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Twisted umbilical cords at risk of cord entanglement to fetal death found at surgery

Original Research

- The difference of Bishop score change and labor event between oral and vaginal misoprostol in pregnancy beyond 41 weeks
- Characteristics of outpatient gynecology oncology services before and after COVID-19 pandemic at Ulin Regional General Hospital, Banjarmasin, Indonesia
- Description of the implementation of complementary therapy in midwifery services in Surabaya, Indonesia
- Is maternal pre-pregnancy Body Mass Index associated with type of Congenital Heart Disease in offspring?
- Testosterone and sexual function in menopausal women based on the Female Sexual Function Index (FSFI) score

Meta-Analysis

- The effect of micronutrients on postpartum pelvic organ prolapse patients

Review Article

- Impact of COVID-19 on the histopathological aspect of the placenta during pregnancy

Case Report

- The management of Monochorionic Monoamniotic (MCMA) twin pregnancy

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Address

Department of Obstetrics and Gynecology
Faculty of Medicine, Universitas Airlangga - Dr. Soetomo General Academic Hospital
Jl. Mayjen Prof dr Moestopo no. 6 – 8, Surabaya 60286, Indonesia. Phone: 62-31-5501185, Facs: 62-31-5037733
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Numerous studies[20-22] have.....
Smith's research .....[21]
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More than 3 authors eg. Smith et al.[24] reports.

ORIGINAL RESEARCH

The difference of Bishop score change and labor event between oral and vaginal misoprostol in pregnancy beyond 41 weeks

Maskasoni[1]*, Julian Dewantiningrum[2]
Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Diponegoro,
Dr. Kariadi General Academic Hospital, Semarang, Indonesia

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***Corresponding author:**
Maskasoni
maskasoni@gmail.com

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ABSTRACT

Objective: To compare Bishop score changes and labor event between oral and vaginal misoprostol in pregnancy beyond 41 weeks.
Materials and Methods: A total of 52 pregnant women with more than 41 weeks of gestation, had a Bishop score less than 5, and were undergoing induction labor were randomly divided into two groups: oral and vaginal misoprostol. In the oral misoprostol group, participants were given 25 mg of misoprostol in a solution with a concentration of 1 ug/ml every 2 hours. In the vaginal misoprostol group, a 25 mg misoprostol tablet was inserted into the posterior fornix every 6 hours. The two groups were compared in terms of Bishop score during the first 6 hours, changes in Bishop score, labor at term events, neonatal outcomes, complications, and side effects after the administration of misoprostol.
Results: The oral group showed significantly higher changes in Bishop score compared to the vaginal group (5.5 vs 3.6; p=0.0001). The median interval times for induction of labor at term, induction at stage II, and induction at birth were found to be shorter in the oral misoprostol group compared to the vaginal group (7.3 hours vs 10.6 hours, 14.0 hours vs 16.8 hours, and 14.6 hours vs 17.6 hours; p=0.002, 0.003, 0.002). Labor at term occurred much more frequently in the oral group (53.8% vs 15.4%). Additionally, the oral misoprostol group had a 3.5 times higher likelihood of experiencing labor at term within the first 6 hours after the initial administration compared to the vaginal group (OR 3.5, 95% CI 1.33-9.23).
Conclusion: Oral administration of misoprostol for cervical ripening has been demonstrated to be more effective than vaginal administration, greater bishop score changes while maintaining an equivalent level of safety.

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doi: 10.20473/mog.V31I22023.61-67.

Highlights:

1. Oral misoprostol is more effective than vaginal misoprostol in cervical ripening as a part of induction of labor.
2. Oral misoprostol is as safe as vaginal misoprostol.

INTRODUCTION

Perinatal mortality and morbidity rates tend to increase in pregnancies that go beyond 41 weeks.[1] Morbidity in such cases can be attributed to issues like placental dysfunction, decreased amniotic fluid volume, and macrosomia.[2-5] Effective management of induction labor and regular antenatal care are crucial strategies for reducing perinatal mortality and morbidity.[6] The use of misoprostol for cervical ripening in the induction of labor for pregnancies beyond 41 weeks with an unfavorable cervix is a well-established approach.[7] Both oral and vaginal administration of misoprostol have been shown to be effective in inducing labor, with oral administration offering the advantages of lower risks of surgical complications and reduced uterine hyper-

stimulation.[5,8] Additionally, the use of oral misoprostol is more convenient for both healthcare providers and patients.[9]

The Bishop score is a widely used scoring system in obstetrics to assess the readiness of the cervix for labor induction. It evaluates specific cervical parameters, including cervical dilation, effacement, consistency, position, and fetal station.[10] Each parameter is assigned a score ranging from 0 to 3 or 4, depending on the scoring system used.

The Bishop score provides valuable information about the cervical status and helps healthcare providers determine the appropriate method and timing of labor induction. Higher Bishop scores indicate a more favorable cervix, which is associated with increased chances of successful induction and shorter labor duration.[10] On the other hand, lower Bishop scores suggest an unfavorable cervix that may require additional cervical ripening methods before proceeding with labor induction.

The changes in the Bishop score over time during labor induction reflect the progress of cervical ripening and readiness for childbirth. As the cervix ripens, it becomes softer, effaced, and dilated, resulting in an increase in the Bishop score. Monitoring the changes in the Bishop score allows healthcare providers to assess the effectiveness of cervical ripening methods and make informed decisions regarding the management of labor induction.[10] The aim of this study was to compare changes in the Bishop score and labor events between patients receiving oral and vaginal misoprostol for labor induction in pregnancies that have gone beyond 41 weeks.

MATERIALS AND METHODS

This experimental study was conducted in maternity room of the Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Diponegoro, Kariadi Hospital, Semarang, Indonesia, and its satellite hospital (Dr. Soeselo Hospital in Slawi, Dr. R Soetrasno Hospital in Rembang, Margono Hospital in Purwokerto, and Semarang Regional Hospital, all in Indonesia), from January 2019 until the desired sample size was fulfilled. The study included pregnant patients with a gestational age of ≥41 weeks, singleton pregnancies, and a Bishop score <5 who were admitted to Dr. Kariadi Hospital and its satellite hospitals for labor induction. Patients with conditions such as premature rupture of membranes, fetal abnormalities, placentomegaly, urinary tract infections, asthma, diabetes, dyslipidemia, obesity, hypotension, anemia, and autoimmune diseases were excluded from the study. Patients were considered drop-outs if they experienced uterine rupture, uterine hyperstimulation, fetal distress, or refused to continue with the induction process.

