HIV, malignancy, ongoing antibiotics or immunosuppressants treatment, and refusal to participate in the study.

The study subjects were selected through history taking, physical examination, and further examinations. Subjects who met the study criteria and signed the consent form were included in the study. The sample size of this study was 21 samples.

Before subjected to the study procedures, each subject received an explanation of the aims, objectives, and procedures of the study. The samples were taken using a vaginal swab kit. Afterward, a culture with agar media, identification tests, and antibiotic susceptibility tests were conducted. Laboratory examinations were carried out in the Microbiology Laboratory of the Faculty of Medicine, Universitas Sam Ratulangi, Manado

Data were collected and recorded in a study data form that has been prepared and then arranged in a master table. Data were analyzed descriptively.

RESULTS

A total of 21 subjects with risk factors for infections were obtained, including six patients for preterm PROM cases, premature contraction cases, five pathological fluor albus cases, and five prolonged labor cases.

Table 1 showed the characteristics of the study subjects. The most common age group was 20 - 35 years, namely 17 patients (80.95%), with five patients (83.33%) of preterm PROM cases and four patients (80%) with premature contraction, pathological fluor albus, and prolonged labor cases. The majority of the study subjects were senior high school (66.67%) and were housewives. The majority of the study subjects were overweight (66.67%).

Table 2 showed the microorganisms observed in this study, including three variants of gram-positive microorganisms, one variant of fungal, and two variants of mixed microorganisms (gram-positive bacteria + fungi). The most common type of microorganism found was Staphylococcus aureus with a total of 12 samples (57.14%), followed by coagulase-negative *Staphylococcus* + *Candida sp* (14.28%), *coagulase-negative Staphylococcus* (9.52%), *Staphylococcus aureus* + *Candida sp* (9.52%), *Bacillus sp* and *Candida sp* (4.76%).

Table 3 showed the distribution of microorganisms by the obstetric cases. In the preterm PROM cases, the growth of *Staphylococcus aureus* was observed in four (66.67%) samples, followed by coagulase-negative *Staphylococcus* and *coagulase-negative Staphylococcus* + *Candida sp,* one sample each (16.67%). In premature contraction cases, two samples (40%) showed the growth of *Staphylococcus aureus* and one sample (20%) with *Staphylococcus aureus* + *Candida sp, coagulase-negative Staphylococcus* + *Candida sp*, and *Candida sp*. In pathological fluor albus cases, there were three samples (60%) with *Staphylococcus aureus* growth, one sample (20%) with *coagulase-negative Staphylococcus aureus* growth, and one sample (20%) with *Staphylococcus aureus* + *Candida sp* growth. In prolonged labor cases, three samples (60%) showed the growth of *Staphylococcus aureus,* followed by one sample (20%) with the growth of *coagulase-negative Staphylococcus* + *Candida sp*, and one sample (20%) with *Bacillus sp.*

Table 4 showed the results of the antibiotics susceptibility test based on the microorganism. For the most common microorganisms, *Staphylococcus aureus,* sensitive antibiotics included Chloramphenicol, Gentamicin, Tobramycin, Levofloxacin, Moxifloxacin, Ampicillin / Sulbactam, and Meropenem antibiotics. Ampicillin / Sulbactam and Meropenem antibiotics are category B in pregnancy and considered safe. Furthermore, resistant antibiotics to *Staphylococcus aureus* were Ceftriaxone, Tetracycline, and Neomycin. *Candida sp*. were sensitive to all anti-fungal groups.

Table 1. Characteristics of Patients

Characteristics	**Diagnosis/Cases**									
	Preterm PROM	%	**Premature Contraction**	%	**Pathological Fluor Albus**	%	**Prolonged labor**	%	**Total**	%
Age (year)										
< 20	1	16,67	0	0	0	0	1	20	2	9.52
20-35	5	83.33	4	80	4	80	4	80	17	80.95
> 35	0	0	1	20	1	20	0	0	2	9.52
Education										
Elementary	0	0	0	0	0	0	1	20	1	4.76
Junior high school	0	0	1	20	1	20	1	20	3	14.28
Senior high school	4	66.67	3	60	4	80	3	60	14	66.67
University/ college	2	33.33	1	20	0	0	0	0	3	14.28
Occupation										
Housewives	4	66.67	3	60	5	100	5	100	17	80.95
Business women	2	33.33	0	0	0	0	0	0	2	9.52
Civil servants	0	0	2	40	0	0	0	0	2	9.52
Body mass index										
Underweight (< 18.5)	0	0	1	20	0	0	0	0	1	4.76
Normal (18.5- 24.9)	1	16.67	0	0	2	40	2	40	5	23.8
Overweight (25-29.9)	4	66.67	4	80	3	60	3	60	14	66.67
Obese (≥ 30)	1	16.67	0	0	0	0	0	0	1	4.76

Table 2. Grouping Types of Microorganisms

Microorganisms		**Total**	**%**
Gram-Positive Bacteria	*Staphylococcus aureus*	12	57.14
	Coagulase-negative Staphylococcus	2	9.52
	Bacillus sp	1	4.76
Fungi	*Candida sp*	1	4.76
Mixed (Gram-Positive bacteria + fungi	*Staphylococcus aureus + Candida sp*	2	9.52
	Coagulase-negative Staphylococcus + Candida sp	3	14.28

Table 3. Distribution of Microorganism Growth by the Type of Cases

Microorganisms	Diagnosis/Cases							
	Preterm PROM	%	**Premature Contraction**	%	**Pathological Fluor Albus**	%	**Prolonged labor**	%
Staphylococcus aureus	4	66.67	2	40	3	60	3	60
Coagulase-negative Staphylococcus	1	16.67	0	0	1	20	0	0
Staphylococcus aureus + Candida sp	0	0	1	20	1	20	0	0
Coagulase-negative Staphylococcus + Candida sp	1	16.67	1	20	0	0	1	20
Bacilus sp	0	0	0	0	0	0	1	20
Candida sp	0	0	1	20	0	0	0	0

Table 4. Susceptibility Test Results by Microorganisms

Antibiotics	Microorganisms														
	S.a			**CoNS**			**S.a + Candida**			**CoNS + Candida**			**B.sp**		
	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R
Chloramphenicol	7	3	2	2	0	0	1	0	1	1	1	1	1	0	0
Erythromycin	1	5	6	0	1	1	0	0	2	0	0	3	0	0	1
Gentamicin	7	4	1	2	0	0	1	0	1	1	1	1	1	0	0
Neomycin	1	2	9	2	0	0	0	1	1	1	0	2	1	0	0
Sulphamethoxazole/ Trimethoprim	3	1	8	0	0	2	2	0	0	1	0	2	1	0	0
Tetracycline	0	3	9	0	0	2	0	0		0	0	3	0	0	1
Tobramycin	6	2	4	1	1	0	1	0	1	1	1	1	1	0	0
Vancomycin	1	7	4	0	2	0	0	1	1	1	0	2	1	0	0
Amikacin	4	3	5	0	1	1	0	0	2	0	1	2	1	0	0
Ciprofloxacin	4	4	4	2	0	0	0	2	0	1	1	1	1	0	0
Cefadroxil	3	1	8	1	0	1	0	0	2	0	0	3	0	1	0
Ampicillin/ Sulbactam	6	1	5	0	0	2	1	0	1	0	0	3	1	0	0
Levofloxacin	6	3	3	1	0	1	1	0	1	1	0	2	1	0	0
Piperacillin/ Tazobactam	4	2	6	0	0	2	1	0	1	0	1	2	1	0	0
Moxifloxacin	6	2	4	0	0	2	0	0	2	1	1	1	1	0	0
Tigecycline	1	4	7	0	1	1	0	1	1	1	1	1	1	0	0
Ceftriaxone	1	2	9	0	0	2	0	0	2	0	1	2	0	1	0
Meropenem	7	4	1	0	0	2	2	0	0	2	0	1	1	0	0

* S = Susceptible, I = Intermediate, R = Resistant, S.a: *Staphylococcus aureus,*
CoNS: *Coagulase-negative Staphylococcus,* B.sp: *Bacillus sp*

DISCUSSION

In this study, 21 pregnant patients met the inclusion and exclusion criteria and had signed the informed consent to participate. The subjects consisted of six preterm PROM cases, five premature contraction cases, five pathological fluor albus cases, and five prolonged labor cases.

The characteristics of the research subjects were assessed in terms of maternal age, education, occupation, and Body Mass Index (BMI). In Table 1, it can be seen that the most common age group was 20 - 35 years (80.95%), with the most common educational background of senior high school (66.67%), housewives as the most common occupation (80.95%). Most of the subjects were overweight (66.67%). Obese pregnant women have a 2.5 to 4.5 times higher risk of infection morbidity than normal-weight patients. Hormonal imbalance may occur in obesity, leading to changes in the balance of normal vaginal flora to pathogenic flora.[6]

In this study, microorganism growth was observed in all 21 samples. These microorganisms included bacteria, fungi, and mixed (bacteria + fungi) (Table 2). Gram-positive bacteria were the dominant microorganisms in this study. A study in Uganda found the highest number of gram-positive bacteria at 63%.[7] The most common microorganism observed in this study was *Staphylococcus aureus* (57.14%). *Staphylococcus aureus* is a gram-positive spherical bacterium with a diameter of 0.8 - 1.0 µm. These bacteria grow at an optimum temperature of 37^0C but form the pigments best at room temperature (20-25^0C). They are mostly observed on the surface of the skin and mucous membranes of humans. *Staphylococcus aureus* is coagulase-positive and the primary pathogen in humans. *Staphylococcus aureus* is a commensal bacteria that is often found on the skin and urogenital tract. The habit of wiping from front to back is thought to cause translocation of commensal germs on the skin of the vulva.[8,9] There were two variants of microorganisms found in this study, including mixed microorganisms (gram-positive bacteria and fungi), namely *Staphylococcus aureus* + *Candida sp* (9.52%) and c*oagulase-negative Staphylococcus* + *Candida sp*. (14.28%). Coinfection of *Staphylococcus sp*. and *Candida sp*. can increase their pathogenic properties. *Staphylococcus aureus,* in particular, binds to the invasive hyphal form of Candida albicans and increases the mortality and systemic spread in the tissue mucosa.[10]

As seen in Table 3, the most common type of microorganisms in preterm PROM cases was Staphylococcus aureus (66.67%). A study in Uganda (2017) found that the most common microorganisms in preterm PROM were *Staphylococcus aureus* (19.4%), followed by *Escherichia coli* (17.9%), *coagulase-negative Staphylococcus* (13.4%), and *Streptococcus pyogenes* (11, 9%).[7]

In cases of premature contraction, the most common germ was *Staphylococcus aureus* (40%). *Staphylococcus sp*. and *Pseudomonas sp*. were most commonly found in pregnant women with preterm labor without premature rupture of membranes. One of the causes of preterm labor is chorioamnionitis. *Staphylococcus aureus* is also a cause of chorioamnionitis associated with preterm labor. *Staphylococcus aureus* infects soft tissue and forms a strong biofilm on the surface, providing an advantage for bacteria and aiding resistance to antimicrobials. Infection of *Staphylococcus aureus* on the pregnancy membrane will induce the release of proinflammatory cytokines, including IL-1β, IL-2, IL-6, TNF-α, and IFN-, this increase can promote the release of MMP neutrophils which directly contribute to preterm labor.[11]

In pathological fluor albus and prolonged labor, the most common germ was *Staphylococcus aureus* (60%). The hygiene of the mother also influences the change in acidity and growth of this microorganism during pregnancy. Rapid pH changes lead to the disturbance of vaginal acid-base and the rapid growth of normal and anaerobic microorganisms, resulting in an increased phagocytosis process and the metabolic results of microorganisms that change the vaginal fluorine albus to alkaline and trigger normal vaginal flora to become parasites in the cervical mucosa and vagina. This situation will change the quality of fluor albus and can be categorized as pathological fluor albus. Infections can be a threat to the mother and the fetus during prolonged labor. Frequent examinations of the cervix using fingers lead to vaginal contamination and entry of bacteria into the vagina and uterus.[12,13]

The antibiotic susceptibility test results showed that *Staphylococcus aureus* was susceptible to Chloramphenicol, Gentamicin, Tobramycin, Levofloxacin, Moxifloxacin, Ampicillin / Sulbactam, and Meropenem antibiotics. Aminoglycoside antibiotics (Gentamicin, Tobramycin) and quinolones (Levofloxacin, Moxifloxacin) are classified into category C or D by the FDA and are not recommended for pregnant women. Ampicillin / Sulbactam and Meropenem antibiotics are category B in pregnancy and are considered safe. Ampicillin / Sulbactam is a combined antibiotic class of the penicillin group with β-lactamase inhibitors. The addition of Sulbactam to Ampicillin will increase the effectiveness of Ampicillin. The predominant microorganisms were *Staphylococcus aureus, Streptococcus sp*., and *Escherichia coli*.

Furthermore, the study stated that the sensitive antibiotics considered safe to use during pregnancy included Ampicillin / Sulbactam, Cefixime, Cefuroxim, and Erythromycin. According to the American College of Obstetricians and Gynecologists (ACOG), the administration of broad-spectrum antibiotics reduces infections in both mothers and newborns and may reduce morbidity in pregnancy. Antibiotic treatment for 7 days with parenteral combination administration of Ampicillin and Erythromycin followed by oral Amoxicillin, and oral Erythromycin is recommended in preterm PROM with gestational age <34 weeks.[14] Meropenem is categorized into the Carbapenem antibiotic class. Carbapenem is a broad spectrum β-lactam drug. The Carbapenem group is the last weapon against bacteria that are resistant to other antibiotics.[8]

The antibiotic susceptibility test results showed that resistant antibiotics to Staphylococcus aureus were Neomycin, Tetracycline, and Ceftriaxone antibiotics. A meta-analysis showed that there were 626 samples from 2032 samples of the *Staphylococcus aureus* that were resistant to Ceftriaxone, and there were 1982 samples from 3019 samples that were resistant to Tetracycline.[15] To minimize the possibility of resistant microbes, proper selection of antibiotics based on their indication, dose, timing, and type must be conducted.

