Editorial

Are Vaccines Safe during Pregnancy ?

Johanes C. Mose

Certain vaccines are safe and recommended for women before, during, and after pregnancy to help keep them and their babies healthy. The antibodies mothers develop in response to these vaccines not only protect them, but also cross the placenta and help protect their babies from serious diseases early in life. Vaccinating during pregnancy also helps protect a mother from getting a serious disease and then giving it to her newborn.

Centers for Disease Control and Prevention (CDC) recommends that pregnant women get two vaccines during every pregnancy: the inactivated flu vaccine (the injection, not the live nasal flu vaccine) and the Tdap vaccine.

Some vaccines, especially live vaccines, should not be given to pregnant women because they may be harmful to the baby. As we know that vaccine recommendations for pregnant women are developed with the highest safety concerns for both mothers and babies.[1]

Some vaccines are not recommended during pregnancy, such as: Human papillomavirus (HPV) vaccine; Measles, mumps, and rubella (MMR) vaccine; Live influenza vaccine (nasal flu vaccine); Varicella (chicken pox) vaccine. Certain travel vaccines: yellow fever, typhoid fever, and Japanese encephalitis. These travel vaccines should generally not be given during pregnancy, unless it is determined that the benefits outweigh the risks. In case of breastfeeding, it is safe to receive routine vaccines right after giving birth, even while you are breastfeeding. However, yellow fever vaccine is not recommended for breastfeeding women unless travel to certain countries is unavoidable and a healthcare provider determines that the benefits of vaccination outweigh the risks.

Pregnant women are at higher risk of getting severe Covid and delivering premature babies. In situations where there is a lot of Covid-19 transmission in the country and a woman is exposed to it, or if she's in a profession like a health care worker or a frontline worker where she's at especially high risk of acquiring the infection, the benefits of getting the vaccine definitely outweigh the risks. Particularly since the platforms that we used currently for vaccines are the mRNA platform, inactivated viruses or the viral vectored platforms or subunit proteins. None of them have a live virus that can multiply within the body and that could potentially create a problem. So, it's important that pregnant women in every country be explained the benefits versus the risks and be offered the vaccine if they would like to take it. And it's probably the right thing to do in many situations, where the pregnant woman is at higher risk of getting the infection and where the vaccines would bring more benefits[2]

CDC recommends that people who are pregnant, breastfeeding, trying to get pregnant now, or might become pregnant in the future be vaccinated and stay up to date with their Covid-19 vaccines, including getting a Covid-19 booster shot when it's time to get one. Evidence shows that Covid-19 vaccination during pregnancy is safe and effective[3,4] CDC recommendations align with those from professional medical organizations serving people who are pregnant, including the American College of Obstetricians and Gynecologists, Society for Maternal Fetal Medicine, and the American Society for Reproductive Medicine, along with many other professional medical organizations.[1]

REFERENCES

1. Centers for Disease Control and Prevention (CDC). Pregnancy or Breastfeeding. Vaccines during Pregnancy FAQs-CDC. https://www.cdc.gov/vaccinesafty/concerns/vaccines-during-pregnancy.html
2. WHO. Episode #41 - Vaccines, pregnancy, menstruation, lactation and fertility. Science Conversation, 4 June 2021. https://www.who.int/vaccine/fertility.
3. Shimabukuro TT, Kim SY, Myers TR, Moro PL, Oduyebo T, Panagiotakopoulos L, et al. Preliminary Findings of mRNA Covid-19 Vaccine Safety in Pregnant Persons. N Engl J Med 2021; 384:2273-82.
4. Theiler RN, Wick M, Mehta R, Weaver AL, Virk A, Swift M. Pregnancy and birth outcomes after SARS-CoV-2 vaccination in pregnancy. Am J Obstet Gynecol MFM. 2021; 3(6): 100467-73.

Research Article

Obstetric Referral System during COVID-19 Pandemic : Tertiary Referral Hospital Perspective

Sistem Rujukan Obstetri dalam Masa Pandemi COVID-19 : Perspektif Rumah Sakit Rujukan Tersier

Arietta R. D. Pusponegoro, Chakti A. Swastika, Junita Indarti

Department of Obstetrics and Gynecology
Faculty of Medicine Universitas Indonesia
Dr. Cipto Mangunkusumo General Hospital
Jakarta

Abstract

Objective: To evaluate the effectiveness of obstetric referrals to the dr. Cipto Mangunkusumo National Central General Hospital (RSCM), Jakarta, Indonesia, during the COVID-19 pandemic.

Methods: This was a cross-sectional that compared the effectiveness of referrals before (July-December 2019) and during the COVID-19 pandemic (March-August 2020) at the National Central General Hospital dr. Cipto Mangunkusumo (RSCM). Referral effectiveness is assessed based on two criteria, namely the suitability of the diagnosis and procedural compliance which includes communication through the integrated emergency response system (SPGDT), delivery by ambulance, and attachment of a referral letter.

Results: The study found 198 referral cases from 464 obstetric cases (42.67%) before the pandemic and 231 referral cases from 486 obstetric cases (47.53%) during the pandemic. The diagnostic concordance increased from 57.58% before the pandemic to 71.00% during the pandemic ($p = 0.004$). Referral procedural compliance increased from 28.28% before the pandemic to 45.45% during the pandemic ($p < 0.001$). Based on these criteria, the effectiveness of referrals at the RSCM during the COVID-19 pandemic era was found to be significantly higher, namely before the pandemic by 21.72% and during the pandemic by 40.26% ($p < 0.001$).

Conclusion: The effectiveness of referral to the RSCM based on the suitability of the diagnosis and the accuracy of the procedure during the COVID-19 pandemic was found to be better than before the pandemic.

Keywords: COVID-19, obstetric referral system, pandemic.

Abstrak

Tujuan: *Untuk menilai efektivitas rujukan obstetri ke Rumah Sakit Pusat Nasional dr. Cipto Mangunkusumo, Jakarta, Indonesia, selama pandemi COVID-19*

Metode: *Penelitian ini merupakan penelitian dengan desain potong lintang yang membandingkan efektivitas rujukan sebelum (Juli-Desember 2019) dan saat pandemi COVID-19 (Maret-Agustus 2020) di Rumah Sakit Umum Pusat Nasional dr. Cipto Mangunkusumo (RSCM). Efektivitas rujukan dinilai berdasarkan dua kriteria, yakni kesesuaian diagnosis dan kepatuhan prosedur yang meliputi komunikasi melalui sistem penanggulangan gawat darurat terpadu (SPGDT), pengantaran dengan ambulans, dan pelampiran surat rujukan.*

Hasil: *Penelitian menemukan 198 kasus rujukan dari 464 kasus obstetri (42,67%) sebelum pandemi dan 231 kasus rujukan dari 486 kasus obstetri (47,53%) saat pandemi. Kesesuaian diagnosis meningkat dari 57,58% sebelum pandemi menjadi 71,00% saat pandemi ($p = 0,004$). Kepatuhan prosedur rujukan meningkat dari 28,28% sebelum pandemi menjadi 45,45% saat pandemi ($p < 0,001$). Berdasarkan kriteria tersebut, efektivitas rujukan di RSCM pada era pandemi COVID-19 ditemukan lebih tinggi secara signifikan, yakni sebelum pandemi sebesar 21,72% dan saat pandemi sebesar 40,26% ($p < 0,001$).*

Kesimpulan: *Efektivitas rujukan ke RSCM berdasarkan kesesuaian diagnosis dan kepatuhan prosedur saat pandemi COVID-19 ditemukan lebih baik.*

Kata kunci: *COVID-19, pandemi, sistem rujukan obstetri.*

Correspondence author. Arietta R.D. Pusponegoro. Department of Obstetrics and Gynecology Faculty of Medicine Universitas Indonesia. Dr. Cipto Mangunkusumo General Hospital. Jakarta
Email: ariettapusponegoro@yahoo.com; chakti.as@gmail.com

Received: October, 2021 Accepted: March, 2022 Published: April, 2022

INTRODUCTION

Based on the 2019 Indonesian Health Profile, the Maternal Mortality Rate (MMR) in Indonesia has decreased from 390 per 100,000 in 1991 to 305 per 100,000 in 2015. However, this figure has not met the 2015 Millennium Development Goals (MDGs) target, which is 102 per 100,000 live births.[1] The MMR in Jakarta Special Capital Region in 2015 was quite good, at 38 per 100,000 live births.[2] This fact indicates that there is still a lot that needs to be improved in maternal health services in Indonesia, especially to achieve the MMR target based on the Sustainable Development Goals (SDGs), which is 70 per 100,000 live births.[3]

According to the International Federation of Gynecology Obstetrics (FIGO), the pillars of emphasis on maternal mortality include women's status and gender equality, family planning and reproductive health, clean, safe, and competent delivery, and basic and comprehensive emergency obstetric and neonatal services.[4] An important aspect of obstetric care is an effective referral system. Regulation of Minister of Health No. 001/2012 concerning the Individual Health Service Referral System states that health services are carried out in stages so that the initial treatment is carried out by primary health facilities.[5] Patients can be referred to a referral health facility based on medical indications and if the referrer is unable to provide health services.[6] This tiered referral system is also supported by the mandatory membership of the Health Social Security Administering Body based on Law no. 40/2004.[7]

The Coronavirus Disease 2019 (COVID-19) pandemic presents its challenges for the health situation in Indonesia. The Task Force for Handling COVID-19 on January 27th, 2021, reported 1,024,298 confirmed cases of COVID-19, 9.6% of whom were pregnant women. A total of 28,855 COVID-19 patients died, 0.3% of whom were pregnant women.[8] The pandemic in particular is feared to have an impact on the obstetrical referral system. Health facilities are not fully prepared to provide adequate obstetric services amid a pandemic due to limited personal protective equipment (PPE), infrastructure, and health workers. Hospitalization capacity is reduced to make room for the handling of COVID-19 patients. This limits the ability of referral health facilities to receive referrals. In response to this, primary-level health facilities are encouraged to conduct planned referrals using information technology and improve service quality to increase referral effectiveness.[9]

Concerns about the referral system are based on data from the Health Social Security Administering Body for the period January-February 2015. Primary health facilities were found to refer 15.3% of cases, higher than the mandated limit, which is below 5%.[10] The same data also found that 1.47% of referral cases did not need to be referred.[11] This shows that primary-level health facilities have not succeeded in becoming gatekeepers even in non-pandemic situations. Some of the reasons for the ineffectiveness of the referral system include the lack of public understanding of the referral system, the tendency of patients towards certain health facilities, non-compliance with standard operating procedures, weak regulations, and inadequate facilities.[12,13] Considering that there has never been an assessment of the effectiveness of the obstetric referral system during the COVID-19 pandemic, this study was conducted to determine the effectiveness of obstetric referrals to the dr. Cipto Mangunkusumo National Central General Hospital (RSCM) during the COVID-19 pandemic.

METHODS

This was a cross-sectional study. This study had been approved by the Ethics Committee of the Faculty of Medicine Universitas Indonesia-RSCM and has received permission to research at the RSCM. The inclusion criteria for this study were all pregnant patients who came to the RSCM Emergency Installation in July-December 2019, March-August 2020 with a referral letter. The selection of the July-December 2019 timeframe as the reference inclusion criteria before the pandemic was carried out, because this timeframe was the closest timeframe before the pandemic which began in January 2020. Meanwhile, the selection of the March-August 2020 timeframe as the referral inclusion criteria during the pandemic was carried out by considering that the first case of COVID-19 in Indonesia only occurred in March 2020, even though the COVID-19 outbreak has spread in many parts of the world since January 2020. Patients with incomplete medical record data were excluded from this study. The research sample was taken by total sampling.

Data was collected from the administration book of the RSCM Emergency Unit and

medical records. The data taken included patient characteristics (age, education, marital status, history of parity, gestational age), data related to referral (origin of the referrer, availability of referral letters, referrals through the integrated emergency response system (SPGDT), transportation), and components of referral letters. (reason for referring, referral diagnosis, treatment, attachment of supporting examination). Referrals are said to be effective by looking at two indicators, namely the suitability of the diagnosis and the compliance of procedures based on three things; referral through SPGDT, transportation by ambulance, and attachment of referral letter.

The data obtained were entered into Microsoft Excel and analyzed using the Statistical Program for Social Sciences (SPSS) version 22.0. The descriptive and analytic statistics were conducted to describe the effectiveness of referrals, appropriateness of diagnosis, compliance with procedures, characteristics of referring health facilities, and cases referred to RSCM.

RESULTS

Table 1. Characteristics of Patients

Variables	Pre-Pandemic		Pandemic	
	N = 198	%	N = 231	%
Age group (y o)				
< 19	4	2.02	2	0.87
19-35	160	80.81	173	74.89
> 35	34	17.17	56	24.24
Marital status				
Unmarried	4	2.02	3	1.30
Married	194	97.98	228	98.70
Education				
Lower education	16	8.08	24	10.39
High school	134	67.68	130	56.28
Diploma/University	48	24.24	77	33.33
Parity				
Nullipara	71	35.86	74	32.03
Primipara	47	23.74	57	24.68
Multipara	80	40.40	100	43.29
Gestational age (weeks)				
< 14	10	5.05	6	2.60
14-28	28	14.14	18	7.79
29-36	90	45.46	88	38.10
≥ 37	70	35.35	119	51.51
Diagnosis				
Abortus	5	2.53	5	2.16
Dystocia	7	3.54	6	2.60
Eclampsia and severe preeclampsia	56	28.28	52	22.51
Ectopic pregnancy	5	2.53	4	1.73
Antepartum hemorrhage	17	8.59	23	9.96
High-risk pregnancy	107	54.04	111	48.05
Suspect COVID-19	0	0.00	24	10.39
Not emergency	1	0.51	6	2.60
Management				
Conservative	6	3.03	9	3.90
Curettage	5	2.53	5	2.16
Spontaneous	37	18.69	43	18.61
Induction	13	6.57	16	6.93
Vacuum	7	3.54	7	3.03
Forcep	0	0.00	1	0.43
C-section	123	62.12	146	63.20
Explorative laparotomy	7	3.54	4	1.73

This study found that RSCM received more referral cases during the pandemic (231/484 cases, 47.53%) than before the pandemic (198/464 cases, 42.67%). Both before and during the pandemic, most of the referred patients were aged between 19-35 years (160/198, 80.81%; 173/231, 74.89%), married (194/198, 97.98%; 228/ 231, 98.70%), and have high school education (134/198, 67.68%; 130/231, 56.28%). Both before and during the pandemic, multiparous patients were the most referred to the RSCM (80/198, 40.40%; 100/231, 43.29%) compared to nulliparous and primiparous patients. Most patients who were 29 weeks gestation or more were referred either before or during the pandemic.

Both before and during the pandemic, high-risk pregnancies were the most common diagnosis of obstetric referral cases found in RSCM (107/198, 54.04%; 111/231, 48.05%). Antepartum hemorrhage was the third most common diagnosis before the pandemic (17/198 cases, 8.59%), while suspicion of COVID-19 was the third most common diagnosis during the pandemic (24/231 cases, 10.39%). Obstetric non-emergency referral cases were found to be higher during the pandemic (6/231 cases, 2.60%) than before the pandemic (1/198 cases, 0.51%). Cesarean section is the most commonly performed treatment for obstetric referral cases at RSCM.

Both before and during the pandemic, most referrals came from type-D hospitals (94/198, 47.47%; 87/231, 37.66%), On the other hand, referrals from type-A hospitals to RSCM were higher during the pandemic (19 /231 cases, 8.23%) compared to before the pandemic (1/198 cases, 0.51%). Both before and during the pandemic, most obstetric patients referred to the RSCM were not delivered via SPGDT (142/198, 71.72%; 126/231, 54.55%) and were not delivered by ambulance (142/198, 71.72%; 126/231, 54.55%). All patients were referred with the attached referral letter.

Table 2. Characteristics of Referrals

Variables	Pre-Pandemic		Pandemic	
	N = 198	%	N = 231	%
Source of referral				
PHCs	42	21.21	70	30.30
Independent midwife practice	13	6.57	15	6.49
Type-D hospital	94	47.47	87	37.66
Type-C hospital	2	1.01	10	4.33
Type-B hospital	46	23.23	30	12.99
Type-A hospital	1	0.51	19	8.23
Communication via SPGDT				
Done	56	28.28	105	45.45
Not done	142	71.72	126	54.55
Patient's transport				
Ambulance	56	28.28	105	45.45
Personal vehicle	142	71.72	126	54.55
Components of Referral Letters Diagnosis				
Included	194	97.98	231	100.00
Not included	4	2.02	0	0.00
Supporting examinations				
Included	153	77.27	192	83.12
Not included	45	22.73	39	16.88
Management				
Included	82	41.41	120	51.95
Not included	116	58.59	111	48.05
Reason of Referral				
Included	171	86.36	202	87.45
Lack of human resources	31	18.13	35	17.33
Lack of facilities	137	80.12	166	82.18
Full capacity	3	1.75	1	0.50
Not included	27	13.64	29	12.55

Both before and during the pandemic, most of the referral letters had included a diagnosis (194/198, 97.98%; 231/231, 100.00%) and supporting examinations (153/198, 77.27%; 192/231, 83.12%). More referral letters included management during the pandemic (12/231 cases, 51.95%) than before the pandemic (82/198 cases, 41.41%). Both before and during the pandemic, most of the referral letters also included the reason for the referral (171/198, 86.36%; 202/231, 87.45%). The absence of the required facilities is the most common reason for the referral of obstetric cases to the RSCM.

This study found more obstetric referrals to RSCM according to procedures during the pandemic (105/231 cases, 45.45%) than before the pandemic (56/198 cases, 28.28%). The accuracy of diagnosis was also found to be higher during the pandemic (164/231 cases, 71.00%) than before the pandemic (114/198 cases, 57.58%). The percentage of effectiveness of obstetric referrals before the pandemic was found to be 21.72% and during the pandemic, it was 40.26%. The bivariate analysis found significant differences in the three variables when compared before and during the pandemic.

Table 3. Effectivity of Referrals

Variables	Pre-Pandemic		Pandemic		*P-values*
	N = 198	%	N = 231	%	
Diagnostic accuracy					0.004
Accurate	114	57.58	57.58	71.00	
Inaccurate	84	42.42	42.42	29.00	
Procedural compliance					<0.001
Compliant	56	28.28	28.28	45.45	
Non-compliant	142	71.72	71.72	54.55	
Referral effectivity					<0.001
Effective	43	21.72	21.72	40.26	
Ineffective	155	78.28	78.28	59.74	

DISCUSSION

This study found that RSCM received more referral cases during the pandemic than before the pandemic, in contrast to several studies that reported a decrease in obstetric cases during the pandemic. Twelve point nine percent reduction in admissions for obstetric cases[14]. Meanwhile, a decrease in obstetric case admissions of up to 49.8%, with the number of referral cases decreasing by 66.4%.[15] The decline in cases in these countries was due to lockdowns that restricted public movement and affected admissions, in contrast to Indonesia, which did not implement a lockdown. Public concerns also affect the decline in admissions.[14,15] On the other hand, although this study and both studies were conducted in a tertiary hospital, the position of the RSCM as the top referral hospital in the Indonesian health system may have caused the admission rate to increase during the pandemic.

Most of the obstetric referral patients were between 19-35 years old, either before or during the pandemic. This finding is almost the same as who reported that the proportion of patients aged 21-35 years was 66.1-78.8%.[16] Most of the referred patients in this study had a high school education. This is different from the findings who reported more patients who graduated from elementary-junior high school (46.3%).[17] This difference can occur considering that this study was conducted at a referral center hospital in Jakarta, in contrast which uses data from the 2016 National Health Indicators Survey taken from all over Indonesia.[17]

Most of the patients referred to RSCM were multiparous patients both before and during the pandemic, in contrast to the findings that most of the referral patients were nulliparous patients, which ranged from 38.1 to 52.4%.[16] On the other hand, this study and the research of Madjid et al16 both reported patients of gestational age 29 weeks or more like the most frequently referred to the RSCM. The diagnosis of most obstetric referral cases is the high-risk pregnancy.[16] On the other hand, this study found the proportion of non-emergency cases was who reported the percentage of non-emergency cases in 2013-2014 of 6.1-6.9%.[16] The majority of referral cases in this study were managed by cesarean section. This figure is relatively higher than the percentage of cesarean sections in 2013-2014 of 35.9-49.6%.

The majority of referral cases came from type-D hospitals, different from the findings of Madjid et al16 in 2013-2014 which reported that most of the referrals came from community

health centers or clinics. With a reduced portion of referrals from community health centers or clinics and an increase in the portion of referrals from type-D hospitals, we suspect an increase in tiered referral compliance.16 On the other hand, an increase in referrals from type-A hospitals to RSCM was found in this study. This is interesting, considering that it is not common for type-A hospitals to make referrals to another type-A hospitals. This could be due to the establishment of several type-A hospitals as COVID-19 referral centers.[18] This causes a limited number of non-COVID-19 patients to be admitted or have to be transferred to other hospitals.

This study found that both before and during the pandemic, most of the obstetric referral cases received by RSCM were not carried out with the right procedure. The procedural errors made were not communicating with SPGDT and not delivering by ambulance, while all of them included a referral letter. Most of the referral letters have included the patient's diagnosis, supporting examinations, and reasons for referral, with an improvement trend during the pandemic. The treatment that has been given is a component that is relatively rarely listed. This finding is almost similar to the study who reported the inclusion of a diagnosis in the referral letter was 98.4%[19]. On the other hand, the inclusion of supporting examinations, reasons for referral, and treatment in the referral letter found relatively higher the inclusion of anamnesis, physical examination, reasons for referral, and therapy in the referral letter was 57.1%, 52.4%, 52.4%, and 30.2%, respectively.[21]

The diagnostic suitability rate in this study was higher during the pandemic. When compared with a diagnostic concordance of 78.0-88.6% in 2013-2014, the diagnostic concordance found in this study was relatively low.[16] The finding of concordance with the diagnosis after the pandemic is slightly higher who reported a 59% percentage of concordance between the referral diagnosis and the diagnosis at admission.[20]

This study found a significant increase in the proportion of effective referrals during the pandemic ($p < 0.001$) based on two criteria; diagnostic suitability ($p = 0.004$) and procedure compliance ($p < 0.001$). The inclusion of procedural compliance considers by-passing, a referral action that skips the level of health services, as one of the problems of the referral system.[21] By-passing causes a disproportionate burden on referral health facilities that should only handle complex cases, such as the RSCM as the top referral health facility in the Indonesian health system. Previous studies have used various definitions of referral effectiveness. Using the appropriateness of the diagnosis as a criterion, found referral effectiveness of 90.3% in 2013 and 83.2% in 2014.[16]

Although few studies have addressed the effects of the pandemic on pregnancy outcomes,[22] admissions,[14] to procedural compliance,[23] Researchers have not found other studies that discuss the effect of the pandemic on the referral system. Therefore, this study is one of the first to discuss the impact of the pandemic on the obstetrical referral system, particularly in Indonesia. However, this study has not explored the reasons for the change in referral effectiveness. Further research needs to be done to study the possible causes, for example, qualitative research using focus group discussions involving health workers in primary and advanced health facilities.

On the other hand, this study also did not measure the impact of the pandemic on obstetric outcomes. Research on a wider scale by measuring the impact of obstetric outcomes needs to be carried out to get a more complete picture of how the reproductive health system in Indonesia is affected by the COVID-19 pandemic. Thus, this series of studies can contribute to preparing the health system in Indonesia, both during this pandemic or in dealing with other global health problems in the future.

CONCLUSIONS

The effectiveness of referral to the RSCM based on the suitability of the diagnosis and compliance with procedures during the COVID-19 pandemic was found to be better. Further qualitative research is needed to find out the factors that increase the effectiveness of obstetric referrals during the pandemic.

REFERENCES

1. Indonesia KK. Profil kesehatan Indonesia tahun 2011.http://perpustakaan.depkes.go.id:8180/handle/123456789/3257
2. Dinas Kesehatan DKI Jakarta. Profil Kesehatan DKI Jakarta Tahun 2015. http://www.depkes.go.id/resources/download/profil/PROFIL_KES_PROVINSI_2015/11_DKI_Jakarta_2015.pdf
3. SDGs http://sdgsindonesia.or.id/index.php/sdgs/itemlist/category/29-sdgs?start=12
4. Kementerian Kesehatan RI. Pedoman Penyelenggaraan Puskesmas Mampu PONED. Jakarta; 2012.