We employed the consecutive sampling method and divided the participants into two groups using a simple randomization method, with each group consisting of a minimum of 20 patients. The first group received oral misoprostol by dissolving 200 µg misoprostol tablets into 200 cc of mineral water, and then 25 cc of the solution was given to the patient every 2 hours, up to a maximum of six doses. Intravaginal placebo tablets were also administered to this group. The second group received oral placebo tablets following a similar method as the first group, along with intravaginal misoprostol tablets. If a patient entered the labor phase, misoprostol administration was discontinued. The Bishop score examination was performed before and after the treatment, and changes in the scores were calculated by subtracting the pre-treatment score from the post-treatment score. The examinations were conducted by a senior resident. To minimize measurement bias we employed Interrater Reliability analysis using the Intraclass Correlation method. A coefficient value above 0.8 was considered indicative of good correlation. The WHO modified Bishop score, as shown in Table 1, was utilized for the assessment.

Table 1. Modified Bishop score

Score	Dilatation	Cervical length (cm)	Station	Consistency	Position
0	0	>4	-3	Firm	Posterior
1	1-2	3-4	-2	Intermediate	Medial
2	3-4	1-2	-1	Soft	Anterior
3	≥5	<1	1/2		

Prior to the study, informed consent was obtained from all participants, ensuring their understanding and voluntary participation. In cases where uterine tachysystole was observed, the patient received 250 µg of the medication intravenously to either manage acute tocolysis or proceed with a cesarean section if necessary. The administration of terbutaline/salbutamol was discontinued if the patient's heart rate exceeded 140 beats per minute. Statistical analysis was performed using the independent t-test for ratio variables and the Chi-square test for nominal variables. Multivariate analysis was conducted using logistic regression analysis to assess the relationships between variables. Results were considered statistically significant if $p<0.05$. This study was approved by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Diponegoro (Approval No: 15/EC/FK-RSDK/1/2019).

RESULTS AND DISCUSSION

A total of 52 people was included in our study, 26 people in the oral misoprostol group and 26 in the vaginal misoprostol group, with the characteristics as seen in Table 2, where there are no significant differences in subjects' age, parity, abortion, gestational age and BMI between the two treatment groups.

Table 2. Subject characteristics.

	Groups						
	Oral			Vaginal			
	Mean ± SD	Median (min-max)	N (%)	Mean ± SD	Median (min-max)	N (%)	P
Age (years)	26 ± 3.0	26 (22.0-32.0)		25 ± 4.0	24 (19-34)		0.14*
Parity		0 (0.0-2.0)			0 (0.0-2.0)		0.71*
Abortion		0 (0.0-1.0)			0 (0.0-1.0)		1.00*
Gestation age (weeks)	41.2 ± 0.37	41 (41.0-42.0)		41.2 ± 0.37	41 (41.0-42.0)		1.00*
BMI	26.3 ± 2.3	26.2 (22.0-32.4)		25.6 ± 1.9	25.8 (20.2-28.3)		0.22#
Normoweight			2 (7.7)			1 (3.8)	
Overweight			7 (26.9)			9 (34.6)	
Obese			17 (65.4)			16 (61.5)	

*Mann Whitney test; # T-Independent test

Table 3. Bishop score differences.

	Group				p
	Oral		Vaginal		
	Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)	
Preripening	1.2 ± 0.99	1.0 (0.0-3.0)	1.0 ± 1.11	1.0 (0.0-3.0)	0.411
After 6 hours	5.5 ± 1.36	5.5 (3.0-7.0)	3.6 ± 1.60	3.0 (2.0-7.0)	0.0001
Bishop score differences	4.3 ± 1.19	4.0 (2.0-6.0)	2.5 ± 0.81	2.0 (1.0-4.0)	0.0001
Induction - first stage labor interval (hours)	7.3 ± 2.80	6.0 (3.5-12.25)	10.6 ± 2.92	11.25 (4.0-14.5)	0.0001
Induction - second stage labor interval (hours)	14.0 ± 2.97	14.4 (8.5-20.0)	16.75 ± 3.95	17.5 (7.5-21.5)	0.003
Induction - delivery (hours)	14.6 ± 3.1	14.75 (8.75-21.0)	17.6 ± 4.03	18.6 (8.0-22.5)	0.002

Mann-whitney test

Table 4. Labor events differences

		Labor		Total	p	OR	IK 95%
		Yes	No				
Treatments	Oral	14 (53.8)	12 (46.2)	26 (100.0)	0.004	3.5	1.33-9.23
	Vaginal	4 (15.4)	22 (84.2)	26 (100.0)			

Chi-square test

Table 5. Neonatal outcomes, complications and side effects of misoprostol

		Groups				p
		Oral		Vaginal		
		n	%	n	%	
Apgar Score	≥7	25	96.2	26	100.0	1.00
First five minutes	<7	1	3.8	0	0.0	
Threated uterine rupture	Yes	0	0.0	0	0.0	
	No	26	100.0	26	100.0	
Hyperstimulation	Yes	0	0.0	0	0.0	
	No	26	100.0	26	100.0	
Meconeum	Yes	0	0.0	2	7.7	0.54
	No	26	100.0	24	92.3	
Nausea and Vomiting	Yes	0	0.0	0	0.0	
	No	26	100.0	26	100.0	
Fever	Yes	2	7.7	0	0.0	0.54
	No	24	92.3	26	100.0	
Diarrhea	Yes	0	0.0	0	0.0	
	No	26	100.0	26	100.0	

Chi-Square test

Table 3 shows significant differences in mean Bishop scores within six hours after misoprostol administration in both groups (p=0.0001). Bishop scores changes in oral group were greater than vaginal misoprostol group (5.5 vs 3.6). The mean interval between induction to first stage labor, induction to second stage labor and induction to delivery was also shorter in oral than vaginal misoprostol group (7.3 hours vs. 10.6 hours, 14.0 hours vs 16.8 hours, and 14.6 hours vs. 17.6 hours; p=0.002; 0.003; 0.002, respectively). Table 3 shows that within six hours of misoprostol administration, labor incidence was greater in the oral compared to the vaginal group (53.8% vs 15.4%). The oral misoprostol group was 3.5 times more likely to be in labor after six hours after the first administration than the vaginal group (OR 3.5 ’95% CI 1.33-9.23).