CONCLUSION

The microorganisms observed in vaginal swab cultures of pregnant women with risk for infections in cases of preterm PROM, premature contraction, pathological fluor albus, and prolonged labor were *Staphylococcus aureus*, coagulase-negative *Staphylococcus*, mixed (*Staphylococcus aureus* + *Candida sp*. and *coagulase-negative Staphylococcus* + *Candida sp*.), *Candida sp*., and *Bacillus sp*. The most common microorganism was *Staphylococcus aureus*. Susceptible and safe antibiotics to *Staphylococcus aureus* were Ampicillin / Sulbactam and Meropenem. Resistant antibiotics to Staphylococcus aureus were Ceftriaxone, Tetracycline, and Neomycin antibiotics. *Candida sp*. were susceptible to all anti-fungal groups.

SUGGESTION

Further studies with a larger sample size are necessary to provide more accurate results in determining the pattern of germs in vaginal swab cultures of pregnant women related to risk factors for infection in preterm PROM cases, premature contraction, pathological fluor albus, and prolonged labor in Manado. Furthermore, antibiotics susceptibility studies, including more antibiotics that are safe for pregnancy, are warranted.

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Research Article

Cesarean delivery Characteristics during JKN Implementation

Karakteristik persalinan sesar selama Implementasi JKN

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Abstract

Objective: To compare the characteristics of cesarean before and during JKN, also analyzes the factors that influence these differences.

Methods: This was a quantitative study with a longitudinal retrospective design and qualitative research used design case studies. The population were delivery women at the Banyuwangi referral hospital before and during JKN. The quantitative data were analyzed firstly by univariable and then bivariable. The bivariable analysis was performed by comparing the prevalence ratio (PR) between two variables.

Results: The proportion of cesarean delivery had increased significantly during the implementation of JKN. 50% of maternal deaths before JKN gave birth using cesarean delivery, this proportion increased significantly to 60% during JKN. Indications of fraud committed by health workers to be a factor in increasing the proportion of cesarean delivery. Other contributing factors were repeated cesarean delivery, delayed referral, and the number of obstetric complications.

Conclusion: There was an increase in the proportion of cesarean deliveries during the implementation of JKN. BPJS Kesehatan needed to re-evaluate the system they had created so far. The quality of service must be emphasized so that the negative impact on women could be minimized.

Keywords: cesarean section, health insurance, maternal mortality.

Abstrak

Tujuan: *Membandingkan karakteristik persalinan sesar sebelum dan selama implementasi JKN, selain itu juga menganalisis faktor-faktor yang berpengaruh.*

Metode: *Studi kuantitatif dengan desain longitudinal retrospective dan studi kualitatif dengan desain case studies. Populasi adalah ibu bersalin di rumah sakit rujukan Kabupaten Banyuwangi sebelum dan selama JKN. Data kuantitatif dianalisis secara univariabel dan bivariabel. Analisis bivariabel dengan membandingkan prevalensi rasio (PR) diantara dua variabel.*

Hasil: *Proporsi persalinan sesar meningkat secara signifikan selama implementasi JKN. 50% ibu yang meninggal bersalin dengan metode sesar, proporsi ini meningkat selama JKN menjadi 60%. Indikasi kecurangan oleh tenaga kesehatan menjadi salah satu faktor yang menyebabkan peningkatan ini. Faktor lain yang berkontribusi adalah persalinan sesar yang berulang, keterlambatan rujukan dan banyakanya komplikasi obstetrik.*

Kesimpulan: *Terdapat peningkatan proporsi persalinan sesar selama implementasi JKN. BPJS Kesehatan perlu mengkaji ulang sistem yang dibuat selama ini. Kualitas pelayanan harus tetap dipertahankan, agar tidak berdampak pada kesehatan ibu.*

Kata kunci: *jaminan kesehatan, kematian ibu, persalinan sesar.*

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INTRODUCTION

The outcome of cesarean delivery is still being debated today. According to the WHO, the impact of cesarean delivery on maternal and perinatal morbidity and psychological disorders is still being debated[1]. Several studies have shown that cesarean delivery can adversely affect maternal health. Cesarean delivery is associated with a higher risk of maternal death than vaginal delivery. Cesarean delivery can also result in postpartum complications such as postpartum infections[2,3]. The World Health Organization (WHO) recommends that national cesarean delivery rates not exceed 10-15%, as higher rates do not reduce maternal and neonatal mortality rates1. Recent evidence indicates that most countries have higher cesarean delivery rates than the WHO recommended rate, with Latin America and the Caribbean region having 40.5%, Northern America having 32.3%, Europe having 25%, and Asia having 19.2 %. In Indonesia, the trend is similar, with the cesarean delivery rate rising from 2% in 1986 to 16% in 2012[4]. In 2018, 17.6% of deliveries in Indonesia used the cesarean method[5].

Health insurance can be an indication of an increase in cesarean delivery, including health insurance initiated by the government[6]. The Indonesian Demographic and Health Survey data shows that women who have and use health insurance are 1.12 times more likely to give birth using the cesarean delivery compared to those without health insurance[7]. WHO states that cesarean delivery is effective in reducing the risk of maternal death, but if there are medical indications[1]. Cesarean surgery without medical indication can be a factor in increasing the number of cesarean delivery[8]. China is an example of a country that has seen an increase in cesarean deliveries since the implementation of national health insurance. National health insurance is one of the factors that contribute to high cesarean deliveries in China [9].

Indonesia implemented national health insurance (JKN) in 2014. JKN implementation is intended to realize universal health coverage so that inequality in getting health services can be reduced. Banyuwangi is an area that provides a reality that JKN does not positively impact maternal health. The number of maternal deaths in Banyuwangi District has stagnated during the implementation of JKN. Several years before the implementation of JKN, maternal mortality in Banyuwangi District was quite low. Maternal mortality in 2011 was 17, 2012 was 15 deaths, an increase in 2013 to 33. At the beginning of the implementation of JKN there was a decline to 22, it has stagnated in the following years. In 2015, there were 23 deaths and stagnant in 2016 with 21 deaths [10].

In this study, we want to analyze the comparison of cesarean delivery characteristics before and during implementation JKN in four referral hospital in Banyuwangi District, Indonesia.

METHODS

This study used mixed methods with a sequential explanatory design. Quantitative research was carried out first, then confirmed by qualitative research. Research design in quantitative research used longitudinal retrospective. Qualitative research used a case studies design.

Quantitative research used secondary data from medical records. This was collected from four referral hospitals in Banyuwangi District (Blambangan government hospital, Genteng government hospital, Muhammadiyah private hospital, Nahdlatul Ulama private hospital). Qualitative data were obtained from interviews with several parties related to the case.

The population in this study was 8676 deliveries before and during JKN implementation. The research sample was taken using a total sampling technique. Total deliveries were 4435 before JKN and 4242 during JKN. The research informants included midwives, obstetricians, Banyuwangi district health offices, traditional birth attendants and cadres. Researchers determine informants using snowball techniques.

Quantitative research used two analyzes. The quantitative data were analyzed firstly by univariable and then bivariable. The bivariable analysis was performed by comparing the prevalence ratio (PR) between two variables, by using the following guidelines: $PR < 0.9$ or $PR > 1.1$: There are differences between the two variables, $0.9 < PR < 1.1$: There is no difference between the two variables.

The analysis in qualitative research used four stages. These stages included data collection, data reduction, data presentation with narrative text, and drawing temporary conclusions. The drawing of temporary conclusions was determined from the results of data reduction and presentation. Temporary conclusions may change if other evidence was found.

RESULTS

Table 1. The Proportion of Cesarean Delivery before and during JKN

JKN Era	Cesarean Delivery		Total Deliveries
	∑	%	
before	2001	45.1	4435
during	2250	53.1	4242
	PR = 1.17		

From quantitative data, it was found that there was an increase in the proportion of cesarean delivery during the implementation of JKN in four referral hospitals in Banyuwangi significantly (PR = 1.17). The number of cesarean delivery before the implementation of JKN was 2001 from 4435 deliveries (45.1%). During JKN implementation, the number of cesarean deliveries was 2250 from 4241 deliveries (53.1%) (Table 1).

Table 2. The Proportion of Cesarean Delivery and Vaginal Delivery in Maternal Death before and during JKN

	Cesarean Delivery				Vaginal Delivery				
	Maternal Death								
JKN Era	∑		%		∑		%		Total Maternal Death
before	4		50		4		50		8
during	6		60		4		40		10
PR	1.2				0.8				
	Time of Death								
	Childbirth		Postpartum		Childbirth		Postpartum		Total Maternal Death
JKN Era	∑	%	∑	%	∑	%	∑	%	
before	2	25	2	25	1	12.5%	3	37.5	8
during	2	20	4	40	2	20	2	20	10
PR	0.8		1.20		0.2		0.5		

Table 2 showed that 50% of maternal deaths before JKN give birth using cesarean delivery, this proportion increased significantly to 60% during JKN (PR = 1.2). This was different from the proportion of vaginal deliveries, where 50% of women who died before JKN gave birth using the vaginal method. The proportion decreased significantly during the implementation of JKN. 40% of women who died gave birth using the vaginal method (PR=0.8).

Table 2 showed 25% of deaths occurred postpartum before JKN delivered using the cesarean delivery. 40% of women who died postpartum during JKN gave birth using cesarean delivery. An increase in this proportion occurred significantly (PR = 1.2). The proportion of vaginal deliveries at the time of delivery to death increased significantly during JKN (PR = 0.2). 12.5% of women who died during JKN delivery gave birth using the vaginal method. This was an increase during JKN, 20% of woman who died postpartum during JKN gave birth using the vaginal method.

Table 3. The Proportion of Causes of Death in Cesarean and Vaginal Delivery before and during JKN

	Cesarean Delivery								
	Postpartum Hemorrhage		Uterine Rupture		Puerperal Sepsis		Preeclampsia/ Eclampsia		Total Maternal Death
JKN Era	∑	%	∑	%	∑	%	∑	%	
before	2	25	1	12.5	0	0	1	12.5	8
during	3	30	0	0	1	10	2	20	10
PR	1.2		0		0		0.2		
	Cesarean Delivery								
	Postpartum Hemorrhage		Uterine Rupture		Puerperal Sepsis		Preeclampsia/ Eclampsia		Total Maternal Death
JKN Era	∑	%	∑	%	∑	%	∑		
before	2	25	1	12.5	1	12.5	0	0	8
during	1	10	3	30	0	0	0	0	10
PR	0.4		2.4		0		0		

Table 3 showed that 25% of women died due to postpartum hemorrhage before JKN gave birth by cesarean surgery. This increased significantly during JKN implementation to 30% (PR = 1.2). Deaths caused by preeclampsia/eclampsia also increased significantly during JKN. 12.5% of deaths caused by preeclampsia/eclampsia delivered with cesarean delivery before JKN, then increased significantly to 20% during JKN (PR = 0.2). There were no deaths caused by puerperal sepsis before the implementation of JKN. 10% of deaths due to puerperal sepsis during JKN delivery by the cesarean delivery method. This increase in the proportion of deaths did not occur significantly (PR = 0).

Table 3 showed that 12.5% of women delivered by vaginal method before JKN died of uterine rupture. There was an increase in the proportion of deaths in vaginal deliveries during JKN due to uterine rupture, the increase in this proportion was more than half of the proportion before JKN significantly (PR = 2.4). 30% of women who died due to uterine rupture during JKN gave birth using the vaginal method.

Reimbursement and Cesarean Delivery without Indication

Doctors felt that service reimbursement was minimal during JKN implementation, one of them was the reimbursement of vaginal delivery services. The operational standards made by the Social Security Administrator for Health (BPJS Kesehatan) as the implementer of JKN did not match the actual conditions. A delivery that was planned vaginally would not get reimbursement if the realization was delivered with cesarean delivery. They had to spend a long time observing vaginal delivery, but this service would not receive reimbursement. They decided to make an adverse selection for this reason.

The hospital complained about several regulations made by BPJS Kesehatan. For example, the hospital avoided delivery induction for normal delivery and instead encouraged mothers to give birth by cesarean delivery method. The hospital did not get reimbursement from BPJS Kesehatan for the induction procedure that was given to the mother who ends up with cesarean delivery.

Delay in Referral and Increased Cesarean Delivery

Most of the cesarean delivery given to women during the implementation of JKN were cesarean delivery emergencies, women who were given cesarean delivery were already in a bad condition. This condition caused the risk of death to increase. Obstetric complications dominated the cause of death in both methods of delivery.

Obstetric complications were another factor contributing to the increasing proportion of cesarean deliveries. Less massive early detection and late referral were the main causes. Women came to the referral hospital in a severe condition so that cesarean delivery was required.

The referral system was strictly implemented during JKN implementation. Women must get services from primary health facilities first, then a referral will be made if there were indications. This regulation caused women to experience delays in getting services because they have to go through a long procedure. Complications would get worse due to delays in therapy. This can be prevented by carrying out massive high-risk early detection. If early detection was not carried out massively, the risk of late referral increased.

Communication problems between health workers in primary and secondary facilities were also a factor in the delay in referrals. Communication content was still a problem regarding reference indications, there was still a miss of communication between the two facilities regarding indications that the referral should be made. This problem caused the mother to go through a long and late referral procedure.

Repeat Cesarean Delivery

A large number of cesarean delivery history becomes a ticking time bomb at subsequent deliveries. If the first child was delivered by cesarean delivery, then subsequent deliveries were most likely cesarean delivery. This was because women who have a history of cesarean delivery indicate another cesarean delivery in their next pregnancy.

Reimbursement and Increased Death due to Uterine Rupture

The increase in vaginal deliveries in deaths caused by uterine rupture was due to the presence of midwives who helped women with a history of cesarean delivery. This condition was caused by various reasons. Women with a history of cesarean delivery still entrusted their delivery to midwives rather than by doctors or hospitals, this was because of excessive fear of giving birth cesarean delivery was back. Service providers also contributed to this condition, especially regional midwives who helped. Regional midwives still forced themselves to give birth to mothers with a history of cesarean delivery. Reimbursement standards made not by real conditions. Services already provided in primary facilities would not get reimbursement if women were referred to secondary facilities. Likewise, for women with a history of cesarean delivery, primary facilities will not get reimbursement for services that have been provided if women are referred to as secondary facilities. This condition was an indication of fraud to continue giving actions to women who previously had a cesarean delivery.