5. Kementerian Kesehatan RI. Peraturan Menteri Kesehatan Nomor 001 Tahun 2012. http://www.fkm.ui.ac.id/sjsn
6. Info BPJS Kesehatan "Kapitasi Berbasis Komitmen Pelayanan Dorong FKTP Tingkatkan Mutu Pelayanan." 2016. 38th ed. :3–4.
7. Presiden RI. Undang-undang Republik Indonesia No. 40 Tahun 2004 tentang Sistem Jaminan Sosial Nasional-[PERATURAN]. 2004 http://perpustakaan.depkes.go.id:8180/bitstream/123456789/1957/1/UU2004-40.pdf
8. Satuan Gugus Tugas Penanganan Covid-19. Data Sebaran 2020. https://covid19.go.id/peta-sebaran
9. Pritasari K. Rujukan maternal di era pandemi COVID-19. Webinar Sistem Rujukan Maternal di Era Pandemi COVID-19; 2020 Apr 24.
10. Badan penyelenggara jaminan sosial kesehatan. Peraturan badan penyelenggara jaminan sosial kesehatan nomor 2 tahun 2015. 2015.
11. Tingkat Rujukan ke RS Tinggi 2015 . http://jkn.jamsosindonesia.com/home/cetak/462/Tingkat%20Rujukan%20ke%20RS%20Tinggi
12. Primasari KL. Analisis Sistem Rujukan Jaminan Kesehatan Nasional RSUD Dr. Adjidarmo Kabupaten Lebak. Jur Admin Kebijakan Kes. 2015;1(2):78–86.
13. Rukmini R, Ristrini R. Implementation of Maternal Reference System at Tambakrejo and Tanah Kali Kedinding Health Centres in Surabaya City. Buletin Penelitian Sistem Kesehatan. 2015;18 :365–75.
14. Anderson TS, Stevens JP, Pinheiro A, Li S, Herzig SJ. Hospitalizations for Emergent Medical, Surgical, and Obstetric Conditions in Boston During the COVID-19 Pandemic. J Gen Intern Med. 2020;35(10):3129–32.
15. Kumari V, Mehta K, Choudhary R. COVID-19 outbreak and decreased hospitalisation of pregnant women in labour. The Lancet Global Health. 2020;8(9):e1116–7.
16. Madjid OA, Pusponegoro ARD, Margatan IS. Evaluation of the Accuracy of Implementation of Obstetric Referral Cases to the Emergency in the JKN Era: Inajog. 2019;7(3):159-65.
17. Suparmi, Rizkianti A, Maisya IB, Saptarini I. Hubungan Kepemilikan Buku KIA Terhadap Peningkatan Pemanfaatan Pelayanan Kesehatan Maternal di Indonesia. Jur Kes Reprod. 2018;9(2):159–66.
18. Dinas Kesehatan DKI Jakarta. Jakarta Tanggap Covid-19. Jakarta Tanggap Covid-19. https://corona.jakarta.go.id/id
19. Nurrizka RH, Setiawati ME. Evaluasi Pelaksanaan Sistem Rujukan Berjenjang dalam Program Jaminan Kesehatan Nasional. Jurnal Kebijakan Kesehatan Indonesia : JKKI. 2019 ;8(1):35–40.
20. Setiawati ME, Nurrizka RH. Evaluasi pelaksanaan sistem rujukan berjenjang dalam program jaminan kesehatan nasional. Jur Kebijakan Kes Indones: JKKI https://doi org/1022146/JKKI. 2019;43843.
21. Ghardallou M, Limam M, Khelifi A, Khairi O, Khairi H, Mtiraoui A, et al. Obstetric referrals to a tertiary care maternity: a descriptive study. Pan Afr Med J. 2019;33(306). https://www.panafrican-med-journal.com/content/article/33/306/full/
22. McDonnell S, McNamee E, Lindow SW, O'Connell MP. The impact of the Covid-19 pandemic on maternity services: A review of maternal and neonatal outcomes before, during and after the pandemic. Eur J Obstet Gynecol Reprod Biol. 2020;255:172–6.
23. Kc A, Gurung R, Kinney MV, Sunny AK, Moinuddin M, Basnet O, et al. Effect of the COVID-19 pandemic response on intrapartum care, stillbirth, and neonatal mortality outcomes in Nepal: a prospective observational study. The Lancet Global Health. 2020 ;8(10):e1273–81.

Research Article

The Impact of Premature Rupture of Membranes (PROM) and Low Birth Weight (LBW) Infant Outcomes to the Survival Rate

Hubungan Ketuban Pecah Dini (KPD) dengan Luaran Bayi Berat Badan Lahir Rendah (BBLR) terhadap Survival rate setelah Satu Minggu Dilahirkan

Hasanuddin[1], Dannu Wijaya[1], Dora Darussalam[2]

[1]Department of Obstetrics and Gynecology
[2]Department of Pediatrics
Faculty of Medicine Universitas Syiah Kuala
dr. Zainoel Abidin General Hospital
Banda Aceh

Abstract

Objective: To determine the impact of premature rupture of membranes and the outcome of low birth weight on the survival rate one week after birth in RSUDZA Banda Aceh.

Method: This study used an observational analytic study with a prospective cohort study design. The research samples were 84 samples that met the inclusion and exclusion criteria. The data source used was primary data obtained by direct examination by weighing the newborn at birth and during visits.

Results: There was an impact of premature rupture of membranes and the outcome of low birth weight on the survival rate of infants after one week. The results showed that the p-value <0.000. The lowest neonatal survival rate was in the group weighing less than 1000 grams, namely 0%. Weight group 1000 grams to 1500 grams with a survival rate of 55% and group weight 1500 grams to 2500 grams with a survival rate of 95%.

Discussion: There was an impact of premature rupture of membranes and the outcome of low birth weight on the survival rate one week after birth in RSUDZA Banda Aceh.

Keywords: low birth weight (LBW), preterm premature rupture of membranes, survival rate.

Abstrak

Tujuan: *Untuk mengetahui dampak ketuban pecah dini dengan luaran berat badan lahir rendah terhadap survival rate satu minggu setelah dilahirkan di RSUDZA Banda Aceh.*

Metode: *Penelitian ini menggunakan studi analitik observasional dengan desain penelitian kohort prospektif. Sampel penelitian sebanyak 84 sampel yang memenuhi kriteria inklusi dan eksklusi. Sumber data yang digunakan adalah data primer yang diperoleh dengan cara pemeriksaan langsung dengan penimbangan bayi saat baru lahir dan ketika kunjungan.*

Hasil: *Ada dampak ketuban pecah dini dengan luaran berat badan lahir rendah terhadap survival rate bayi setelah satu minggu didapatkan hasil bahwa p-value <0,000. Survival rate neonatal terendah pada kelompok berat badan di bawah 1000 gram yakni 0%. Kelompok berat badan 1000 gram sampai di bawah 1.499 gram memiliki survival rate 55% dan kelompok berat badan 1.500 gram sampai 2.499 gram memiliki angka survival rate 95%.*

Diskusi: *Ada dampak ketuban pecah dini dengan luaran berat badan lahir rendah terhadap survival rate satu minggu setelah bayi dilahirkan di RSUDZA Banda Aceh.*

Kata kunci: *berat badan lahir rendah (BBLR), ketuban pecah dini, survival rate.*

Correspondence author. Hasanuddin. Department of Obstetrics and Gynecology
Faculty of Medicine Universitas Syiah Kuala Dr. Zainoel Abidin General Hospital. Banda Aceh
Email: i744nu@gmail.com

Received: March, 2021 Accepted: March, 2022 Published: April, 2022

INTRODUCTION

Premature rupture of membranes (PROM) is a condition in which the membranes break before childbirth. Premature rupture of membranes that occurs before 37 weeks of gestation was called a preterm premature rupture of membranes (PPROM).[1] The prevalence is different in each country.[2] According to the World Health Organization (WHO), data on spontaneous early PROM were more prevalent in developing countries.[3] Based on data from the Ministry of Health of the Republic of Indonesia (KEMENKES RI) in 2013, the incidence of premature rupture of membranes in Indonesia is reported to vary, ranging from 6% to 10%.[4,5]

PROM complications can occur in both mother and fetus. In the mother, PROM can cause intrauterine infection, whereas, in the fetus, PROM will cause preterm labor and low birth weight (LBW)[2]. Low birth weight is a baby born weighing less than 2500 grams.[6] The prevalence of LBW according to WHO is estimated to be 17% of the 25 million births in the world annually, where 95% of them occur in developing countries and 11.6% of all cases of LBW worldwide are in Southeast Asia. The incidence of LBW in Indonesia was 11.1%. LBW incident at the dr. Zainoel Abidin Regional General Hospital (RSUDZA) Banda Aceh is still quite high, it was found that out of 1441 births, 248 (17.2%) were LBW babies while out of 1763 births there were 267 (15.1%) cases of LBW babies[6].

Low birth weight is one of the main causes of neonatal mortality. Until now, the infant mortality rate (IMR) in Indonesia is high compared to other countries in the Association of Southeast Asia Nations (ASEAN). There are multiple risk factors for neonatal mortality including LBW. LBW is not only a direct cause of death but also a major factor that threatens the chance of the newborn's survive.[7] LBW babies are babies who are susceptible to disease and have low survival. Some studies suggest that this survival rate is related to the management of infants in health services.[8] This study was conducted to assess the impact of PROM and LBW infant outcomes to the survival rate one week after birth at RSUDZA Banda Aceh.

METHODS

This study was an observational analytic study of primary data with a prospective cohort study design. This research was conducted from January 1, 2020, to September 30, 2020, at the dr. Zainoel Abidin Banda Aceh after receiving ethical approval from the Health Research Ethics Committee (HREC), Faculty of Medicine, Syiah Kuala University. The design was chosen because the researchers wanted to see the role of time (one week) in health services as exposure to LBW with PROM and assess the survival rate. This research was conducted at RSUDZA Banda Aceh from January to September 2020 with 97 research samples, but 13 samples did not follow the follow-up examination (lost to follow-up) so that the total sample that met the inclusion and exclusion criteria was 84 research samples. Infants with intrauterine growth restriction (IUGR), newborns with congenital abnormalities, mothers with other diseases such as severe preeclampsia, hyperthyroidism, heart disease, and patients who did not undergo further examination (loss to follow up) were excluded in this study.

The data was processed by univariate and bivariate methods, using survival analysis. Survival analysis aims to estimated the probability of survival, recurrence, death, and other events over a certain period. The statistical method used to see the probability of survival rate was the Kaplan Meier method. Also, the association between the independent and dependent variables will be assessed using bivariate analysis with the cox proportional hazard model method to identify the effect of birth weight on neonatal survival. Cox Proportional Hazards regression or better known as the Cox regression model were used to determine the relationship between the dependent variable and the independent variable, where the data used in the Cox Proportional Hazards regression was in the form of survival time data from an individual.

RESULTS

This research was conducted at RSUDZA Banda Aceh from January to September 2020 with 97 research samples, but 13 samples did not follow the follow-up examination (lost to follow-up) so that the total sample that met the inclusion and exclusion criteria were 84 research samples. The general characteristics of research subjects in this study were grouped based on maternal age, parity, gestational age, method of delivery, birth weight, and complete newborn outcome were listed in table 1.

Table 1. General characteristics of the research subject

Respondent characteristics	Total (n=84)	(%)
Maternal age (y o)		
15-20	4	4.7
21-25	19	22.6
26-30	23	27.4
31-35	22	26.2
36-40	12	14.2
41-45	4	4.7
Parity		
Primipara	27	32.1
Multipara	57	67.9
Gestational Age (weeks)		
Preterm (<37)	67	79.8
Early Term (37^{+0}-38^{+6})	17	20.2
Method of Delivery		
Pervaginam	33	39.2
Perabdominal	51	60.8
Birth Weight (grams)		
<1.000	4	4.8
1.000-1.500	9	10.7
1.500-2.500	71	84.5
Newborn Outcome		
Alive	68	81
Dead	16	10

Based on Table 1, the most maternal age group was 26-30 years old, namely, 27.4%, while for the lowest age group were 15-20 years and 41-45 years, 4.7% respectively. Of the 84 samples, it was dominated by multiparous as many as 57 samples. A total of 67 patients (79.8%) experienced premature rupture of membranes during preterm gestation. Cesarean section was a separate choice where as many as 51 samples (60.8%) underwent the procedure. Most low birth weight newborns were in the range 1,500-2,500 grams. A total of 68 samples of this study were declared alive.

The characteristics of the research variables in this study were grouped based on the APGAR score and birth weight were listed in table 2.

Table 2. Characteristics of the research variables

Characteristics	Total (n=84)	(%)
APGAR Score		
Severely depressed (0-3)	3	3,6
Moderate depressed (4-6)	13	15,4
Excellent condition (7-10)	68	81,0
Birth Weight (grams)		
Extremely low birth weight (<1000)	4	4,8
Very low birth weight (1000 - <1500)	9	10,7
Low birth weight (1500 - <2500)	71	84,5

Table 2 showed that the highest APGAR score was in excellent condition (7-10) with a percentage of 81%. For the characteristics of birth weight in the sample of this study, there were 84.5% with birth weight in the low birth weight group (LBW) or 1500-2500 grams and there were 4.8% with extremely low birth weight (ELBW) or below 1000 grams.

The complete distribution between the variables of gestational age and birth weight can be seen in table 3.

Table 3. Distribution of Gestation Age Against Birth Weight

Gestational Age	Birth Weight						Total	
	ELBW		VLBW		LBW			
	n	%	n	%	n	%	n	%
Preterm	4	4.8	5	6	58	69	67	79.8
Early Term	0	0	0	0	17	20.2	17	20.2
Total	4	4.8	5	6	75	89.2	84	100

The distribution of subjects based on the variable gestational age to birth weight is categorized as extremely low birth weight (ELBW) where the birth weight is less than 1000 grams, the birth weight is very low (VLBW), namely birth weight ranges above 1000 grams but below 1500 grams, and low birth weight (LBW), namely birth weight above 1500 to less than 2500 grams, the results show that babies with low birth weight were born with a gestational age below 37 weeks or preterm as much as 69%, in which there were 4.8% of the sample. The total sample who had low birth weight in the category of LBW with 89.2% followed by 6% VLBW, and 4.8% ELBW. In the early term sample, 17 samples (20.2%) had low birth weight (LBW).

The data was processed using the Cox Proportional Hazards Regression method to determine the impact of the dependent variable and the independent variable. After processing the cox regression data to assess the impact of newborn weight and preterm premature rupture of membranes on the survival rate of infants after one week, the results show that the p-value is less than 0.05 indicating that the dependent variable and the independent variable have an impact.

In this study, observations were made on all samples, namely 84 samples, it was found that 16 samples died under the age of 7 days. From a total of 16 samples who died, it was found that the lowest birth weight was 530 grams. From the results of the research that has been done, the sample who died was dominated by the female gender as much as 56.2% and the average body weight ranged from 1500 grams to 2500 grams.

Table 4. Characteristics of Study Variables who Died with in the First 7 Days

Characteristics	Total (n=84)	(%)
Gender		
Boys	7	43.8
Girls	9	56.2
Birth Weight (grams)		
ELBW (<1000)	4	25
VLBW (1000 - <1500)	5	31.25
LBW (1500 - <2500)	7	43.75

DISCUSSIONS

In this study were grouped characteristics based on maternal age, parity, gestational age, method of delivery, birth weight, and newborn outcome. The largest group of maternal age was the 26-30 year age group, namely 27.4%, while the least age group was the 15-20 years and 41-45 years age group, namely 4.7% respectively (Table 1). Meanwhile, Radha Y. Aras showed that pregnancies at extreme reproductive ages - young adolescents and older women (after 40 years) - were at high risk of giving birth to low birth weight babies so community-based awareness were needed for the prevention of teenage pregnancy and prevention of pregnancy after 40 years of maternal age and will carry important public health significance in reducing low birth weight infants, thereby avoiding further consequences for low birth weight infants.[9]

Of the 84 samples, it was dominated by multiparous as many as 57 samples. The highest percentage of parity status was multigravida with a rate of 67.9%, primigravida was 32.1%. Atiya and Sutjhata showed the risk of maternal parity on the fetal outcome with 365 samples, the results were 52.81% multigravida. Cesarean section was a separate choice where as many as 51 samples (60.8%) underwent the procedure. Most low birth weight newborns were in the range 1,500-2,500 grams.

A total of 67 patients (79.8%) experienced premature rupture of membranes during preterm gestation. On the characteristics based on gestational age, the highest results were obtained, namely the Preterm group (<37 weeks) as much as 79.8%. This was consistent with the theory that premature rupture of membranes were leading cause of preterm birth in the United States, based on gestational age, babies born prematurely can be small or large during gestation but most cases of preterm or premature babies will be born with low birth weight. Many studies have been conducted regarding the association of prematurity with neonatal morbidity and mortality. Mosammat et al, investigated 100 samples to assess maternal factors in preterm and low birth weight infants found a mean gestational age of 27 weeks.[10] Also, Tanushree et al's study on 213 samples with very, very low birth weight found a mean gestational age of 27 weeks with an average birth weight of 783 grams.[11]

Based on table 4.2, showed that the highest APGAR scores were in excellent condition (7-10) with a percentage of 81%. This was not in line with a retrospective study conducted by Bernard et al with a sample of 1237 newborns with very low birth weight who were found to have the highest APGAR scores, namely 0-3 or severely depressed. Samples with severely depressed APGAR scores who were unable to survive were 68.1%.[12] However, this is in line with this study where preterm birth was associated with low birth weight (LBW).

For the characteristics of birth weight in the sample of this study, there were 84.5% with birth weight in the 1500–2500 grams group and there were 4.8% birth weight below 1000 grams. This is in line with research conducted by Andhikary et al where their study was a cross-sectional study of 50 pregnant women with gestational age more than 28 weeks who had PROM, where the results showed that perinatal mortality increased if PROM appeared when the fetus was not yet viable for extrauterine conditions. Also, the study observed that 45.8% neonates weight less than 2500 grams, and 2.08% have a bodyweight below 1500 grams.[12] In theory, neonates weighing less than 1000 grams have a 95% risk of death and according to the ACOG, the risk of death was increased in infants with birth weight less than 750 grams.[13]

Based on table 4.3, the results showed that babies with low birth weight were born with a gestational age of fewer than 37 weeks or preterm as much as 76.1%, in which 4.7% of the samples were born with ELBW. Meanwhile, of the total sample with low birth weight, the largest percentage was in the LBW category, namely 65.5% followed by VLBW 5.9%, and ELBW 4.7%. This was in line with the theory, namely, birth weight was categorized into extremely low birth weight (ELBW) where the birth weight was less than 1000 grams, very low birth weight (VLBW), i.e. birth weight was around 1000 grams but below 1500 grams, and low birth weight (LBW),

namely birth weight over 1500 grams to less than 2500 grams.

Table 4 showed that of the 84 samples, 16 samples died under the age of 7 days. From a total of 16 samples who died, it was found that the lowest birth weight was 530 grams. From the results of the research that has been done, the sample who died was dominated by the female gender as much as 56.2%. There was no significant difference in mortality and morbidity between male and female newborns, even after considering other risk factors such as gestational age, birth weight, and the delivery process using logistic regression methods and linear.[14] Besides, there was no sex association with neonatal mortality.[15] The same results, namely, there was no gender relationship with neonatal mortality.[16] The male gender, mothers whose age at pregnancy were too young or too old, multiparity, and deprivation contribute to the increased mortality rate in infants with VLBW and LBW.[17] Similar to the study conducted by D'Sa et al, namely gender was not a contributing factor to the incidence of neonatal mortality.[18]

Table 4.4 showed the average newborn body weight ranging from 1500 grams to 2500 grams. This was in line with research conducted by Vilanova et al. where low birth weight was closely related to infant mortality, especially in infants born to young mothers and born in public hospitals.[19] Besides, according to research by Mosammat et al. that low birth weight carries a relatively large risk in the perinatal period and increases neonatal morbidity and mortality. The study was also aimed at assessing maternal risk factors resulting in low birth weight where 33% of the causes of low birth weight were PROM. From a total sample of 100 infants with low birth weight, 52 boys and 48 girls, the survival rate was 87%, with the main cause of death being septicemia (30%).[10] In line with Abebaw's study on determinants of neonatal mortality in the intensive care unit, the neonatal mortality rate was around 38%.[20] Idrisa et al also assessed neonatal outcome in PROM cases and found that PROM had a significant effect on the perinatal, peripartum, and neonatal periods. Morbidity and mortality associated with PROM were ARDS, LBW, IUGR, and sepsis.[21] Heny et al. In a cohort study to assess the survival rate of low birth weight infants without major morbidity with a total sample of 49,333 had a 62.2% survival rate.[22]

Survival was correlated with gestational age for infants according to gestational age. In 2010, the infant mortality rate was 24 times higher for infants with low birth weight (<2500 grams) and 100 times higher in infants with very low birth weight (<1500 grams) than for infants with birth weight 2500 grams or more. First-year survival was 15.5% for infants weighing less than 500 grams. Infants with extremely low birth weight (ELBW) are more susceptible to all complications of preterm birth, both in the immediate neonatal period and after discharge from intensive care.[23,24] A meta-analysis by Laswell et al showed that VLBW infants and very preterm infants had an increased likelihood of death if they were not born in a grade III hospital. Also, significant rates of intraventricular bleeding (IVH) and periventricular leukomalacia (PVL), were associated with less than optimal neurodevelopmental outcomes, increase.[22]

The survival function was obtained from the Kaplan Meier described the probability of survival of the individual being the object of the study. Figure 4.1 showed the Kaplan Meier curve to assess the survival rate of infants with low birth weight in the first 1 week, the results were obtained where the survival rate was 81.0%.

In this study, after performing a statistical test with the Kaplan Meier method, the lowest neonatal survival rate was obtained in the group with body weight below 1000 grams where the survival rate for this group was 0%. This indicates that 4 samples with a birth weight below 1000 grams experienced death within the first 7 days / early neonatal death. Meanwhile, the group weighing 1000 grams to below 1500 grams had a survival rate of 55%, and the group weighing 1500 grams to below 2500 grams had a survival rate of 95%. The results of this study were in line with the theory and supported by other studies in which WHO estimates that out of about 130 million babies born worldwide, 4 million die at neonatal age, most (98%) occur in developing countries.[25] There were multiple risk factors for neonatal mortality including low birth weight (LBW). It was not only a direct cause of death but also a major factor that threatens the newborn's chance of survival.[26] WHO also says that 60–80% of the infant mortality rate (IMR) was caused by low birth weight.[25]

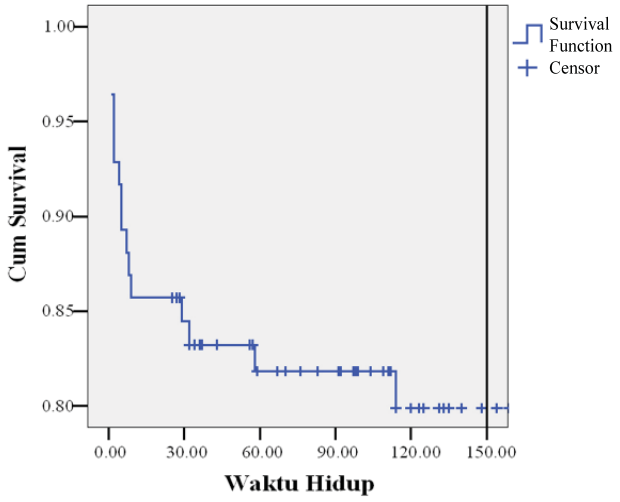

Figure 1. Survival Function

The lower the birth weight, the lower the probability of neonatal survival. The probability of survival increases with higher birth weight. This was supported by Alhassan et al. In a retrospective study to assess risk factors and neonatal outcomes in NICU care, the overall survival rate was 60.73%. The lowest survival rates were in the very low birth weight (14.3%) and very premature (20%) groups. A significant association was observed between birth weight, gestational age, and survival.[27]

Zhang et al in their study said that the increased survival rate of neonates with a low birth weight with or without major morbidity has increased. This point was associated with perinatal care and neonates that have changed in the last 2 decades. However, late-onset sepsis was still a major concern.[16] Also, in a longitudinal observational study that included 2,390 extremely preterm infants (gestational age <27 weeks), Pappas et al. Reported that antenatal exposure to chorioamnionitis appears to increase the likelihood of cognitive impairment as well as death/neurodevelopmental disorders.[25]

Although the mortality rate was greatly reduced with surfactant use, the proportion of surviving infants with severe sequelae, such as chronic lung disease, cognitive delay, cerebral palsy, and neurosensory deficits, did not increase significantly. Although there have been reports of improved neurodevelopmental outcomes in a few small studies, these improvements have not been seen on a global scale.[24]

CONCLUSIONS

This study concludes that there was an impact of newborns weight and premature rupture of membranes on the survival rate of infants after one week after being born in RSUDZA Banda Aceh and the survival rate for low-birth-weight babies with premature rupture of membranes one week after birth has a survival rate of 81%.

SUGGESTIONS

Suggestions that could be given from this study are the need for further research by adding variable characteristics, namely the cause of death of the sample and further research on the care of neonates with low birth weight at the Dr. Zainoel Abidin Regional General Hospital Banda Aceh.

ACKNOWLEDGEMENTS

The author would like to thanks the Department of Obstetrics and Gynecology, Faculty of Medicine, Syiah Kuala University/ RSUDZA Banda Aceh for helping and collaborating to complete this research. In this study, there was no conflict of interest.

REFERENCES

1. Laura M, Lauren R. Characteristics, Properties, And Functionality of Fetal Membranes: An Overlooked Area in The Field of Parturition. In: Encyclopedia of Reproduction. Elsevier. 2018: 1-12.
2. Himpunan Kedokteran Fetomaternal P. Pedoman Nasional Pelayanan Kedokteran Ketuban Pecah Dini. Perkumpulan Obstetri dan Ginekologi Indonesia. Jakarta.Perkumpulan Obstetri dan Ginekologi Indonesia. 2016.
3. Boskabadi H, Zakerihamidi M. Evaluation of Maternal Risk Factors, Delivery, and Neonatal Outcomes of Premature Rupture of Membrane. A Systematic Review Study. J Pediatr Review. 2019;7(2):77–88.
4. WHO. Newborns: improving survival and well-being. Child Health. 2020;19(5):1–6.
5. Rohmawati N, Wijayanti Y. Ketuban Pecah Dini di Rumah Sakit Umum Daerah Ungaran. HIGEIA (Journal of Public Health Research and Development). 2018;2(1):23–32.
6. Cutland C, Lackritz E, Mallett-Moore T, Bardají, A Chandrasekaran R, Lahariya C, Nisar M, et al. Low birth weight: Case definition & guidelines for data collection, analysis, and presentation of maternal immunization safety data. Vaccine. 2017;35(48):6492–500.