First five-minute APGAR score <7 was only found in the oral misoprostol group (3.8%; p=1.00). Meconeum stain in amniotic fluid occurred in 2 patients in vaginal misoprostol group (7.7%; p=0.54) and 2 cases of fever in the oral misoprostol group (7.7%; p=0.54). The administration of oral misoprostol was as safe as vaginal misoprostol in terms of fetal outcome, complications and side effects of the drug.

Several maternal characteristics were associated with successful cervical ripening and labor induction, including: parity and gestational age. Age and pre-pregnancy body mass index (BMI) also related to successful cervical ripening and labor induction.[11-13] In our study, age, parity, BMI, and pre-ripening Bishop scores variables did not show any significant differences between two groups. Therefore, it can be excluded as confounding factor.

The clinical parameters commonly used to predict successful labor induction are Bishop scores. The relationship between Bishop scores and successful labor induction varies.[14] In our study we found that Bishop scores mean difference in the oral group were greater than in the vaginal group (5.5 vs 3.6). The mean interval between induction to first stage labor, induction to second stage labor and induction to delivery also shorter in the oral misoprostol than in the vaginal group (7.3 hours vs. 10.6 hours, 14.0 hours vs 16.8 hours, and 14.6 hours vs. 17.6 hours, respectively).

Cochrane Systematic Review by Alfirevic's et al, from nine RCT studies found that oral misoprostol was more effective than placebo.[15] RCTs showed that oral misoprostol is as effective as vaginal misoprostol.[4,15] WHO recommendation in labor induction was to use 25 µg misoprostol oral, and compared to placebo, oral misoprostol reduced the risk of 24 hours vaginal delivery failure six times greater than placebo.[4] Compared to vaginal misoprostol, oral misoprostol has similar efficacy.[15]
Abbassi’s study that compared safety and effectivity of oral and vaginal misoprostol for labor induction at term pregnancy showed that Bishop scores changes after six hours were greater in the oral group than in the vaginal group (3.6 ± 3.09 vs. 3.3 ± 3.45). Induction to delivery interval was shorter in the oral compared to vaginal group (7.5 ± 4.4 hours vs. 7.5 ± 4.4 hours).[16] Successful vaginal delivery in the oral group was greater than in the vaginal group (95 % vs 80%).[13] Paungmora et al. found that the induction to delivery interval in the oral misoprostol group was shorter than the vaginal group (14.3 hours vs. 15.8 hours).[17]

Oral misoprostol efficacy is due to the fast-oral absorption. It reaches peak concentration after 12 minutes, half-life of 20-30 minutes). Misoprostol vaginal takes longer to work, has a lower peak value with peak concentration after 60 minutes, but the effect

is more persistent. Vaginal misoprostol had greater reproductive tract effects than gastrointestinal tract will decrease. If a misoprostol tablet is placed in the posterior fornix of the vagina. The plasma concentration of misoprostol reaches a peak after two hours and will slowly decreases. Vaginal administration of misoprostol causes slow increase of plasma concentration and its peak value was also lower compared to oral administration, but the overall effect of the drug is higher.[18]

Misoprostol as a cervical ripening agent, stimulate fibroblasts to synthesize hyaluronan through EP4 receptors. Hyaluronan (HA) is a glycosaminoglycan that will draw water into the cervical stroma and soften the cervix.[18-22] Degradation of hyaluronan by hyaluronidase enzyme into small molecules will trigger an inflammatory response in the cervix, followed by leukocytes influx. Degranulation of neutrophils will release collagenase enzyme (MMP-8) and trigger IL-6 and IL-8 cytokines production, followed by disorganization of extra cellular collagen matrix. Inflammatory cells influx is also triggered by misoprostol via EP-2 receptors by increasing capillary permeability in order to facilitate leukocyte diapedesis.[21]

In our study, we found first five-minute APGAR score <7 in 3.8% of oral misoprostol group and meconium amniotic fluid stain in 7.7% of the vaginal misoprostol group, but both of them were not statistically significant. Similar to our findings, a meta-analysis by Alfirevic et al. also showed first five-minutes APGAR scores <7 as neonatal outcomes after labor induction with oral misoprostol was lower compared to vaginal misoprostol (RR 0.6 CI 95% 0.44-0.82).15 Meconium excretion risk was also higher in the oral misoprostol group (RR 1.22 CI 95% 1.03-1.44). Compared to placebo, the complications of uterine hyperstimulation in labor induction with oral misoprostol did not differ significantly (RR 4.78 CI 95 % 0.73-31.32) from that in vaginal misoprostol group (RR 2.67 CI 95% 0.73-9.76).[15] In our study, the uterine hyperstimulation complications did not occur in either group of study subjects.

Side effects of misoprostol administration in our study were fever in 7.7% oral misoprostol group, while gastrointestinal side effects did not occur. From this result, in terms of fetal outcome, drug complications and side effects, the safety of oral misoprostol administration was similar to vaginal misoprostol. Our results also confirmed a study by Alfirevic et al which found that nausea, vomiting, diarrhea and shivering in oral misoprostol induction was similar in oral and vaginal misoprostol administration.[15]

Prostaglandin E increased thermostat set point, resulted in body shivering and increased body temperature. This side effects is related to dosage and route of administration.[23] Per rectal misoprostol administration appears to be associated with lower serum concentrations and milder side effects compared to oral administration.[24] Clinical trials in the United Kingdom report that the side effects of shivering are more common in 600ug oral compared to vaginal misoprostol. These side effects were independent with per rectal route dose.[18] Shivering is self-limiting side effect and does not need further treatment, and the outcome as good as other cases without fever.[23] Some pathogenesis of the fever was unknown. Genetic and environmental factors may influence the occurrence of these side effects which requires further research.[23]

Misoprostol may cause diarrhea because it has an effect to increase cyclic AMP in gastrointestinal tract. This increment will cause secretion of CL- and HCO3-, also passive expenditure of Na+, K+, and water, and inhibits Na+ and CL- into the erythrocyte.[25]