DISCUSSION

An increase in the proportion of cesarean delivery during JKN occurred significantly in four Banyuwangi referral hospitals. Several factors caused an increase in the proportion of cesarean deliveries in these four referral hospitals. The adverse selection indication made by doctors and hospitals. The causes of this were that the cesarean delivery reimbursement during JKN did not match the real cost. This funding complaint was an indication of fraud by doctors and hospitals to make cesarean delivery decisions without action so that the proportion of cesarean delivery has increased. Financing problems have indeed become an indication for health workers and health facilities to carry out the adverse selection and moral hazard [11]. Payment affected health facilities in the decision-making process. Doctors as the main decision-maker in carrying out medical actions were the determinants of the services to be provided to patients, as well as cesarean surgery [12]. A study in China states that the number of unsuitable claims would be the cause of the increase in cesarean delivery. This was related to the perception built by doctors about the higher income received when giving cesarean delivery compared to vaginal deliveries. A vaginal delivery also required a longer observation time than a cesarean delivery [9]. High obstetric complications forced the hospital to perform cesarean delivery procedures. Most of the cesarean surgery during JKN at the four Banyuwangi referral hospitals were emergency cesarean. Women came to the hospital already in a bad condition, this condition forced the hospital to do cesarean surgery. Cesarean delivery tended to occur in women with complicated pregnancies, one of which was obstetric complications[13]. Women with pregnancy complications had a 1.12 times greater risk of delivering with cesarean delivery. Women with labour complications had a greater risk of cesarean delivery, they had a 6.63 times greater risk [7].

Delay in referral was a determinant of emergency cesarean delivery. The tiered referral standard that was too strict makes it difficult for women to make referrals. This condition was also a determinant of increasing mortality during the implementation of JKN. The delay in getting adequate action tends to give birth to the cesarean method, 33.1% of women with near-miss gave birth using the cesarean method [14]. The three delays theory also explained that delays in getting action could increase the risk of death[15]. Prevention of late referral was not optimal, especially in the early detection of high-risk pregnancies. Early detection can prevent obstetric complications, unqualified early detection will increase the risk of obstetric complications and lead to death [14,16].

Repeat cesarean delivery was one of the causes of an increase in the proportion of cesarean deliveries during the implementation of JKN. The same conditions were found in different settings. One study stated that women who previously had a cesarean delivery had a greater risk of having a cesarean delivery in a subsequent pregnancy. Only one-third of women who previously had a cesarean delivery was allowed to have a vaginal delivery, only 63.3% had a successful vaginal delivery [17].

Indications of fraud also occurred in primary care, midwives in primary care provided delivery actions for women with previous cesarean delivery. This was why the proportion of vaginal deliveries among women who die from uterine rupture increased during JKN. American College of Obstetricians and Gynecologists made guideline that Vaginal Birth After Cesarean Delivery (VBAC) was allowed, but it must meet several condition[16]. The Indonesian Ministry of Health also established guidelines that women who previously had cesarean delivery should be referred to secondary health facilities [18]. Cesarean delivery must be accompanied by medical indications, delivery that was not accompanied by medical indications will hurt the mother. Some of the risked that could be obtained from childbirth that was not accompanied by medical indications include maternal death, intensive care unit care, blood transfusions to hysterectomy[19]. Cesarean delivery also has an impact on the psychological disorders of both mother and baby, especially in emergency cesarean delivery. Women would experience trauma, anxiety, and even problems in giving breastfeeding to their baby [20].

CONCLUSIONS

During the implementation of JKN in four secondary referral hospitals in Banyuwangi, the proportion of cesarean deliveries increased significantly. The number of mothers with a history of cesarean delivery and delays in referrals that result in complications suggests a medical indication for the number of cesarean deliveries during JKN. However, there are some indications of moral hazard and adverse selection due to the BPJS policy. Inappropriate reimbursement of health care costs is one indication of this. As the JKN policy's implementer, BPJS Kesehatan must review the standards established, one of which is the system and amount of reimbursement. Banyuwangi District's local government must also improve health services, particularly early detection of high-risk pregnant women. As a result, referral delays can be reduced and complications avoided.

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Research Article

How the Type of Surgery and Adherence to the Clinical Pathway Correlate with Quality Control and Cost Control in Endometriosis Surgery

Bagaimana Jenis Pembedahan dan Kepatuhan pada Clinical Pathway Berhubungan dengan Kontrol Kualitas dan Kontrol Biaya pada Operasi Endometriosis

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Abstract

Objective: This study examined the correlation of the type of surgery and adherence to the clinical pathway corresponding to the national guidelines in terms of quality and cost control.

Methods: Quantitative economic evaluation was conducted to assess the type of surgery and adherence to clinical pathways in terms of quality and cost control. The data were analyzed using the chi-square or Mann–Whitney test.

Result: Of the sample of 82 patients who had undergone laparoscopy or laparotomy, 54.9% had a laparoscopic procedure, while 45.1% had undergone laparotomy ; only 25.6% of the case procedures adhered to the clinical pathway. In general, it can be interpreted that, in a laparoscopy procedure, the potential risk that a mismatch will occur in quality control is up to 32 times that of a laparotomy procedure. Moreover, good adherence to the clinical pathway does not correlate with good cost control. Overall, of the 82 cases, only three (3.7%) showed a good fit for both quality control and cost control.

Conclusion: The type of surgery correlates with quality and cost control, whereas adherence to the clinical pathway does not correlate with either quality or cost control.

Keywords: endometriosis, laparoscopy, laparotomy, narional health insurance, surgery.

Abstrak

Tujuan: *Studi ini menguji korelasi jenis operasi dan kepatuhan terhadap jalur klinis yang sesuai dengan pedoman nasional dalam hal kontrol kualitas dan biaya.*

Metode: *Evaluasi ekonomi kuantitatif dilakukan untuk menilai jenis operasi dan kepatuhan terhadap jalur klinis dalam hal kualitas dan pengendalian biaya. Data dianalisis menggunakan uji chi-square atau Mann-Whitney.*

Hasil: *Dari sampel 82 pasien yang pernah menjalani laparoskopi atau laparotomi, 54,9% menjalani prosedur laparoskopi, sedangkan 45,1% pernah menjalani laparotomi ; hanya 25,6% dari prosedur kasus yang mengikuti jalur klinis. Secara umum dapat diartikan bahwa, dalam prosedur laparoskopi, potensi risiko terjadinya ketidaksesuaian dalam kontrol kualitas adalah hingga 32 kali lipat dari prosedur laparotomi. Selain itu, kepatuhan yang baik terhadap jalur klinis tidak berkorelasi dengan pengendalian biaya yang baik. Secara keseluruhan, dari 82 kasus, hanya tiga (3,7%) yang menunjukkan kesesuaian yang baik untuk pengendalian kualitas dan pengendalian biaya.*

Kesimpulan: *Jenis pembedahan berkorelasi dengan kualitas dan pengendalian biaya, sedangkan kepatuhan terhadap jalur klinis tidak berkorelasi dengan kualitas atau pengendalian biaya.*

Kata kunci: *endometriosis, jaminan kesehatan nasional, laparoskopi, laparotomi, pembedaahan.*

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INTRODUCTION

Endometriosis is a benign gynecological disease characterized by the presence of glands and stroma similar to those of the endometrium outside the uterine cavity; it is associated with pelvic pain and infertility. It has several clinical manifestations, with numerous progressions and recurrences.[1-3] The incidence of endometriosis is difficult to diagnose with certainty; this difficulty may be due to the lack of epidemiological studies that can be used as a reference and the invasive procedure that must be performed for diagnosing it.[1] Globally, it is estimated that 10% of women of reproductive age and around 30%–50% of women with infertility suffer from endometriosis.[4] In Indonesia, it is estimated that endometriosis incidence occurs among 13.6%–69.5% of the population with infertility.

Supporting examinations for diagnosing endometriosis can be performed using transvaginal ultrasonography, magnetic resonance imaging (MRI), and biochemical markers; however, since a definitive diagnosis can only be ascertained via laparoscopic procedures, many patients are not diagnosed until 4–10 years from the onset of symptoms.[5] Endometriosis surgery can be performed using a laparotomy or laparoscopy method. Previous studies have shown that laparoscopy surgery will allow the patients to lead a better life, and it is considered an effective procedure.[6,7] However, until now, there have been no data reported on the relationship between the type of surgery chosen in endometriosis cases and quality and cost control. Systematic studies reveal that pain, infertility and the length of time required for diagnosing the condition, as well as the high recurrence rate, may lead to a decrease in quality of life and are the major factors in predicting the associated healthcare budget.[8]

In addition, there are currently no data on the economic burden caused by endometriosis in Indonesia, but studies in the United States show that the costs for managing endometriosis patients could reach up to $2,801 US per year, and it is estimated that around $1,023 US or 86.4 hours per year are lost because of a decrease in productivity among endometriosis patients.[9] Medical practices in Indonesia are regulated by Law No. 24 of 2009, where article 44 states that doctors or dentists who perform medical practices must follow the prescribed medical service standards, which are further regulated by the Minister of Health Regulation No. 1438 of 2010 concerning medical service standards. Indonesian medical service standards consist of the National Guidelines for Medical Services and the Standard Operating Procedure (SOP), where the SOP is derived from the national guidelines. These procedures are delineated as practices in local health facilities, expressing the national guidelines in the form of Clinical Pathway or Clinical Practice Guidelines.

The national guidelines for dealing with endometriosis were established in 2013 by the Indonesian Society for Reproductive Endocrinology and Infertility, followed by the formulation of national guidelines for endometriosis management at Dr. Cipto Mangunkusumo Genaral Hospital. To this day, the national guidelines for endometriosis management have never been evaluated. Moreover, quality and cost controls at Dr. Cipto Mangunkusumo Genaral Hospital have not been evaluated, but internal data from 2014 reveal that there is a significant disparity between the total claim filed by Indonesian Case Base Groups (INA-CBGs) and the real cost borne by the National Hospital. Quality and cost control have been the major outcomes in health services management following the enactment of the National Health Insurance scheme in 2014; therefore, the application of national guidelines serves as a tool for providing proper health services that are consistent with the existing standards. Meanwhile, quality control is defined as a system that guarantees the delivery of effective, efficient, and good-quality health services that meet the patients' needs, while cost control is a system that guarantees the health care costs paid by the patients will result in services that fulfill their needs. Based on the issues mentioned above, this study explores the relationship between the type of surgery and adherence to national guidelines on the one hand and quality control and the cost of surgical procedures in on the other endometriosis cases at the Department of Obstetrics and Gynecology at Dr. Cipto Mangunkusumo Genaral Hospital.

METHODS

The research comprised a quantitative economic evaluation with a cross-sectional study design and an unpaired comparative categorical analytic method. Comparative analysis was carried out to examine the correlation between the types of surgery (laparotomy or laparoscopy) and quality control and cost control. A comparative analysis was also conducted on the adherence to national guidelines with quality control and cost control. The sample in the study comprised endometriosis patients who underwent either laparotomy or laparoscopy surgeries at Dr. Cipto Mangunkusumo Genaral Hospital in 2016. The study's inclusion criteria covered patients with typical endometriosis complaints, that is, women who had been diagnosed with endometriosis. The laparoscopic or laparotomy surgical procedures were all performed at Dr. Cipto Mangunkusumo Genaral Hospital and paid for by the National Health Insurance System. The exclusion criteria were women who needed intensive care or suffered from other comorbid diseases that could affect the treatment cost, as well as women whose post-surgery diagnosis revealed conditions other than endometriosis.

The operational definition regarding adherence to guidelines is defined as good if 80% of the guidelines' components are carried out. The type of surgery covered in the study was based on HIFERI's National Guidelines for Medical Services for endometriosis and Dr. Cipto Mangunkusumo Genaral Hospital medical service guidelines. Meanwhile, as mentioned above, quality control was defined as a system that provides effective, efficient, and quality health services that meet patients' needs; the level of quality is measured from three components, that is, the complications that may arise during the surgery, duration of treatment after surgery, and mortality. In contrast, cost control is a system that guarantees that the amount paid by patients exclude the taxes, will give them health care that fulfills their needs.[10] Cost conformity is the entire cost of disease management, from initial diagnosis until surgery, incurred by the hospital for patient management consisting of medical, pharmaceutical, laboratory, and radiological services. The financing standards used in Dr. Cipto Mangunkusumo Genaral Hospital refer to the hospital's costing unit and INA-CBGs standard payment rates, which are based on the Regulation of the Minister of Health No. 59 of 2014.

Statistical analysis was carried out using the chi-square and Mann–Whitney tests while considering the distribution of data. The outcome of the study is expected to show the proportions of relative risks with p-values and confidence intervals. The data were processed using SPSS version 20.

Ethical Clearance

Ethical approval was granted by the ethics committee of the Faculty of Medicine, University of Indonesia (code: 18/UN2.F1/ETIK/2016). Informed consent was obtained from all of the participants.

RESULTS

This study was carried out on 82 patients who met the inclusion criteria. All subjects followed the study to completion.

Table 1. Research Subjects' Characteristics

	Total Number	%
Age (year)		
>50	6	7.3
<50	76	92.7
Type of Surgery		
Laparoscopy	45	54.9
Laparotomy	37	45.1
Adherence to Clinical Practice Guidelines		
Yes	21	25.6
No	61	74.4
Cost Control		
Adhering to PPK guidelines	9	11.0
Not adhering to PPK guidelines	73	89.0
Quality Control		
Adhering to PPK guidelines	28	34.1
Not adhering to PPK guidelines	54	65.9

Table 1 shows that most of the cases were women of premenopausal age, aged less than 50 years old, with 92.7% of the sample belonging to this group. The type of surgery was quite balanced, where 54.9% of the patients underwent a laparoscopy procedure, whereas the remaining 45.1% had laparotomy. Moreover, in the 82 cases, only 25.6% of the surgeries adhered to the national guidelines, which shows low compliance with the prevailing guidelines.