7. Ida F. Bayi Berat Lahir Rendah Beserta Determinannya Sebagai Faktor Resiko Kematian Bayi Di Indonesia Analisis Lanjut SDKI 2012. Maternal and Child Health. 2018;3(1):15273562.
8. Suraya I. Kelangsungan Hidup Bayi dengan Berat Lahir Rendah (BBLR) Neonatal Berdasarkan Aspek Pelayanan Kesehatan. Media Penelitian dan Pengembangan Kesehatan. 2017;27(4):217–22.
9. Goisis A, Remes H, Barclay K, Martikainen P, Myrskylä M. Advanced Maternal Age and the Risk of Low Birth Weight and Preterm Delivery: a Within-Family Analysis Using Finnish Population Registers. American Journal of Epidemiology [Internet]. 2017 Dec 1;186(11):1219–26. Available from: https://doi.org/10.1093/aje/kwx177
10. Jinnat MA, Ahmed S, Monira S, Haque MM, Musharraf M, Hasan MR. Maternal Risk Factors, Clinical Profile and Short-Term Outcome of Pre-Term Low Birth Weight Babies. KYAMC Journal. 2020;11(2):77–82.
11. Sahoo T, Anand P, Verma A, Saksena M, Sankar MJ, Thukral A, et al. Outcome of extremely low birth weight (ELBW) infants from a birth cohort (2013–2018) in a tertiary care unit in North India. Journal of Perinatology [Internet]. 2020;40(5):743–9. Available from: http://dx.doi.org/10.1038/s41372-020-0604-6
12. Adhikary S, Tanira S, Sultana A, Wazed F. Fetal Outcome in Premature Rupture of Membrane - A Study conducted in a tertiary level hospital in Bangladesh. Mediscope. 2020;7(2):108–12.
13. Kliegman R, Lye P, Bordini B, Toth H, Basel D. Nelson Pediatric Symptom-Based Diagnosis. 1st ed. Elsevier Inc; 2017. 944 \1126.
14. Barzilay B, Shirman N, Bibi H, Abu-Kishk I. Newborn gender as a predictor of neonatal outcome in mixed-gender twins born with very low birth weight. BMC Pediatrics. 2019;19(1):1–7.
15. Stuti G, Mehrotra G, Mulye S, Shrivastav A. Effect of gender and gestational age on short term morbidities and mortality in extremely low birth neonates. International Journal of Contemporary Pediatrics. 2017;4(3):993.
16. Zhao D, Zou L, Lei X, Zhang Y. Gender Differences in Infant Mortality and Neonatal Morbidity in Mixed-Gender Twins. Scientific Reports [Internet]. 2017;7(1):3–8. Available from: http://dx.doi.org/10.1038/s41598-017-08951-6
17. Watkins WJ, Kotecha SJ, Kotecha S. All-Cause Mortality of Low Birthweight Infants in Infancy, Childhood, and Adolescence: Population Study of England and Wales. PLoS Medicine. 2016;13(5):1–19.
18. D'Sa S, Pinto D, Anousha A, Baliga B. Effect of low birth weight on neonatal mortality in preterm and small for gestational age babies in a tertiary neonatal intensive care unit in India. International Journal of Contemporary Pediatrics. 2016;3(3):735–8.
19. Vilanova CS, Hirakata VN, De Souza Buriol VC, Nunes M, Goldani MZ, Da Silva CH. The relationship between the different low birth weight strata of newborns with infant mortality and the influence of the main health determinants in the extreme south of brazil. Population Health Metrics. 2019;17(1):1–12.
20. Alemu AY, Belay GM, Berhanu M, Minuye B. Determinants of neonatal mortality at neonatal intensive care unit in Northeast Ethiopia: Unmatched case-control study. Tropical Medicine and Health. 2020;48(1).
21. Idrisa A, Pius S, Bukar M. Maternal and Neonatal Outcomes in Premature Rupture of Membranes at University of Maiduguri Teaching Hospital, Maiduguri, North-Eastern Nigeria. Tropical Journal of Obstetrics and Gynaecology. 2019;36(1):1–20.
22. Zhang T, Chen J, Wu H, Pan W, Yang X, Li Y, et al. Improved Survival and Survival Without Bronchopulmonary Dysplasia in Very Low Birth Weight Infants after Active Perinatal Care. Nigerian Journal of Clinical Practice. 2020;23(7):980–7.
23. Jiang M, Mishu MM, Lu D, Yin X. A case control study of risk factors and neonatal outcomes of preterm birth. Taiwanese Journal of Obstetrics and Gynecology [Internet]. 2018;57(6):814–8. Available from: https://www.sciencedirect.com/science/article/pii/S1028455918302328
24. Zhang G, Feenstra B, Bacelis J, Liu X, Muglia LM, Juodakis J, et al. Genetic Associations with Gestational Duration and Spontaneous Preterm Birth. New England Journal of Medicine. 2017;377(12):1156–67.
25. Liu P-C, Hung Y-L, Shen C-M, Chen P-C, Hsieh W-S. Histological chorioamnionitis and its impact on respiratory outcome in very-low-birth-weight preterm infants. Pediatrics & Neonatology [Internet]. 2021;62(3):258–64. Available from: https://www.sciencedirect.com/science/article/pii/S1875957221000036
26. American Obstetrician and Gynecologists. Practice Bulletin No. 160: Premature Rupture of Membranes. New York: American College of Obstetricians and Gynecologists; 2016. p. 39–51.
27. Hartiningrum I, Fitriyah N. Bayi Berat Lahir Rendah (BBLR) di Provinsi Jawa Timur Tahun 2012-2016. Jurnal Biometrika dan Kependudukan. 2018;7(2).

Research Article

Progress of Labor Onset with Combination of Pregnancy Massage and Acupressure

Kemajuan Awal Persalinan dengan Kombinasi Pijat Kehamilan dan Akupresur

Milatun Khanifah, Nur Chabibah, Siti Khuzaiyah

Department of Midwifery
Faculty of Health Science
Universitas Muhammadiyah Pekajangan Pekalongan

Abstract

Objective: To investigate effectiveness of complementary therapy combination pregnancy massage and acupressure on the onset of labor in primigravida pregnant women.

Methods: The population was pregnant women in all regions of Pekalongan Regency at more than 39 weeks' gestation, using random cluster sampling. Data collect use an observation sheet to measure the start time of labor and also check the implementation of massage and acupressure in pregnancy. Treatment was carried out every 2-3 days from 39 weeks of gestation until labor occurs. This study was quantitative quasi-experimental with control group design with a cohort approach.

Result: The results of the bivariate analysis showed that there were significant differences in the onset of childbirth in the intervention group with the control group (p-value; 0.003; CI -8.59 - (- 2.07)). It was concluded that complementary therapy combined therapy of pregnancy massage and acupressure could be used as an alternative therapy to prevent overdue pregnancy.

Conclusion: These findings confirm that complementary therapy combination pregnancy massage and acupressure could faster the onset of labor.

Keywords: acupressure, complementary therapy, onset labor, pregnancy massage.

Abstrak

Tujuan: *Untuk mengetahui efektivitas terapi komplementer kombinasi pijat kehamilan dan akupresur pada permulaan persalinan pada ibu hamil primigravida.*

Metode: *Populasi dalam penelitian ini adalah ibu hamil di seluruh wilayah Kabupaten Pekalongan dengan usia kehamilan lebih dari 39 minggu, dengan menggunakan sampel cluster random. Pengumpulan data menggunakan lembar observasi untuk mengukur waktu mulai persalinan serta memeriksa pelaksanaan pijat dan akupresur pada kehamilan. Pengobatan dilakukan setiap 2-3 hari dari usia kehamilan 39 minggu sampai terjadi persalinan. Penelitian ini merupakan penelitian kuasi eksperimental kuantitatif dengan desain kelompok kontrol dengan pendekatan kohort.*

Hasil: *analisis bivariat menunjukkan terdapat perbedaan yang signifikan timbulnya persalinan pada kelompok intervensi dengan kelompok kontrol (p-value; 0,003; CI -8,59 - (- 2,07)). Disimpulkan bahwa terapi komplementer terapi kombinasi pijat kehamilan dan akupresur dapat digunakan sebagai terapi alternatif untuk mencegah terjadinya kehamilan terlambat.*

Kesimpulan: *Temuan ini mengkonfirmasi bahwa terapi komplementer kombinasi pijat kehamilan dan akupresur dapat mempercepat terjadinya persalinan.*

Kata kunci: *akupresur; awalan persalinan, pijat kehamilan, terapi komplementer.*

Correspondence author. Nur Chabibah. Department of Midwifery Faculty of Health Science, Universitas Muhammadiyah Pekajangan Pekalongan. Email: nchabibah@ymail.com

Received: April, 2021 Accepted: March, 2022 Published: April, 2022

INTRODUCTION

Postterm pregnancy is one of the high-risk pregnancies. This is closely related to mortality, perinatal morbidity, or macrosomia. The risk for mothers with postterm pregnancies can be in the form of postpartum bleeding or increased obstetric procedures.[1] There were 24 mothers with serotinous pregnancies of 87 (28%) women giving birth, of 24 women with pregnancies serotinus, 18 (75%) infants had asphyxia.[2] A relationship between late pregnancy and severe preeclampsia with asphyxia incident.[3] Women in the post-term had a significantly higher rate of caesarean section and operative vaginal delivery. Post-term pregnancy versus full-term pregnancy was associated with an increased risk of NICU admission, respiratory morbidity, and infectious morbidity. Post-term pregnancy versus late-term pregnancy was similarly associated with an increased risk of NICU admission, respiratory morbidity, and infectious morbidity (and with hypoglycemia).[4]

Labor induction is a measure to stimulate uterine contraction using any medical procedure or by attempting any mechanical alteration prior to normal uterine contraction for labor. One is mechanical using membrane pressure manipulation, and the other is pharmaceutical using prostaglandin and oxytocin hormone stimulation. However, these pharmaceuticals pose some risks. Among those risks is that the administration of synthetic oxytocin may reach its maximum level that the body can tolerate, which in turn increases the likelihood of cesarean section and hence, greater risk of bleeding. A latest research finds that the risk of uterine tear due to labor induction is 77% among patients undergoing cesarean section.[5] In Indonesia, the SC number in the last five years reached 15.3% of 20.591 deliveries, while the target of the World Health Organization (WHO) SC number was 5-15%. SC labor will have an impact on the length of the healing process of the post-partum, the risk of infection with SC wounds, disruption of the breastfeeding process, and affect the low degree of maternal and child health.[6]

Currently, the services needed by the community are not only for healing, but the highest hope of the community is the comfort that is obtained in the services they receive so that side effects are not felt by the client on treatment and also become a pain prevention measure that will be accepted. This is proven by using Complementary and Alternative Medicine (CAM) by women about 48.9% compared with men 37.8%. Can be concluded that the use of alternative complementary therapies in women can be used as indicators of use alternative complementary therapies at a time when will come. This includes the use of complementary therapies in problems of pregnancy, childbirth and breastfeeding.[7]

The presence of this complementary therapy is expected to be able to provide alternative measures in the prevention of labor complications in preventing late pregnancy and the impact of late pregnancy. Complementary care in childbirth includes: endorphin massage, oxytocin massage, giving dates, birth ball therapy, giving aromatherapy, therapy Murottal Al-Qur'an provides significant results on client comfort, maximizes the role of the midwife, minimizes trauma, increases energy in maternal labor and shorter time of delivery.[8]

One of the massages that is known to increase hormones that help the birth process namely the hormone oxytocin is a massage in the back area. The massage in question is an oxytocin massage. Oxytocin can increase the influx of calcium ions into the intracellular. With the release of the hormone oxytocin will strengthen actin and myosin bonds. This will make the uterine contractions stronger. This is in accordance with the theory that oxytocin massage carried out on inpartum mothers has an effect on his frequency and his duration in pregnant women.[9] Another massage used in labor is endorphin massage which makes reduced labor pain. Endorphin massage can stimulate the body releases endorphins which are pain reliever so feel reduced labor pain. Touch and massage can make mothers feel calm and comfortable during childbirth. Massage endorphins do not cause side effects which harms the mother. Endorphin massage too can reduce anxiety so that pain that the mother feels during childbirth can be reduced.[8] In the results of the study it was stated that massage endorphins affect the decrease intensity of labor pain in primiparous mothers.[10] As post-term pregnancy is an important factor in perinatal mortality and has undesirable maternal and neonatal results, this study was conducted to identify the effect of combination pregnancy massage and acupressure inducing labor in primigravida with 39-40 weeks of pregnancy in 2018.

METHODS

Study design in this research was using quasi experimental with control group design with a cohort approach. The sample was determined from the population of primigravida pregnant women with gestational age ≥39 weeks taken at random with the Cluster random sampling technique. After the random cluster, three public health centers working were selected as research locations, including Buaran, Kedungwuni I, and Kedungwuni II public health center. A population of 212 primigravida pregnant women was obtained in ones years at random to participate in the study.

Determination of the sample size is calculated using the Stata 12 software based on the proportion approach with 80% power and a degree of significance (α) 0.05. The proposed sample size in this study is 50 for the intervention group and 50 for the control group. However, until this July, there are 4 respondents in the intervention group were lost to follow-up, 8 not finished the intervention, and 13 respondents who had given birth before the target intervention has been completed. So, Big of sample in intervention group just 25 until the finish of study.

This study was endorsed by the institutional Ethics and Research Committee. All volunteers signed a consent form to declare a voluntary agreement with all procedures implicated in this project. Participants were informed that they participation could be voluntarily terminated at any time without any consequence. Procedure In this study, researchers conducted an initial meeting of the first trimester pregnant women in the class of pregnant women in three public health centers. Researchers explain the preparation of labor and explain the flow of research on prospective clients. Clients who are willing to take part in the research are welcome to write down their address and contact number. The researcher randomized the group of pregnant women who were willing to participate in the study in two groups, namely, the intervention group and the randomized control group. In the intervention group, the combination of Pregnancy, Massage, and Acupressure was given to the treatment group, once every 2-3 days since 39 weeks of gestation until the time of delivery. The control group was given standard pregnancy care with antenatal care services and classes of pregnant women with the main theme of labor preparation in the third trimester of pregnancy, The intervention was carried out by a certified acupressure therapist in a standardized antenatal care room. Before and after the intervention, check the fetal heart rate and blood pressure of the client. After three interventions, the client is asked to inform the date of delivery.

The data was collected through three instruments. The first instrument was a general data collection sheet that was used as an instrument for recording general client data. The second instrument was an observation sheet of vital signs and signs of labor that were measured by the therapist before and after the intervention. The third instrument checks the implementation of pregnancy, massage, and acupressure as a time recording and scheduling of subsequent therapy. These three instruments were arranged by the researcher and the team and conducted a common perception of the therapist as an enumerator and executor of the intervention. The intervention was carried out according to standard operational procedures that the research team had compiled. The intervention was carried out every 2-3 days starting at 39 weeks' gestation until delivery.

The first instrument examines general data such as client biographical data including name, age of last education, and occupation. in the second part of this instrument asks client knowledge about labor preparation, which contains twenty question items with yes and no answer choices. The third part of this instrument explores the preparation of childbirth that the client and family have planned in accordance with the birth planning and complications prevention program known in Indonesia as P4K. This section asks about planned birth attendants, where the place of delivery is planned, what vehicles are planned to go to, where birth attendants are planned, and whether there was an insurance preparation and or delivery cost. At the end of this instrument, there is an instrument to assess client anxiety using the Halminton Ranting Scale and current pregnancy history.

The second instrument was a checklist for recording the results of antenatal care carried out before and after the implementation of the intervention. A pregnancy check-up involves asking for complaints related to the signs of labor that the client may experience and measuring blood pressure, fetal heart rate, and uterine contractions.

The third instrument was a checklist for recording the date the client arrived and the

intervention carried out, which was accompanied by the signature of the client and therapist and recording the date of the next intervention agreed by the client and therapist. Data collection using three instruments that have been prepared to measure the prefix time of delivery, also using a checklist for pregnancy massage and accupressure. The treatment is carried out every 2-3 days starting at 39 weeks of gestation until delivery occurs. Analysis of respondent characteristics was performed in frequency distribution of age, educational background, working status, and onset of labor. The data were analyzed using t-test independent to see differences labor onset in intervention and control group. The level of significance used in this test is p-value <0.05 in the 95% confidence interventions. Statistical analysis was conducted via Stata 12 software.

RESULTS

The findings indicated there was significant statistical differences between the two groups (25 pregnant women receiving pregnancy massage, acupressure and antenatal visit versus 25 receiving antenatal visit only) in terms of demographic data such as age, BMI, education levels, employment, knowledge of labour preparation, preparation of labor and gestational age at enrollment (Table 1).

Table 1. Demographic Data

Groups	Intervention	Controls	*P-value*
Age, y o	25.32(4.488)	27.16(4.525)	0.152
BMI, kg/m^2	23.28(2.137)	22.43(4.351)	0.356
Education			0.341
Elementary School	4(16)	4(16)	
Middle school	6(24)	11(44)	
High School diploma	12(48)	7(28)	
University	3(12)	3(12)	
Employment			0.022
Home work	15(60)	19(76)	
Employed	10(40)	6(24)	
Knowladge of Labor Preparation			0.073
Good	13(52)	12(48)	
Lacking	12(48)	13(52)	
Preparation of Labour			0.299
Already	22(88)	19(76)	
Not Yet	3(12)	6(24)	
Gestasional Age at enrollment	273.68(4.347)	280.20(5.431)	0.000

*Categorical data describe by numbers and percentages, Numeric data describe by mean and deviation standard

Tabel 2. Fetal Heart Rate and Blood Pressure in the Intervention Group

Variable	Mean ± SD		*P-value*	mean	CI 95%
	Pre	Post			
Fetal Heart rate Intervention I	138.28 ±6.419	135.28 ± 7.817	0.209	2.4	-1.445 to 6. 245
Fetal Heart rate Intervention II	139.24 ± 5.783	135.64 ± 8.036	0.029	3.6	0.392 to-6.808
Fetal Heart rate Intervention III	137.32 ± 6.644	132.48 ± 6.165	0.000	4.84	2.512 to-7.158
Sitole blood pressure I	108.8 ± 13.013	102.24 ± 13.371	0.000	6.56	3.976 to-9.144
Sitole blood pressure II	108.8 ± 12.356	102.24 ± 14.347	0.000	4.84	3.909 to-9.211
Sitole blood pressure III	108.8 ± 12.355	102.04 ± 12.888	0.000	6.76	4.165 to-9.355
Diastole blood pressure I	71.92 ± 9.6	67.2 ± 9.473	0.000	4.72	2.253 to-7.187
Diastole blood pressure II	72.32 ± 8.826	68 ± 10.408	0.001	4.32	1.940 to-6.699
Diastole blood pressure III	72.32 ± 8.826	67.8 ± 9.691	0.000	4.52	2.095 to-6.944

At each time the intervention was examined, fetal heart rate and blood pressure, which can be observed in table 2 that there was a change in the mean value of interventions I, II and III. In the first intervention, there were insignificant changes in fetal heart rate (p-value; 0.209; CI -1.445 – 6.245), but there were significant changes in systolic (p-value; 0.000; CI 3.976 – 9.144) and diastolic blood pressure (p-value; 0.000; CI 2.253 - (7.187). In the second intervention there were significant changes in fetal heart rate (p-value; 0.029; CI 0.392 – 6.808), and systolic (p-value; 0.000; CI 3.909 – 9.211), and diastolic blood pressure(p-value; 0.001; CI 1.940 – 6.699). In the second intervention there were significant changes in fetal heart rate.

Table 3. Effectiveness of Complementary Combination Therapy Pregnancy Massage with Acupressure with Labor Onset

Variable	Mean ± SD		*P-value*	mean	CI 95%
	Control	Intervention			
Labor onset (Days)	280.20 ±5.431	273 ± 4.347	0.000	-6.52	-9.541 to -3.498
Long active phase of labor (Hour)	11.66 ± 5.503	6.52 ± 5.876	0.016	-5.14	-9.220 to-1.059

Table 3 showed that the combination of pregnancy massage and acupressure therapy is effective in increasing the onset of labor. The findings showed that mean labor started in intervention group 273 days (p-value; 0.000; CI -9.541 - (- 3.498).

DISCUSSION

This research was done to study the effect pregnancy, massage, and acupressure therapy with labor onset. The findings showed that mean labor started in intervention group 273 days (p-value; 0.000; CI -9.541 - (- 3.498) after third treatment. Research conducted by giving massage interventions for 20 minutes every week for a period of 16 weeks, showed a significant decrease in the decrease in cortisol levels, anxiety, and depression. Massage can reduce anxiety so that pain What mothers feel during childbirth can be reduced.[8]

Research conducted on women who have entered the onset of labor with the opening of the first 3-4 cm does not have an impact on shortening the duration of the period I. In addition to the incidence of labor onset, the study also observed that the average distance of labor with the last treatment in the intervention group was 4 days. 26.67% of them respond less than 24 hours to spontaneous labor. Research conducted on first-stage maternity showed that acupressure on SP6 for 30 minutes when contractions appear can significantly reduce pain and shorten the duration of time I. The location of SP6 is located on the inner leg of approximately four fingers above the ankle. Emphasis was carried out using the thumb, given with the strength of 2150 mmHg by the right finger and 1911 mmHg by the left thumb.[11,12]

This study also showed an effect on changes in fetal anther, pulse, and blood pressure in the group receiving pregnancy massage therapy and acupressure before and after therapy. Pregnancy massage provides a sense of relaxation and dilation of blood vessels in maternal patients pregnant so that indirectly there is a blood pressure that influences the hormone endorphin that comes out when the patient feels relaxed will help dilate blood vessels and lower the patient's blood pressure. Massage therapy has the advantage that it can reduce levels of the stress hormone cortisol, and depression levels, anxiety decreases, decreases the risk of heart attack, kidney failure, and stroke, and smooth blood flow. Thus, pregnancy massage can be used in therapy reducing the blood pressure of a pregnant patient.[13]

The results also showed that by providing pregnancy, massage therapy and acupressure on an ongoing basis can prepare the pregnant woman's physical health more optimally so that the readiness to face childbirth is getting better. This is indicated by the results of shortening the active phase of labor during its shorter time compared to the control group. The average score for the group receiving pregnancy, massage, and acupressure therapy was 6.52 hours (p-value; 0.016; CI -9.220 - (-1.059. This is in line which results that maternity mothers who are given counter pressure massage experience the first stage of active phase which is faster than the control group who were not given counter pressure massage. Massage sends neurotransmitter impulses to the limbic system, and then to the amygdala. The hypothalamus is then relayed to the anterior pituitary. With this massage, the pituitary anterior produces higher amounts of endorphins. Endorphins other than helps reduce labor pain, it also enhances the action of endogenous oxytocin in helps stimulate myometrial contractions in the process of cervical dilatation. This causes the first stage of the active phase to be shorter.[14] Eight respondents who were given prenatal massage, as many as 7 respondents (87.5%). Of the 8 respondents who were not given prenatal massage, some with delivery experienced dystocia, namely 4 respondents (50%). There is an effect of prenatal massage on the delivery process with a significant value of 0.006.[15]

Therefore that, Induction of labor with non-pharmacological techniques is not without its risks and may well contribute to prevent complications when used more widely and in

normal, unwarranted cases. As in other procedures or treatments used within conventional medicine for complex/abnormal cases, there is a tendency for them to be incorporated as routine practice. In contrast, there also needs to be a change in society's expectations of 'the expected date' and 'being overdue' so that it is not viewed as abnormal. The role of self-help techniques and the safe use of complementary therapies is critically explored within a model of enhanced hormonal activity and reduction of stress hormones during the postdates period, in conjunction with a more conservative approach of care for uncomplicated postdates pregnancy.

CONCLUSIONS

There was a significant difference in the onset and long active phase of labor between groups that were given complementary therapy with a combination of pregnancy massage and acupressure. Complementary therapy for combination pregnancy, massage, and acupressure can be an alternative in preventing pregnancy over time.

REFERENCES

1. Nurhidayati, T., Astyandini, B., & Setiasih S. Identifikasi Penanganan Kehamilan Serotinus di RSUD Dr. H Soewondo Kendal. Midwifery Care J. 2019;1(1):10-8.
2. Wulansari, A., Tonasih, T., & Ratnasari E. Hubungan antara Kehamilan Serotinus dengan Kejadian Asfiksia Pada Bayi Baru Lahir Di Rsud Indramayu Periode 01 September-30 November Tahun 2014. Midwife's Res. 2019;3(2):15-23.
3. Mandasari P. Hubungan Kehamilan Lewat Waktu dan Preeklampsia Berat (PEB) dengan Kejadian Asfiksia Neonatorum. Citra Delima J Ilm Stikes Citra Delima Bangka Belitung. 2020;4(1):36–40.
4. Linder, N., Hiersch, L., Fridman, E., Klinger, G., Lubin, D., Kouadio, F. & Melamed N. Post-Term Pregnancy Is An Independent Risk Factor For Neonatal Morbidity Even In Low-Risk Singleton Pregnancies. Arch Dis Childhood-Fetal Neonatal Ed. 2017;102:F286-F90.
5. Citrawati, D. H. D. & Martanti Le. Complementary Therapies For Labor Induction And Their Legality In Indonesia: A Literature Review. Proc Int Conf Appl SCI Heal. 2019:476–91.
6. Kementrian Republik Indonesia. Riset Kesehatan Dasar (Riskesdas) 2018. Jakarta; 2018.
7. Septiani, R., & Lestari Gi. Hubungan Karakteristik Bidan Dengan Praktik Kebidanan Komplementer Di Praktek Mandiri Bidan. J Ilm Keperawatan Sai Betik. 2020;15(2):114-9.
8. Puspitasari, N. A., & Hukmilah H. Pengalaman Ibu yang Melahirkan dengan Asuhan Kebidanan Komplementer Tahun 2021. J Asuhan Ibu dan Anak,. 2022;7(1):1-10.
9. Qonitun, U., & Qiftiyah M. Pengaruh Pijat Oksitosin terhadap Frekuensi His, Durasi His pada Ibu Inpartu di BPM Asri Tuban. Jur Keb. 2021;10(1):75.
10. Fitriana, F., & Putri Na. Pengaruh Pijat Endorphin (Endorphin Massage) Terhadap Intensitas Nyeri Kala I Pada Ibu Primipara. Jur Ilmu Keperawatan Sai Betik,. 2018;13(1):31-4.
11. Chabibah, N. & Khanifah M. Efektivitas Pregnancy Massage Terhadap Tekanan Darah Pada Ibu Hamil Trimseter Iii. Proceeding Urecol. 2019:360–5.
12. Ernawati, E. & Safitri D. Manfaat Teknik Relaksasi Massage Muscullus Trapezius dengan Aromaterapi Mawar terhadap Perubahan Tekanan Darah pada Ibu Hamil. Jur Keb. 2017;6:23–7.
13. Firyadhonah PN. Perbedaan Lama Persalinan Kala I antara Diberi dan tidak diberi Massage Effluerage di Fundus Uteri pada Ibu Multipara di Puskesmas Halmahera Semarang. Semarang. 2016.
14. Merry, Y. A., Bebasari, M., & Ridanta OR. Pengaruh Massage Counter Pressure Terhadap Lama Kala 1 Fase Aktif Persalinan Normal. Jur Ilmu Keb (J Midwifery). 2021;9(1):38-45.
15. Sudarnanik S. Pengaruh Prenatal Massage terhadap Proses Persalinan di Pustu Kedungprimpen Kecamatan Kanor Kabupaten Bojonegoro. STIKES Insan Cendekia Medika Jombang. 2020.