Our study was a second phase clinical trial in phase III humans to compare the efficacy of standard treatment method of vaginal misoprostol and oral misoprostol for labor induction. Screening for several confounding factors and maternal characteristics, which may have affected our study results, were done through inclusion and exclusion criteria as well as through the comparison study between maternal characteristics in both treatment group and control group. Randomization and blinding were also performed to reduce the selection bias in our study. The power in our study was set to 80% with type I error 5%. Bias found in the study was caused by Bishop Score measurement and treatment was delivered by one appointed research assistant, a yellow pin, operator level, obstetric resident. Several limitations in our study were Bishop Score parameter and labor measurement still used traditional methods by cervical examination and uterine contraction palpation. These methods were very subjective. However, they were still the standard method in obstetric department. The more objective alternative for Bishop score measurement is ultrasonography and chemical biomarker, which are still under research. The administration of vaginal misoprostol tablet of 25 mg was divided into 8 parts (200 mg) by research assistant. Thus, the allocation may not be equal and it was one of the limitations in our study. Then, oral administration of 25 ug was given every 2 hours. Thus, the cumulative dosage in oral misoprostol group was higher than in vaginal misoprostol group, even though the clearance effect in oral misoprostol group is about ± 2 hours. This may be a factor that needs further investigation.

CONCLUSION

Oral misoprostol administration as a cervical ripening agent may be more effective compared to vaginal administration. Furthermore, in oral misoprostol treatment group there was greater change in Bishop score and shorter interval time of induction to first stage of labor as well as shorter induction to second stage of labor and induction to delivery. The output for neonates, maternal complications, and adverse events of medication suggested that oral misoprostol administration is as safe as misoprostol administered vaginally.

DISCLOSURE

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Conflict of interest

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ORIGINAL RESEARCH

Characteristics of outpatient gynecology oncology services before and after COVID-19 pandemic at Ulin Regional General Hospital, Banjarmasin, Indonesia

Setyo Teguh Waluyo[1]*, Ferry Armanza[1], Hariadi Yuseran[1], Kevin Stanley Halim[2]
[1]Department of Obstetrics and Gynecology, Lambung Mangkurat University, Ulin Regional General Hospital Banjarmasin, South Kalimantan, Indonesia.
[2]Medical Education Program, Department of Obstetrics and Gynecology, Lambung Mangkurat University, Ulin Regional General Hospital Banjarmasin, South Kalimantan, Indonesia.

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***Corresponding author:**
Setyo Teguh Waluyo
setyo.teguh.waluyo-2021@fk.unair.ac.id

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ABSTRACT

Objective: The aim of this study was to investigate the characteristics of the Gynecology Oncology Outpatient Clinic at Ulin Hospital Banjarmasin before and after the COVID-19 pandemic.

Materials and Methods: This descriptive study utilized existing patient data from the Gynecology Oncology Outpatient Clinic at Ulin Hospital Banjarmasin covering the period from March 2019 to February 2021. The study received ethical approval from the Ulin General Hospital ethics committee with clearance number 10/I-Reg Research/RSUDU/23. The collected data was presented in a tabular format to compare the service characteristics before the pandemic (March 2019 - February 2020) and after the pandemic (March 2020 – February 2021).

Results: During the periods of March 2019 – February 2020 and March 2020 – February 2021, there was a reduction of 19% in patient visits. The number of patients undergoing treatment also decreased, from 1081 patients (53.9%) in the period of March 2019 – February 2020 to 926 patients (46.1%) in the period of March 2020 – February 2021. Notably, there was a decrease in the number of patients undergoing surgical procedures, dropping from 76 patients (70.4%) in the period of March 2019 – February 2020 to 32 patients (29.6%) in the period of March 2020 – February 2021. A similar trend was seen in patients receiving chemotherapy, with the count decreasing from 1005 patients (52.9%) in the period of March 2019 – February 2020 to 894 patients (47.1%) in the period of March 2020 – February 2021. These changes were attributed to various hospital measures implemented to address the COVID-19 pandemic, including a reduction in outpatient clinic visits and the temporary suspension of surgical procedures from March 2020 to October 2020 to minimize potential exposure.

Conclusion: The study highlights a noticeable decline in both the frequency of visits to the Gynecology Oncology Outpatient Clinic at Ulin Regional General Hospital Banjarmasin and the number of patients receiving treatment during the periods before and after the onset of the COVID-19 pandemic.

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Highlights:

1. The characteristics of gynecology oncology services at Ulin Regional General Hospital before and after the COVID-19 pandemic were evaluated.
2. There was a decrease of 19% in the number of visits by Gynecology Oncology Clinic patients at Ulin Regional General Hospital between the period of March 2019 - February 2020 and March 2020 - February 2021.

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is a global health issue that affects many aspects of life. Since its first appearance in Wuhan City, China, at the end of 2019, the number of morbidities and deaths due to COVID-19 has continued to grow. The number of COVID-19 patients in Indonesia has reached 1.76 million patients, with the number of patients dying reaching 48,876 people on May 21, 2021.[1]

The risk of COVID-19 complications is greater in groups with certain comorbidities, for example patients with a history of malignancy. Research by O'Neill, et al. stated that mortality due to COVID-19 with patients with cancer was 7.6%, relatively high compared to the mortality rate of COVID-19 in patients without comorbidities of 1.4%.[2] Research by Leibold et al involving six hospitals in New York stated that patients with gynecological cancer had more severe COVID-19 infection, of which 54.5% of patients needed hospitalization, 30.3% needed treatment in an intensive care unit, and 14% died from complications of COVID-19, showing a mortality rate much higher than the general population.[3] Cancer patients were 3.56 times more likely to suffer from severe symptoms than patients without a history of malignancy. This is suspected due to the presence of an active malignancy as well as oncology therapy that gives rise to a decrease in physical capacity and immunosuppression status. For this reason, interruption of therapy should be considered in patients with active COVID-19 infection until the patient recovers, especially if the therapy used is an immunosuppressive therapy that is cytotoxic.[4]