Table below showed the cost incurred by Cipto Mangunkusumo National Hospital and the amount paid by BPJS (National Insurance).

Table 2. Analysis of the Disparity between the Cost by Dr. Cipto Mangunkusumo General Hospital and the Amount Reimbursed by BPJS

	Median	Minimum	Maximum
Percentage of the cost incurred by Cipto Mangunkusumo National Hospital and the amount reimbursed by BPJS (%)	75.05	15.78	139
Cost disparity (Rp)	−5,160,954	−32,072,899	6,032,713
Adhering to PPK guidelines (Rp)	−6,872,183	−23,834,347	−320,395
Not adhering to PPK guidelines (Rp)	−4,343,356	−32,072,899	6,032,713

From Table 2, we may deduce that the disparity between the cost incurred by Cipto Mangunkusumo National Hospital and the amount reimbursed by BPJS is quite large, where the hospital only received 75% of the cost on average, up to Rp 5,160,954. The biggest loss that was borne by the National Hospital was Rp 32,072,899 (only 15.78% of the hospital's cost is reimbursed by National Insurance). The data revealed that there were only nine cases (10.9%) where National Insurance overpaid the cost incurred by the National Hospital.

From Table 3, we may conclude that, in most endometriosis surgeries, the costs borne by the National Hospital are higher than the reimbursement paid by National Insurance, which leads to a substantial loss to Dr. Cipto Mangunkusumo General Hospital.

Table 3. Correlation between the Type of Surgery and Adherence to PPK with Cost Control

Cost Control	Laparoscopy (*n* = 45)		Laparotomy (*n* = 37)		Total		*P-value*
	n	%	n	%	N	%	
Not adhering to PPK guidelines	39	86.7	34	91.9	73	89.0	
Adhering to PPK guidelines	6	13.3	3	8.1	9	11.0	0.503
	Good adherence to PPK guidelines (*n* = 21)		**Poor adherence to PPK guidelines (*n* = 61)**		**Total**		***P-value***
	n	**%**	**n**	**%**	**N**	**%**	
Not adhering to PPK guidelines	20	95.2	53	86.9	73	89.0	
Adhering to PPK guidelines	1	4.8	8	13.1	9	11.0	0.435

Only 11% of the cases have proper cost control (13.3% in laparoscopy cases and 8.1% in laparotomy cases), illustrating that cost control still leaves much to be desired. The uniform data distribution ultimately yields an insignificant *p*-value of 0.503, which means that neither laparoscopy nor laparotomy procedures have any effect on cost control. It is also apparent that there is only a single case with a good adherence to the PPK guidelines in addition to having a proper cost control and eight cases where adherence to the PPK guidelines is poor and cost control is also at odds with the PPK guidelines. Therefore, the conclusion is that good adherence to the PPK guidelines does not correlate with good cost control, but neither does poor adherence to the PPK guidelines correlate with poor cost control, where the lack of correlation is shown by the *p*-value of 0.435.

Table 4. Correlation between the Type of Surgery and Adherence to PPK with Quality Control

Quality Control	**Laparoscopy**		**Laparotomy**		**Total**		***P-value***	**RR (Confi-dence Level 95%)**
	n	**%**	**n**	**%**	**n**	**%**		
Not adhering to PPK guidelines	44	97.8	10	27.0	54	65.9	0.001	32 (4-230)
Adhering to PPK guidelines	1	2.2	27	73.0	28	34.1		
	Good adherence to PPK guidelines (n = 21)		**Poor adherence to PPK guidelines (n = 61)**		**Total**		***P-value***	
	n	**%**	**n**	**%**	**n**	**%**		
Not adhering to PPK guidelines	15	71.4	39	63.9	54	65.9	0.532	
Adhering to PPK guidelines	6	28.6	22	36.1	28	34.1		

Table 4 shows that, from the perspective of quality control between laparoscopy and laparotomy, only 2.2% of the cases were managed according to the PPK guidelines for laparoscopy procedures and 73% for laparotomy procedures; the overall percentage of the correlation between the type of surgery and adherence to the PPK guidelines with the total percentage of quality control is 34.1%, with a significant *p*-value at 0.001. It can be interpreted that, in a laparoscopy procedure, there is a potential risk that a mismatch in quality control will occur reaching 32 times that of a laparotomy procedure. From the perspective of adhering to the PPK guidelines, 6 cases showed good adherence to the guidelines and good quality control, whereas 22 cases showed poor adherence to the PPK guidelines and good quality control. After analyzing the correlation between adherence to PPK, wherein the outcome is evaluated from three components that is, complications that may arise after surgery, duration of treatment during the surgery, and mortality we learn that there is no correlation between good adherence to PPK with good quality control and vice versa, with a *p*-value of 0.532.

Table 5. Evaluation of the Type of Surgery and Adherence to PPK with Quality Control and Cost Control

	Laparoscopy		**Laparotomy**		**Total**		***P-value***
	N	**%**	**n**	**%**	**n**	**%**	
Cost control and quality control fail to meet PPK guidelines	39	86.7	9	24.4	48	58.5	<0.001
Cost control meets PPK guidelines	5	11.1	1	2.7	6	7.3	0.215
Quality control fails to meet PPK guidelines	0	0.0	25	67.6	25	30.5	<0.001
Cost control and quality control meet PPK guidelines	1	2.2	2	5.4	3	3.7	0.586
	Good adherence to PPK guidelines		**Poor adherence to PPK guidelines**		**Total**		***P-value***
Cost control and quality control do not meet PPK guidelines	14	66.7	34	55.7	48	58.5	0.447
Cost control meets PPK guidelines	1	4.8	5	8.2	6	7.3	1.000
Quality control meets PPK guidelines	6	28.6	19	31.1	25	30.5	1.000
Cost control and quality control meet PPK guidelines	0	0	3	4.9	3	3.7	0.566

From Table 5, we can still see a mismatch between cost control and quality control in the total cases (58.5%); meanwhile, only three samples (3.7%) show a proper match between quality control and cost control. Other data also show that the figure for cost control's adherence to PPK, at 7.3%, is far lower than the figure for quality control, which reaches 30.5%. There is a relationship between the type of surgery and quality control and cost control, where a laparoscopy surgery will produce quality control and cost control that does not meet the PPK guidelines, with a *p*-value < 0.001. It is also apparent that there is no relationship between good adherence to the PPK guidelines and quality or cost control, with a *p*-value = 0.566. Therefore, we may conclude that the type of surgery correlates with quality control and cost control, whereas adherence to PPK does not correlate with quality control or cost control.

DISCUSSIONS

We included 82 patients, where 45 had undergone a laparoscopy procedure and 37 a laparotomy procedure. These were cross-sectional samples taken from patients who underwent surgical procedures at Dr. Cipto Mangunkusumo General Hospital in 2016. It should be noted that the collected sample size was higher than the calculated sample size to avoid the possibility of data deficiency in some patients. However, as it turned out, all 82 samples could be analyzed in their entirety. Demographically, the patients were quite uniform, where 92.7% of them were of premenopausal age; this shows that endometriosis is a disease that is closely related to reproductive hormones and patients' menopausal status.

The data in the study showed a prevalence of endometriosis cases in postmenopausal women of 7.3%, which is in line with the findings in a study [10,11]. Which pointed to a figure of around 2.55%. The types of surgery were evenly distributed, with 54.9% of the patients undergoing a laparoscopy procedure and 45.1% undergoing a laparotomy procedure. As expected with the initial sample size of 35 women in the laparoscopy group and 35 women in the laparotomy group, the actual samples collected satisfied the data collection requirement, and the data could be analyzed further.

Evaluation of the adherence to the PPK guidelines revealed that only 23.6% of the services adhered to the current PPK guidelines, which is a rather low rate. This figure is consistent with those of other studies conducted in two hospitals in Indonesia, where the adherence to the PPK guidelines ranged from 0% to 28.12%[10,12]. In their study, Joris et al. stated that adherence to PPK is still controversial, where adherence is associated with improvement in some outcomes in some cases but not in all applications. A systematic review showed that the integration of PPK guidelines with information technology improves the outcomes of the services[13,14].

The poor adherence to the PPK guidelines we found in the study may be caused by several factors, that is, the heavy load and diverse cases that must be managed, the number of healthcare professionals involved, and finally, a lack of training on the procedure. These are the crucial points that show where improvement can be made by adjusting the PPK guidelines and intensifying the training on the guidelines; if these changes are made, all the physicians at Dr. Cipto Mangunkusumo General Hospital will be able to comply with the guidelines. Adjustment and adherence to the PPK guidelines can only be imposed by the institution's policymakers in conjunction with the proper use of information technology. Via such measures, all healthcare professionals will be aware of the guidelines and adhere to these standards. When good adherence to the PPK guidelines has been achieved, then we may know the effect on the existing patient services outcomes.

Analysis of the correlation between the type of surgery with quality control and cost control reveals that the laparoscopy procedure is at odds with the PPK guidelines, with a mismatch between quality control and cost control. This is contrary to HIFERI's recommendation that endorses laparoscopy as the preferred procedure because the potential for complication is lower and the procedure requires a shorter hospital stay. Analysis of the correlation between adherence to PPK guidelines and quality control and cost control revealed no discernible link between the two variables. This finding invalidates the researchers' initial hypothesis that a correlation would be present between good adherence to the PPK guidelines and quality and cost control. Therefore, we may conclude that the type of surgery correlates with quality and cost control, whereas adherence to PPK does not correlate with quality and cost control. The limitation of this research was that the costs were not calculated according to the actual unit cost. Instead, they were based on the total costs incurred by Dr. Cipto Mangunkusumo General Hospital.

CONCLUSION

Laparoscopic surgery and adherence to PPK does not correlate with good quality control or cost control. In contrast, laparotomy does not correlate with good cost control, but it does correlate with good quality control. The median disparity between the cost incurred by Cipto Mangunkusumo National Hospital and the reimbursement paid by BPJS was Rp 5,160,954. Percentage wise, BPJS reimbursed only 75.05% of the total costs incurred by Dr. Cipto Mangunkusumo General Hospital. The level of adherence based on services performed to the PPK guidelines in the study was 25.6%. A detailed financial evaluation that calculates the real unit cost is important to prevent a deficiency in the funding; hence, it is crucial for a team to be set up in each department to manage the finances and discuss the matter directly with the P2JK Office (Health Insurance Financing Center) at the Ministry of Health. The level of adherence to the PPK guidelines was 25.6%, which has not been able to improve the evaluation of quality control and cost control, and as a consequence, it may be necessary to adjust and reformulate the existing PPK guidelines by incorporating the classification of endometriosis severity, allowing the quality control and cost control to be adjusted accordingly. Socialization of PPK guidelines must be carried out thoroughly to ensure that all healthcare professionals at Cipto Mangunkusumo National Hospital become familiar with the guidelines. More studies on INA-CBG's claim evaluation and financing in other fields and cases with a high prevalence are highly recommended to prevent further deficits in the hospital's finances.

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CONFLICT of INTERESTS

The author reports no conflicts of interest in this work.

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Case Report

Prenatal Differential Diagnosis and Prospective Management of Hydranencephaly

Diagnosis Diferensial Prenatal dan Manajemen Prospektif dari Hidranensefali

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Abstract

Objective: To report a rare case of hydranencephaly that was diagnosed during prenatal period. We also provided further review of differential diagnosis and management performed in Ende District General Hospital, based on appropriate literatures and guidelines available.

Methods: Case Report.

Case: A 27-year old primigravida women was diagnosed with term pregnancy (37 weeks of gestation) and intra-uterine singleton live fetus with hydranencephaly via ultrasonography. In this patient, emergency caesarean section (CS) was performed to prevent complication of cephalo-pelvic disproportion (CPD), involving teamwork between obstetrics and perinatology. A male neonate was born weighing 3000 grams, head circumference of 32 cm, and APGAR score of 2/4/7/8 suggestive of asphyxia and respiratory distress. The newborn was immediately transferred to Neonatal Intensive Care Unit (NICU) for further resuscitative management and observation. The newborn remains in stable condition after resuscitative management was given. Post-natal transcranial sonography (TCS) of the newborn was performed by a pediatrician, and the diagnosis of hydranencephaly was confirmed. The newborn was later referred to facilities with neurosurgery department for further evaluation and intervention.

Conclusion: Early prenatal recognition of hydranencephaly and exclusion of similar differential diagnosis, which includes: hydrocephalus, holoproscencephaly, porencephaly and schizencephaly, are fundamental in formulating proper multidisciplinary management with pediatric and neurosurgery department, which may consequently improve the newborn's life expectancy.

Keywords: differential diangnosis, hydranencephaly, management.