Research Article

The Role of Placental TLR-7 Expression with Cord Blood HBV DNA and Placental HBV DNA

Peran Ekspresi TLR-7 Plasenta dengan HBV DNA Tali Pusat dan HBV DNA Plasenta

Naeny Fajriah[1], Maisuri T. Chalid[1], Lenny Lisal[1], Efendi Lukas[1], St. Nur Asni[1], Rina Masadah[2]

[1]Department of Obstetrics and Gynecology
[2]Department of Pathology
Faculty of Medicine Universitas Hasanuddin
Dr. Mohamad Hoesin General Hospital
Makassar

Abstract

Objective: To determine the role of TLR-7 expression on intrauterine vertical transmission in pregnancy through identification of serum hepatitis B markers in both maternal and umbilical cord blood.

Methods: Analysis of TLR expression was performed on 38 paraffin block samples of placental tissue acquired from mothers with HBV using TLR immunohistochemical staining.

Results: 16 of 38 samples were acquired from mothers aged 26-30 years-old. Most of the samples were from primiparous mothers (52.6%). This study found no significant association between TLR-7 expression and HBV DNA in the placenta and cord blood (p = 1.000). However, we found a significant association between placental TLR-7 expression and maternal HBV DNA (p = 0.034). Meanwhile, placental HBeAg and HBV DNA were not associated with placental TLR-7 expression (p = 0.082; p = 1.000).

Conclusion: There was no significant association between TLR-7 expression and HBV DNA in the placenta and cord blood, but we found a significant association between TLR-7 expression and maternal HBV DNA.

Keywords: HBV DNA, Hepatitis B, intrauterine infection, placental toll-like receptor (TLR) 7,umbilical cord.

Abstrak

Tujuan: *untuk melihat peran ekspresi TLR-7 terhadap transmisi vertikal intrauterina pada kehamilan melalui identifikasi marker serum hepatitis B pada darah ibu dan talipusar.*

Metode: *Analisis ekspresi TLR dilakukan pada 38 sampel blok paraffin jaringan plasenta ibu yang menderita HBV dengan memakai pewarnaan imuhohistokimia TLR.*

Hasil: *16 dari 38 sampel berusia 26-30 tahun. Sebagian besar sampel merupakan kelompok primipara (52.6%). Penelitian ini tidak menemukan hubungan yang signifikan antara ekspresi TLR-7 di plasenta dan HBV DNA darah tali pusat (p = 1.000). Tapi, kami menemukan hubungan yang signifikan antara ekspresi TLR-7 plasenta dan HBV DNA ibu (p = 0,034). Sedangkan HBeAg dan HBV DNA plasenta tidak berhubungan dengan ekspresi TLR-7 plasenta (p = 0,082; p = 1.000).*

Kesimpulan: *Tidak ada hubungan yang signifikan antara ekspresi TLR-7 dan DNA HBV di plasenta dan tali pusat, tetapi kami menemukan hubungan yang signifikan antara ekspresi TLR-7 dan DNA HBV ibu.*

Kata kunci: *HBV DNA, Hepatitis B, infeksi intrauterina, plasenta, tali pusat, toll-like receptor (TLR) 7.*

Correspondence author. Naeny Fajriah. Department of Obstetrics and Gynecology
Faculty of Medicine Universitas Hasanuddin Dr. Mohamad Hoesin General Hospital. Makassar
Email: fajriahnaeny@yahoo.com

Received: May,2021 Accepted: March,2022 Published: April,2022

INTRODUCTION

Hepatitis B virus (HBV) infection is a serious public health problem, where more than one million people die every year due to this disease. Chronic HBV infection affects more than 350 million people worldwide, leading to a range of liver diseases, including chronic hepatitis, fulminant liver failure, cirrhosis of the liver, and hepatocellular carcinoma[1].

Chronic hepatitis B, as a worldwide health problem, is a disease that begins in the prenatal period, and its complications gradually become apparent later in life[2,3]. The prevalence of HBV in pregnant women is about 5% and varies from 0.6% in low-incidence areas to more than 20% in areas with a higher incidence such as eastern and African regions[2]. Indonesia is considered as a country with a high incidence of hepatitis along with 11 other countries in Southeast Asia. The Indonesian Health Profile data for 2018 further shows that the national prevalence of Hepatitis B in pregnant women reaches 1.88%. South Sulawesi Province is ranked 12th among other Indonesian provinces for having the most pregnant women with hepatitis B (2.51%)[4].

Hepatitis B vertical transmission mechanism into three gestational periods at conception where germ-line infection occurs, during pregnancy through contamination of maternal blood and transplacental transmission, and at birth via membrane rupture and vaginal delivery. The transmission rate through these three mechanisms is associated with positive HBeAg status and high levels of Hepatitis B Virus (HBV) DNA[5,6].

There are many serum markers to indicate the risk of vertical transmission of hepatitis B virus via intrauterine such as maternal viral load and HBeAg. High viral load values indicate an increased risk of vertical transmission and positive HBeAg. Both of these are closely related to the levels of HBV DNA in cord blood[7]. Based on previous studies, intrauterine infection and vertical transmission occur when HBV DNA titer is detected in neonatal peripheral venous blood or umbilical cord blood[8]. However, studies suggest that the detection of HBV DNA levels in umbilical cord blood is not considered as an absolute marker of intrauterine infection but suggests a risk of hepatitis B virus transmission in the placenta[9].

Infants whose mothers were HBeAg positive and cord blood HBV DNA positive but at the time of placental examination did not develop an intrauterine infection suggests that there is an unexplained mechanism that appears to protect the fetus from intrauterine HBV infection. The mechanism by which HBV passes across the placental barrier and infects the fetus is still unknown. However, it has been demonstrated that HBV infects trophoblasts in vivo and in vitro, and this infection is the first and most crucial step of intrauterine HBV infection[1].

The placenta is considered a specific component during the pregnancy which has an innate immune system and contains mechanical and immunological barriers restricting entry to the fetus. A study revealed the function of placental trophoblasts as macrophages in recognizing and responding to pathogens through the expression of toll-like receptors (TLRs), and primary placental trophoblasts are more resistant to viral infection than non-trophoblastic cells. The mechanism by which placental trophoblasts combat viruses, including HBV, needs to be elucidated. However, TLRs on trophoblasts can play a vital role[1].

Based on this background, research is needed to evaluate the role of TLR-7 expression on intrauterine vertical transmission in pregnancy through the identification of serum hepatitis B markers in maternal and umbilical cord blood so that in the future, the necessary treatment can be given to reduce mother-to-child HBV transmission. Research data regarding placental TLR-7 expression on umbilical cord hepatitis B virus detection in Indonesia, especially in Makassar, has never been reported to the best of the authors' knowledge.

METHODS

This was a cross-sectional study. The study was conducted in four hospitals in Makassar from September 2019 to March 2020. Our population consisted of HbsAg-positive pregnant women in Makassar. In this study, the inclusion criteria were women with term pregnancy who were infected with hepatitis B virus with positive HBsAg test results, who had never received antiviral therapy before, were willing to participate in the study by providing written consent after receiving thorough explanation of the study. The exclusion criteria in this study were women who received antiviral therapy within six months to recruitment; were receiving interferon therapy; had pregnancy complications (preterm labor, premature rupture of membranes, and preeclampsia); fetal distress;

had an autoimmune disease, HIV, syphilis, or other infectious diseases; and had abnormal liver and kidney function. Incomplete data including those who did not follow all required procedures as well as those who withdrew form this study for any reason were not included in our analysis. Sampling was carried out using the purposive sampling technique. The number of samples in this study was 38 subjects. Data analysis used STATA 14. Univariate analysis was conducted to determine baseline characteristics, while the relationship between placental TLR-7 expressions and maternal, umbilical cord, and placental HBV-DNA were analyzed using the Fischer-exact test.

Instruments and Procedures

All pregnant women who met the inclusion criteria described above who have agreed to participate in this study were asked to sign an informed consent form. We conducted history taking, physical examination, and laboratory tests (HBsAg and HBV DNA) on all participants. Pregnant women who have previously been diagnosed with HBV infection confirmed by a positive HBsAg result during pregnancy, then had their blood samples took and analyzed for HBV markers. Blood samples were taken when the patient was admitted to the hospital. The blood sample is then centrifuged after leaving it for at least 30 minutes at room temperature. HBsAg markers were routinely examined using ELISA (enzyme-linked immunosorbent assays), and HBV DNA levels were assessed using real-time quantitative PCR.

After the baby is born, either by vaginal delivery or surgery, the umbilical cord blood is collected after cutting the cord and before the placenta is separated from the uterus for HBV DNA examination. HBV DNA markers were quantified using a qualitative serological test. A placenta sample is taken as soon as the placenta is delivered. The placental cotyledons were dissected in the middle zone, washed thoroughly with cold normal saline after separation from the amniotic membrane, decidua, and connective tissue. Then frozen with liquid nitrogen and then stored at -800C until ready for inspection. The tissue in the paraffin block was cut to a size of 5 µm and glued to a poly-L-lysine slide, and then deparaffinized. Immunohistochemical staining was carried out using the standard avidin-biotin-peroxidase complex (ABC) method. The unstained slides were incubated with peroxidase-1 for 5 minutes at room temperature, after which an ABC procedure was followed. Immunohistochemical staining used monoclonal TLR-7 antibody concentrated with a 1:100 dilution. The results of immunohistochemical staining were evaluated using light microscopy by two pathologists and researchers.

RESULTS

This study involved 38 pregnant women who had hepatitis B based on history taking, physical examination, and confirmed by laboratory examination. Sample characteristics were grouped according to age, parity, gestational age, and hepatitis risk factors, including a history of hepatitis and family history of hepatitis.

We divided our samples into five age groups: <20 years-old, 21-25 years-old, 26-30 years-old, 31-35 years-old, and> 35 years-old. Most of our samples were in the 26-30 years-old age group (42.1%), and only one sample was in the <20 years-old age group (2.6%). In this study, the youngest patient was 18 years-old, and the oldest was 39 years-old with a mean ± standard deviation of 28.78 ± 4.70 years. More than half of our samples were primiparous (52.6%), and two samples were grand-multiparous. About 34.2% of our samples had a history of hepatitis, and only two subjects had a family history of hepatitis (Table 1).

Table 1. Sample Characteristics

Variables	Frequency (n=38)	(%)
Age (y o)		
<20	1	2.6
21-25	8	21.1
26-30	16	42.1
31-35	9	23.7
>35	4	10.5
Parity		
Primiparous	20	52.6
Multiparous	16	42.1
Grand-multiparous	2	5.3
History of Hepatitis		
Yes	13	34.2
No	25	65.8
Family History of Hepatitis		
Yes	2	5.3
No	36	94.7

Based on the following table, it can be seen that there is no significant relationship between HBV-DNA cord blood levels and TLR-7 expression in the placenta with a p-value = 1.000 (p> 0.05) (Table 2).

Table 2. Relationship between HBV-DNA Cord Blood Levels and TLR-7 Expression

Variable		HBV-DNA Cord Blood		Total	*P-value*
		Positive	**Negative**		
Positive TLR-7 expression	n	2	23	25	1.000
	%	8	92	100.0	
Negative TLR-7 expression	n	1	12	13	
	%	7.7	92.3	100.0	
Total	n	3	25	38	

*Fisher-exact test

Based on table 3, it can be seen that there is a significant relationship between the risk of transmission based on maternal HBV-DNA levels and the expression of TLR-7 in the placenta with a p-value value of 0.034 (p <0.05). There was no significant relationship between HBeAg levels and TLR-7 expression in the placenta where the p-value was 0.118 (p> 0.05). There was no significant relationship between placental HBV-DNA levels and TLR-7 expression in the placenta where the p-value was 1.000 (p> 0.05).

Table 3. Relationship between Risk of Intrauterine HBV Exposure Based on Maternal HBV-DNA, HbeAg and Placental HBV-DNA Levels with TLR-7 Expression

Variable		TLR-7 expression		Total	*P-value*
		Positive	**Negative**		
Maternal HBV-DNA	Positive	8 (100.0)	0 (0.0)	8 (21.1)	0.034
	Negative	17 (56.7)	13 (43.3)	30 (78.9)	
HBeAg	Positive	9 (90.0)	1 (10.0)	10 (26.3)	0.82
	Negative	16 (57.1)	12 (42.9)	28 (73.7)	
Placental HBV-DNA	Positive	9 (69.2)	4 (30.8)	13 (34.2)	1.000
	Negative	16 (64.0)	9 (36.0)	25 (65.8)	

*Fisher-exact test

DISCUSSION

Our samples were mostly obtained from mothers aged between 26-30 years-old (16 people (42.1%)), and the least were aged <20 years-old (one person (2.6%)). This finding is in line with a research where the highest incidence of HBsAg was found among those within the 30 to 34-year-old age group with a percentage of 23.3% followed by the second largest age group, the 25 to 29-year-old age group with a percentage of 16.9%. According to Kolawole et al., this age group has the highest peak of social activity or is considered the productive age, therefore that the risk of virus transmission through sexual contact is also fairly high[10].

Based on parity status, a majority of our samples consisted of primiparous women (20 people (52.6%)), and in the grand-multiparous group, only two samples (5.3%) were obtained. Whereas the prevalence of HBV-positive was more common in multiparous women due to repeated pregnancy and labor, which put pregnant women at a greater risk of HBV infection due to examination procedures and childbirth 11. However, it was found that there was no difference between primiparous and multiparous HbsAg-positive women[12].

Based on table 2, there was no significant relationship between cord blood HBV-DNA levels and TLR-7 expression in the placenta. However, we found that the percentage of mothers with a negative cord blood HBV-DNA gave more positive TLR-7 expression results. Our finding is in line where mothers infected with the hepatitis B virus who gave birth to infants without a HBV infection (infants who were not intrauterine infected) had higher levels of TLR-7 expression than infants with an intrauterine infection[1].

The factor underlying the insignificant relationship in this study was the maturity of the endosomal to express TLR-7. Endosomal immaturity is influenced by several genes and maternal immunity factors that may differ in our samples. TLR-7 is expressed in the intracellular compartment such as the endosome, by hence to identify ligands, and ligands require endosomal maturation recognized by hepatitis B. Thus the expression of TLR 3,7,8, and 9 can be used as parameters of infection or exposure to hepatitis B virus[13].

We found that based on the percentage of positive TLR-7 expression, a majority had a negative cord blood HBV-DNA. This occurs where positive HBV DNA indicates HBV exposure to the placenta (risk of transmission), not an intrauterine infection. Because it has crossed the placental barrier generally increases TLR-7 expression. TLR-7, in particular, has an intracellular signaling mechanism by recognizing nucleic acids from the virus when it infects cells. Viruses that penetrate cells activate IFN. IFN activation will result in the expression of TLR-7 on lysosomes which will signal inflammatory cytokines and chemokines, which will inhibit transcription of viral RNA. The inhibition of viral transcription resulted in a decline of viral load[9,14,15].

In this study, it was found that there was a significant correlation between HBV DNA titers >200,000 IU/ml and the expression of TLR-7 levels (Table 3). This finding is in where the expression of placental TLR-7 and TLR-8 was significantly increased in women with positive HBV DNA. Significant results in this study occurred as a result of the immune response to HBV by the placental trophoblast, which is the center for preventing intrauterine infection of HBV through upregulation of TLR7 as an immune response to HBV infection 1. HBV DNA >2x 105 has a high risk of intrauterine infection affecting the placental immune response through a positive expression of TLR-7 on the placenta. Isogawa et al. conducted an in vivo study in mice and found a significant effect of TLR-7 expression on HBV virus replication. TLR-3, TLR-4, TLR-5, TLR-7, and TLR-9 all modulate replication against hepatitis B virus[16].

A similar study revealed a significant relationship between TLR-9 and TLR-3 expression and the risk of intrauterine infection. Gao et al. described the influence of the role of genes in the risk of vertical transmission and their relationship with TLR-3 and TLR-9 expression. That large sample size was required to determine the mechanism of TLR expression and its relationship to intrauterine transmission[17].

We also found no significant relationship between maternal HBeAg levels and TLR-7 expression in the placenta, as shown in Table 3. This is likely due to genetic and immunity factors where the number of APC cells, such as dendritic cells is produced less or still immature. The Tfh cell and B-cell related gene factors affect the number of APC cells, which will later affect the expression of TLR-7 because it is known that TLR-7 is found in the intracellular antigen-presenting cell (APC), especially in the endosomal. In immature APCs, there is also an irregularity in the activation signal for TLR-7[18].

Another similar study was also conducted by Wu et al. In that study, and it also assessed the relationship between placental Toll-Like receptor-3 with HbeAg among HbeAg-positive mothers. In this study, a negative correlation was found between a positive-HBeAg status and TLR-3, where the expression of TLR-3 decreased in mothers with positive HBeAg. However, this study did not explain the mechanism underlying the decrease in placental TLR-3 expression[19]. Research on maternal HBeAg and its relation to TLR-7 expression is still lacking, therefore further research is needed in this regard.

In this study, there was no significant relationship between placental HBV-DNA levels and the expression of TLR-7 in the placenta (see table 3). Our findings contradicted other studies where it was found that there was an increase in placental TLR-7 expression levels in placental trophoblast cells exposed to hepatitis B virus in vitro[1].

The insignificant association between placental HBV DNA levels and TLR-7 activation occurred because TLRs belong to the pattern recognition receptor (PRR) family, responsible for pathogen-related molecular inheritance pattern recognition (PAMPs). PAMP is a protein, lipid, polysaccharide, DNA, or RNA present in the membrane or envelope of pathogenic microorganisms. TLR is also able to recognize damage-related molecular patterns (DAMPs)[20]. Based on the ligand domain that TLR can recognize, TLR-7 and TLR-8 can recognize ssRNA, and TLR-9 can recognize viral DNA ligands, while in our study the identified virus was hepatitis B virus, which is a dsDNA virus. Therefore, based on the mechanism of ligand recognition, it appears that TLR-7 is not expressed at the time of exposure to hepatitis B virus−a dsDNA virus that TLR-9 generally recognizes−in the placenta[13].

The limitation of this study is that we did not conduct an analysis related to maternal genetic factors, considering that genetic factors play a role in the immune response mechanism and its relation to TLR-7 expression. This study also did not take HBV DNA or HBsAg samples directly from infants to determine the risk of vertical transmission and did not follow-up on infants whose mothers had a high risk of HBV exposure. Further research is needed to explain

the association of HBV DNA levels in the mother, placenta, and cord blood with the expression of TLR-7 as assessed quantitatively. Proof of intrauterine infection by examining samples in infants such as HBsAg and HBV viral load is required in future studies. Other factors related to the risk of vertical transmissions such as genetic factors, history of anti-hepatitis B treatment, clinical symptoms, and liver function can affect the expression of TLR-7 and should be further studied and investigated.

CONCLUSION

We did not find a significant association between TLR-7 and HBV DNA expression in either the placenta or cord blood. However, we did find a significant association between the expression of TLR-7 and maternal HBV DNA.

REFERENCES

1. Tian T, Sun D, Wang P, Wang H, Bai X, Yang X, et al. Roles of Toll-like Receptor 7 and 8 in Prevention of Intrauterine Transmission of Hepatitis B Virus. Cell Physiol Biochem. 2015;37(2):445–53.
2. Abdi F, Novin MG, Afrakhteh M, Khorvash F. Hepatitis B and pregnancy: An update review article. World J Obstet Gynecol. 2015;4(1):1.
3. Sepehri Z, Kiani Z, Alavian SM, Arababadi MK, Kennedy D. The link between TLR7 signalling and hepatitis B virus infection. Life Sci. 2016 Aug;158:63–9.
4. Kementrian Kesehatan Republik Indonesia. Situasi dan Analisis Hepatitis. 2014.
5. Cheung KW, Seto MTY, Wong SF. Towards complete eradication of hepatitis B infection from perinatal transmission: review of the mechanisms of in utero infection and the use of antiviral treatment during pregnancy. Eur J Obstet Gynecol Reprod Biol. 2013 Jul;169(1):17–23.
6. Khumaedi AI, Gani RA, Hasan I. Pencegahan Transmisi Vertikal Hepatitis B: Fokus pada Penggunaan Antivirus Antenatal. J Penyakit Dalam Indones. 2017 Jan 27;3(4):225.
7. Geffert K, Maponga TG, Henerico S, Preiser W, Mongella S, Stich A, et al. Prevalence of chronic HBV infection in pregnant woman attending antenatal care in a tertiary hospital in Mwanza, Tanzania: a cross-sectional study. BMC Infect Dis. 2020 Dec 5;20(1):395.
8. Nie R, Jin L, Zhang H, Xu B, Chen W, Zhu G. Presence of hepatitis B virus in oocytes and embryos: a risk of hepatitis B virus transmission during in vitro fertilization. Fertil Steril. 2011 Apr;95(5):1667–71.
9. Liu J, Xu B, Chen T, Chen J, Feng J, Xu C, et al. Presence of hepatitis B virus markers in umbilical cord blood: Exposure to or infection with the virus? Dig Liver Dis. 2019 Jun;51(6):864–9.
10. Kolawole OM, Wahab AA, Adekanle DA, Sibanda T, Okoh AI. Seroprevalence of hepatitis B surface antigenemia and its effects on hematological parameters in pregnant women in Osogbo, Nigeria. Virol J. 2012 Dec 27;9(1):317.
11. Dortey BA, Anaba EA, Lassey AT, Damale NKR, Maya ET. Seroprevalence of Hepatitis B virus infection and associated factors among pregnant women at Korle-Bu Teaching Hospital, Ghana. Chemin I, editor. PLoS One. 2020 Apr 22;15(4):e0232208.
12. Luuse A, Dassah S, Lokpo S, Ameke L, Noagbe M, Adatara P, et al. Sero-prevalence of hepatitis B surface antigen amongst pregnant women attending an antenatal clinic, Volta region, Ghana. J Public Health Africa. 2017 Jan 19;7(2).
13. Ma Z, Cao Q, Xiong Y, Zhang E, Lu M. Interaction between Hepatitis B Virus and Toll-Like Receptors: Current Status and Potential Therapeutic Use for Chronic Hepatitis B. Vaccines. 2018 Jan 16;6(1):6.
14. Petes C, Odoardi N, Gee K. The Toll for trafficking: Toll-like receptor 7 delivery to the endosome. Frontiers in Immunology. 2017.
15. Mei C, Yang W, Wei X, Wu K, Huang D. The Unique Microbiome and Innate Immunity During Pregnancy. Front Immunol. 2019 Dec 17;10.
16. Isogawa M, Robek MD, Furuichi Y, Chisari F V. Toll-Like Receptor Signaling Inhibits Hepatitis B Virus Replication In Vivo. J Virol. 2005 Jun 1;79(11):7269–72.
17. GAO Y, GUO J, ZHANG F, GUO Z, ZHANG L-R, WANG T, et al. Evaluation of neonatal Toll-like receptors 3 (c.1377C/T) and 9 (G2848A) gene polymorphisms in HBV intrauterine transmission susceptibility. Epidemiol Infect. 2015 Jul 12;143(9):1868–75.
18. Vyas AK, Negi P, Patra S, Maras JS, Ramakrishna G, Sarin SK, et al. Maternal Immunity Influences Vertical Transmission of Hepatitis B to Newborns. Hepatol Commun. 2019 Jun 16;3(6):795–811.
19. Wu L, Zhang R, Feng Y, Yao T, Yi L, Wan H, et al. Impaired trophoblast Toll-Like Receptor 3 signaling pathway involves in hepatitis B vaccine non- or hypo-response of infants born to HBsAg-positive mothers. 2020;1–23.
20. Anwar MA, Shah M, Kim J, Choi S. Recent clinical trends in Toll-like receptor targeting therapeutics. Med Res Rev. 2019 May 18;39(3):1053–90.

Research Article

Estradiol on Day Seven is a Good Predictor for Oocyte Maturation Rate in In Vitro Fertilization Program

Kadar estradiol hari ketujuh sebagai prediktor tingkat kematangan oosit pada program Fertilisasi In Vitro

Betaria R. Prima, Andon Hestiantoro, Eka R. Gunardi, Yudianto B. Saroyo, Muharam Natadisastra

Department of Obstetrics and Gynecology
Faculty of Medicine Universitas Indonesia
Dr. Cipto Mangunkusumo General Hospital
Jakarta

Abstract

Objective: To determine which factors influence the rate of oocyte maturation in In Vitro Fertilization (IVF) program.

Methods: A retrospective cohort study was conducted using secondary data from IVF participants at the Yasmin Fertility Clinic, Dr. RSUP. Cipto Mangunkusumo, Jakarta, Indonesia during the period January 2019 to December 2020, as recorded in the InaRepromed archive. The variables analyzed were age, body mass index, and hormone levels on day 1, day 7, and day hCG, with oocyte maturation rate as the main outcome. Correlation test was performed between several variables and the level of oocyte maturation rate and followed by multivariate analysis to assess the factors that were closely related to oocyte maturation rate.

Result: Data from 52 subjects were collected for the study. Positive correlation was observed between oocyte maturation rate and estradiol on day 7 (r = 0.229), while negative correlation was observed between oocyte maturation rate and progesterone/estradiol ratio on day 7 (r = -0.289) and luteinizing hormone on day 1 (r = -0.265). Multivariate analysis revealed that higher estradiol on day-7 was associated with better oocyte maturation rate (p = 0.047).

Conclusion: Higher estradiol level on day 7 was associated with better oocyte maturation rate in IVF.

Keywords: Assisted reproductive technology (ART), estradiol, in vitro fertilization (IVF), progesterone.