COVID-19 has had a devastating impact on all aspects of health services, including gynecology oncology services. A survey by the Italian Society of Gynecology (SIGO) stated that the impact of COVID-19 on gynecology oncology service practices reached 70%, and the decline in service quality reached 46%.[5] A survey by the Indian Association of Gynecology Oncology also stated that there were barriers to service during the COVID-19 pandemic. 71% of practitioners delayed elective surgery services. 52% of practitioners delayed new patient diagnostic services for up to two weeks, and even 27% of practitioners delayed services for up to six weeks. 54% of practitioners delayed the control schedule of patients who had been declared disease-free.[6] Research by Khazaeipour et al based in Iran states that visits to gynecology oncology clinics decreased by 63% in 2020 compared to 2019.[7]

Hospitals are one of the significant places of transmission of COVID-19, therefore high standards are needed to protect patients and staff of health workers. This can be an obstacle to providing services to patients, especially gynecology oncology patients, because it is necessary to select interventions based on disease priorities to minimize the transmission of COVID-19. Gynecology oncology health services, especially surgical therapy, need to be studied based on a priority scale, namely: availability of resources, prevalence of disease, characteristics of patients and diseases, and prediction of disease output if delayed. Top priority is given to patients with minimally invasive treatment as well as a prediction of short hospitalization times. Priority is also given to curative procedures with a high success rate at early-stage malignancies, as well as malignancies that require cytoductative surgery after neoadjuvant chemotherapy.[8]

Service management is also one of the important elements in preventing the transmission of COVID-19 during therapy. Health protocols and efforts to minimize contact are recommended to prevent transmission, for example: the implementation of consultations with telephone agreements, the use of indoor N95 masks, the implementation of social distancing, conducting remote consultations (if possible), reduction of procedures aimed at screening only (e.g. mammography and pap-smear in healthy patients), delays in measures in COVID-19 patients (except when in the emergency), separation of emergency operating rooms and elective surgeries, and so on.[9] People whose treatment for cancer is delayed by even one month have in many cases a 6 to 13% higher risk of dying, a risk that keeps rising the longer their treatment does not begin. The need for better understanding of the impact of treatment delay on outcomes has come into focus during the COVID-19 pandemic because many countries have experienced deferral of elective cancer surgery and radiotherapy as well as reductions in the use of systemic therapies, while health systems have directed resources to preparing for the pandemic. Based on this background, this study aims to see and evaluate the characteristics of outpatient gynecology oncology services at Ulin Regional General Hospital before and after the COVID-19 pandemic.

MATERIALS AND METHODS

This research was an analytical descriptive study conducted during the period from March 2019 to February 2021 at the Ulin Regional General Hospital, Banjarmasin, Indonesia, and had been registered to the Ulin General Hospital ethics committee with ethical clearance number 10/I-Reg Research/RSUDU/23. This study used secondary data from Gynecology Oncology Clinic patients at Ulin Regional General Hospital for the period of March 2019 – February 2021. The data

obtained in this study was in the form of descriptive data. The statistics used were descriptive statistics by describing the collected data and presenting them in tables.

RESULTS AND DISCUSSION

The data were divided into two distinct time frames: the pre-COVID-19 pandemic interval (March 2019 to February 2020) and the COVID-19 pandemic interval (March 2020 to February 2021). Within the Ulin Regional General Hospital, a total of 6833 patients were treated for gynecology oncology conditions. Specifically, during the period spanning from March 2019 to February 2020, there were 4069 patients (59.5%), and during the period from March 2020 to February 2021, there were 2674 patients (40.5%).

The dominant diagnosis observed throughout both time periods was cervical cancer, accounting for 1622 patients (57.2%) between March 2019 and February 2020, and 1212 patients (42.8%) between March 2020 and February 2021. The second most prevalent diagnosis in both intervals was ovarian cancer, comprising 896 patients (60.1%) from March 2019 to February 2020, and 596 patients (39.9%) from March 2020 to February 2021. Conversely, the least common diagnosis across both periods was uterine corpus cancer, encompassing 14 patients (93.3%) between March 2019 and February 2020, and 1 patient (6.7%) between March 2020 and February 2021.

Among the cohort of 2007 gynecology oncology patients treated at Ulin Regional General Hospital, 1081 patients (53.9%) received treatment during the March 2019 to February 2020 period, while 926 patients (46.1%) received treatment during the March 2020 to February 2021 period. A total of 76 patients (70.4%) underwent surgical intervention from March 2019 to February 2020, which decreased to 32 patients (29.6%) from March 2020 to February 2021. Similarly, 1005 patients (53.9%) underwent chemotherapy between March 2019 and February 2020, and 926 patients (46.1%) underwent chemotherapy between March 2020 and February 2021.

From 2007 gynecology oncology patients who underwent surgery and chemotherapy at Ulin Regional General Hospital, the outcomes, as detailed in Table 3, were as follows. In the period from March 2019 to February 2020, 918 patients (84.92%) experienced clinical improvement, and 68 patients (89.47%) received treatment in the postoperative intensive care unit (ICU). Notably, there were no reported deaths following procedures during this period. In contrast, during the period from March 2020 to February 2021, 648 patients (69.27%) were treated in the postoperative ICU, and no instances of disease stage progression were observed. Regrettably, there were 9 patients (0.97%) who succumbed to their conditions after receiving gynecology oncology therapy within the March 2019 to February 2021 period.

Table 1. Data on gynecology oncology patients at Ulin Regional General Hospital for the period of March 2019 – February 2021.

Diagnosis	March 2019 - February 2020		March 2020 - February 2021	
	n	%	n	%
Cervical cancer	1622	57.2	1212	42.8
Ovarian cancer	896	60.1	596	39.9
Cystic ovary neoplasm	812	60.4	533	39.6
Solid ovary tumor	310	70.9	127	29.1
Endometrial cancer	177	71.1	72	28.9
Vaginal cancer	74	67.9	35	32.1
Uterine corpus cancer	14	93.3	1	6.7
Gestational trophoblastic neoplasm	164	46.6	188	53.4
Total	4069	59.5	2764	40.5

Table 2. Data on gynecology oncology measures at Ulin Regional General Hospital for the period of March 2019 – February 2021

Treatment	March 2019 - February 2020		March 2020 - February 2021	
	n	%	n	%
Surgery	76	70.4	32	29.6
Chemotherapy	1005	52.9	894	47.1
Total	1081	53.9	926	46.1

Table 3. Output data of gynecology oncology therapy at Ulin Regional General Hospital for the period of March 2019 – February 2021.