Abstrak

Tujuan: *Melaporkan suatu kasus langka hidranensefali yang kami diagnosa dalam periode prenatal; dan memberikan ulasan lanjut mengenai diagnosis diferensial dan manajemen yang kami kerjakan di Rumah Sakit Umum Ende, berdasarkan literatur dan pedoman ilmiah yang tersedia.*

Metode: *Laporan Kasus.*

Kasus: *Seorang perempuan primigravida berusia 27 tahun di diagnosa dengan kehamilan aterm (37 minggu gestasi), janin tunggal hidup intrauterin dengan hidranensefali via ultrasonografi. Pada pasien ini dilakukan Sectio Caesarea (SC) cito untuk mencegah komplikasi dari disproporsi kepala-panggul dengan kerjasama tim kebidanan dan perinatologi. Lahir bayi laki-laki dengan berat badan 3000 gram, lingkar kepala 32 cm, dan skor APGAR 2/4/7/8 dengan kesan asfiksia dan distres pernapasan. Bayi segera dipindahkan ke Neonatal Intensive Care Unit (NICU) untuk penanganan resusitatif lanjut dan observasi. Bayi tetap bertahan dalam kondisi stabil setelah diberikan manajemen resusitatif. Pemeriksaan sonografi transkranial pasca-natal dilakukan oleh dokter anak, dan diagnosis hidranensefali terkonfirmasi. Bayi kemudian di rujuk ke fasilitas dengan ketersediaan departemen bedah saraf untuk evaluasi dan intervensi lanjut.*

Kesimpulan: *Deteksi dini prenatal hidranensefali dan eksklusi diagnosis diferensial serupa, yang mencakup: hidrosefalus, holoprosensefali, porensefali, dan skizensefali, adalah dasar dari formulasi manajemen multidisiplin yang baik antara departemen pediatrik maupun bedah saraf, sehingga dapat meningkatkan kualitas dan ekspektasi hidup bayi baru lahir.*

Kata kunci: *diagnosis diferensial, hidranesefali, manajemen.*

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INTRODUCTION

Hydranencephaly (HE) is a condition most commonly associated with cerebral cortex absence in bilateral hemispheres or unilateral hemisphere (Hemi-Hydranenchephaly / HHE) in rare occasions. Cerebral cortex tissue is replaced with cerebrospinal fluid, necrotic glial, and/or ependymal debris filled sac covered in membranous leptomeninges.[1,2] It is one of the most rare severe forms of bilateral cerebral cortical anomaly which only affects approximately 2.1 to 20 out of 100,000 births or pregnancies; and shares close resemblance with other conditions, such as: hydrocephalus, holoproscencephaly, porencephaly and schizencephaly.[2,3] A specific incidence especially in Indonesia is still difficult to determine with very limited data, and currently no case has been reported. Despite recent medical advancements, doubts still persist on etiopathogenetic, onset, and diagnostic aspects of HE due to its similarity with conditions mentioned above.[1] HE commonly has a poor prognosis; since most affected individuals died in-utero or have a life expectancy of 1 year at most with a burden of developmental delay, drug-resistant seizures, spastic displegia, severe growth failure and respiratory infections. However, some survivors with proper maintenance of brainstem functions (temperature, blood pressure, and cardiovascular function) have been reported to survive at the age of 20, 22, and 32 years old respectively.[4]

Based on these reports, recognizing hydranencephaly from its differential diagnosis is fundamental in formulating proper multidisciplinary management with pediatric and neurosurgery department, which may consequently improve the newborn's life expectancy. In this paper, we reported a case of at term fetus with prenatal and postnatal sonographic findings consistent with hydranencephaly in our obstetrics and gynecology department.

CASE

A 27-year old primigravida women on her 37th week of gestation was referred by a private midwife practice for the first time to our labor and delivery unit in Ende District General Hospital due to prolonged active phase labor with cephalo-pelvic disproportion suspicion. The patient had experienced signs of labor such as constant progressive uterine contractions with bloody show for the past two days, and fluid leakage symptom was denied; throughout the pregnancy, the patient felt normal fetal movements. The patient rarely had prenatal check-up visits; only visited once in each first and second trimesters respectively with no third trimester prenatal visits. The patient also denied having history of previous ultrasound examinations throughout her pregnancy. The patient had previously done laboratory blood hemoglobin (Hb) examination during her sixth week of gestation to which her Hb was 12 g/dL; previous urine dipstick, Hepatitis B Surface Antigen (HbsAg), anti-syphilis (VDRL) and anti-HIV showed no significant abnormalities; She recalled having tetanus toxoid injection once during her sixth week prenatal check-up visit. The patient denied having previously tested for TORCH (Toxoplasma, Rubella, Cytomegalovirus and Herpes Simplex). The patient admitted that she skipped routine folic acid and ferrous sulfate medication due to rare prenatal check up visits.

Physical examination and vital signs were within normal limit. The patient's height and weight measured 147 cm and weight 46 kg respectively, which is considered to be normal. The clinical obstetric examination revealed oblique lie fetus with hardly distinguishable fetal presentation and it still floats beyond upper pelvic outlet. Vaginal examination revealed her cervix was dilated at 4 cm with intact amniotic membrane, with confirmed head presentation still floating higher than hodge 1 pelvic plane suggestive of cephalo-pelvic disproportion, and occipital fontanel facing the left side of the patient.

2D-Transabdominal ultrasonography was performed, revealed a singleton intrauterine pregnancy in oblique lie position, with fetal heart rate of 134 beats per minute (M-Mode) and fetal movement was unremarkable. Fetal biometry was equivalent to 37 weeks of gestation (Hadlock Standard). Intracranial sonography showed fluid filled cranial cavity with absent of most bilateral cerebral cortex and falx cerebri disruption; thalami and midbrain structures were still present; cerebellum and other posterior fossa structures were still present **[Figure 1]**. Amniotic fluid index was measured 150 mm still within normal range with no polyhydramnios present. Overall sonography results was suggestive of hydranencephaly.

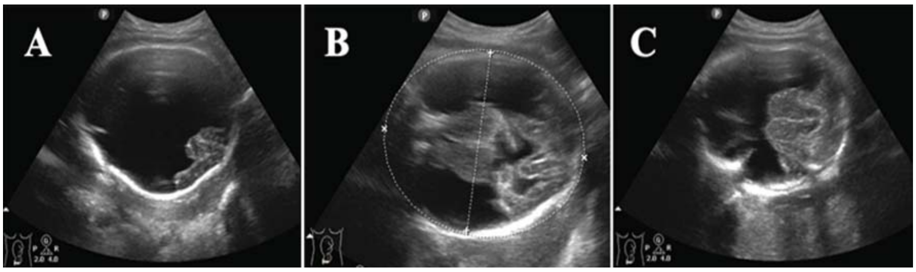

Figure 1. 2D Transabdominal Ultrasound of fetal head (Axial View) at 37 weeks' gestation: (A) transventricular plane showing absent of bilateral cerebral cortex with no intact cortical rim and falx cerebri disruption, (B) transthalamic plane showing thalami and midbrain structures were still present, (C) transcerebellar plane showing cerebellum and other posterior fossa structures were still present.

Given the severity of the clinical picture, we convinced the patient to undergo emergency caesarean section (CS) since the patient's gestational age is at term and to prevent further obstetric complications that may arise from cephalo-pelvic disproportion. The patient's pre-operative blood work revealed O positive blood group with blood count results within normal range; urinalysis, anti-HIV and HbsAg infection markers were confirmed uneventful. The Pediatric-Perinatology department was informed of the about the situation and parents were given proper counseling regarding the child's poor prognosis and potential post-natal management. The newborn was a 3000 grams male, with normal physical appearance **[Figure 2]**. The head of the newborn was of normal size (head circumference = 32 cm), however the head was particularly transilluminated. Placenta and umbilical cord appearances were normal. Post-operative course of the patient (mother) was uneventful.

The newborn was immediately transferred to the neonatal intensive care unit (NICU) due to moderate asphyxia and respiratory distress, with APGAR score of 2/4/7/8. At birth, the newborn was cyanotic, weakly crying when stimulated, with slow heart rate and respiratory below 100 bpm and 60 bpm respectively; however the condition improved after proper neonatal management was given. Continuous positive airway pressure (CPAP) was installed with positive expiratory end pressure (PEEP) of 7, oxygen flow rate (FLOW) of 6 L/min, and fraction inspired oxygen (FiO2) of 30%. The newborn was advised for oral fasting and oral-gastric tube (OGT) was installed to minimize risk of aspiration; fluid administration of intravenous 10% dextrose solution (D10%) was given at a starting rate of approximately 7 cc/hours (60 cc/kg/24 hours with increments of 10 cc/kg/24 hours). Antibiotic injections of ampicillin 150 mg/12 hours (50 mg/kg/12 hours) and gentamicin 15 mg/24 hours (5 mg/kg/24 hours) for at least 7 days were given since the newborn showcased potential signs of neonatal sepsis. The newborn's postpartum blood work were within normal range, further laboratory analysis of TORCH (toxoplasma, rubella, cytomegalovirus, and herpes simplex) infections were advised but the patient refused for checkup. Transcranial sonography (TCS) of the newborn was performed by a pediatrician one day after delivery. TCS revealed fluid filled cranial cavity with absent of most bilateral cerebral cortex and falx cerebri disruption; however, midbrain structures, cerebellum and other posterior fossa structures were less visible this time **[Figure 2]**. TCS therefore confirmed the prenatal diagnosis of hydranencephaly. The newborn was observed for seven days before getting referred to facilities with neurosurgery department to further diagnostic evaluation the case and perform surgical intervention if indicated.

Figure 2. (A) General Appearance of The Newborn, (B) (C) 2D Transcranial Sonography (TCS) of The Newborn's Head (Mid-Coronal View) and (Mid-Sagittal View) respectively revealed absent of bilateral cerebral cortex with falx cerebri disruption; while midbrain structures, cerebellum and other posterior fossa structures are less visible.

DISCUSSION

Hydranencephaly (HE) is a condition most commonly associated with cerebral cortex absence in bilateral hemispheres or unilateral hemisphere (Hemi-Hydranenchephaly/HHE) in rare occasions. It is one of the most rare severe forms of bilateral cerebral cortical anomaly which only affects approximately 2.1 out of 100,000 births or pregnancies. The etiopathogenesis of HE remains unknown; however, there are some hypothesized theory, which includes: vascular accident/circulation developmental theory, early organogenesis disruption theory and encephaloclastic destruction theory. Many reports suggested that vascular accident has been associated with: intrauterine infections (toxoplasmosis, enterovirus, adenovirus, parvovirus, cytomegalovirus, herpes simplex, Epstein Barr and respiratory syncytial virus), toxic exposures (smoking, cocaine abuse, estrogen, sodium valproate), and other risk factors (young maternal age, mono-chorionic twin pregnancy, factor XIII deficiency and prior intra-cerebral hemorrhage).[2,3]

Prenatal Differential Diagnosis

Prenatal diagnosis of hydranencephaly (HE) can be determined early during prenatal period by ultrasonography (US). Maternal clinical manifestations during pregnancy are unreliable in determining diagnosis, since mother typically feels normal fetal movements just similar to this case; unless there is a decrease or absent in fetal movements with suspicion of intra-uterine fetal demise, which promotes further ultrasonography examination. Fetus with HE mostly died before birth, however those who survive do not initially show evident clinical or neurological signs; in this case, the newborn has a normal head circumference at birth, without any evident disturbance in archaic reflexes, extremity movements, and sucking-swallowing reflexes. Subtle signs such as feeble crying, feeding difficulty, hypotonia or wide anterior fontanel may be seen at birth and more rapidly pronounced after a few days; consequently progress to severe hypotonia, irritability, and seizure; these signs were not found in this case throughout a week of observation.[3]

Ultrasonography (US) can detect abnormal features of HE for as early as 21st – 23rd weeks of gestation with impressions of absent cerebral hemispheres without any intact cortical rim, which is replaced by homogenous echogenic materials (cerebrospinal fluid, necrotic glial tissues and/or ependymal debris) filling the supratentorial space with preserved brain stem (midbrain), thalamus, basal ganglia, choroid plexus and cerebellum in most cases. Cerebral cortex is fully absent in most cases; but there may be partial preservation of frontal, occipital, or both lobes. Our case presented prenatal ultrasonography with impressions of bilateral cerebral cortex absences without any intact cortical rim; while thalami, midbrain structures, cerebellum and other posterior fossa structures were still present. Falx cerebri is still commonly present; however in some reported cases including this case, falx cerebri is shown partially or completely disrupted with unclear anterior or posterior margins.[3] Diagnosis of HE should be narrowed down from many other similar differential diagnosis in order to plan proper post-natal management; which includes **[Figure 3]**[3]:

Hydrocephalus is defined as a progressive enlargement of ventricular system due to inadequate passage of cerebrospinal fluid (CSF) from its production site within cerebral ventricles to its site of absorption into the systemic circulation, resulting in abnormally accelerated head growth.[8] It is still considered as a common problem in fetus and newborns; which accounts for approximately 2,7 out of 1,000 births globally, in which the incidence of congenital hydrocephalus was approximately 1,2 out of 1,000 births.[5] classified based on its etiology as congenital/developmental (intrinsic causes) and acquired (extrinsic causes); traditionally it was also classified based on its pathogenesis (obstructive or non-obstructive) and genetics (syndromic or non-syndromic). The pathogenesis of hydrocephalus is the consequence of imbalance in intracranial CSF inflow and outflow, classified into: (1) CSF flow obstruction (non-communicating), (2) impaired CSF absorption (communicating, due to subarachnoid villi inflammation or venous sinus pressure elevation), and (3) CSF overproduction (communicating, due to functional choroid plexus papilloma). Prenatal diagnosis of congenital hydrocephalus is done by ultrasonography (US) with persistent enlargement of posterior horn lateral ventricle width (atrial width) measured 10-15 mm (mild ventriculomegaly), > 15 mm (severe ventriculomegaly); however these findings must also be accompanied by increase in post-natal head size and tense major fontanelle (due to increase in intracranial pressure). Unlike hydranencephaly, hydrocephalus has increase in head size due to increase in intracranial pressure with intact cortical rim and intracranial structures including the ventricle is still distinguishable.[6]

Holoprosencephaly (HPE) is described as incomplete cleavage of prosencephalon; hence it does not clearly divide in diencephalon, two halves of telencephalon and lateral ventricles; resulting in complete or partial union of forebrain with only a single ventricle instead of two. It is the most common forebrain developmental malformation, affecting 1 out of 250 prenatal fetus and only 1 out of 6000 live births.[7] HPE is classified into three main types and one variant: alobar, semi-lobar, lobar, and inter-hemispheric average fusion variant. Prenatal diagnosis with ultrasound reveals presence of midline malformation and brainstem anomalies, which are preserved in holoprosencephaly. In alobar HPE, ultrasonography reveals a single primitive ventricle structure with fused thalamus in the midline and complete absence of: inter-hemispheric fissure, corpus callosum, septum pellucidum, neuropophysis, third ventricle, olfactory bulb, and tract. Inter-hemispheric fissure is still partially preserved posteriorly in semi-lobar HPE and in anterior-posteriorly in lobar HPE. Unlike in hydranencephaly, HPE especially in alobar HPE is also associated with facial abnormalities such as cyclopia (one middle eye), proboscis (middle anterior appendage structure), etmocephaly (extremely close ocular distance with proboscis), cebocephaly (close ocular distance with single nostril), anophthalmia/ microphthalmia (very small or no eyeballs), cleft lip and absence of nose.[8]