Abstrak

Tujuan: *Untuk menentukan faktor-faktor yang mempengaruhi tingkat pematangan oosit dalam program Fertilisasi In Vitro (FIV).*

Metode: *Desain penelitian adalah kohort retrospektif, menggunakan data sekunder peserta bayi tabung Klinik Fertilitas Yasmin, RSUP Dr. Cipto Mangunkusumo, Jakarta, Indonesia selama periode Januari 2019 hingga Desember 2020, yang tercatat di dalam arsip InaRepromed. Variabel yang dianalisis adalah umur, indeks massa tubuh, dan kadar hormon pada hari ke-1, hari ke-7, dan hari ke-hCG, dengan tingkat maturasi oosit sebagai luaran utama. Dilakukan analisis korelasi antara beberapa variabel dengan tingkat maturasi oosit, dan dilanjutkan dengan analisis multivariat untuk menilai faktor-faktor yang berhubungan kuat dengan tingkat maturasi oosit.*

Hasil: *Data dari 52 subjek dikumpulkan untuk penelitian ini. Dijumpai korelasi positif antara tingkat maturasi oosit dan estradiol pada hari ke 7 (r = 0,229), sedangkan korelasi negatif diamati pula antara tingkat maturasi oosit dan rasio progesteron/estradiol pada hari ke 7 (r = -0,289) dan hormon luteinisasi pada hari 1 (r = -0,265). Analisis multivariat mengungkapkan bahwa estradiol yang lebih tinggi pada hari ke-7 dikaitkan dengan tingkat maturasi oosit yang lebih baik (p = 0,047).*

Kesimpulan: *Kadar estradiol yang lebih tinggi pada hari ke 7 dikaitkan dengan tingkat pematangan oosit yang lebih baik pada program FIV.*

Kata kunci: *Teknologi Reproduksi Berbantu (TRB), estradiol, Fertilisasi In Vitro (IVF), progesteron.*

Correspondence author. Andon Hestiantoro. Department of Obstetrics and Gynecology
Faculty of Medicine Universitas Indonesia Dr. Cipto Mangunkusumo General Hospital.Jakarta
Email:hestiantoro@gmail.com

Received: February, 2021 Accepted: March, 2022 Published: April, 2022

INTRODUCTION

Infertility is categorized as a disease by the World Health Organization, in the form of disability in partners who are regularly sexually active and do not use contraception to achieve clinical pregnancy after 12 months (<35 years) or 6 months (>35 years).[1,2] Epidemiologically, infertility is experienced by 15% of all couples of different sex globally.2 As a problem including couples, infertility may be caused by either female and male. Therefore, a thorough evaluation of both husband and wife is needed.[1,2.]

There are several methods of treating infertility, one of which is the assisted reproductive technology (ART) program as a treatment for infertility caused by both male factor and female factor.[2,3] ART might be considered as one of the options in some cases, such as uncorrected tubal occlusion, moderate endometriosis, sperm factors, or repeated failure of intrauterine insemination.[3] The philosophy of ART is to grow several oocytes simultaneously, which start at the early follicular phase so that some of the collected mature eggs can be fertilized with spermatozoa. This technology requires a controlled ovarian hyperstimulation (COH) approach.

The quality of oocytes in the ART program is one of the most important things in predicting the success of the ART program.[4] There are several oocytes produced in the ART program through a controlled ovarian hyperstimulation process. Some of these oocytes are retrieved together, fertilized, and cultured until they become embryos which will be returned eventually to the mother's endometrial cavity.[5] The maturation level of oocytes is one of the factors affecting quality of oocytes. The success of ART generally depends on three main factors, namely oocyte quality, sperm quality, and uterine quality.[4,5] These three factors will be influenced by various characteristics of the patient, such as genetics, age, body mass index, and other comorbidities.[6]

Ovarian reserve and the sensitivity of the follicular response to growth after COH are factors that strongly influence the oocyte maturation rate, and this condition can be reflected in the reproductive hormones levels of each participant in the ART program. This study aimed to determine which factors associated with oocyte maturation rate on ART participants.

METHODS

This is a retrospective cohort study, conducted using secondary data from IVF participants in Yasmin Fertility Clinic, Dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia during the period of January 2019 to December 2020. Data were collected from the Ina-Repromed archive.

This study used 5% error bound and 95% confidence interval limit, with power of the test considered to be 90%. This study was conducted at Yasmin Clinic, dr. Cipto Mangunkusumo National General Hospital, Jakarta, Indonesia on January 2019 to December 2020. The inclusion criteria for this research were all ART participants aged 30 to 45 years old and having undergone in vitro fertilization (IVF) program using frozen embryo transfer (FET) or intracytoplasmic sperm injection (ICSI), with antagonist protocol. Subjects with incomplete medical record data were excluded from the study.

Variables analyzed in this study were age, body mass index, day 1; anti-mullerian hormone (AMH), follicle stimulating hormone (FSH), luteinizing hormone (LH), day 7; estradiol, progesterone, progesterone-to-estradiol ratio, and day hCG; estradiol, progesterone, progesterone-to estradiol ratio, FSH, LH level.

All human studies had been approved by the Research Ethics Committee of Faculty of Medicine, Universitas of Indonesia. All patients who were included in this study had given the informed consent prior to the study.

Collected data were then analyzed using SPSS for Macintosh ver. 20. Characteristics of subjects and examination results were analyzed descriptively. Correlation between variables and oocyte maturation rate was calculated. Multivariable analysis was done in order to determine factors associated with oocyte maturation rate.

RESULTS

On the course of this study, a total of 52 subjects were included in this study. Baseline characteristics of subjects can be found on Table 1. Based on the analysis, it was found that the average age of subjects were 37 years old with normal body mass index, and having hormonal level within normal limit.

Table 1. Characteristics of Subjects

Characteristics	Characteristics
Age (years)	36.93 + 4.31
Body mass index (kg/m^2)	24.35 (16.1 – 37.7)
AMH day 1 (ng/mL)	3. 09 (0.02 – 18.9)
FSH day 1 (mIU/mL)	8.32 (1.90 – 17.4)
LH day 1 (mIU/mL)	4.55 (1.32 – 18.47)
Estradiol day 7 (pg/mL)	123.1 (9.98 – 40.0)
Estradiol day hCG (pg/mL)	1.763 (619 -5.187)
Progesterone day 7 (ng/mL)	0.58 (0.1 – 1.98)
Progesterone day hCG (ng/mL)	0.84 (0.3 – 5.5)
Progesterone-to-estrogen ratio day hCG	0.51 (0.18 – 2.71)
Mature oocyte number	5 (1 – 29)
Total oocyte number	7 (1 – 32)
Oocyte maturation rate	0.79 (0.1 – 1)

All of the variables in this study were analyzed for correlation with oocyte maturation rate. Based on the analysis, it was found that positive correlation was observed between oocyte maturation rate and estradiol on day 7 (r = 0.229), while negative correlation was observed between oocyte maturation rate and progesterone/ estradiol ratio on day 7 (r = -0.289) and luteinizing hormone on day 1 (r = -0.265). The result of this analysis can be found on Table 2.

Table 2. Correlation between variables and oocyte maturation rate

Variables	Oocyte Maturation Rate	
	r	*P-value*
Age (years)	- 0.103	0.469
Body mass index (kg/m^2)	- 0.187	0.185
AMH day 1 (ng/mL)	- 0.165	0.244
Estradiol day 7 (pg/mL)	0.229	0.102
Progesterone day 7 (ng/mL)	- 0.111	0.434
Progesterone-to-estrogen ratio day 7	- 0.289	0.038
FSH day 1 (mIU/mL)	0.173	0.221
LH day 1 (mIU/mL)	- 0.265	0,057
Estradiol day hCG	- 0.112	0.430
Progesterone day hCG	-0.189	0.179
Progesterone-to-estrogen ratio day hCG	-0.056	0.694
FSH day hCG (mIU/mL)	-0.138	0.331
LH day hCG (mIU/mL)	-0.052	0.715

Additionally, multivariable analysis revealed that higher estradiol on day-7 was associated with better oocyte maturation rate (p = 0.047). The result of this analysis can be found on Table 3 and 4.

Table 3. Multivariable Analysis Result: Step 2

	Unstandardized Coefficients		Standardized Coefficients		
Variables	**B**	**Standard Error**	**Beta**	**T**	***P-value***
Estradiol day 7	0.001	0.000	-0.306	2.267	0.028
Progesterone day hCG	-0.049	0.030	-0.216	-1.598	0.116
Constant	0.755	0.054	-	14.029	0.000

Table 4. Multivariable Analysis Result: Step 2

	Unstandardized Coefficients		Standardized Coefficients		
Variables	**B**	**Standard Error**	**Beta**	**T**	***P-value***
Estradiol day 7	0.001	0.000	0.270	2.041	0.047
Constant	0.710	0.046		15.266	0.000

DISCUSSION

In this study, it was found that the variable that can be used to predict the oocyte maturation index of subjects with controlled ovarian hyperstimulation (COH) is estradiol on day 7. Although one of the previous multivariate analysis steps had shown the effect of progesterone on the hCG day on the oocyte maturation rate, the last step of the multivariate analysis only showed that estradiol on day 7 was the dominant factor to predict the oocyte maturation index in COH.

Estradiol level is one of the parameters that can determine the aging of follicular cells, because granulosa cells are the main source of follicular estrogen (E2 - estradiol). Increased levels of estrogen are associated with follicular cells that are getting more mature or experiencing atresia. Therefore, estrogen might be used as one of the parameters of the proportion of maturation.[7]

Research conducted on sheep oocytes found that estradiol levels were directly related to the stimulation of oocyte maturation.[8] Other studies on in vitro fertilization of bull and ewe oocytes found that oocytes having richer estradiol environment will have higher nucleus maturation rate than oocytes with low environmental estradiol levels.[9] However, excessive concentration of estradiol

would actually inhibit oocyte maturation.[10]

The results showed that higher serum estradiol level in women undergoing assisted reproductive technology programs would not inhibit the maturation level of oocytes, but directly increase the number of mature oocytes obtained, thereby increasing the maturation level of oocytes.[13] The pathophysiology underlying more mature oocytes in ART participants who have higher estradiol levels is based on the growth and development of dominant follicles. The growth of dominant follicles will cause the secretion of estradiol and inhibin A. This secretion indicates better cytoplasmic maturation and more advanced folliculogenesis.[9]

In this study, it was also known that progesterone level did not affect oocyte maturation rate. Previous studies has shown that progesterone level in ART program participants was one of the variables that have been widely studied to affect the number of oocytes obtained, the maturation level of the oocytes, the fertilization rate, and the success of pregnancy. This phenomenon is associated with the incidence of premature luteinization.[11,12] Premature luteinization is a term used to refer to a premature LH surge (LH surge), with serum progesterone levels being used as an indication of premature luteinization in various studies.[11,12]

CONCLUSIONS

It is concluded in this study that higher estradiol level on day 7 was associated with better oocyte maturation rate on ART participants with COH.

DECLARATIONS

The data used in this study can be requested from corresponding author upon reasonable request.

CONFLICT of INTEREST

Authors declare that there is no conflict of interest in this study.

FUNDING STATEMENT

All of the funding for this research was financed by authors.

ACKNOWLEDGEMENTS

Authors would also like to express sincere gratitude to all participating patients and medical staffs on the Department of Obstetrics and Gynecology, Faculty of Medicine Universitas Indonesia Dr. Cipto Mangunkusumo National General Hospital who willingly support this study.

REFERENCES

1. American Society of Reproductive Medicine. Definitions of infertility and recurrent pregnancy loss: a committee opinion. Fertil Steril. 2020;1(1):1-2.
2. American College of Obstetricians and Gynecologists. ESHRE guideline: ovarian stimulation for IVF/ICSI. Obstet Gynecol. 2019;133(6):377-384.
3. Kemal A, Soebadi D, Afdal, , et al. Konsensus Penanganan Infertilitas. Jakarta: Himpunan Endokrinologi Reproduksi dan Fertilitas Indonesia (HIFERI): 2013.
4. Vaegter KK, Lakic TG, Olovsson M, et al. Which factors are most predictive for live birth after in vitro fertilization and intracytoplasmic sperm injection (IVF/ICSI) treatments? Analysis of 100 prospectively recorded variables in 8,400 IVF/ICSI single-embryo transfers. Fertil Steril. 2016;107(3):641-50.
5. Okeigwe I, Marsh EE. Disparate IVF Outcomes and the Role of Uterine and Oocyte Factors. Current Women Health Rev. 2018;14:251-60.
6. Evans MB, Healy MW, DeCherney AH, Hill MJ. Adverse effect of prematurely elevated progesterone in in vitro fertilization cycles: a literature review. Biol Reprod. 2018; 99(1):45-51.
7. Bosch E, Broer S, Griesinger G,. et al. ESHRE guideline: ovarian stimulation for IVF/ICSI. Hum Reprod Open. 2020:1-13.
8. Rehman R, Zafar A, Ali AA, Baig M, Alam F. Impact of serum and follicular fluid kisspeptin and estradiol on oocyte maturity and endometrial thickness among unexplained infertile females during ICSI. PloS One 2020;15(10):e0239142.
9. Maksudra H, Akon N, Islam MN,. et al. Effects of estradiol on in vitro maturation of buffalo and goat oocytes. Reprod Med Biol. 2020;00:1-9.
10. Imudia AN, Goldman RH, Awonuga AO, Wright DL, Styer AK, Toth TL. The impact of supraphysiologic serum estradiol levels on peri-implantation embryo development and early pregnancy outcome following in vitro fertilization cycles. J Assist Reprod Genet 2014;31:65-71.
11. Arroyo A, Kim B, Yeh J. Luteinizing Hormone Action in Human Oocyte Maturation and Quality: Signaling Pathways, Regulation, and Clinical Impact. Rep Sci. 2020; 27: 1223-52.
12. Evans MB, Healy MW, DeChemey AH, Hill MJ. Adverse effect of prematurely elevated progesterone in in vitro fertilization cycles: a literature review. Bio Reprod 2018;99(1):45-51.

Research Article

The Efficacy of Chemotherapy in Advanced-Stage Cervical Cancer on Vitamin A Serum

Efektivitas Kemoterapi pada Karsinoma Serviks Stadium Lanjut terhadap Serum Vitamin A

Raissa Nurwany, Rizal Sanif, Amirah Noviliani, Theodorus

Department of Obstetrics and Gynecology
Faculty of Medicine Universitas Sriwijaya
Dr. Mohammad Husein General Hospital
Palembang

Abstract

Objective: To determine the efficacy of neoadjuvant chemotherapy on changes of vitamin A serum in advanced cervical carcinoma patient.

Methods: A randomized clinical trial was performed in the Oncology Gynecology Polyclinic and Ward of Dr. Mohammad Hoesin General Hospital, Palembang from September 2019 to September 2020. There were 30 subjects of advanced cervical carcinoma. Vitamin A levels and tumor volume subjects were assessed before and 1 month after 3 cycles of NAC and analyzed using the Paired T Test and Wilcoxon test. The correlation between vitamin A levels and tumor volume was analyzed by using Spearman's Rho test. Data analysis was using SPSS version 22.0.

Results: This study showed statistically not significant increase on vitamin A levels after 3 cycles of NAC chemotherapy (p=0.515). However, there was a significantly decrease in tumor volume after 3 cycles of NAC (p=0.000). In addition, there was a moderate negative correlation between tumor size and vitamin A (r=-0.475; p=0.008).

Conclusion: It can be concluded that there was significantly decrease in tumor volume after 3 series NAC chemotherapy and the smaller tumor size, the higher level of vitamin A serum.

Keywords: cervical cancer, neoadjuvant chemotherapy, randomized clinical trial, vitamin A.

Abstrak

Tujuan: *Untuk mengetahui efektivitas kemoterapi neoadjuvan terhadap perubahan kadar serum vitamin A pada karsinoma servik stadium lanjut.*

Metode: *Penelitian uji klinik tanpa pembanding telah dilakukan di Poliklinik dan Bangsal Onkologi Ginekologi RSUP Dr. Muhammad Hoesin Palembang sejak September 2019 hingga September 2020. Didapatkan 30 sampel karsinoma serviks stadium lanjut. Kadar vitamin A dan volume tumor dinilai sebelum dan 1 bulan setelah 3 siklus NAC dan dianalsis menggunakan uji Paired T Test dan Wilcoxon. Korelasi antara Kadar vitamin A dan volume tumor sampel dianalisis menggunakan uji Spearman Rho's. Analisa data menggunakan SPSS versi 22.0.*

Hasil: *Pada penelitian ini terdapat peningkatan tidak signifikan kadar vitamin A setelah kemoterapi (p = 0,515). Terdapat penurunan secara signifikan volume tumor sebelum dan sesudah kemoterapi NAC 3 seri (p = 0,000). Selain itu, didapatkan korelasi negatif sedang yang bermakna antara ukuran tumor dan kadar vitamin A (r = -0,475 ; p = 0,008).*

Kesimpulan: *Disimpulkan bahwa terdapat penurunan volume tumor setelah kemoterapi NAC 3 series dan semakin kecil ukuran tumor maka semakin tinggi kadar vitamin A dalam serum.*

Kata kunci: *kanker serviks, kemoterapi neoadjuvan, uji klinik tanpa pembanding, vitamin A.*

Correspondence author. Raissa Nurwany. Department of Obstetrics and Gynecology
Faculty of Medicine Universitas Sriwijaya. Dr. Muhammad Hoesin General Hospital. Palembang.
Email. raissa.nurwany@gmail.com

Received: October, 2020 Accepted: March, 2022 Published: April, 2022

INTRODUCTION

Cervical cancer ranked the fourth most common cancer in women worldwide after breast, colorectal, and lung cancer, where there were around 604,127 cases with 341,831 cervical cancer deaths in 2020. Deaths from cervical cancer are projected to continue to increase and estimated to reach 481 thousand deaths in 2040 if not treated properly. The incidence of cervical cancer in Indonesia is estimated to have 36,600 new cases in 2020 and the death rate is estimated to reach 75% in the first year. These deaths are mainly associated with the majority of cervical cancer stages (70% of cases) are invasive, advanced, and even terminal at the time of diagnosis.[1-3]

The optimal treatment for the early stages (stages IA1, IA2 and IB1) consists of radical surgery or chemoradiation. In advanced stage cervical cancer (IIB-IVB), where surgery is not possible, primary therapy is generally performed with chemoradiation or in combination with chemotherapy and radiation. Because most cervical cancers are diagnosed at an advanced stage, it creates various obstacles in the availability of facilities and infrastructure. The administration of neoadjuvant chemotherapy (NAC) alone in late advanced cervical carcinoma (LACC) is still a matter of debate and has not been included in therapeutic recommendations by various international oncology organizations. Cancer treatment delay is a worldwide problem. The limitations of radiation facilities in Indonesia cause chemotherapy as the only therapeutic modality, which can be offered. The effectiveness of giving chemotherapy itself is still questionable, whereas at Mohammad Hoesin General Hospital Palembang, the only available radiotherapy facilities are external radiation with Cobal 60 which is problematic so chemotherapy is the main choice.[4-7]

Cisplatin is often used as a single chemotherapy regimen. Carboplatin has effectiveness in cervical cancer with a response rate of up to 20%. While paclitaxel is known to have moderate effectiveness in cervical cancer with a response rate of up to 17%. The success of the paclitaxel-carboplatin combination is higher in squamous cell carcinoma because each of these agents has high cytotoxic activity as a single agent. Neoadjuvant chemotherapy in patients with late advanced cervical cancer has a beneficial effect by increasing the willingness to undergo surgery, reducing the risk of surgery and at a young age, it helps influence the patient's psychology.[7-9]

Retinoic acid (RA), an active metabolite of vitamin A, is an important signaling molecule involved in the differentiation, proliferation, and apoptosis processes of almost all cell types. Regulation by retinol or retinoic acid includes controlling cell proliferation through activities that stimulate resting G1 phase and resting S phase. This mechanism occurs because retinol or retinoic acid has a role in strengthening p53 expression, activating p21, and activating cyclin suppression. A study revealed that improving nutritional status plays a role in the prevention and improvement of cervical dysplasia. Improvement of mild and moderate cervical dysplasia has been seen in patients who received vitamin A supplements within a few months. Therefore, a number of clinical studies have shown that topical application of vitamin A to the cervix results in the improvement of cervical dysplasia in 50% of cases.[9-14]

The main objective of administering chemotherapy or chemoradiation is abnormal cell death which will also affect normal cells, especially proliferating cells such as intestinal cells and hepatocyte cells. They are very important in the absorption and metabolism of vitamin A, so that this will cause serum vitamin A to decrease. Because of the role of vitamin A in the cell cycle, which is very important, it can be predicted that cell death will be disrupted, so that carcinoma treatment will be disrupted. In other words, the response to therapy will be less good.[13,14]

Based on the above reasons, the researchers conducted a study to see how the efficacy of neoadjuvant chemotherapy on changes in vitamin A level in advanced cervical carcinoma at dr. Mohammad Hoesin General Hospital as a successful predictor of chemotherapy.

METHODS

This study was a clinical trial without comparison. The research was conducted at the Oncology Outpatient Clinic and Ward, Department of Obstetrics and Gynecology, Dr. Mohammad Hoesin Palembang. Data collection and observations were carried out from September 2019 to September 2020.

Subjecst were all cervical carcinoma patients who were treated at the Oncology Outpatient Clinic and Ward, Department of Obstetrics and Gynecology, Dr. Mohammad Hoesin Palembang

from September 2019 until September 2020. Patients with advanced-stage cervical carcinoma (stage IIB to IVA according to FIGO classification in 2018), treated with 3 series of neoadjuvant chemotherapy, and willing to participate in the study by signing the consent form were included in this study.

Patients with early-stage cervical carcinoma, advanced-stage with chronic renal failure, an advanced-stage with severe systemic disease, and advanced-stage cervical carcinoma who were on radiation were the exclusion criterias in this study. In addition, the drop out criterias in this study were advanced cervical carcinoma patients who did not complete treatment and advanced-stage cervical carcinoma who died before completing treatment.

Subjects were collected by consecutive sampling. In this study, there were 38 subjects who met the inclusion criterias, 4 people dropped out due to death, 4 people dropped out due to not completing chemotherapy. A total of 30 patients with advanced-stage cervical carcinoma who were treated with 3 series of neoadjuvant chemotherapy were taken as research subjects.

All patients who will be included in this study were asked several questions (name, age, address, parity, last menstrual period, and previous medical history), physical examination (general condition, blood pressure, pulse rate, respiration rate, temperature, body weight, and height). Then, the patient was asked to have fasting (they were not allowed to eat and drink, except drinking water) for 12-14 hours before taking 3 ml of the cubital venous blood sample. The venous blood sample was then immediately taken to the Prodia laboratory and tested for serum vitamin A using the HPLC (High-Performance Liquid Chromatography) method.

The patient is then subjected to an ultrasound examination before chemotherapy treatment to determine the size of the tumor by a consultant oncologist and gynecologist or fetomaternal consultant. The size of the tumor mass was calculated in 3 sections, namely superior-inferior, lateral-lateral, and anterior-posterior by transabdominal ultrasound. Then, chemotherapy was given every cycle until the 3rd cycle. After 1 month post 3 cycles of NAC, another ultrasound examination was performed to assess tumor size after 3 cycles of chemotherapy by a consultant oncologist and gynecologist or fetomaternal consultant in the same way. The patient was then checked for vitamin A levels by the Prodia Laboratory by doing the same examination and an evaluation of the chemotherapy response based on the size of the tumor mass.

After the data were collected, we did a statistical analysis using SPSS, where continuous variables used student t-test using p 0.05 to assess significance. The categorical variables used the Chi-square test to assess differences between treatment groups. Presentation of data used tables to facilitate data reading and analysis of results.

RESULTS

A total of 30 subjects were treated with 3 series of neoadjuvant chemotherapy were sampled. Vitamin A levels and tumor mass size were assessed before and 1 month after 3 NAC cycles.

In this study, the mean age of the patient with advanced cervical carcinoma was 54.23 ± 13.09 years with an age ranged of 35 to 81 years. The majority of the subjects were married (93.3%) and the highest parity was multiparous (60%), and as many as 6 subjects had history of abortion. The largest sample stage in this study was stage IIIB (70%) and the majority of patients had squamous cell carcinoma based on histopathology examination (83.3%) and received Paclitaxel-Carboplatin chemotherapy (93.3%) (Table 1).

Vitamin A levels and sample mass size were assessed before and 1 month after 3 NAC cycles. In this study, the levels of vitamin A before chemotherapy were found to be 450.03 ± 167.18, after chemotherapy the levels of vitamin A increased to 478.37 ± 197.25. With statistical analysis, it was found that there was no change in vitamin A levels before, and after 3 series of NAC chemotherapy, vitamin A levels increased after chemotherapy but it was not statistically significant (p = 0.515). A total of 15 subjects had increased vitamin A and 15 other subjects had decreased vitamin A (Table 2).

Table 1. Demographic Characteristics of the Subject

Characteristics	Total	%
Age, mean ± SD	**54.23 ±13.098**	
Occupation		
Housewife	29	96.7
Entrepreneur	1	3.3
Address		
Palembang	11	36.7
Outside Palembang	19	63.3
Marital Status		
Unmarried	2	6.7
Married 1 time	24	80.0
Married 2 times	4	13.3
Parity		
Nulliparity	4	13.3
Primiparity	2	6.7
Multiparity	18	60.0
Grand multiparity	6	20.0
Abortion		
Negative	24	80
Positive	6	20
Stage		
III A	1	3.3
II B	8	26.7
III B	21	70.0
Concomitant Diseases		
Positive	7	23.3
Negative	23	76.7
Chemotherapy regimen		
Paclitaxel-Carboplatin	28	93.3
Paclitaxel-Cisplatin	1	3.3
Cisplatin-Ifosfamid Mesna	1	3.3
Histopathology		
Squamous Cell Carcinoma	25	83.3
Non Squamous Cell Carcinoma	5	16.7

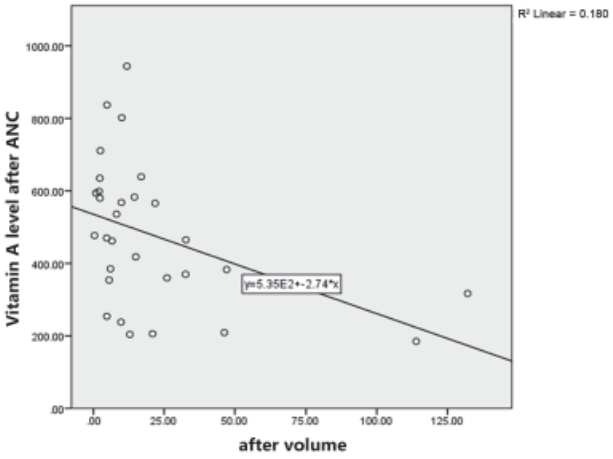

Figure 1. Correlation Graph of Vitamin A Levels And Tumor Volume

In this study, from 29 subjects who had decreased tumor volume, 14 subjects (48.3%) experienced a decrease in vitamin A levels and 15 subjects (51.7%) did not experience a decrease in vitamin A levels. Meanwhile, there was 1 sample who experienced an increase in tumor volume and also decreased levels of vitamin A. With statistical analysis, it was found that a significant negative correlation between tumor size and vitamin A (r = -0.475; p = 0.008), which meant that the smaller the tumor size was, the higher the level of vitamin A was in the serum (Table 3 and Figure 1).