Outcome	March 2019 - February 2020		March 2020 - February 2021	
	n	%	n	%
Clinical improvement	918	84.92	648	69.97
Intensive care post-surgery	68	89.47	0	0
Death	0	0	9	0.97

Global trends revealed a decline in gynecology oncology patient visits across diverse regions. Research by Rimmer et al., in the United Kingdom, underscored the impact of the COVID-19 pandemic on gynecological service units. An extensive 79.1% of units reduced in-person clinic interactions, while 88.5% deferred elective gynecology services, and 55.4% curtailed schedules for oncological interventions.[10] A survey conducted by the Italian Society of Gynecology (SIGO) further substantiated these observations, indicating that 70% of practices experienced COVID-19-induced modifications, accompanied by a 46% deterioration in service quality.[5] Similarly, the Indian Association of Gynecology Oncology reports that 71% of practitioners delayed elective surgeries, 52% delayed new patient diagnostic services for up to two weeks, and 27% extended service delays to six weeks. Furthermore, 54% of practitioners postponed follow-up appointments for previously cleared patients.[6] A study conducted by Khazaeipour et al. in Iran revealed a substantial 63% reduction in gynecology oncology clinic visits during 2020 compared to the pre-pandemic year of 2019.[7] The reduction in oncology patient visits is not solely attributed to external factors; patient concerns contributed significantly. Investigations by Lou et al. in the United States underscored the challenges imposed by the pandemic, with 50.8% of respondents encountering impediments to cancer therapy due to COVID-19 fears. Of those actively receiving cancer treatment, 71.9% expressed apprehension about contracting COVID-19 within healthcare settings, and 90.8% expressed anxiety over severe manifestations if infected.[11]

Correspondingly, Ray et al.'s research in an Indian cancer oncology center disclosed that 78% of patients apprehended COVID-19 exposure, with 51% manifesting profound fear due to concerns about fatal outcomes. This apprehension lead into delays in disease monitoring and evaluation. Gultekin et al.'s study underscored patients' cognizance of cancer as a COVID-19 vulnerability (73.2%), though only 17.5% demonstrated greater fear of COVID-19 than their cancer condition. In contrast, 71% manifested anxiety concerning cancer progression due to potential treatment delays. The average HADS (Hospital Anxiety and Depression Scale) scores reflected considerable anxiety and depression, registering at 8.8.[13]

In line with previous studies, this study underscored a pronounced decrease in patient visits post-COVID-19. Comparing patient visits between March 2019 to February 2020 and March 2020 to February 2021 revealed a significant 19% reduction. This decline was due to the imposition of patient visit limits, with a maximum of 25 patients at the Gynecology Oncology Clinic of Ulin Regional General Hospital, aimed at curtailing COVID-19 transmission.

Comparable patterns were found when considering procedural uptake, evidenced by a decrease from 1081 patients (53.9%) in March 2019 - February 2020 to 926 patients (46.1%) in March 2020 - February 2021. Remarkably, a policy shift temporarily suspended gynecology oncology surgeries from March 2021 to October 2021, resulting in a decline from 76 patients (70.4%) to 32 patients (29.6%). A similar decline in patients undergoing chemotherapy was also observed, from 1005 patients (52.9%) in March 2019 - February 2020 to 894 patients (47.1%) in March 2020 - February 2021.

The pandemic-induced condition was reflected in patient outcomes, revealing increased mortality rates during the pandemic (9 patients, 0.97%), surpassing pre-pandemic levels. Notably, the number of patients experiencing clinical improvement dropped from 918 (84.92%) to 648 (69.97%). Correspondingly, the rate of postoperative ICU treatments diminished due to a decline in surgical cases, potentially stemming from prolonged delay of elective services. The reduction of face-to-face clinic interactions further compounded delays in disease detection and therapeutic intervention.

In the context of the COVID-19 pandemic, service adaptations are imperative, guided by established standards, to both mitigate virus transmission and deliver optimal care. Institutional adherence to well-constructed Standard Operational Procedures (SOPs), informed by ethical principles and procedural values, underpins health facility readiness and excellence, in alignment with national guidelines. These SOPs should

allow for swift revisions, if warranted, within a 3–4-week timeframe to effectively respond to evolving pandemic dynamics.[14] The preparedness evaluation for health facilities embraces multiple facets, including the availability of personal protective equipment (PPE), functional blood banks, proficient surgical teams, nursing support, sterile equipment, room capacity, negatively pressurized operating rooms, specialized treatment spaces, and prompt emergency management. Effective scheduling, in accordance to available resources and individual patient needs, must be orchestrated across the hospital system to ensure patient-specific care.[15] Services falling short of minimal standards may detrimentally affect patients and potentially amplify viral transmission.[16]

Adjustments to therapy management for gynecology oncology patients during the COVID-19 pandemic are needed to ensure that each patient continues to receive optimal, adequate, and appropriate therapy according to patient needs. Various ways can be done to prevent the transmission of COVID-19 in health facilities, for example in outpatient clinics. It is necessary to limit visits, for example, only accepting new patient visits, consultations on acute oncology problems, as well as patients in active therapy programs. Restrictions on the number of clinicians, supporting health workers, residents and students (where possible) need to be carried out to prevent exposure. Face-to-face meetings should be diverted to telemedicine whenever possible, or done by appointment and limit the number of introductions.

Restrictions on examination measures that are not strictly necessary in asymptomatic patients also need to be considered, for example routine imaging examinations or serum markers.[17] The study by Quam et al. collected data through a survey of 188 gynecological cancer patients regarding the satisfaction rate of telemedicine use and obtained results that 80.5% of the participants were satisfied with telemedicine use and 54.8% recommended for telemedicine use in patients with similar conditions. The rest expressed concern that something would go wrong if they did not have face-to-face meetings, but in practice, telemedicine requires an adaptation, a thorough evaluation of the patient's condition and education of the patient.[18]

The operation is best done on a priority scale. Elective surgery can be delayed for 4 weeks in cases such as germ cell tumors, early-stage cervical cancer, high-risk uterine cancer, early-stage ovarian cancer, primary vulvar tumor resection. A longer delay (10 to 12 weeks) can be made in cases of early-stage uterine cancer or microinvasive cervical cancer that can be treated by local excision measures. Chemotherapy is preferred for patients with a percentage of chemotherapy success of more than 50% or adjuvant therapy which increases the probability of recovery by as much as 50% after surgery or radiotherapy. The lowest priority is given to patients receiving non-curative or palliative therapy with a moderate cure rate (15% - 50%) or life expectancy of less than one year.[19]