Porencephaly/pseudo-porencephaly is a very rare condition affecting only approximately 5.2 out of 100,000 live births; described as the presence of cystic cavities that usually communicate with ventricular system, subarachnoid space or both within brain parenchyma.[2,9] pseudo-porencephaly (encephaloclastic / porencephalic cysts) is different from schizencephaly / true porencephaly in the lining of the cavity, which usually contains white matter instead of gray matter; and is not associated with neuronal migration abnormality. Fetal ischemic stroke and middle cerebral artery occlusion was postulated as the main cause of porencephalic cyst. Prenatal diagnosis with ultrasound reveals cystic cavity(s) within the brain that usually interconnects with ventricular system and located in middle cerebral artery territory accompanied by ischemic infarcts. This condition is hardly differentiated with hydrancephaly in severe cases, usually parieto-occipital cortex is still preserved in porencephaly. Further evaluation with post-natal MRI can be used to precisely differentiate this condition with other similar abnormalities.[9]

Schizencephaly / true porencephaly is a condition characterized by full thickness, gray matter-lined clefts of cerebral mantle; which is often bilateral and symmetric, providing communication between lateral ventricles and external subarachnoid space. It is a very rare condition, which only affects 1 out of 100,000 live births. Agenetic/developmental anomaly (familial chromosomal abnormality) is believed to be the cause of schizencephaly.[2,9] Schizencephaly is further classified into type 1 (fused clefts in cerebral mantle) and type 2 (majority of cases, in which clefts are separated in cerebral mantle with associated ventriculomegaly). Prenatal diagnosis with ultrasound reveals clefts in the area of sylvian fissures, connecting enlarged lateral ventricles medially and subarachnoid space laterally; bilateral frontal horns may be fused with absent septum pellucidum. It is often difficult to differentiate with lobar holoproscencephaly and large porencephalic cysts or intracranial cysts in sylvian fissure area. Further evaluation with post-natal MRI is required to precisely differentiate this condition with other similar abnormalities.[9]

	Hydranencephaly	Hydrocephalus	Holoproscencephaly	Porencephaly	Schizencephaly
Head Circumference	Normal or slightly smaller	Larger	Normal	Normal	Normal
Midline Malformations	Absent	Absent	Present	Absent	Absent
Brainstem Anomalies	Absent	Absent	Present	Absent	Absent
Intact Cortical Rim	Absent	Present	Present	Present	Present
Ventricular System Abnormality	Lateral ventricle structures are irregular and indistinguishable Third ventricle remain intact and not-dilated	Lateral ventricle structures are regular with persistent enlargement Third Ventricle enlargement only present in obstructive forms	Overall abnormal ventricular system, structures are irregular and indistinguishable	Lateral ventricles and subarachnoid space enlargement Frontal horns not fused	Lateral ventricles and subarachnoid space dilatation Frontal horns fused in some cases.
Angiographic Investigation	Bilateral internal carotid artery occlusion (Not Always)	Normal	Normal	Involvement of middle cerebral artery resulting in localized areas of cortical destruction	Normal
Other Fetal Malformations	Absent	Absent	Present	Absent	Absent

Figure 3. Differential Diagnosis of Hydranencephaly

Prospective Management

Post-natal diagnostic evaluation of HE with magnetic resonance imaging (MRI) or computed tomography (CT) is considered as gold standard, which allows precise differentiation of HE with severe congenital hydrocephalus, holoprosencephaly, porencephaly and schizencephaly. Other diagnostic evaluation includes electroencephalogram (EEG), brainstem auditory evoked response test, digital subtraction angiography (DSA) and brain magnetic resonance angiography (MRA). Since our facility (type C hospital) has limited diagnostic resources and technology, only transcranial sonography (TCS) was performed by a pediatrician. Coronal and sagittal plane TCS confirmed the diagnosis of HE by revealing fluid filled cranial cavity with absent most of bilateral cerebral cortex and falx cerebri disruption; however progression was shown, since midbrain structures, cerebellum and other posterior fossa structures were less visible this time. Nevertheless these findings were less reliable in excluding differential diagnosis of HE and the newborn was referred to facilities with appropriate diagnostic technology for further evaluation.[3,10]

Post-natal management ranges from supportive non-surgical interventions (initial neonatal resuscitation, physiokinesthetherapy, drugs for epileptic seizure and nutritional interventions) and neurosurgical interventions. Surgical interventions must be considered in cases with evidence of intracranial hypertension, which include: ventriculo-peritoneal shunting (VP-Shunting), choroid plexus coagulation with endoscopic third ventriculostomy (ECPC), and choroid plexectomy (CP). VP-shunts are commonly associated with complications such as: secondary infection and malposition, which therefore requires regular replacement and re-positioning. ECPC was reported with better success rate of 50-80% when compared to VP shunting, therefore ECPC is considered as a standard treatment for hydranencephaly. Anatomic characteristics that provides advantage for ECPC over VP-Shunting are lack of septum pellucidum (hemispheric separation) and brain parenchyma in hydranencephaly, which allows easy access to bilateral choroid plexus. Arachnoid collapse is a complication commonly associated with ECPC, which occurs when the opened dura liberates intracranial pressure, consequently lead to difficulty in coagulating the choroid plexuses. A few neurosurgeons have reported that repeated complex surgeries such as choroid plexectomy (CP) may be useful.[3,10,11]

In this case, the newborn patient was observed in NICU for a week with unremarkable progression in clinical status. The newborn was later referred to facilities with neurosurgery department to further evaluation and surgical intervention if indicated. Prognosis determination and proper post-natal management, which will consequently improve the newborn's life expectancy, are achievable through precise diagnosis of HE and exclusion of differential diagnosis.[3,10,11]

CONCLUSION

Early prenatal recognition of hydranencephaly and exclusion of similar differential diagnosis, which includes: hydrocephalus, holoproscencephaly, porencephaly and schizencephaly, are fundamental in formulating proper multidisciplinary management with pediatric and neurosurgery department, which may consequently improve the newborn's life expectancy.

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Case Report

Clinical Pregnancy Rate in in-Vitro Fertilization (IVF) among Endometrioma Patients Underwent Cystectomy Laparoscopy

Kejadian Kehamilan Klinis setelah Fertilisasi In Vitro pada Pasien Endometrioma Postsistektomi Laparoskopi

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Abstract

Objective: to discuss the clinical pregnancy rate and factors influencing fecundity among endometriosis women having cystectomy laparoscopically who underwent IVF.

Methods: The search was conducted on Pubmed®, EBSCOhost®, and Proquest®, Cochrane Library®, ClinicalKey® using MeSH.

Case: A 38-years woman, P0A0 come to the gynecology clinic with a chief complaint of primary infertility for eight years. The patient had undergone a bilateral endometrial cyst resected with laparoscopy and failed for two cycles of IVF. What is the clinical pregnancy rate of women that undergo IVF with a history of ovarian endometrioma cystectomy?

Results: There were six articles appropriate to the inclusion criteria and further appraised using the Centre for Evidence-Based Medicine, University of Oxford appraisal tools. The studies consisted of five prognostic studies and one meta-analysis. The studies were appraised for their validity, Importance, and Applicability.

Conclusion: The pregnancy rate in patients undergoing IVF after ovarian cystectomy ranges from 14%-45.2%. A prudent consideration and carefulness during cystectomy surgery are essential for patients that wish to be fertile.

Keywords: clinical pregnancy rate, endometrioma, in vitro fertilization, laparoscopy, ovarian cystectomy.

Abstrak

Tujuan: *Untuk menelaah tentang kemungkinan terjadinya kehamilan secara klinis pada perempuan yang menjalani IVF dengan riwayat laparoskopi sistektomi dan faktor-faktor yang mempengaruhi kesuburannya.*

Metode: *Pencarian jurnal dilakukan dengan menggunakan search engine Pubmed®, EBSCOhost®, dan Proquest®, Cochrane Library®, ClinicalKey® menggunakan MeSH.*

Kasus: *Perempuan P0A0 berusia 38 tahun datang ke poliklinik dengan keluhan utama infertilitas selama delapan tahun. Pasien memiliki riwayat kista endometrioma bilateral yang sudah di kistektomi dengan laparoskopi dan dua kali gagal menjalani siklus IVF. Berapa kemungkinan terjadinya kehamilan secara klinis pada perempuan yang menjalani IVF dengan riwayat kistektomi endometrioma?*

Hasil: *Dari hasil pencarian didapatkan enam artikel jurnal yang sesuai dengan kriteria inklusi dan dianalisis lebih lanjut menggunakan telaah kritis Evideence-Based Medicine, University of Oxford. .Terdapat lima jurnal studi prognostic dan satu meta-analisis. Studi-studi tersebut akan ditelaah kritis lebih lanjut berdasarkan validitas, kepentingan, dan aplikabilitasnya*

Kesimpulan: *Kemungkinan terjadinya kehamilan secara klinis pada pasien yang menjalani IVF setelah kistektomi endometrioma ovarium adalah 14%-45,2%. Pertimbangan yang bijaksana dan hati-hati diperlukan untuk melakukan operasi kistektomi pada pasien yang mengalami endometrioma dan ingin tetap subur.*

Kata kunci: *endometrioma, fertilisasi in vitro, kehamilan klinis, kistektomi ovarium, laparoskopi.*

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INTRODUCTION

Endometriosis is characterized by endometrial-like tissue in both glands and stroma outside the uterus, which induces a chronic inflammatory reaction, scar tissue, and adhesion.[1] Although endometriosis could be asymptomatic, many complain about abdominal pain, painful periods, dyspareunia, dyschezia, and infertility.[2,3] From that complaint, infertility in endometriosis may pose a chronic and complicated socioeconomic and health problem for women. Among 30-50% of endometriosis women who had infertility, and vice versa, 25-40% of infertile women, had endometriosis.[4,5] Thus, we should be careful about ovarian function in deciding on a therapeutic approach in endometriosis women complicated with infertility. Women with endometriosis often require assisted reproduction technology (ART), and the severity of endometriosis has been linked to the outcome. Although the exact mechanism in endometriosis that affects fecundity is still unclear, several reasons tried to explain this phenomenon, such as altered folliculogenesis resulting in reduced quality oocytes, mechanical interference with oocyte pickup and transportation, exposure to a hostile environment of macrophages, cytokines, and vasoactive substances in peritoneal fluid, and peritubular and ovarian adhesions.[6]

Endometriosis usually presents in different entities that may appear together or alone, such as a peritoneal lesion, deep endometriosis, and ovarian endometriotic cysts or endometriomas.[7] From all those entities, endometriomas is the most common form of endometriosis, with the prevalence of 17%-44% of women who has endometriosis.[8] Because endometriomas are cysts, visualization of the cyst's color and location is essential. Some imaging modalities, such as transvaginal ultrasound, are commonly used. The endometrioma lesion may appear as a low-level homogenous echo with ground glass appearance with no vascularity in ultrasound and Doppler flows. The gold standard of examination uses laparoscopy with biopsy to perfectly visualize the cysts and their severity. Endometriomas typically appear blue or black or, in rare cases, may appear into red, white, or non-pigmented lesions.[3,7]

In infertile patients with endometriosis, laparoscopic treatment is superior to diagnostic laparoscopy regarding clinical pregnancy and live birth. It improves in vitro fertilization (IVF) outcomes in minimal-mild endometriosis and deep infiltrative disease.[2,9] Several approaches to endometriomas include aspiration, cystectomy, fenestration, and ablation of the cyst; nevertheless, there is no consensus on which approach is the best to preserve ovarian reserve and subsequent ART outcome. Cystectomy is commonly performed for endometriomas more than 3 cm in diameter before the ART procedure.[10] However, it has detrimental effects of excision on the ovarian function, which is signed by serum anti-Mullerian hormone (AMH) level. Some studies found 40-60% decreased AMH levels from baseline after endometrioma surgery. Furthermore, endometrioma patients had significantly lower levels than their counterparts, amplifying the detrimental effects after endometrioma surgery.[4,5]

The benefits and harms of surgery in endometrioma should be carefully considered, as the goal is future fertility. Although IVF may be offered an increased chance of conception in infertile patients, the rate of pregnancy in endometrioma resected patients should be calculated to educate the patients in making choices. Therefore, this evidence-based case report would like to discuss the clinical pregnancy rate and factors influencing fecundity among endometriosis women having cystectomy laparoscopically who underwent IVF.

CASE

A 38-year-old P0A0 woman came to the gynecology clinic for eight years due to primary infertility. She had ever performed bilateral endometrial cyst via laparoscopy 12 years ago. She only complained of dyspareunia without dysmenorrhea, dyschezia, and dysuria. We did not find any abnormal uterine bleeding and no palpable mass. Patients already underwent two cycles of IVF. In 2015, we obtained seven oocytes in the first ovum pick up (OPU), but after ICSI, the eggs were unfertilized. In the second IVF in 2019, there were five oocytes after OPU, after ICSI 4 unfertilized, and one fertilized; unfortunately, no clinical pregnancy was found. In physical examination, she had a normal BMI. Her gynecological examination was a cystic nodule on the left adnexa, sized 4 cm. Ultrasonography examination shows normal shape and size of the uterine cavity, left endometrial cyst with 24x22x33mm, and adhesion of right ovarium with posterior corpus. Laboratory parameter showed low AMH level (0.17 ng/mL). The couples had undergone infertility investigation resulting from bilateral varicocele from malefactors, submucosal leiomyoma, and ovarian endometrioma from female factors. Bilateral varicocele has been repaired with sperm analysis showed normal limit. Submucosal leiomyoma has been resected through operative hysteroscopy. Therefore, the diagnosis was primary infertility for 8 years due to female factors (ovarian endometrioma, poor ovarian reserve) and a history of failed IVF two times. She planned for performing IVF.