Table 2. Effectiveness of the 3rd Neoadjuvant Chemotherapy

Characteristics	Period		*P-value*
	before NAC	**after NAC**	
Vitamin A Level			
Mean ± SD	450.03 ±167.18	478,37 ± 197,25	0.515*
Median (Min-Max)	444.5 (158 - 780)	467,5 (185 – 944)	
Tumor Volume			
Mean ± SD	94.07 ± 114.19	20.84 ± 30.57	0.000**
Median (Min-Max)	57.43 (12.31 – 581.57)	9.97 (0.39 – 132.14)	

In addition, in this study, the tumor volume before chemotherapy was 94.07 ± 114.19, after chemotherapy the tumor volume decreased to 20.84 ± 30.57. With statistical analysis, it was found that there was a change in tumor volume before and after 3 series of NAC, the tumor volume decreased significantly after chemotherapy (p = 0.000).

Table 3. The Relationship between Tumor Size and Vitamin A Levels

Characteristics	Tumor Size	Vitamin A Level	r	*P-value*
Mean ± SD	20.84 ± 30.57	478.37 ± 197.25		
Median (Min – Max)	9.97 (0.39 – 132.14	467.5 (185 – 944)	-0.475	0.008

Spearman Rho's, p = 0.05

DISCUSSION

The cervix is the lower third of the uterus, is cylindrical in shape, protrudes and connects to the vagina via the external orificium of uterus. Cervical cancer is a malignancy that originates from the cervix. Globally, the average age at diagnosis of cervical cancer was 53 years, ranging from 44 years to 68 years.[1,13] In this study, the average age of patients with advanced cervical cancer was approximately 54 years with a range of 35 to 81 years. The results of this study were not much different from the research which reported the average age of women with CIN III/ CIS/cervical cancer was 56.7 years.[14]

The age in this study was slightly greater than the that the mean age of cervical cancer patients was 48.30 ± 9.67 years with a range of 32 to 72 years.[15] The results of this study were similar from the mean age of cervical cancer patients in Canada where the mean age of patients was 45.9 years.[16] This similarity was probably due to the younger age of cervical cancer patients who were included in this study, namely between 15 to 49 years.

Labor contributed to the risk of cervical carcinogenesis in addition to the risks associated with persistent HPV infection. Delivery might increase the risk of direct precursor lesions to cervical cancer, especially in women with persistent high-risk HPV infection.[17] Women with parities greater or equal to three had 2.4 times higher odds of developing cervical cancer.[18] In addition, high parity was associated with the risk of adenocarcinoma or adenosquamous cervical carcinoma which had increased over the past two or three decades.[18,19] In this study the most parity was multiparous. In line with the results of this study, found that the majority of cervical cancer patients were multiparous except 2% nulliparous patients and only 15% had single parity.[19] Previous research in South Sumatera concluded that multiparity (parity of 3 times or more) was associated with 4.55 times greater risk of cervical cancer. Therefore, cervical cancer screening was recommended to focus on high-risk groups, including women with more than three parity.[20]

The optimal treatment for the early stages (stages IA1, IA2, and IB1) consisted of radical surgery or chemoradiation. In advanced-stage disease (IIB-IVB), where surgery was not possible, primary therapy was generally performed with chemoradiation or in combination with chemotherapy and radiation. In this study, 3 series of neoadjuvant chemotherapy were given, the majority of the subjects received Paclitaxel-Carboplatin chemotherapy. The success of the Paclitaxel-Carboplatin combination was higher in squamous cell carcinoma because each of these agents had high cytotoxic activity as a single agent.[21]

The most histopathological type in this study was squamous cell carcinoma (83.3%). These results were in line that the most histopathological types in cervical cancer patients, namely squamous cell carcinoma (75-90%).[22] The histology results of cervical cancer patients as much as 83% was squamous cell carcinoma, 17% of patients had adenocarcinoma and adenosquamous cell carcinoma.[23]

Vitamin A or retinol was a polyisoprenoid compound containing a cyclohexinyl ring.24 Examination of vitamin A status could be done by examining the relative dose response (RDR). With the RDR method could estimate retinol deposits in the liver and low deposits indicate a long enough deficiency.[25] Retinoic acid (RA) played a role in cancer regulation which can be either promotion or suppression. RA induced protocogene and tumor suppressor.[26-29]

The chemotherapy or chemoradiation was given because abnormal cell death will also affect normal cells, especially proliferating cells such as intestinal cells and hepatocyte cells which are very important in the absorption and metabolism of vitamin A. Thus, this will cause serum vitamin A to decrease. However, in this study, it was found that vitamin A levels after chemotherapy increased compared with before chemotherapy but it was not statistically significant. Thus, the chemotherapy given did not affect the level of vitamin A in the blood of cervical cancer patients. A significant increase in vitamin A levels in cervical cancer patients after 3 months of chemotherapy follow-up, but during and after chemotherapy the levels of vitamin A in cervical cancer patients in all stages were lower than before chemotherapy.[30]

In patients with advanced-stage cervical carcinoma who were given neoadjuvant chemotherapy (NAC) Cisplatin and Paclitaxel with additional vitamin A, after 3 cycles of chemotherapy, there was a change in tumor volume size in the neoadjuvant chemotherapy group plus vitamin A greater than the neoadjuvant chemotherapy group alone. ($p = 0.04$). This suggested that the addition of vitamin A also affects changes in the mass volume of cervical cancer mass.[31,32]

In this study, there was a decrease in tumor volume after 3 series of neoadjuvant chemotherapy. The change in tumor volume was 73.56 ± 24.69 with the largest change of 99.34% and the smallest was 11.53% and 1 patient experienced an increase in tumor volume by 4.59%. The results of this study were similar which showed that the tumor size decreased significantly in the neoadjuvant chemotherapy group.[33]

In this study, a significant negative correlation was found between tumor volume and vitamin A levels, from 29 subjects with decreased tumor volume by more than 50% experienced an increase in vitamin A levels. The smaller the tumor size after 3 series of neoadjuvant chemotherapy was, the higher the vitamin A levels were. However, the correlation between these two variables was only a moderate correlation possibly because only part of the sample experienced an increase in vitamin A levels. It was found that during the follow-up period after chemotherapy, serum vitamin A levels showed a significant increase. This increase in concentration might be caused by the death of tumor cells due to radiation or cessation of tumor growth by chemotherapy agents. Decreased levels of vitamins played a role in the etiology and development of cervical cancer.[30]

Retinol and vitamin A derivatives affected cell differentiation, proliferation, and apoptosis and played an important physiological roles in various biological processes. Retinoids had many important and diverse functions throughout the body including roles in the regulation of cell proliferation and differentiation, and the activation of tumor suppressor genes. Natural and synthetic retinoids had been used as potential chemotherapeutic or chemopreventive agents due to their differentiating, antiproliferative, proapoptotic, and antioxidant effects. Thus, it could be concluded that increased levels of vitamin A correlated with a decrease in tumor size which indicated the effectiveness of treatment.

There were several limitations in this study, namely the absence of a comparison group that received 3 series of neoadjuvant chemotherapy with additional vitamin A supplementation so that we could see the role of vitamin A in tumor development. In addition, checking vitamin A levels was only done before and after 3 series of chemotherapy, it would be better if vitamin A levels were checked during chemotherapy and was also followed up a few months after chemotherapy.

CONCLUSION

In this study, the average age of patients with advanced cervical cancer was approximately 54 years with 63.3% of the subjects coming from outside Palembang. The most histopathological type in this study was squamous cell carcinoma (83.3%). There was no change in vitamin A levels before and after 3 series of neoadjuvant chemotherapy, vitamin A levels increased after chemotherapy but it was not statistically significant. There was a change in tumor volume before and after 3 series of neoadjuvant chemotherapy, the tumor volume decreased significantly after chemotherapy. There was moderate negative correlation between tumor volume and vitamin A levels. The smaller the tumor size after 3 series of neoadjuvant chemotherapy, the higher the vitamin A levels were.

SUGGESTIONS

Further large-scale studies and longer study time are needed to investigate the effectiveness of 6-series of neoadjuvant chemotherapy by assessing the evaluation of clinical responses to changes in vitamin A levels in advanced stage cervical carcinoma. An analysis is needed by taking into account all the factors that affect serum vitamin A levels in order to obtain more accurate results. Additional vitamin A supplementation can be given in patients with cervical cancer to help increase the success rate and response to therapy.

REFERENCES

1. GLOBOCAN. The Global Cancer Observatory: All Cancer. 2020. https:// gco.iarc.fr/today/data/factsheets/cancers/39-all-cancers-fact-sheet.pdf.
2. GLOBOCAN. The Global Cancer Observatory: Cervix Cancer. 2020. https://gco.iarc.fr/today/data/factsheets/cancers/23-Cervix-uteri-fact-sheet.pdf
3. GLOBOCAN. The Global Cancer Observatory : Cancer Today. Estimated number of new cases in 2020, Indonesia, both sexes, all ages. 2020. https://gco.iarc.fr/today/online-analysis-map?v=2020&mode=population&mode_population.
4. Koh W, Abu-Rustum NR, Bean S, et al. Cervical Cancer, Version 3.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2019;17(1):64-84. doi:10.6004/jnccn.2019.0001

5. Hanna T P, King W D, Thibodeau S, Jalink M, Paulin G A, Harvey-Jones E et al. Mortality due to cancer treatment delay: systematic review and meta-analysis. BMJ. 2020;371:m4087 doi:10.1136/bmj.m4087
6. Jhawar S, Hathout L, Elshaikh MA, Beriwal S, Small W, Mahmoud O. Adjuvant chemoradiation therapy for cervical cancer and effect of timing and duration on treatment outcome. Int J Radiat Oncol Biol Phys.2017;98:1132-41. doi:10.1016/j.ijrobp.2017.03.045
7. Chen C-P, Kung P-T, Wang Y-H, Tsai W-C. Effect of time interval from diagnosis to treatment for cervical cancer on survival: a nationwide cohort study. PLoS One. 2019;14:e0221946. doi:10.1371/journal.pone.0221946
8. Tao W, Yang J, Jiang Y, Chen W, Wang Y. Paclitaxel, Carboplatin, and Bevacizumab in Advanced Cervical Cancer: A Treatment Response and Safety Analysis. Dose-Response. 2020. doi:10.1177/1559325820941351
9. Salihi R, Leunen K, Moerman P, et al. Neoadjuvant Weekly Paclitaxel-Carboplatin Is Effective in Stage I–II Cervical Cancer. Int J Gynecol Cancer. 2017;27:1256-60.
10. Chaninya W, Nasamon W, Jira C, Yong P. Retinoic acid receptor beta promoter methylation and risk of cervical cancer. World J Virol. 2018; 7(1): 1–9.
11. Everts, H.B.; Akuailou, E.-N. Retinoids in Cutaneous Squamous Cell Carcinoma. Nutrients. 202; 13:153. https://doi.org/10.3390/ nu13010153 .
12. Hunsu,V.O,Facey,COB, Fields, JZ, Boman, BM. Retinoids as Chemo-Preventive and Molecular-Targeted Anti-Cancer Therapies. Int. J. Mol. Sci. 2021;22:7731.https:// doi.org/10.3390/ ijms22147731
13. Arbyn, M., Weiderpass, E., Bruni, L., de Sanjosé, S., Saraiya, M., Ferlay, J., & Bray, F. Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. *The Lancet Global Health*.2020; 8(2), e191–e203.
14. El-Moselhy, E., Salim, S., & Hagrass, S. Prevalence and Risk Factors of Cervical Intraepithelial Neoplasia and Cervical Cancer among Ever Married Adult Females in Egypt : A Survey Study. *J Comprehensive Cancer Research*.2017; 1(1): 1–15.
15. Sanif, R., & Nurwany, R. Prognostic significance of CD4/ CD8 ratio in patients with advanced cervical cancer. *J Physics Conference Series*. 2019;1246(1): 0–8.
16. Cusimano, M. C., Baxter, N. N., Gien, L. T., Moineddin, R., Liu, N., Dossa, F., et al. Impact of surgical approach on oncologic outcomes in women undergoing radical hysterectomy for cervical cancer. AJOG. 2019;221(6):619. e1-619.e24. https://doi.org/https://doi.org/10.1016/j. ajog.2019.07.009
17. Baskaran, K., Kumar, P. K., Santha, K., & Sivakamasundari, I. 2019. Cofactors and their association with cancer of the uterine cervix in women infected with high-risk human papillomavirus in south India. *Asian Pacific J Cancer Prev. APJCP*. 2019; 20(11): 3415.
18. Tekalegn, Y., Sahiledengle, B., Woldeyohannes, D., Atlaw, D., Desta, F., Bekele, K., ... & Gezahegn, H. High parity is associated with increased risk of cervical cancer: Systematic review and meta-analysis of case-control studies. 2021. https://assets.researchsquare. com/files/rs-397999/v1/93bf5bfb-33ce-47e3-8f2f-2db0c8158ede.pdf?c=1631880610.
19. Rajeswari, R. An Evaluation of Risk Factors for HPV (Human Papilloma Virus) and its Association with Development of Cervical Carcinoma. Sch Int J Obstet Gynecol. 2021; 4(4): 90-4. doi: 10.36348/sijog.2021. v04i04.002
20. Agustiansyah, P., Sanif, R., & Nurmaini, S. 2021. Epidemiology and Risk Factors for Cervical Cancer. *Bioscientia Medicina. J Biomed Translational Research*. 2021; 5(7): 624-31.
21. Hacker NF. Principles of Cancer Therapy. Essentials of Obstetrics and Gynecology.6th ed. Philadelphia ; Saunders W.B. Company. 2018.
22. Teixeira, J. C., Santos, D. Z., Campos, C. S., Vale, D. B., Bragança, J. F., & Zeferino, L. C. 2021. Cervical cancer in women under 25 years of age and outside the screening age: Diagnosis profile and longçterm outcomes. *Int J Gynecol Obstet*. 2021; 154(1): 150-6.
23. Voinea, S., Herghelegiu, C. G., Sandru, A., Ioan, R. G., Bohilțea, R. E., Bacalbașa, et al. 2021. Impact of histological subtype on the response to chemoradiation in locally advanced cervical cancer and the possible role of surgery. *Experimental Therapeutic Med. 2021; 21*(1): 1-1.
24. Rosmiati H, Wardhini BP. Vitamin A. Farmakologi dan terapi. Edisi 3. FK. Universitas Indonesia.1987:657-60.
25. Sheftel, J., & Tanumihardjo, S. A. 2021. Systematic review and meta-analysis of the relative dose-response tests to assess vitamin A status. *Advances Nutr*. 2021; 12(3): 904-41.
26. Ozgun, G., Senturk, S., & Erkek-Ozhan, S. 2021. Retinoic acid signaling and bladder cancer: Epigenetic deregulation, therapy and beyond. *Int J Can*. 2021; 148(10): 2364-74.
27. Wang, C., Zhao, D., Wang, K., Gao, L., He, Y., Wu, H., et al. All-Trans Retinoic Acid Rescues the Tumor Suppressive Role of RAR-β by Inhibiting LncHOXA10 Expression in Gastric Tumorigenesis. *Nutr Can*. 2021; 73(10): 2065-77.
28. Chinapayan, S. M., & Prabhakaran, P. 2019. Anticancer effects of retinoic acid in cervical cancer cells. *Jur Teknol*. 2019; 81(2).
29. Dou, Y., Huang, D., Zeng, X., Zhou, Y., Jiang, X., Yue, C., et al. All-trans retinoic acid enhances the effect of Fra-1 to inhibit cell proliferation and metabolism in cervical cancer. *Biotechnol Letters*. 2020; 42(6): 1051-60.
30. Shrivastava, A., Pradhan, S., Mishra, S. P., Asthana, A. K., Choudhary, S., Zahra, K., et al. Serum vitamin A, E and C status in cervical cancer patients undergoing Concurrent Chemo-Radiotherapy, an institutional study. *J Nutr Intermed Metabol*. 2019; 18: 100107.
31. Sanusi, R. S. 2019. Outcome of combined neoadjuvant chemotherapy and vitamin a in advanced cervical carcinoma: a randomized double-blind clinical trial. APJCP. 2019; 20(7):2213.
32. Ono, A., Koshiyama, M., Nakagawa, M., Watanabe, Y., Ikuta, E., Seki, K., et al. The preventive effect of dietary antioxidants on cervical cancer development. *Medicina*. 2020; 56(11): 604.
33. Huang, Y., Liu, L., Cai, J., Yang, L., Sun, S., Zhao, J., & Wang, Z. The efficacy and response predictors of platinum-based neoadjuvant chemotherapy in locally advanced cervical cancer. *Can Management Research*. 2020;12: 10469.

Research Article

High Random Blood Glucose Level before Surgery as a Risk Factor for Recurrent Event in Epithelial Ovarian Carcinoma

Kadar Gula Darah Sewaktu yang Tinggi sebelum Operasi sebagai Faktor Risiko Kejadian Residif pada Pasien Karsinoma Ovarium Tipe Epitelia

Anggiyasti V. Hapsari, Teuku M. Iskandar

Department of Obstetrics and Gynecology
Faculty of Medicine Universitas Diponegoro
Dr. Kariadi General Hospital
Semarang

Abstract

Objective: To investigate the high random blood glucose level as a risk factor for recurrent disease in EOC patient at Kariadi General Hospital.

Methods: Sixty six patients diagnosed as EOC in Kariadi General Hospital were divided into 2 groups: 30 patients with recurrent disease and 30 patients without recurrent disease after completing chemotherapy cycles. We analysed correlation between age of diagnosis, tumour mass location, Ca-125 level, histological subtype and random blood glucose level before surgery with recurrent disease.

Results: There is no significantly difference in age of diagnosis, tumour mass location and histological subtypes between two groups. However, recurrent EOC patients have higher Ca-125 level significantly than non-recurrent patients (327.8±250.5 vs 183.5±212.1 respectively; p = 0,01). Mean of random blood glucose level of recurrent patients is also higher than non-recurrent patients significantly (150.5 ±79 vs 110.8 ± 31.1 respectively; p = 0.006). Patient with random blood glucose level > 110 mg/dl have 3 times more likely to develop recurrence in EOC patient significantly with 95% CI.

Conclusion: The mean of random blood glucose level in recurrent EOC patients is significantly higher than non-recurrent EOC patients. Patient with random blood glucose level > 110 mg/dl have 3 times more likely to develop recurrence in EOC patient.

Keywords: cepithelial ovarian cancer, random blood glucose level, recurrent.

Abstrak

Tujuan: *Untuk membuktikan kadar glukosa darah sewaktu yang tinggi sebagai faktor risiko kejadian residif pada pasien karsinoma ovarium epitelial di RSUP dr. Kariadi.*

Metode: *Enam puluh pasien yang telah didiagnosis sebagai karsinoma ovarium epitelial di RSUP dr. Kariadi dibagi menjadi 2 kelompok: 30 pasien pada kelompok residif dan 30 pasien pada kelompok non-residif berdasarkan evaluasi setelah menyelesaikan siklus kemoterapi. Data yang dianalisis meliputi usia saat terdiagnosis, lokasi tumor, kadar Ca-125, subtipe histologi, kadar gula darah sewaktu (GDS) sebelum operasi dan hubungannya dengan kejadian residif.*

Hasil: *PTidak terdapat perbedaan yang bermakna dalam usia saat diagnosis, lokasi tumor dan subtipe histologis diantara kedua kelompok. Namun, kelompok pasien residif memiliki kadar Ca-125 yang lebih tinggi secara bermakna dibandingkan kelompok pasien non-residif (327,8 ± 250,5 vs 183,5 ± 212,1; p = 0,01). Rerata kadar GDS pada kelompok pasien residif juga lebih tinggi secara bermakna daripada kelompok non-residif (150,5 ± 79 vs 110,8 ± 31,1; p = 0,006). Pasien dengan kadar GDS > 110 mg/dl memiliki risiko 3 kali lipat untuk menjadi residif secara bermakna dengan tingkat kepercayaan 95%.*

Kesimpulan: *Rerata kadar GDS pada kelompok pasien residif lebih tinggi secara bermakna dibanding kelompok pasien non-residif. Pasien dengan kadar GDS > 110 mg/dl memiliki risiko 3 kali lipat untuk menjadi residif.*

Kata kunci: *kadar gula darah sewaktu, karsinoma ovarium epitelial, residif.*

Correspondence author. Anggiyasti V. Hapsari, Teuku M. Iskandar,Department of Obstetrics and Gynecology
Faculty of Medicine Universitas Diponegoro. Dr. Kariadi General Hospital. Semarang.
Email: anggiyastivh@gmail.com

Received: May, 2021 Accepted: March, 2022 Published: April, 2022

INTRODUCTION

Epithelial ovarian cancer is the fifth most common cause of death in women in America, and is the leading cause of death in gynecological malignancies.[1,2] In Indonesia, ovarian cancer ranks fourth of all malignancies. Epithelial ovarian cancer accounts for more than 90% of all malignancies in the ovary. About 70% of cases of ovarian cancer were diagnosed at an advanced stage, the 5-year survival rate is below 30%.[3-5] Recent clinical studies show that plasma glucose levels in cancer patients can be important prognostic indicators related to reduced survival life and recurrence in patients. In addition, hyperglycemia is thought to have an important role in triggering residual events in epithelial ovarian cancer through glucose transporter protein 1 (GLUT 1).[6,7] The objective of this study is to prove high blood glucose levels before surgery as a risk factors for recurrent events in epithelial ovarian carcinoma patients in Dr. Kariadi General Hospital.

METHODS

This is an observational study with case control research design. The sample of this study were 60 patients who had been diagnosed as epithelial ovarian carcinoma based on histopathological examination and hospitalized at Dr. Kariadi General Hospital Semarang, had undergone complete surgical staging or cytoreduction surgery, had completed the chemotherapy cycle and was willing to be the subject of research with informed consent. The sample will be divided into 2 groups, firstly the recurrent group which had recurrent disease based on the evaluation results after complete remission and secondly the non-recurrent group which had no recurrent disease based on the evaluation results were not found after remission. Data collection included patient age of diagnosis, tumor location, histological subtype, Ca-125 plasma level and random blood sugar level before surgery or treatment. The collected data will be analyzed by chi square test and Odds Ratio value were calculated for risk estimation.

RESULTS

In this study, we analysed 60 study subjects with 30 cases of recurrent epithelial ovarian carcinoma as a recurrent group and 30 cases of non-recurrent epithelial ovarian carcinoma as a non-recurrent group. Data of patient's characteristics in this study can be seen in table 1. In the recurrent group, the mean age of diagnosis patients was slightly higher than the non-recurrent group with a non-significant difference (50.8 ± 7.2 vs 49.3 ± 9.5 years). There were no differences in tumor location between the recurrent and non-recurrent groups where there were 23 unilateral cases (76.7%) and 7 bilateral cases (23.3%). The most histological subtypes of the recurrent group were endometrioid carcinoma types (33.3%), whereas in the most non- recurrent group were serous carcinoma types (40%), but there were no significant differences between the two groups. The mean level of Ca-125 in the recurrent group was significantly higher than in the non- recurrent group (327.8 ± 250.5 U / ml vs. 183.5 ± 212.1 U / ml).

Table 1. Characteristics of subjects

Characteristics		Group		*P-value*
		Control (N=30) Non Recurrent	**Case (N=30) Recurrent**	
Age (years old)		49.3 ± 9.5 Median: 47.5	50.8 ± 7.2 Median: 52	0.496[a]
Ca-125 Level (U/ml)		183.5 ± 212.1	327.8 ± 250.5	0.010[b]
Location	Unilateral	23 (76.7)	23 (76.7)	1.00[c]
	Bilateral	7 (23.3)	7 (23.3)	
Hitological	Serous Ca	12 (40.0)	7 (23.3)	
Subtype	Muscinous Ca	9 (30.0)	6 (20.0)	
	Endometrioid Ca	7 (23.3)	10 (33.3)	0.220[c]
	Clear Cell Ca	2 (6.7)	5 (16.7)	
	others	0 (0)	2 (6.7)	

The mean and median values of random blood glucose levels of recurrent epithelial ovarian carcinoma patients had significantly higher compared to random blood glucose levels of non-recurrent epithelial ovarian carcinoma (110.8 ± 31.1 vs. 150.5 ± 79).

Table 2. The Difference in Mean GDS Levels of Residual and non-Residual Ovarian Carcinoma Patients

	Control (N=30) Non Recurrent	Case (N=30) Recurrent	*P-value*
Random blood glucose levels (mg/dl)	110.8 ± 31.1	150.5 ±79	0.006**
Normality test	0.038*	0.001*	

When random blood glucose levels from both groups of patients were categorized into high and low random blood glucose levels with a cut-off value of 110 mg / dl, carcinoma patients with recurrent epithelial ovarian carcinoma with random blood glucose levels > 110 mg / dl were significantly more likely to have recurrent disease compared to patients who had random blood glucose levels <110 mg / dl. The OR value analysis of the relationship between random blood glucose levels and recurrent event in epithelial ovarian carcinoma patients is 3.00, which means patients with epithelial ovarian carcinoma who have random blood glucose levels more than 110 mg / dl have a 3.00-fold risk of being recurrent than those with random blood glucose levels less than 110 mg / dl. Level of significance shows p = 0.041 (p <0.05), so that at a 95% confidence level, OR values are considered significant or meaningful which means they can represent the entire population.