Protection of health workers needs to be carried out optimally. The use of personal protective equipment is carried out anytime and anywhere, as well as providing training on the use of personal protective equipment and identification of patients suspected of COVID-19. Personnel with significant immunocompromised and comorbid conditions are transferred to the administrative department, as well as the implementation of strict self-isolation in case of illness. Refreshment of insights about COVID-19 needs to be done regularly with online-based seminars.[20]

CONCLUSION

There was a decrease in the number of visits by Gynecology Oncology Clinic patients at Ulin Regional General Hospital, Banjarmasin, Indonesia, between the period of March 2019 - February 2020 and March 2020 - February 2021, as much as 19% due to the restrictions on the number of visits aimed at reducing exposure and preventing the transmission of COVID-19 during the pandemic. The service of gynecology oncology patients during the COVID-19 pandemic was carried out with health protocols and good service management to prevent the transmission of COVID-19. Preventive efforts carried out including limiting face-to-face meetings and regular supporting diagnostics in asymptomatic patients, conducting remote consultations or telemedicine whenever possible, providing surgical and chemotherapy therapy according to the priority scale, as well as protecting health workers through the use of personal protective equipment, dividing tasks according to health conditions, and providing training for health workers.

DISCLOSURES

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Conflict of interest

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Author Contribution

All authors have contributed to all processes in this research, including preparation, data gathering and analysis, drafting and approval for publication of this manuscript.

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ORIGINAL RESEARCH

Description of the implementation of complementary therapy in midwifery services in Surabaya, Indonesia

Annisa' Wigati Rozifa*, Nova Elok Mardliyana, Irma Maya Puspita
Midwifery Study Program, Faculty of Health Sciences, Universitas Muhammadiyah Surabaya, Surabaya, Indonesia

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***Corresponding author:**
Annisa' Wigati Rozifa
annisa_wigati_rozifa
@um-surabaya.ac.id

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ABSTRACT

Objectives: This study aimed to describe the implementation of complementary therapy among the independent midwifery practices in Surabaya, Indonesia.
Materials and Methods: Employing a quantitative approach with a survey methodology, this study involved data collection through surveys administered to independent midwives practicing in Surabaya and midwives affiliated with independent midwifery practices. The questionnaires were containing the characteristics of the participants, the implementation of complementary therapies, and the complementary therapies integrated into the practice settings.
Results: The findings revealed that 25 midwives (comprising 52%) provided complementary midwifery services, whereas 23 midwives (comprising 48%) abstained from incorporating complementary midwifery services into their independent midwifery practices. The types of complementary therapies implemented consisted of aromatherapy, hypnotherapy, herbal medicine, baby massage and spa, maternity massage, oxytocin massage, and yoga.
Conclusion: This study concluded that 52% of independent midwives in Surabaya applied complementary therapy into their practices.

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Highlights:

1. Midwifery services are carried out by combining conventional and complementary midwifery services.
2. Types of complementary therapies applied by 52% of independent midwifery services in Surabaya consisted of aromatherapy, hypnotherapy, herbal medicine, baby massage and spa, maternity massage, oxytocin massage, and yoga.

INTRODUCTION

Midwifery services are an integral part of the health care system for pregnant women, maternity mothers, postpartum mothers, newborns, infants and children, women of reproductive age and the elderly. Currently, midwifery services combine conventional and complementary, which have become an essential part of midwifery practice.[1]

By the Regulation of the Minister of Health of the Republic of Indonesia, No. 1109/Menkes/Per/IX/2007, what is meant by complementary and alternative medicine is non-conventional medicine aimed at improving public health status, including promotive,

preventive, curative and rehabilitative with quality, safety, and high effectiveness.

In Indonesia, no law specifically regulates the implementation of complementary midwifery services.[2–7] Still, the implementation of complementary medicine, in general, has been regulated by the Minister of Health of the Republic of Indonesia, No. 1109/Menkes/Per/IX/ 2007 concerning complementary alternative medi-cine. People are attracted to complementary midwifery services because they are considered to have minimal effects than conventional or medical services. The increasing community needs and the development of research on complementary therapies are opportunities for midwives to participate according to community needs.[8]

In Indonesia, under the national program for Traditional and Complementary Medicine, the Center of Traditional Medicine Development (*Sentra Penapisan dan Pengembangan Penyehatan Tradisional*/SP3T) has implemented traditional medicine (TM) practice at 13 provinces since 1995 and complementary medicine (CM) practices were introduced in 12 pilot hospitals in 2010. This shows how national program for Traditional and Complementary Medicine has been distributed among the WHO regions. However, there was no data showing the overall number of midwives who apply complementary therapies in Indonesia.

The development of midwifery services through complementary midwifery services can be carried out in various forms, including massage for pregnant women and postpartum mothers, baby massage, and acupressure. Complementary midwifery services are an effort to increase added value, market competitiveness, and innovative advantages for the independent practice of midwives according to the expectations of users of midwifery services.[9] This study aimed to describe the implementation of complementary therapy at the independent midwife practices in Surabaya, Indonesia.

MATERIALS AND METHODS

This research was conducted using a survey method. Data collection was carried out by surveying midwives who had independent practice and midwives who were partners of midwife independent practice centers in Surabaya. The survey was conducted by distributing questionnaires containing the characteristics of the respondents, the implementation of complementary therapies and the types of complementary therapies applied to their practice.

The subjects in this study were midwives who had independent midwife practices and midwives who were partners of independent midwife practices. The research subjects consisted of population and sample. The population in this study were 177 midwives who had independent midwife practices and partners of independent midwife practices in the city of Surabaya, Indonesia. The samples were recruited using a purposive sampling technique and a total sample of 48 midwives was obtained. The inclusion criteria in this research included: Midwives registered and have permission to be able to carry out midwifery practices independently; active in professional organizations, and carry out midwifery practices in accordance with midwifery service standards; carrying out overall midwifery services (pregnancy, childbirth, infants and toddlers, and female reproductive health, and are willing to work with researchers to become respondents), while the exclusive criteria were respondents who did not fill out and did not follow a complete series of research.