CLINICAL QUESTIONS

What is the clinical pregnancy rate of women that undergo IVF with a history of ovarian endometrioma cystectomy?

Searching strategy To answer the clinical question, the search was conducted on Pubmed®, EBSCOhost®, and Proquest®, Cochrane Library®, ClinicalKey® (figure 1). The searching strategy was performed on August 15th, 2020, there were five studies in Pubmed®, two studies in Cochrane Library®, 80 studies in Clinical Key®, 10 Studies in EBSCOhost®, and 79 studies in Proquest®; respectively. The articles were screened using the criteria consisting of abstracts answering the clinical question, written in the English language, full-text paper availability, and omitting all duplication papers. After screening, there were six articles inappropriate to the inclusion criteria. It consisted of 2 retrospective cohort studies, three retrospective, and one meta-analysis study. Critical appraisal determining the validity, importance, and applicability (VIA) was conducted by two independent authors. The critical appraisal steps are used in this article as prognostic studies.

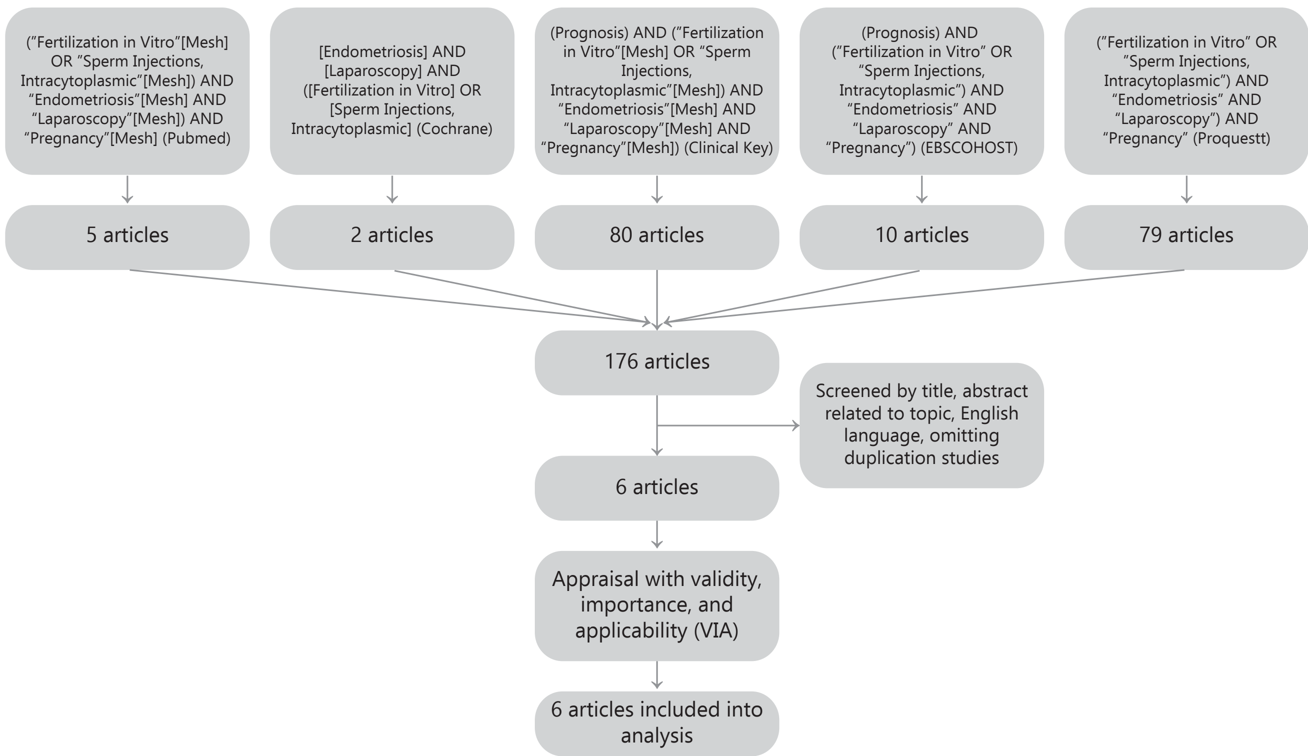


Figure 1. Flowchart of searching strategy

RESULTS

There were six studies appraised using VIA criteria based on critical appraisal of the systematic review and prognostic studies by the Centre for Evidence-Based Medicine, University of Oxford, 2010. From the systematic review form, the study was valid and important. In prognostic appraisal form, all studies were valid and important. All prognostic studies could apply to our patients. Table 1 describes the characteristics of studies, table 2 and 3 show the result of appraisal form on prognostic studies—meanwhile, the result of the pregnancy rate of each study is described in tables 4 and figure 2.

Table 1. Characteristics of each Study Included in this Evidence-Based Case Report

Study	Design	Intervention	Population	Study group	Control group	Cystic size cm	Outcomes
Loo TC, et al.[11]	Retrospective cohort study	Controlled ovarian stimulation (COS) by long agonist protocol	Patient who had at least one endometrioma larger than 3 cm	Laparoscopic ovarian cystectomy for endometrioma	Tubal occlusion	>3	Implantation and pregnancy rate per cycle
Esinler I, et al.[12]	Retrospective case-control study	Controlled ovarian hyperstimulation (COH) and recombinant FSH and intracytoplasmic sperm injection (ICSI)	Women <40 years, Unilateral/bilateral endometrial cyst >3cm histopathology of endometrioma First ICSI cycle	Unilateral or bilateral laparoscopy cystectomy	Tubal factor infertility	>3 in diameter	Cycle cancellation rate, number of oocytes, fertilization rate, embryo quality, clinical pregnancy rate (PR), implantation rate
Nakagawa K, et al.[13]	Retrospective case-control study	Hyperstimulation protocol with GnRH agonist	Women with inadequate tubal patency or severe pelvic adhesion	Ovarian endometrioma who received laparoscopic cystectomy	Expectant management	4.3 ± 2.1	Cumulative pregnancy rate
Harada M, et al.[14]	Retrospective case-control study	COS by daily injection of hMG with GnRH agonist or antagonist	Unilateral endometrioma >3cm. No other intervention before for ovaries. Absence of endometrioma when IVF conducted.	Excision of unilateral endometrioma by laparoscopically	Healthy ovaries	>3 in diameter	Number of oocytes, clinical pregnancy/ embryo transferred, on-going pregnancy/ embryo transferred
Guler I, et al[15]	Retrospective cohort study	COS (either antagonist or long GnRH analog)	-	Minimal peritoneal endometriosis and endometrioma underwent laparoscopic ablation and unilateral/ bilateral cystectomy	Expectant management	>3	Clinical pregnancy and live birth rates
Nickkho-Amiry M, et al.[16]	Systematic review and meta-analysis		Subfertile women with endometrioma undergoing ART	Surgical removal of endometrioma	Expectant management		Clinical pregnancy rate, pregnancy rate, live birth rate, number of oocytes retrieved and number of embryos, and

Table 2. Validity of Systematic Review and Meta-analysis Included in this Evidence Based Case Reports

Study	Validity					Results
	PICO	Relevant studies	Criteria for inclusion appropriate	Included studies valid	Similar from study to study	
Nickkho-Amiry M, et al.[16]	Impact of surgical management of endometrioma on the outcome of ART	Yes	Yes	Yes Original paper and clinical study about ovarian endometrioma	Yes	Below

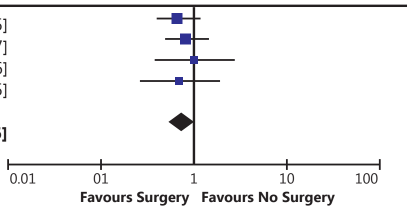
Table 3. Validity and Applicability of Prognostic Study included in this evidence based case reports

Study	Validity				Applicability	
	Representative sample	Follow-up sufficiently long and complete	Outcome applied in "blind" fashion	Adjustment for prognostic factors	Different patient	Clinically important to patient
Loo TC, et al. [11]	Yes	Yes	Yes	Yes	No	Yes
Esinler I, et al. [12]	Yes	Yes	Yes	Yes	No	Yes
Nakagawa K, et al. [13]	Yes	Yes	Yes	Yes	No	Yes
Harada M, et al. [14]	Yes	Yes	Yes	Yes	Yes	Yes
Guler I, et al. [15]	Yes	Yes	Yes	Yes	No	Yes

1. Live birth rate / cycle

Study or Subgroup	Treated Endometrioma Events	Treated Endometrioma Total	Non Treated Endometrioma Events	Non Treated Endometrioma Total	Weight	Odds Ratio M-H, Random, 95% CI
Bongioannil 2011	29	112	49	142	39.4%	0.66 [0.38, 1.15]
Dong 2014	58	153	29	68	34.8%	0.82 [0.46, 1.47]
Lee 2014	12	36	12	36	12.3%	1.00 [0.38, 2.66]
Tinkanen 2000	11	55	12	45	13.5%	0.69 [0.27, 1.75]
Total (95% CI)		**356**		**356**	**100.0%**	**0.75 [0.54, 1.06]**
Total events	110		102			

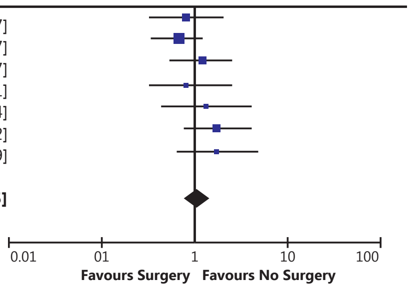
Heterogeneity. Tau²=0.00; Chi²=0.65, df =3 (P=0.88); I²=0%
Test for overall effect: Z=1.61 (P=0.11)



2. Clinical Pregnancy / cycle

Study or Subgroup	Treated Endometrioma Events	Treated Endometrioma Total	Non Treated Endometrioma Events	Non Treated Endometrioma Total	Weight	Odds Ratio M-H, Random, 95% CI
Demirol 2005	17	49	19	50	12.8%	0.87 [0.38, 1.97]
Dong 2014	66	153	35	68	26.3%	0.72 [0.40, 1.27]
Garcia-Velasco 2004	37	147	14	63	17.6%	1.18 [0.58, 2.37]
Lee 2014	13	36	14	36	9.5%	0.89 [0.34, 2.31]
Pabuccu 2004	11	44	8	40	8.1%	1.33 [0.47, 3.74]
Pabuccu 2007	27	81	15	67	15.9%	1.73 [0.83, 3.62]
Wong 2004	17	36	13	38	9.8%	1.72 [0.67, 4.39]
Total (95% CI)		**546**		**362**	**100.0%**	**1.08 [0.80, 1.45]**
Total events	188		118			

Heterogeneity. Tau²=0.00; Chi²=5.17, df =6 (P=0.52); I²=0%
Test for overall effect: Z=0.50 (P=0.62)



3. Pregnancy / cycle

Study or Subgroup	Treated Endometrioma Events	Treated Endometrioma Total	Non Treated Endometrioma Events	Non Treated Endometrioma Total	Weight	Odds Ratio M-H, Random, 95% CI
Bongioannil 2011	41	112	59	132	32.7%	0.81 [0.49, 1.35]
Garcia-Velasco 2004	44	147	18	63	24.9%	1.07 [0.56, 2.05]
Suganuma 2002	18	62	11	30	14.2%	0.71 [0.28, 1.78]
Tinkanen 2000	12	55	17	45	15.3%	0.46 [0.19, 1.11]
Wong 2004	18	36	13	38	13.9%	1.92 [0.75, 4.90]
Total (95% CI)		**412**		**318**	**100.0%**	**0.88 [0.60, 1.29]**
Total events	133		118			

Heterogeneity. Tau²=0.05; Chi²=5.43, df =4 (P=0.25); I²=26%
Test for overall effect: Z=0.66 (P=0.51)

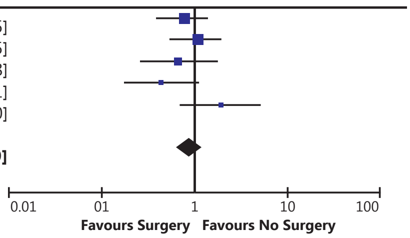


Figure 2. Importance of Nickkho-Amiry M, et al. study

Table 4. Clinical Pregnancy Rate in Prognostic Study Included in this Evidence Based Case Reports

Study	Clinical Pregnancy Rate: Study Group (n,%)	Clinical Pregnancy Rate: Control Group(n,%)	*P-Value*
NS	Endometrioma group (27/85 – 31,8)	Tubal group (21/71 - 29.6)	NS
NS	Unilateral (34, 45.2) Bilateral (23, 44.4)	Tubal Factor (99, 47.8)	NS
NS	IVF in laparoscopy cystectomy (50)	Expectant Management (41.4)	NS
NS (*P*=0.39)	Endometrioma-excised (4/10 – 40)	Healthy ovaries (6/24 – 25)	NS (*P*=0.39)
NS (*P*=0.056)	Operated endometrioma (8.14)	Expectant Management (11. 25)	NS (*P*=0.056)

*NS: Not significant (p>0.05)

DISCUSSION

Nowadays, 10% of the world's population is affected by infertility. Fifty million couples worldwide were infertile. Almost half of infertility is caused by the female factor, with 33.33% having unexplained causes of infertility. The common etiologies coming from female factor includes ovary (ovulatory disorder, PCOS, endometrioma), tube (tubal abnormalities/ blockage, endometriosis), and other (Endocrine or uterine abnormalities). Similar to the other study, endometriosis affects 15% of infertile women, the second-highest prevalence after ovulatory disorders (25%). This finding proves that after PCOS, Endometriosis is one of the leading causes of fertility.[17,18] Current treatment of endometriosis-associated infertility focuses on improving fecundity by removing or reducing ectopic endometrial implants and restoring normal pelvic anatomy. The goal can be achieved by surgical treatment with or without fertility preservation techniques such as oocyte cryopreservation. If after the surgery women could not conceive naturally, assisted reproductive technology such as intrauterine insemination or In-Vitro Fertilization.[19,20]

First, clinicians should decide which patient is eligible or benefit from IVF after surgery. First of all, endometrioma size is essential to assess, in which large endometrioma sized more than 4-5 cm limits the access to retrieve oocyte. Furthermore, oocytes that had been exposed to endometrioma fluid could be damaged.[16,21] After size, other indication to resect an endometrioma was the rapid growth of the mass, malignancy feature in imaging, disturbing symptoms such as pain, and reducing risk for rupture during pregnancy.[16,21] At last, it is necessary to put on utmost care that clinicians should carefully resect the endometrioma since careless dissecting may hazard healthy ovarian tissue.