Table 3. Different Categories of GDS Levels in Patients with Residual and non-Residual Epithelial Type Ovarian Carcinoma

	Control (N=30) Recurrent	Case (N=30) Non Recurrent	OR	*P-value*
High Glucose Level (> 110 mg/dl)	20	12	3.000*	0.041*
Low Glucose Level (> 110 mg/dl)	10	18		

Based on the results of bivariate analysis, it appears that Ca-125 levels and high random blood glucose levels were significantly associated with recurrent events in epithelial ovarian carcinoma patients (p <0.05). High levels of random blood glucose are the most influential factor for the recurrent event, compared with the factor of Ca-125 levels, with a higher OR value. Patients with high levels of Ca-125 have a risk of being 1.003 times more likely to be recurrent than those with lower levels of Ca-125, whereas patients who have high levels of random blood glucose (more than 110 mg / dl) have a 3,445-fold risk of being recurrent than those with lower random blood glucose levels (less than 110 mg / dl).

Table 4. Results of Multivariate Analysis of Ca-125 Levels and GDS Levels with Residual Events in Epithelial Type Ovarian Carcinoma Patients

	P-value	OR	CI 95%	
			Lower	Upper
High Ca-125 Level	0.019	1.003	1.000	1.005
High Glucose Level	0.032	3.445	1.112	10.739

* = Uji *Logistic Regresion*

DISCUSSION

This study determined high random blood glucose levels as a risk factor for recurrent occurrence in patients with epithelial ovarian carcinoma, as well as other factors that influence it, which is age of diagnosis, location, levels of Ca-125 and histological subtypes. The age of diagnosis patients in both groups did not differ significantly (p> 0.05). This indicates that age does not affect the incidence of recurrent ovarian carcinoma in this study. In another study, it was found that the mean age of diagnosis patients with recurrent epithelial ovarian carcinoma was slightly higher than that of non-recurrent, with a median residual patient age: 61 years.8 These results are comparable to this study, where the median age of recurrent epithelial ovarian carcinoma patients is higher than the non-recurrent, with a median residual patient age: 52 years.

Similarly, the location of the tumor and the histological subtypes. In both groups, the location and histological examination were not

significantly different (p> 0.05). This indicates that the location of the tumor and histopathological subtype did not affect the incidence of recurrent ovarian carcinoma in this study. Another similar study showed that the most common histological subtype among those who experienced recurrent disease was clear cell carcinoma, whereas in this study it was found that the most common histological subtype in the recurrent group was endometrioid carcinoma.[8,9]

The results of the analysis of Ca-125 levels in both groups showed a significant difference. This shows that Ca-125 levels affect the incidence of recurrent ovarian carcinoma. This finding is consistent with other previous studies that concluded that in patients with recurrent ovarian cancer there was an increase in CA-125 levels. If CA-125 levels are above 35 U / mL, the clinician must have suspected recurrent event. An increase in CA-125 levels of 10 U / mL or an increase of 100% from the previous level is an accurate predictor of recurrent ovarian cancer. In another study, it was also stated that elevated serum CA-125 levels during follow-up can be used as a marker of recurrent event in epithelial ovarian carcinoma.[9,10]

Based on the analysis of the relationship between random blood glucose level and the incidence of recurrent epithelial ovarian carcinoma, we found that the mean random blood glucose levels in the recurrent epithelial ovarian carcinoma group were significantly higher than in the non-recurrent group. In addition, with a cut-off value of GDS 110 mg / dl, patients with random blood glucose levels > 110 mg / dl had a three-fold risk of developing recurrent event compared to patients with random blood glucose levels < 110 mg / dl. This shows that high level of random blood glucose influence and become a risk factor for recurrent event in patients with epithelial ovarian carcinoma. The results of this study are consistent with previous studies by Lambkin, et al where higher glucose levels were significantly associated with shorter survival times and patients with glucose levels of > 140 mg / dL had 2.48 times the risk of developing recurrent ovarian cancer. In addition to ovarian carcinoma patients, high blood glucose levels are also a risk factor for poor survival time and residual events in malignant cases in the head, neck, stomach and leukemia areas.[11-15]

Plasma glucose levels in cancer patients can be important prognostic indicators related to reduced survival and recurrence in patients. It is known that cancer cells have a significant increase in glycolysis compared to normal cells, and in general it has been shown that inside cancer cells has increased uptake and glucose metabolism is significant compared to normal cells. Hyperglycemia is thought to have an important role in triggering residual events in epithelial ovarian cancer through glucose transporter protein 1 (GLUT 1), the transmembrane protein responsible for glucose uptake. Increased expression of GLUT1 is associated with shorter survival times in ovarian cancer patients and predicts a shorter time for recurrence (DFI) in patients who achieve remission.[16-20]

REFERENCES

1. Sung Y, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. Ca Cancer J Clin. 2021;71:209–49.
2. Islami F, Guerra CE, Minihan A, Yabroff R, Fedewa SA, Sloan K, et al. American Cancer Society's report on the status of cancer disparities in the United States. Ca Cancer J Clin. 2022;72:112–43
3. Chang LC, Huang CF, Lai MS, Shen LJ, Wu FL, Cheng WF. Prognostic factors in epithelial ovarian cancer: A population-based study. PLoS One. 2018;13(3):e0194993.
4. Ebrahimi V, Khalafi-Nezhad A, Ahmadpour F, Jowkar Z. Conditional disease-free survival rates and their associated determinants in patients with epithelial ovarian cancer: A 15-year retrospective cohort study. Cancer Rep (Hoboken). 2021;4(6):e1416.
5. Yang SP, Su HL, Chen XB, Hua L, Chen JX, Hu M, et al. Long-Term Survival Among Histological Subtypes in Advanced Epithelial Ovarian Cancer: Population-Based Study Using the Surveillance, Epidemiology, and End Results Database. JMIR Public Health Surveill. 2021;7(11):e25976.
6. Wang L, Zhong L, Xu B, Chen M, Huang H. Diabetes mellitus and the risk of ovarian cancer: a systematic review and meta-analysis of cohort and case-control studies. BMJ Open. 2020;10(12):e040137.
7. Linkeviciute-Ulinskiene D, Patasius A, Zabuliene L, Stukas R, Smailyte G. Increased Risk of Site-Specific Cancer in People with Type 2 Diabetes: A National Cohort Study. Int J Environ Res Public Health. 2019;17(1):246.
8. Flaum N, Crosbie EJ, Edmondson RJ, Smith MJ, Evans DG. Epithelial ovarian cancer risk: A review of the current genetic landscape. Clin Genet. 2020;97(1):54-63.
9. Charkhchi P, Cybulski C, Gronwald J, Wong FO, Narod SA, Akbari MR. CA125 and Ovarian Cancer: A Comprehensive Review. Cancers (Basel). 2020;12(12):3730.
10. Kim B, Park Y, Kim B, Ahn HJ, Lee KA, Chung JE, et al. Diagnostic performance of CA 125, HE4, and risk of Ovarian Malignancy Algorithm for ovarian cancer. J Clin Lab Anal. 2019;33(1):e22624.
11. Kellenberger LD, Petrik J. Hyperglycemia promotes insulin-independent ovarian tumor growth. Gynecol Oncol. 2018;149(2):361-70.

12. Lee DY, Lee TS. Associations between metabolic syndrome and gynecologic cancer. Obstet Gynecol Sci. 2020;63(3):215-24.
13. Supabphol S, Seubwai W, Wongkham S, Saengboonmee C. High glucose: an emerging association between diabetes mellitus and cancer progression. J Mol Med (Berl). 2021;99(9):1175-93.
14. Wang J, Wang P, Liu X, Wang H, Wu X. Correlations between postoperative recurrence of ovarian cancer and immune function, inflammatory factors and glucose metabolism. Minerva Endocrinol. 2020;45(3):275-6.
15. Lamkin DM, Spitz DR, Shahzad MM, Zimmerman B, Lenihan DJ, Degeest K, et al. Glucose as a prognostic factor in ovarian carcinoma. Cancer. 2009;115(5):1021-7.
16. Pizzuti L, Sergi D, Mandoj C, Antoniani B, Sperati F, Chirico A, et al. GLUT 1 receptor expression and circulating levels of fasting glucose in high grade serous ovarian cancer. J Cell Physiol. 2018;233(2):1396-401.
17. Antoun S, Atallah D, Tahtouh R, Assaf MD, Moubarak M, Ayoub EN, et al. Glucose restriction combined with chemotherapy decreases telomere length and cancer antigen-125 secretion in ovarian carcinoma. Oncol Lett. 2020;19(2):1338-50.
18. Baczewska M, Bojczuk K, Kołakowski A, Dobroch J, Guzik P, Knapp P. Obesity and Energy Substrate Transporters in Ovarian Cancer-Review. Molecules. 2021;26(6):1659.
19. Jammal MP, Martins Filho A, Bandeira GH, Murta BMT, Murta EFC, Nomelini RS. Laboratory predictors of survival in ovarian cancer. Rev Assoc Med Bras. 2020;66(1):61-6.
20. Dauer P, Lengyel E. New Roles for Glycogen in Tumor Progression. Trends Cancer. 2019;5(7):396-9.

Case Report

Treatment Approach for a Rare Case of Cervical Cancer in Pregnancy

Pendekatan Terapi pada Kanker Serviks dalam Kehamilan

Yuannita I. Putri, Gumilang Wiranegara

Badan Pengusahaan Batam Hospital
Batam

Abstract

Objective: To add a new overview of cervical cancer in pregnancy and to review several treatment approaches using available guidelines.

Methods: Case report.

Case: A 29 years old woman, gravida 3 para 2 in 10 weeks of pregnancy, was presented with vaginal bleeding and bloody vaginal discharge. Ultrasound examination showed a 10 weeks single live intrauterine fetus and a mass on the cervix. The histopathological report revealed a poorly differentiated cervical adenocarcinoma without invasion of lymphovascular space. Patient was diagnosed with cervical carcinoma FIGO stage IB3 in 10 weeks of pregnancy. The patient opted to unpreserved the pregnancy. Radical hysterectomy with fetus in situ and bilateral pelvic lymphadenectomy was performed. Patient was referred to undergo adjuvant radiation therapy.

Conclusion: Cervical cancer in pregnancy is a rare and special condition that requires individual planning for the diagnostic and treatment approaches.

Keywords: cervical cancer, cervical cancer in pregnancy, fetus in situ hysterectomy, pregnancy, radical hysterectomy.

Abstrak

Tujuan: *Untuk menambah gambaran kasus mengenai kanker serviks dalam kehamilan serta membahas pendekatan terapi menggunakan pedoman – pedoman yang ada.*

Metode: *Laporan kasus.*

Kasus: *Seorang perempuan berusia 29 tahun dengan G3P2 usia kehamilan 10 minggu datang dengan keluhan perdarahan pervaginam dan keputihan bercampur darah. Hasil dari USG menunjukkan adanya janin berusia 10 minggu serta massa pada serviks. Hasil pemeriksaan histopatologi menunjukkan adanya adenokarsinoma serviks berdiferensiasi buruk tanpa invasi limfovaskuler. Pasien didiagnosis dengan kanker serviks stadium FIGO IB3 dalam kehamilan 10 minggu. Pasien setuju untuk dilakukan terminasi kehamilan. Pada pasien kemudian dilakukan laparotomi histerektomi radikal dengan fetus in situ serta limfadenektomi pelvik bilateral. Pasien kemudian dirujuk untuk dilakukan terapi ajuvan dengan radiasi.*

Kesimpulan: *Kanker serviks pada kehamilan merupakan suatu kondisi khusus sehingga perencanaan diagnostik dan manajemen terapi membutuhkan perencanaan secara individual di setiap kasusnya.*

Kata kunci: *Kanker, kanker serviks, kanker serviks dalam kehamilan, kehamilan, , histerektomi radikal, histerektomi dengan fetus in situ.*

Correspondence author. Yuannita I. Putri. Badan Pengusahaan Batam Hospital. Batam
Email: yuannitaip@gmail.com

Received: February, 2021 Accepted: March, 2022 Published: April, 2022

INTRODUCTION

Cervical cancers are the second commonest cancer in Indonesian women. The incidence rate of cervical cancer in Indonesia is increased 17% between 1990 and 2017. The mortality rate is also increased, which 3,3 per 100.000 in 1990 and 3,7 per 100.000 in 2017.[1] The incidence rate of cervical cancer in pregnancy is extremely low. Of all women who were diagnosed with cervical cancer, 1 – 3% were diagnosed when pregnant or postpartum.[2] Cervical cancer is the most common gynecological cancer founded in pregnancy with incidence rate of 1,5 – 12 per 100.000 pregnancies.[3]

Studies regarding cervical cancer in pregnancy are still limited. Many treatment approaches of cervical cancer in pregnancy still aroused many controversies. This paper aims to add a new overview of cervical cancer in pregnancy and to review several treatment approaches using available guidelines.

CASE

A 29-year-old woman with gravida 3 para 2 was presented with vaginal bleeding. The bleeding had been occurred for 3 months even before the pregnancy. The patient has been experiencing irregular menstrual bleeding for one year. Patient also complained of having bloody vaginal discharge frequently. The patient had menarche at 14 years old. She was married at the age of 18. Her obstetric history shows that the patient had two children, who had been delivered by spontaneous vaginal delivery. She was using IUD as a contraceptive method and had been removed one year ago. Ultrasound examination showed a 10 weeks single live intrauterine fetus and a mass on the cervix. The measurement of the mass is 7 x 6 x 6 cm. The patient underwent cervical biopsy afterward. The histopathological report revealed a poorly differentiated cervical adenocarcinoma without invasion of lymphovascular space. Patient was diagnosed with cervical carcinoma FIGO stage IB3 in 10 weeks of pregnancy.

After the patient was educated and counseled regarding her condition, she opted to end the pregnancy. Radical hysterectomy with fetus in situ and bilateral pelvic lymphadenectomy was performed. Post-surgical histopathological report revealed cervical adenocarcinoma with an invasion of lymphovascular space, remaining of the implantation in the endometrium, absen of pelvic lymph nodes metastasis, no parametrium invasion, and negative surgical margin. Patient was referred to undergo adjuvant radiation therapy.

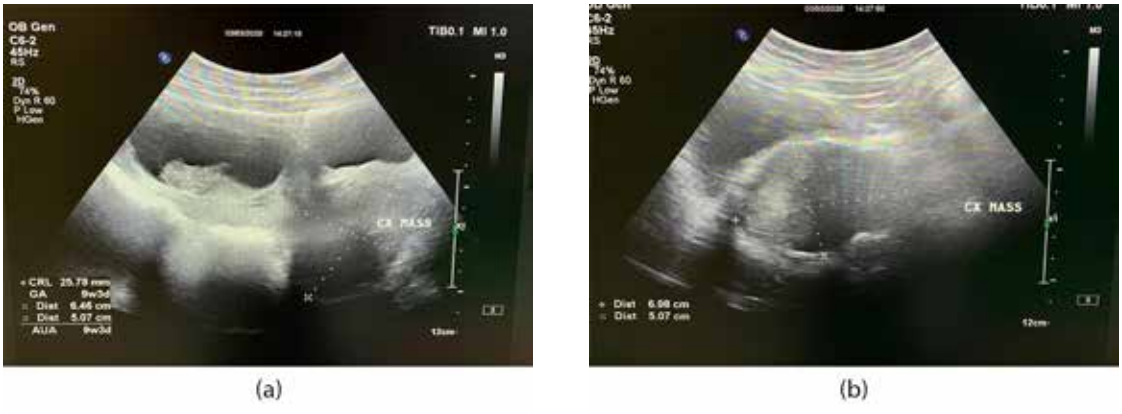

Figure 1. Ultrasound examination: (a) 10 weeks fetus with a cervical mass, (b) cervical mass with measurement 7x6x6 cm

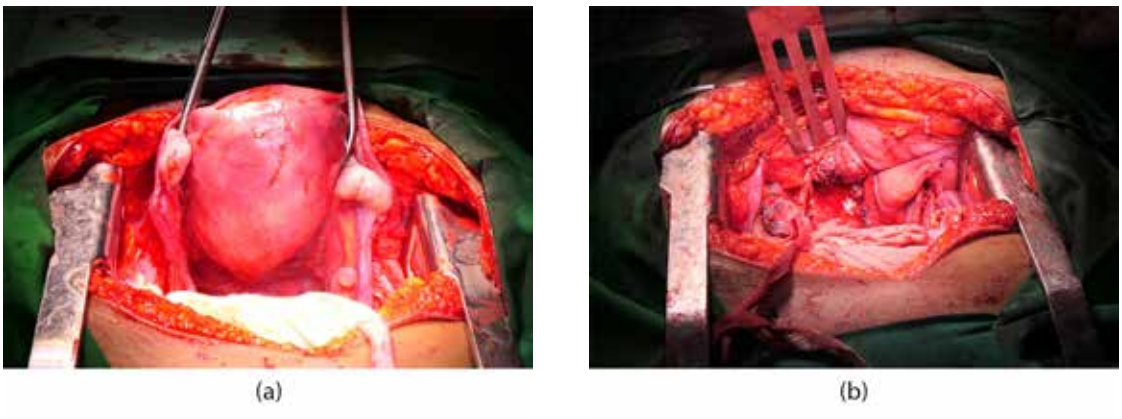

Figure 2. Intraoperative: (a) Fetus in situ radical hysterectomy, (b) Absent of metastatic tumors macroscopically after radical hysterectomy

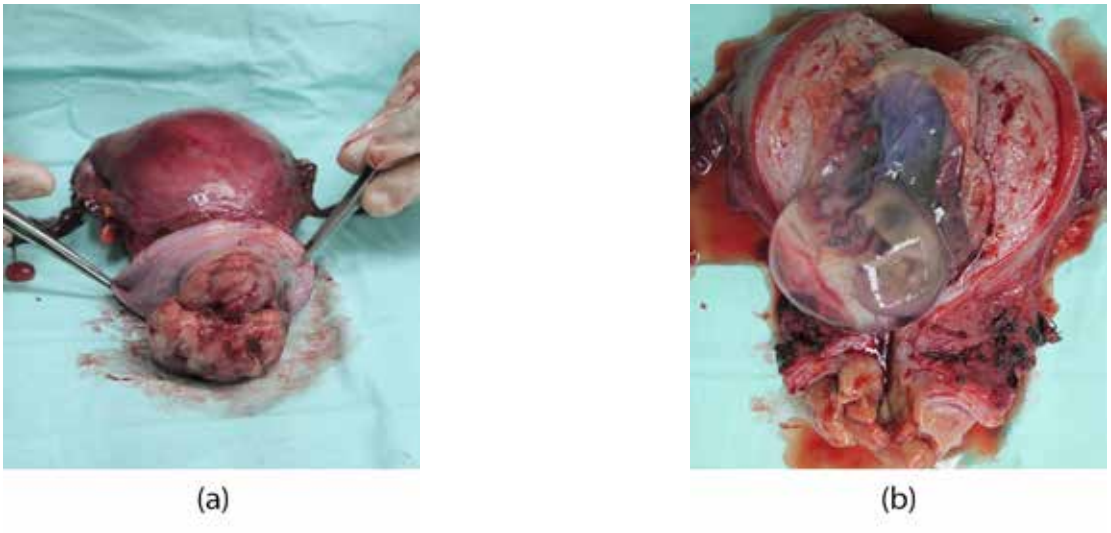

Figure 3. Radical hysterectomy specimen: (a) cervical mass, (b) fetus in situ

DISCUSSION

Many factors had to be considered when selecting the best treatment for cervical cancer in pregnancy. Stage of the disease, lymph nodes status, histological subtype, gestational age, obstetric complication, and patient's desire to continue or stop the pregnancy will affect the treatment options.[4] Pregnancy can affect cervical cancer treatment and vice versa. However, the course of the disease and the disease prognosis are similar in pregnant and non-pregnant women.[5]

In this case report, the patient underwent a cervical biopsy to confirm the diagnosis. Cervical biopsy in pregnant women did not increase obstetric complications, miscarriages, and preterm labor. However, the sample collection must be done cautiously because the cervix during pregnancy is prone to bleeding. It is recommended that the depth of biopsy should less than 1 cm should not be too large so that the bleeding can be easily controlled.[2] Staging was determined using FIGO 2018 stage based on patient's histopathological result. Stage IB3 was the final diagnosis because clinically the tumor is limited on the cervix uteri with > 4 cm size and there is no sign of lymph node metastasis or distant metastasis.[6]

Treatment considerations of this patient were the gestational age (10 weeks of pregnancy), stage IB3, negative lymph nodes status, adenocarcinoma type of tumor, and patient's desire. A case in Portugal also reported the same treatment in 16 weeks pregnant woman with cervical carcinoma FIGO stage IB1 who decided not to continue the pregnancy. Radical hysterectomy has been proved to be the best option for early-stage cervical cancer in patient who desired not to continue the pregnancy.[7] Study from Maryland recommends immediate definitive treatment should be undergo in patient with endophytic, deeply invasive, poorly differentiated squamous cell tumor or adenocarcinoma. Radical hysterectomy with fetus in situ can be performed at gestational age below 20 weeks. In patient with undesired pregnancy with cancer diagnosed above 20 weeks, evacuation of the implantation in the uterus should be performed prior to radical hysterectomy.[8] Indication of post-operative adjuvant radiotherapy has been determined by evaluating prognostic risk factors for recurrence.[9] This patient has been met intermediate-risk group criteria because of the lymphovascular space invasion in the post operative hystopathologic result. A study shows that adjuvant radiotherapy administration can decrease the risk of recurrence by 47%.[9]

Delayed treatment to wait for fetal maturity can be beneficial to the fetus but may affect the tumor progression.[7] Study shows the 5 years disease specific survival for delayed treatment is 61%, whereas for the immediate action is 86%.[10] Administration of NACT can help to control the tumor progression. NACT has been applied in a case of 21 weeks pregnant woman with cervical carcinoma FIGO stage IB1 in China, who wanted to continue the pregnancy. The patient had been delivered a live male baby via transabdominal cesarean section. Radical hysterectomy, bilateral salpingectomy, bilateral ovarian transposition, and pelvic lymphadenectomy

were also performed in this patient. The patient subsequently underwent 35 sessions of radiation therapy. In 3 years of follow up, there are no recurrency on the patient and the neonate has a good prognosis.[11] Another case involving NACT administration in cervical carcinoma stage IIB in desired pregnancy, presented a good outcome for the mother and the neonate.[12] Some studies showed that delayed treatment after delivery without NACT administration had been given a bad prognosis.[7,13]

In 2014, International Institute of Gynecological Oncology (IGCS) dan European Society of Gynecological Oncology (ESGO) established fetal preservation program as a treatment approach for cervical cancer in pregnancy. This program focused on the administration of neoadjuvant chemotherapy (NACT) until the fetus is matured.[2] In 2018, Chinese Anti-Cancer Association (CACA) established a new guideline of cervical cancer in pregnancy treatment. The highlights of this guideline are patient with stage IA2 – IV within first 20 weeks of pregnancy, continuing the pregnancy is not recommended. Whereas treatment for second trimester of pregnancy still aroused controversies. Patient with stage IA – IIA who desired to continue the pregnancy, pregnancy can be continued with strict monitoring. Patient with stage IIB and above, continuing the pregnancy is not recommended. However, if the patient strongly desired the pregnancy, NACT can be applied as proposed by the European consensus.[11] The newest guideline was established in 2019 by International Network on Cancer, Infertility, and Pregnancy (INCIP) based on The Third International Consensus Meeting. In this guideline, stage of the disease and the gestational age are crucial points in treatment determination. It is recommended to use updated FIGO 2018 to stage the disease. Pelvic lymph node dissection is recommended for stage IA2, IB1, and IB2 below 22 weeks of pregnancy. If there is positive lymph node, termination of pregnancy is required. If the lymph node involvement is absent, simple trachelectomy or delayed treatment after delivery can be applied. For the same stages but with gestational age above 22 weeks, NACT or delayed treatment after delivery can be applied. For stage IB3, NACT can be applied or termination of pregnancy can be performed in gestational age below 22 weeks. For gestational age above 22 weeks, NACT or delayed treatment after delivery can be applied. Termination of pregnancy is recommended in advanced stages (stage IIB and above), presence of lymph nodes metastasis, or if the patient desires to stop the pregnancy. In some operable cases (stage IA2 – IB2), radical hysterectomy with fetus in situ can be performed in first trimester and early second trimester. Whereas for stage IB3 and above, chemoradiation therapy should be done prior.[14] In Indonesia, diagnostic and treatment approaches for cervical cancer in pregnancy have been using a guideline from Indonesian Society of Gynecologic Oncology. The treatment approach in this guideline is based on stage of the disease and gestational age. At 16 – 20 weeks of gestation, it is recommended to perform immediate surgery or chemoradiation. In second trimester of pregnancy and afterward, surgery and chemotherapy can be applied in certain cases to preserve the pregnancy. Above 20 weeks of pregnancy, delayed treatment can be opted in stage IA2 and IB1. When the fetus is viable, transabdominal cesarian section can be performed followed by radical hysterectomy. Adjuvant chemotherapy is recommended in locally advanced disease.[15]

CONCLUSIONS

Cervical cancer in pregnancy is a rare and special condition that requires individual planning for the diagnostic and treatment approaches. Patients' desire for pregnancy must be included in consideration of the treatment approach in addition to the stage, gestational age, lymph nodes status, and histologic types. Updated guidelines that can be a reference are guidelines from INCIP, IGCS, ESGO, CACA, and PNPK HOGI. For patients who don't desire to continue the pregnancy, radical hysterectomy with or without radiation therapy can be opt in early trimester. Currently, NACT administration for cervical cancer to preserve pregnancy has been applied in many cases. However, studies regarding the outcome of NACT administration are still limited, particularly in Indonesia. Further studies regarding NACT administration and outcomes in Indonesia should be developed to complement the current guideline.

REFERENCES

1. Wahidin M, Febrianti R, Susanty F. Burden Cervical Cancer in Indonesia: Findings from the Global Burden Disease Study 1990 - 2017. Advances Health Sci Research. 2020;22:213-6.
2. Beharee N, Shi Z, Wu D, Wang J. Diagnosis and Treatment of Cervical Cancer in Pregnant Women. Cancer Med. 2019;00(1-6).
3. Hunter M, Tewari K, Monk B. Cervical Neoplasia in Pregnancy. Part 2: Current Treatment of Invasive Disease. Am J Obstet Gynecol. 2008 ;199(1):10-8.
4. Han S, Gziri M, Calsteren KV, Amant F. Cervical Cancer in Pregnant Women: Treat, Wait, or Interrupt? Assessment of Current Clinical Guidelines, Innovations, and Controversies. Ther Adv Med Oncol. 2013 ;5(4):211-9.
5. Hopkins M, Morley G. The Prognosis and Management of Cervical Cancer Associated with Pregnancy. Obstet Gynecol. 1992;80:9-13.
6. Bhatla N, Berek JS, Fredes MC, Denny LA, Grenman S, Karunaratne K, et al. Revised FIGO Staging for Carcinoma of The Cervix Uteri. Int J Gynecol Obstet. 2019;145:129-35.
7. Ribeiro F, Correia L, Paula T, Santana I, Pinto L, Borrego J, et al. Cervical Cancer in Pregnancy: 3 Cases, 3 Different Approaches. J Low Genit Tract Dis. 2013;17(1):66-70.
8. Nguyen C, Montz F, Bristow R. Management of Stage I Cervical Cancer in Pregnancy. Obstet Gynecol Surv. 2000 ;55(10):633-43.
9. Takekuma M, Kasamatsu Y, Kado N, Kuji S, Tanaka A, Takahashi N, et al. The Issues regarding Postoperative Adjuvant Therapy and Prognostic Risk Factors for Patients with Stage I-II Cervical Cancer: A Review. J Obstet Gynaecol Res. 2017 ;43(4):617-26.
10. Ma J, Yu L, Xu F, Yi H, Wei W, Wu P, et al. Treatment and Clinical Outcomes of Cervical Cancer during Pregnancy. Ann Transl Med. 2019;7(11):241.
11. Han J, Hu X, He X, Wang J, Mueller M, Papadia A, et al. Cervical Cancer in Pregnancy: One Case Report and A Review of Current Treatment Recommendations. Gynecol Pelvic Med. 2019;2(10).
12. Palaia I, Pernice M, Graziano M, Bellati F, Panici P. Neoadjuvant Chemotherapy Plus Radical Surgery in Locally Advanced Cervical Cancer during Pregnancy: A Case Report. Am J Obstet Gynecol. 2007;197(4):5-6.
13. Elhassan E, Mirghani O, Mohamadani A, Ahmed B, Miskeen E. Cervical Carcinoma in Pregnancy: Case Report. Gynecol Perinatol. 2009;18(2):93-5.
14. Amant F, Berveiller P, Boere I, Cardonick E, Fruscio R, Fumagalli M, et al. Gynecologic Cancers in Pregnancy: Guidelines Based on A Third International Consensus Meeting. Ann Oncol. 2019 1;30(10):1601-12.
15. HOGI. Pedoman Nasional Pelayanan Kedokteran Kanker Ginekologi. 2018.

Literature Review

Prevention and Treatment of Venous Thromboembolism in Pregnancy

Pencegahan dan Tatalaksana Tromboemboli Vena pada Kehamilan

Erna Suparman

Department of Obstetrics and Gynecology
Faculty of Medicine Sam Ratulangi University
Prof. Dr. R. D. Kandou General Hospital
Manado, North Celebes

Abstract

Objective: To determine prevention and treatment of venous thromboembolism in pregnancy.

Methods: Literature Review.

Results: The diagnosis of TEV, both deep vein thrombosis (DVT) and pulmonary embolism (PE) was clinical and confirmed by imaging. D-dimers commonly used in the non-pregnant population are less useful in pregnant women. Prevention needs to be done by assessing the risk of TEV in pregnant women and giving thrombophylaxis according to risk. Treatment of TEV in pregnant women mainly uses heparin, either unfractionated heparin (UFH) or low molecular weight heparin (LMWH).

Conclusion: The ASH recommends the use of LMWH compared with UFH for the management of acute VTE in pregnancy, in once-daily or divided doses. The recommended method of delivery for pregnant women receiving anticoagulant therapy should be planned delivery.

Keywords: vein thromboemboli, deep vein thrombosis, pulmonary embolism, pregnancy.

Abstrak

Tujuan: *Mengetahui bagaimana pencegahan dan tatalaksana tromboemboli vena pada kehamilan.*

Metode: *Kajian Pusataka.*

Hasil: *Diagnosis TEV, baik Deep vein thrombosis (DVT) dan pulmonary embolism (PE) berdasarkan klinis dan dikonfirmasi dengan pencitraan. D-dimer yang biasa digunakan pada populasi non-hamil kurang berguna pada ibu hamil. Pencegahan perlu dilakukan dengan menilai risiko TEV pada ibu hamil dan memberikan trombofilaksis sesuai dengan risiko. Tatalaksana TEV pada ibu hamil terutama menggunakan heparin, baik unfractionated heparin (UFH) maupun low molecular weight heparin (LMWH).*

Kesimpulan: *ASH merekomendasikan penggunaan LMWH dibandingkan dengan UFH untuk pengelolaan VTE akut pada kehamilan, dalam dosis sekali sehari atau terbagi. Metode persalinan yang direkomendasikan untuk ibu hamil yang menerima terapi antikoagulan harus direncanakan persalinan.*

Kata kunci: *tromboemboli vena, deep vein thrombosis, pulmonary embolism, kehamilan.*

Correspondence. Erna Suparman; ernasuparman@yahoo.com

Received: September, 2021 Accepted: March, 2022 Published: April, 2022

INTRODUCTION

Venous thromboembolism (VTE), especially pulmonary thromboembolism which often originates from deep vein thrombosis (DVT), is one of the most common causes of death in pregnant women. Research in America with data from 1998-2013 showed maternal mortality due to pulmonary thromboembolism is 1.5 - 1.6 deaths per 100,000 live births. The risk of death from pulmonary thromboembolism is higher in the postpartum period. A total of 8.8% of deaths in pregnancy were due to PTE in the postpartum period compared to 6.7% at the time of delivery. In the period 2004-2014, the incidence of VTE was around 5.7 cases per 10,000 deliveries. The incidence of DVT itself decreased (5.3 to 4.4 cases per 10,000 deliveries) after the clinical community followed the guidelines and recommendations for thromboprophylaxis in pregnant women, but the incidence of pulmonary thromboembolism tends to be the same.[1] Approximately 15-24% of cases of DVT will develop into pulmonary thromboembolism if left unchecked.[2]

Pregnant women have a risk of VTE 4 – 4.6 times compared to women of the same age who are not pregnant. The risk of developing VTE increases with advancing gestational age, peaking at 1-3

weeks postpartum. In the 3-month postpartum period, the risk of VTE increased up to 60-fold (OR 60.1; 95% CI). This risk is increased because of vascular damage at the time of delivery.3 The risk then decreases and is the same as the risk in the nonpregnant state at 12 weeks postpartum.1 Risk factors that increase the incidence of VTE in the nonpregnant population also increase the risk of VTE in pregnant women, such as old age, anemia, obesity, smoking, and other factors.[3]

The most important factor in the incidence of VTE in pregnant women is a previous history of VTE. The incidence of VTE in pregnant women with a history of VTE and who were not given thromboprophylaxis was found to be very high, around 1000 cases per 10,000 pregnant women (10%). The second important factor in VTE in pregnant women is hereditary thrombophilia. The risk of VTE in pregnant women with thrombophilia is much higher than in pregnant women in general (OR 15.4, 95% CI).3 History of cardiovascular disease is the third highest risk factor with an incidence of 100-200 cases per 10,000 pregnant women. Preeclampsia, one of the most common complications of pregnancy, also increases the risk of VTE. The study of Kane et al. showed that preeclampsia increased the risk of VTE in the postpartum period by 1.6 times, but not in the prenatal/antepartum period.4 Another risk factor that significantly increases the risk of VTE in pregnant women is a cesarean section, but this risk was found to decrease with thromboprophylaxis according to recent guidelines.[3]

The increased risk of VTE in pregnant women, especially those accompanied by other risk factors and the high morbidity and mortality of VTE, requires early diagnosis, prevention, and appropriate management. The purpose of this review is to discuss the diagnosis, prevention, and management of thromboembolism in pregnancy.

Table 1. Risk factors for venous thromboembolism in pregnancy [1,3,4]

Risk Factors
Previous VTE history
Hereditary hemophilia
History of cardiovascular disease
Post-partum
Pre-eclampsia
Elderly
Anemia
Obesity
Smoking

METHODS

The method in this research is to use literature review from various references.

RESULTS

PATHOGENESIS OF THROMBOEMBOLISM IN PREGNANCY

Pregnancy and the postpartum period are prothrombotic conditions characterized by an increase in the three components of Virchow's triad, namely venous stasis, endothelial damage, and hypercoagulation. Venous stasis in the lower extremities occurs in pregnancy due to progesterone-induced venous-vasodilation and compression of the large veins by the gravid uterus. Although blood volume and venous return are increased, the linear velocity of the lower extremity veins is reduced because of increased venous capacity. This venous stasis lasts up to about 6 weeks postpartum.[5]

Endothelial damage that occurs during labor on the uteroplacental surface may increase the risk of VTE in the postpartum period. The use of assistive devices such as forceps, vacuum, or surgery can exacerbate these risks. The increased blood volume in pregnancy may also cause shear stress on the blood vessels.[6]

Pregnancy is a hypercoagulable condition characterized by an increase in pro coagulation factors such as factors V, VII, VIII, IX, X, XII, and von Willebrand factor. This condition is also accompanied by reduced anticoagulation factors, namely protein S. Fibrinolysis is also reduced due to increased activity of plasminogen activator inhibitor types I and II, and reduced activity of tissue plasminogen activator.6 These changes are physiological to prepare for blood clotting during labor, which is characterized by an increase in D-dimer and prothrombin fragments.

DIAGNOSIS OF VTE IN PREGNANCY

Deep vein thrombosis (DVT)

The most common complaint in more than 80% of pregnant women with DVT is pain and swelling in the extremities. However, this complaint is also often complained by pregnant women without DVT. A unilateral calf circumference difference of more than 2 cm is a sign suggestive of lower extremity DVT. In the guidelines of the American College of Obstetricians and Gynecologists

(ACOG), the initial investigation recommended in patients presenting with suspected DVT is compression ultrasonography (CUS). Thromboembolism in pregnant patients is usually found in the iliofemoral or ileal, in contrast to the general population, which is usually found in the distal.

When CUS results are negative or doubtful and iliac vein thrombosis is suspected (swelling of the whole leg with or without back, waist, or buttocks pain), the next investigation recommended is iliac vein Doppler ultrasonography, venography, or magnetic resonance imaging (MRI). Empirical anticoagulation may also be given in some cases. When the results are negative and there is no suspicion of iliac vein thrombosis, re-examination can be performed on day 3 and day 7.[7]

The D-dimer examination is less useful in ruling out VTE in pregnant women because normal pregnancy is accompanied by a progressive increase in D-dimer, so it is not recommended.[7] The use of a scoring system such as the Wells score needs to be interpreted with caution as this score was not validated for the pregnant maternal population.[8] The use of clinical prediction LEFt (Left leg, Edema [calf diameter difference 2cm], First trimester) can help in predicting DVT in pregnant women. In a study of 194 pregnant women, DVT was not found in patients with a score of 0. However, this system should not be used as the sole means of excluding DVT. This tool also still needs further validation.[9]

Pulmonary Embolism / PE

PE symptoms such as dyspnea, palpitations, chest pain that is aggravated by movement are often found in pregnant women with non-thrombotic causes, such as gastroesophageal reflux or discomfort due to an enlarged uterus. This causes the diagnosis of PE in pregnant women to be difficult.[8] In addition, scoring systems such as Wells or Geneva are not validated for pregnant patients. Clinicians need to consider the diagnosis of PE in pregnant women who present with these symptoms given the high mortality. Symptoms that can be found in PE include palpitations, anxiety, pleuritic chest pain, cyanosis, and cough with or without hemoptoe. On physical examination, usually found tachypnea, crackles, decreased breath sounds, and tachycardia. In some cases, signs of right ventricular failure can also be found, such as a split-second heart sound, jugular venous distension, parasternal removal, and hepatomegaly.[2]

Investigations such as blood gas analysis (BGA) are neither sensitive nor specific for the diagnosis of PE. Patients with PE usually develop a respiratory alkalosis, similar to that found in normal pregnancy. Normal PO2 and PCO2 levels are often found in patients with PE, so normal BGA levels cannot rule out PE.[10] Examination of D-dimer, such as in DVT is difficult to do because there is no normal value of D-dimer in pregnant women.[11]

According to ACOG guidelines, ventilation-perfusion scanning (V/Q scanning) and computed tomographic pulmonary angiography (CTPA) examinations can be performed in pregnant women with suspected PE. Clinical practice guidelines from the American Thoracic Society recommend a chest X-ray in all pregnant patients with suspected PE without DVT symptoms. If the photo is abnormal, it is recommended to continue with CTPA examination, while the normal photo is followed by V/Q scanning.[12]

PREVENTION OF THROMBOEMBOLISM IN PREGNANCY

Not all pregnant or postpartum women require thromboprophylaxis. ACOG recommends assessing VTE risk factors for all pregnant women before or in early pregnancy.[7] One tool that can be used to assess this risk is to use the modified Padua or Caprini scoring system for the pregnant woman population. ACOG also recommends the assessment of thrombophilia in pregnant women with a previous history of VTE.[13]

Thrombophylaxis in Cesarean Section

In cesarean delivery, ACOG and the American College of Chest Physician (ACCP) recommend using pneumatic compression devices and early mobilization for all pregnant women who are not receiving pharmacological thromboprophylaxis.[13] In pregnant women at high risk of VTE, the recommendations are not clear. ACOG recommends a combination of pneumatic compression and low molecular weight heparin (LMWH).[7] ACCP recommends combination thromboprophylaxis for patients with a score of 5 or more. In pregnancy, this score is usually found in patients with a history of VTE or a family history or with thrombophilia.[13]

Antepartum and Postpartum Thrombophylaxis

Pharmacological thromboprophylaxis can be given to pregnant women with a high risk of

VTE. The recommendations from ACOG 2018 regarding pregnant women who are indicated for pharmacological thromboprophylaxis can be seen in Table 2. These recommendations consider the advantages of preventing VTE and the disadvantages of fetal complications and bleeding.[7]

Table 2. Pharmacological thromboprophylaxis recommendations in pregnancy and the puerperium [7]

Clinical Scenario	Antepartum	Postpartum Management
	Management	
No history of VTE or thrombophilia	Supervision, without pharmacological therapy	Postpartum prophylactic anticoagulation monitoring or therapy may be considered if the patient has multiple risk factors for VTE*
VTE diagnosed during pregnancy	LMWH/UFH therapeutic dose	LMWH/UFH therapeutic dose at least 6 weeks postpartum. The duration of administration may be longer. Oral anticoagulants may be considered.
History of one episode of VTE precipitated by causes other than estrogen or pregnancy (surgery, trauma, immobilization), without thrombophilia	Supervision, without pharmacological therapy	Postpartum prophylactic anticoagulation monitoring or therapy may be considered if the patient has multiple risk factors for VTE*
History of one unprovoked VTE episode, including pregnancy-related or hormonal contraceptives	LMWH/UFH moderate prophylactic dose or therapeutic dose	LMWH/UFH prophylactic dose, moderate dose, or therapeutic dose for 6 weeks postpartum
Low-risk thrombophilia** with no history of VTE	Supervision, without pharmacological therapy	Postpartum prophylactic anticoagulation monitoring or therapy may be considered if the patient has multiple risk factors for VTE*
Low-risk thrombophilia with a nuclear family history of VTE	Surveillance or prophylactic LMWH/UHF	Postpartum prophylactic anticoagulation therapy or moderate dose LMWH/UFH
High-risk thrombophilia*** no history of VTE	Prophylactic or moderate dose LMWH/UFH	Postpartum prophylactic anticoagulation therapy or moderate dose LMWH/UFH
High-risk thrombophilia with a history of one episode of VTE/ nuclear family history	LMWH/UFH prophylactic dose, moderate dose, or therapeutic dose	Prophylactic postpartum anticoagulation therapy or moderate/therapeutic doses of LMWH/UFH for 6 weeks (level of therapy should be similar to antepartum management)
History of two or more VTE episodes	Moderate/therapeutic dose LMWH/UFH	Postpartum anticoagulation therapy with moderate/ therapeutic doses of LMWH/ UFH for 6 weeks (level of therapy should be similar to antepartum management)
History of two or more VTE episodes – being on long-term anticoagulant medication	LMWH/UFH therapeutic dose	Continue long-term anticoagulant therapy.

*Obesity, prolonged immobilization, cesarean delivery, family history of VTE
** Low-risk thrombophilia: Factor V Leiden heterozygous; heterozygous G20210A prothrombin gene mutation; protein C or protein S deficiency; antiphospholipid antibodies.
*** High-risk thrombophilia: Homozygous Factor V Leiden; homozygous G20210A prothrombin gene mutation; Heterozygous Factor V Leiden plus heterozygous G20210A prothrombin gene mutation; antithrombin deficiency.

MANAGEMENT OF THROMBOEMBOLISM IN PREGNANCY

Initial VTE management in pregnant women depends on the degree of suspicion of PE. In cases with a strong suspicion of PE, empiric anticoagulation is given until there is no evidence of VTE. In patients with suspected PE but who have contraindications to anticoagulation, a diagnostic evaluation is preceded by administration of therapy without anticoagulation (eg inferior vena cava filter) after VTE is confirmed.

When anticoagulation is indicated, the recommended initiation of anticoagulation by both ACCP and ACOG is subcutaneous therapeutic dose LMWH.[7,14] LMWH is preferable to intravenous (IV) Unfractionated Heparin (UFH) because it has a better efficacy and safety profile. These findings were obtained by extrapolating a meta-analysis from 22 randomized clinical trials with the general (nonpregnant) population. The use of subcutaneous LMWH has a lower mortality rate, lower recurrent thrombosis, and lower heavy bleeding compared to IV UFH.[15] In patients with PE or situations requiring immediate delivery, surgery, or thrombolysis, IV UFH is preferred because it has a shorter half-life and can be discontinued protamine when necessary. Oral anticoagulants are avoided in pregnancy because of the unknown safety profile. The use of warfarin is avoided because it is teratogenic, especially in the first trimester.[7]

In patients who are about to give birth, the administration of LMWH should be discontinued at least 12 hours before induction. Discontinuation for 24 hours is recommended for the use of therapeutic doses. In the use of heparin 7500 U SC twice daily or more, discontinuation should be carried out for 12 hours with an evaluation of coagulation status. This discontinuation is done to avoid spinal hematoma in the administration of neuraxial anesthesia.[7]

After delivery, the heparin regimen should be restarted after 12 hours of cesarean section or 6 hours after vaginal delivery, unless significant bleeding occurs. For LMWH administration, the consensus of the Society for Obstetric Anesthesia and Perinatology recommends delaying reinitiation for at least 24 hours or using IV UFH if earlier initiation is desired.16 In patients requiring anticoagulation for longer than 6 weeks, bridging to warfarin or direct oral anticoagulation (if not breastfeeding) may be considered. The initial dose of warfarin is 5 mg once daily, with subsequent doses determined by the international normalized ratio (INR).[7]

Thrombolysis / Thrombectomy

Thrombolytic agents are known to have side effects, namely severe maternal bleeding, so they are only given to life-threatening acute PE. Thrombectomy can be performed to save lives if other attempts fail. Thrombectomy is a procedure in which an intravenous catheter is inserted to reach the thrombus, then placing a thrombolytic agent around the thrombus in the hope that the thrombus will lysis. In a literature review, Catheter Directed Thrombolysis (CDT) had a lower risk of bleeding but the possibility of systemic spread of the thrombolytic agent was possible.[17]

ANTICOAGULANT REGIMEN IN PREGNANCY

The use of anticoagulants in pregnant women is different from the general population. The benefits and risks need to be considered for both the fetus and the mother. Heparin is the recommended anticoagulant in pregnancy. The pharmacokinetics of heparin will change in pregnancy as the total blood volume and glomerular filtration rate increase. This causes heparin to have a lower half-life and peak plasma concentration, so larger doses are required. The therapeutic dose of heparin was adjusted according to the activated partial thromboplastin time (aPTT), while the LMWH was adjusted according to the mother's weight. At prophylactic doses or moderate doses, the dose given is specific according to the type of drug given. The American Society of Hematology (ASH) recommends the use of LMWH over the use of UFH in the management of acute VTE, with the LMWH dose being once or divided into twice-daily doses.[18] For pregnant women receiving anticoagulant therapy, the ASH recommends scheduled delivery, with stopping anticoagulation a few days before delivery.18 Management of acute VTE in the anticoagulant regimen taken from the ACOG practical bulletin can be seen in Table 3.[7]

Table 3. Anticoagulant regimen [7]

Anticoagulant regimen	Dose
Prophylactic LMWH	Enoxaparin, 40 mg SC once daily Dalteparin, 5,000 U SC once daily Tinzaparin, 4,500 U SC once daily Nadroparin, 2850 U SC once daily
LMWH moderate dose	Enoxaparin, 40 mg SC every 12 hours Dalteparin, 5,000 U SC every 12 hours
LMWH therapeutic dose	Enoxaparin, 1 mg/kg every 12 hours Dalteparin, 200 U/kg once daily Tinzaparin, 175 U/kg once daily Dalteparin, 100U/kg every 12 hours Anti-Xa targets in a therapeutic range of 0.6-1.0U/ml 4 hours after injection at twice-daily doses; dose increase may be required for daily dosing.
Prophylactic UFH	UFH 5,000-7,000 U SC every 12 hours in the first trimester UFH 7,500-10,000 U SC every 12 hours in the second trimester UFH 10,000 U SC every 12 hours in the third trimester, unless the aPTT is elevated
UFH therapeutic dose	UFH 10,000 U or more SC every 12 hours with dose adjusted to aPTT in the therapeutic range (1.5-2.5x control) 6 hours after injection
Postpartum anticoagulation	Prophylactic, moderate, or therapeutic doses of LMWH for 6-8 weeks as indicated. Oral anticoagulation may be considered according to the duration of therapy, lactation, and patient preferences

CONCLUSIONS AND SUGGESTIONS

VTE risk assessment in all pregnant women needs to be done at the first antenatal visit or before pregnancy. Further assessment of thrombophilia needs to be carried out in pregnant women with a previous history of VTE. Thromboprophylaxis with heparin is indicated in patients at high risk of VTE, eg those with a history of high-risk thrombophilia and a history of recurrent VTE. The ASH recommends the use of LMWH compared with UFH for the management of acute VTE in pregnancy, in once-daily or divided doses. The recommended method of delivery for pregnant women receiving anticoagulant therapy should be planned delivery.

REFERENCES

1. Abe K, Kuklina EV, Hooper WC, Callaghan WM. Venous thromboembolism as a cause of severe maternal morbidity and mortality in the United States. Semin Perinatol. 2019;43(4):200–4.
2. Agnesha F, Rahardjo S. Tromboemboli pada kehamilan. Jurnal Komplikasi Anestesi. 2018;5:11.
3. Parunov LA, Soshitova NP, Ovanesov MV, Panteleev MA, Serebriyskiy II. Epidemiology of venous thromboembolism (TEV) associated with pregnancy. Birth Defects Res C Embryo Today. 2015;105(3):167–84.
4. Kane EV, Calderwood C, Dobbie R, Morris C, Roman E, Greer IA. A population-based study of venous thrombosis in pregnancy in Scotland 1980-2005. Eur J Obstet Gynecol Reprod Biol. 2013;169(2):223–9.
5. Devis P, Knuttinen MG. Deep venous thrombosis in pregnancy: incidence, pathogenesis and endovascular management. Cardiovasc Diagn Ther. 2017;7(Suppl 3):S309–19.
6. Dado CD, Levinson AT, Bourjeily G. Pregnancy and Pulmonary Embolism. Clin Chest Med. 2018;39(3):525–37.
7. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin No. 196: Thromboembolism in Pregnancy. Obstet Gynecol. 2018;132(1):e1–17.
8. Chan W-S. Diagnosis of venous thromboembolism in pregnancy. Thromb Res. 2018;163:221–8.
9. Chan W-S, Lee A, Spencer FA, Crowther M, Rodger M, Ramsay T, et al. Predicting deep venous thrombosis in pregnancy: out in "LEFt" field? Ann Intern Med. 2009;151(2):85–92.
10. Stein PD, Goldhaber SZ, Henry JW, Miller AC. Arterial blood gas analysis in the assessment of suspected acute pulmonary embolism. Chest. 1996;109(1):78–81.
11. Damodaram M, Kaladindi M, Luckit J, Yoong W. D-dimers as a screening test for venous thromboembolism in pregnancy: is it of any use? J Obstet Gynaecol. 2009;29(2):101–3.

12. Leung AN, Bull TM, Jaeschke R, Lockwood CJ, Boiselle PM, Hurwitz LM, et al. An official American Thoracic Society/Society of Thoracic Radiology clinical practice guideline: evaluation of suspected pulmonary embolism in pregnancy. Am J Respir Crit Care Med. 2011;184(10):1200–8.
13. D□Alton ME, Friedman AM, Smiley RM, Montgomery DM, Paidas MJ, D□Oria R, et al. National Partnership for Maternal Safety: Consensus Bundle on Venous Thromboembolism. Obstet Gynecol. 2016;128(4):688–98.
14. Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos A-M, Vandvik PO. TEV, Thrombophilia, Antithrombotic Therapy, and Pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. CHEST. 2012;141(2):e691S-e736S.
15. Middeldorp S. How I treat pregnancy-related venous thromboembolism. Blood. 2011 ;118(20):5394–400.
16. Leffert L, Butwick A, Carvalho B, Arendt K, Bates SM, Friedman A, et al. The Society for Obstetric Anesthesia and Perinatology Consensus Statement on the Anesthetic Management of Pregnant and Postpartum Women Receiving Thromboprophylaxis or Higher Dose Anticoagulants. Anesth Analg. 2018;126(3):928–44.
17. Maurizka AD. Catheter directed thrombolysis terapi emboli paru pada ibu hamil. Wellness And Healthy Magazine. 2020;2(1):41–8.
18. Shannon M. Bates, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism : venous thromboembolism in the context of pregnancy. 2018;2(22) : 3317-3358.