The surgery for endometrioma can be both diagnostic and therapeutic, in which surgery through laparoscopy is preferred due to less pain, shorter hospital stay, and quicker recovery. Several techniques can be performed, such as cystectomy, drainage and coagulation, and laser vaporization. Cystectomy is preferred as the mainstay of treatment because of lower recurrence rate, decreasing pain, and increased spontaneous pregnancy.[22] Nowadays, using hemostatic agents such as thrombin-gelatin matrix or fibrin sealant for hemostasis when doing ovarian cystectomy also minimizes damage given to healthy ovarian tissue rather than bipolar energy.[23] Furthermore, hemostatic agent oxidized regenerated cellulose or surgicel® can be used after drainage or cystectomy to reduce the risk of endometriomas recurrence compared with cystectomy only (Hazard ratio cystectomy only 0.806 vs Drainage and surgicel® 0.355 vs cystectomy and surgicel® 0.271 $p = 0.02$).[22] This opens a new option to decrease the risk of recurrence endometriosis.

In the light of this study, surgery may not improve clinical pregnancy in IVF. A meta-analysis found that clinical pregnancy/cycle in IVF was not statistically significant between treated endometrioma and non-treated endometrioma (OR 1.08; 95% CI 0.80-1.45).[16] Our appraisal also showed no significant difference in fertility outcome between patients undergoing IVF with a history of endometrioma cystectomy and patients with tubal factors. The difference in clinical pregnancy rate between the post-operative endometrioma and tubal factor group was not significant.[11,12,15] Patients performing cystectomy continued with IVF had a clinical pregnancy rate of 50% in 12 months and higher than the control group about 41.4%. There was also no significant difference in clinical pregnancy per embryo transfer from endometrioma and healthy ovarian (4/10 and 6/24; respectively), although the number of oocytes retrieved in healthy ovarium was higher than in endometrioma ovarium significantly.[14] At last, the number of antral follicles and AMH levels respectively in bilateral groups was significantly lower than unilateral groups. Although bilateral endometrioma has a more deleterious effect than unilateral endometrioma, the clinical pregnancy rate compared to tubal factor was not significantly different.[12]

The effect of endometriosis and its effect on achieving pregnancy during IVF is controversial. In our study, IVF patients with endometrioma had similar pregnancy rates among patients with a tubal factor or even non-operated endometrioma. Another study also reported that the birth rate of women with endometriosis is higher than other factors tubal/unexplained (42.5% vs 38.7% and 39.6%). Although women with endometriosis and one other etiology (tubal/unexplained) had the worst birth rate, 33.4% after IVF.[24] It was expected since the more pathology they had, the worse the outcome. In IVF endometriosis patients, the pregnancy and birth rate are most likely affected by the oocyte quality and impaired implantation. In endometriosis patients, the oocyte yield after stimulation was likely lower than with patients with tubal or unexplained causes. Also, the impaired implantation is caused by altered HOXA 10 gene expression, a transcription factor that stimulates $\alpha v\beta 3$ expression to promote uterine receptivity. Furthermore, some transplantation factors are disrupted in endometriosis patients, such as glycodelin A, osteopontin, leukemia inhibitory factor, and lysophosphatidic receptors 2 and 4.[25]

Finally, the strength in our appraisal is that there is a meta-analysis/systematic review journal. The study compared much research about clinical pregnancy rate among patients undergoing IVF after endometrioma laparoscopy and homogenous criteria for cystic size in endometrioma more than 3 cm. The limitation is that the studies appraised had some control groups starting from tubal factor, healthy ovarian, and expectant management, and it can be attributed to a different outcome of clinical pregnancy rate.

CONCLUSION

The pregnancy rate in patients undergoing IVF after ovarian cystectomy ranges from 14%-45.2%. Endometriomas should not be routinely resected in patients undergoing ART. Some indications to perform cystectomy before ART are improving access to ovarium, the rapid growth of endometrioma, suspicion of malignancy, disturbing symptoms such as pain that cannot be relieved by medication, and prevention of rupture during pregnancy. A prudent consideration and carefulness during cystectomy surgery are essential for patients that wish to be fertile.

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Systematic Review

EMA and EMACO Chemotherapy in High Risk Gestational Trophoblast Disease, which Better?

Kemoterapi EMA dan EMACO dalam Risiko Tinggi Penyakit Trofoblas Gestasional, Mana yang Lebih Baik?

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Abstract

Objective: Determine the best effectiveness and efficacy between EMA and EMACO for patients with high-risk GTN.

Results: GTN patients who received EMA showed remissions as high as 74.4% - 96.6% of cases. The side effects of anemia in EMA were less toxic than EMACO, but it wasn't the case in neutropenia. Two studies showed that 57,1% and 87% patients relapse within 2 years, while none in 5 years and 7 years follow-ups.

Discussion: With EMACO use, it has been observed to result in increased morbidity and increased health care costs and when patients experience complications while staying overnight in the hospital, they are not monitored by a good specialist team. Patients treated with EMACO had more peripheral neuropathy as result of vincristine than EMA. The use of EMA certainly requires further evaluation.

Conclusion: Patients with High-risk GTN who treated first-line with EMA or EMACO have an excellent prognosis. Both regiments are equally effective. There were differences in treatment scheduling, hospitalization requirements, and toxicity between regimens.

Keywords: EMA, EMACO, gestational trophoblastic neoplasia.

Abstrak

Tujuan: *Mengetahui efektivitas dan efikasi terbaik diantara EMA dan EMACO untuk pasien dengan NTG berisiko tinggi.*

Hasil: *Pasien dengan NTG yang menerima EMA menunjukkan remisi setinggi 74.4%-96.6% dari kasus. Efek samping anemia dari EMA lebih tidak toksik dibandingkan EMACO, namun tidak dengan neutropenia. Dua studi menunjukkan bahwa 57.1% dan 87% pasien mengalami kekambuhan dalam 2 tahun, namun tidak ada dalam follow up 5 tahun dan 7 tahun.*

Diskusi: *Dengan penggunaan EMACO, dapat diobservasi bahwa terdapat peningkatan morbiditas dan peningkatan biaya pelayanan kesehatan, dan ketika pasien mengalami komplikasi pada saat rawat inap di rumah sakit, mereka tidak dimonitor oleh tim spesialis yang baik. Pasien yang diterapi dengan EMACO memiliki efek samping neuropati perifer lebih tinggi yang disebabkan oleh vinkristin, dibandingkan EMA. Penggunaan EMA membutuhkan evaluasi lebih lanjut.*

Kesimpulan: *Pasien dengan NTG berisiko tinggi yang diterapi dengan lini pertama EMA atau EMACO mempunya prognosis yang baik. Kedua regimen tersebut efektif. Ada perbedaan dalam penjadwalan terapi, kebutuhan rawat inap dan toksisitas antara regimen.*

Kata kunci: *EMA, EMACO, neoplasia trofoblastik gestasional.*

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INTRODUCTION

Gestational Trophoblast Neoplasia (GTN) is a malignant form of Gestational Trophoblast Disease (GTD). GTN refers to a spectrum of diseases mainly including invasive mole, choriocarcinoma, placental-site trophoblastic tumor, and epithelioid trophoblastic tumor. GTN is a rare disease. Estimated incidence is 1 case per 40,000 pregnancies. This condition usually occurs after a previous pregnancy with a history of miscarriage and an ectopic or molar pregnancy.[1]

Guidelines from the International Federation of Gynecology and Obstetrics (FIGO) are used to guide treatment decisions.[2] Patients with a FIGO score ≤ 6 should be treated with single agent chemotherapy. Furthermore, a FIGO score ≥ 7 indicates a high risk of resistance to single agent chemotherapy and this also requires multi-agent chemotherapy. However, if a FIGO score ≥

12 indicates a high risk of treatment failure and a poor prognosis.[2] GTN is highly curable with chemotherapy even with extensive metastases.[2] With proper treatment, survival rates are as high as 90-100%.[2] Previous research report better survival rates for high-risk patients which seen in patients treated with multiagent regimens as much as 65-70% compared to single agent regimen is 14-39%.[3] For this reason, multiagent regimens are recommended as first-line treatment in high-risk GTN.[4]

RESULT

Evidence of efficacy and tolerable toxicity suggests EMACO (etoposide, methotrexate, actinomycin-D with cyclophosphamide and oncovin/vincristine) is the most widely used multiagent regimen for GTN. Previous studies reported that GTN patients who received EMA showed remissions 74.4 to 96.6% of cases. Previous data suggest the side effects of anemia in EMA are less toxic than EMACO, but not for neutropenia.5 Four other studies also report comparable remission rates in patients receiving EMA: 89.7% (United States), 74.4% (Japan), 75.5% (UK), and 96% (South Korea).[5] EMA and EMACO have comparable remission rates as the first-line multiagent regimen in GTN.[7]

Treatment variables and outcomes with EMA vs EMACO.[4]

Variables and outcomes	EMA (n = 44)	EMACO (n = 39)	*P-value*
Variables			
Time to start chemotherapy (days)	4(0.8)	6 (0.12)	0.388
Proportion of delayed CMT cycles/ total			0.059
cycles	18/151(11.9)	12/208 (6.4)	
Adjuvant surgery (yes/no)	4(9.1)	8 (20.5)	
Hysterectomy	2	7	0.211
Lobectomy	1	1	
Craniotomy	1	0	
Embolization	0	1	
Tumor debulking	0	3	
Outcomes			
Complete remission rates	43 (97.7)	28 (71.8)	
Median time to complete remission	12 (95% CI, 10.53-13.47)	13.1 (95% CI, 9.31-16.98)	0.001
(weeks)	3 (2.5)	5 (4.7)	
Number of CMT (cycles)	1/43 (2.3)	6/28 (21.4)	<0.001
Relapse rate	29.9	6.2 (3.1,27.1)	0.013
Time to relapse (months)	0	3	
0-6	0	1	
>6-12	0	0	
>12-24	1	2	
>24-60	1 (2.3)	2 (5.1)	
Death rate	0	2	
Disease-related death	1	0	0.599
Non-disease-related death	5	6	
Subsequent pregnancy (pregnancies)	2	1	
Abortion	3	5	
Normal pregnancy			

Data are n(%) or median (p25, p75).
E=etoposide; M=methotrexate; A=actinomycin-D; C=cyclophosphamide; O=vincristine; CMT=chemotherapy.
Bold values were considered statistically significant at p-values <0.05

This study report that time required to complete remission between the two groups was similar. This raises the logical question whether the EMA can be considered as an alternative to EMACO. Theoretically, EMA is simpler and cheaper way. However, it does vary depending on the local payment environment and practice patterns. In addition, EMA does not use cyclophosphamide which associated with gonadotoxicity and premature ovarian failure.[6] This study also show the long-term outcome relapse in patients receiving EMACO was greater than EMA. Total of 7 patients who relapse, 4 patients (57.1%) relapse within 2 years. Furthermore, there was no relapse after 5 years of follow-up. This data relates to recent study which show 87% GTN patients relapse within 2 years and subsequently had no relapse after 7 years.[7] This study conclude that EMA and EMACO had same remission rates and time to complete treatment. EMA is associated with a high incidence of neutropenia and its toxicity can be minimized with routinely use of CGSF (colony-granulocyte stimulating factors). In order to directly compare the efficacy between EMA and EMACO, it is important to compare outcomes in contemporary groups, even in non-randomized observational study settings.[4]

DISCUSSION

Gestational Trophoblastic Neoplasia (GTN) comprises of malignancies related to pregnancy. GTN is estimated to have an incidence of 1 case per 40,000 pregnancies, making it a rare condition. GTN, even with widespread metastasis, has a high rate of cure. Overall survival rate can be as high as 90-100% with appropriate and timely treatment.[4]

However, estimation of survival rate is misleading because the prognosis of patients with FIGO scores ≥12 is significantly worse than patients with FIGO scores <12.[2,8] Subsequent studies show the mortality rate of patients with FIGO score > 13 was significantly higher than FIGO score <13.[9] FIGO Cancer define very high risk GTN is a subgroup with a FIGO score ≥13.[2]

Health care policies are implemented to improve patient safety, quality, effectiveness, and patient satisfaction. A strong rationale reason for changing the EMACO regimen is to reduce the length of a patient's hospital stay.[10] With EMACO, it has been observed to result in increased morbidity and increased health care costs and when patients experience complications while staying overnight in the hospital, they are not monitored by a good specialist team.[10]

Patients treated with EMACO had more peripheral neuropathy as result of vincristine than EMA. Neurotoxicity in GTD patients has a negative impact on the patient's health-related quality of life (HRQoL). In a systematic review, HRQoL in GTD patients who received more intensive chemotherapy had worse quality of life outcomes including physical, social, and psychosocial functioning.[11]

The use of EMA certainly requires further evaluation. As a direct result of the COVID-19 pandemic, Singh *et al* have temporarily changed the first-line treatment protocol for high-risk GTN to 2-day EMA every 2 weeks with 5 days of 5 mcg / kg / day CGSF support and remove CO to reduce myelosuppression potential and number of hospital visits.[4,7]

CONCLUSION

Patients with high-risk GTN who treated first-line with EMA or EMACO have an excellent prognosis. EMA was associated with less toxicity and treatment delay, although with a similar duration of treatment to EMACO. Use of EMACO was associated with increased neutropenia, non-neutropenic grade 3-4 infections, peripheral neuropathy, delayed treatment, and longer non-elective nights in hospital. Both regimens are equally effective. There were differences in treatment scheduling, hospitalization requirements, and toxicity between regimens. This can be considered according to the patient's personal, social and family circumstances to optimize treatment.

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