The measuring instrument used in this study was the questionnaire that was compiled by the authors. The questionnaires were distributed to the respondents. The questions given were closed and open questions, which were answered directly by the respondents. The research data were displayed in the form of a frequency distribution, using SPSS 23 application. Chairman of the research ethics committee Universitas Muhammadiyah Surabaya, Indonesia, stated that this study was approved to be implemented, the approval was set on 19 October 2021 with the number: 021/KET/II.3/AU/F/ 2021.

RESULTS AND DISCUSSION

There were 25 midwives (52%) who carried out complementary therapy at independent midwife practices and 23 midwives (48%) who did not (Table 1). Midwives who did not apply complementary therapy because there was no high demand from the community in their surroundings for complementary therapy treatment. Besides, the professional organizations also do not require every midwifery service practice to apply complementary therapy.

Table 1. Implementation of complementary therapy in midwifery services at midwife independent practices

No	Implementation of Complementary Therapy	Frequency	Percentage (%)
1	Implemented	25	52
2	Not Implemented	23	48
	Total	48	100

Table 2 shows that the types of complementary therapy services applied by 25 midwives in their practice were 25 baby massage and spa by as many as nine midwives (36%), oxytocin massage by six midwives (24%), and followed by aromatherapy, hypnotherapy, herbal medicine, and yoga by two midwives (8%).

Table 2. Types of complementary therapies applied by midwifery services in midwives' independent practices

No	Types of complementary therapy	Frequency	Percentage (%)
1	Aromatherapy	2	8
2	Hypnotherapy	2	8
3	Herbal Medicine	2	8
4	Baby massage and spa	9	36
5	Maternity massage	2	8
6	Oxytocin massage	6	24
7	Yoga	2	8
	Total	25	100

Complementary and Alternative Medicine (CAM) is a broad collection of healthcare practices that are not part of a country's traditions and are not integrated into the dominant healthcare system.[10] Regulation of the Minister of Health of the Republic of Indonesia Number 15 of 2018 defines Complementary Traditional Health Services as the application of traditional health that utilizes biomedical and biocultural science. Its benefits and safety are scientifically proven.[11] Based on the results of the National Socio-Economic Survey (SUSENAS) on the use of traditional medicine, including complementary and alternative medicine, the traditional medicine have been used by 40% of the Indonesian population, and it is also increasing from year to year.[12]

By 2018, more than 85% of the total member states in the WHO African Region and South-East Asia Region reported having a national policy for Traditional and Complementary Medicine. In the WHO Western Pacific Region and the Eastern Mediterranean Region, 63% and 43% of member states, respectively, had a national policy framework in place, while in the WHO Region of the Americas and the European Region the percentages were 31% and 21%, respectively.[12]

The purpose of complementary therapy is to improve the function of the body's systems, especially the immune and defense systems so that the body can heal itself when it is sick by listening and responding with good and complete nutritional intake and proper care.[12] The role that midwives can provide in complementary or alternative therapies can be adapted to the current care role according to the limits of their abilities. The increasing needs of the community and the development of research on complementary therapies are opportunities for midwives to participate according to community needs. Midwives can act as consultants to clients in selecting appropriate alternatives or help provide direct therapy. Complementary midwifery services are an option to reduce medical interventions during pregnancy and childbirth as has been shown by experience.[13–20] However, this needs to be further developed through research so that it can be applied to provide better midwifery therapy.[21]

The results showed that some midwives still apply complementary therapies in their practice. This is in line with research by Holden, which states that the interest of the public who wants to use complementary therapy services is only one-third of the total number of people. The rest of the community still uses conventional therapy.[22]

In addition, there are still many midwives who have yet to apply complementary therapies in their practice. This can be due to the lack of a strong legal basis for complementary midwifery services, so they are doubtful in their application even though they get maximum results. Complementary therapy service providers or so-called alternative, complementary medicine still needs to be clarified, and licensing is not easy. Health professional organizations have various interpretations of the Regulation of the Ministry of Health No. 1109 of 2007. Alternative complementary health workers are health workers with more value than traditional healers, which can be done by anyone who is not a health worker.[23]

Based on the study results, it was shown that complementary therapies widely applied were baby massage as much as 36% and oxytocin massage of 24%. Baby massage is a touch or massage for babies that provides continuous body contact that provides many physical and psychological benefits for babies.[24] Stimulation or touch on the baby's body will stimulate the vagal nerve to increase the production of digestive enzymes and improve the baby's digestive system, which influences the baby's growth and development.[25,26] Many midwives apply this therapy in their practice is because it is easy to implement and does not require much equipment. In addition, the community is also starting to feel the benefits, so high interest encourages midwives to apply this therapy in practice.

There were, however, some limitations of this study. This study had not examined whether each complementary therapy had been carried out according to the procedure or not, had not explored how the patient responded, and there had been no regular quality assessment. Further research should include

examination whether the complementary therapy has been carried out according to the procedure, in-depth explanation related to the patient's response to complementary therapy services applied by midwives, as well as considering the use of analytical research designs to obtain more optimal research results.

CONCLUSION

There were 52% of midwives who applied complementary therapy in independent practice midwives in Surabaya, Indonesia. There were seven types of complementary therapies from 25 midwives who carry out the complementary therapies in midwifery independent practice centers in Surabaya, i.e., aromatherapy, hypnotherapy, herbal medicine, baby massage and spa, massage for pregnant women, oxytocin massage, and yoga. In providing midwifery services, midwives can apply complementary therapies in their services to minimize the use of medical drugs. This also needs to be supported by professional organizations in providing policies related to complementary midwifery services.

DISCLOSURES

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Conflict of interest

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Author Contribution

All authors have contributed to all processes in this research, including preparation, data gathering and analysis, drafting and approval for publication of this manuscript.

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ORIGINAL RESEARCH

Is maternal pre-pregnancy Body Mass Index associated with type of Congenital Heart Disease in offspring?

Nofita Fachryandini[1], Taufiq Hidayat[2]*, Ernawati[3], Mahrus A Rahman[2]
[1]Medical Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.
[2]Department of Pediatric, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.
[3]Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.

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***Corresponding author:**
Taufiq Hidayat
taufiq-h@fk.unair.ac.id

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ABSTRACT

Objectives: This study aimed to determine the association between maternal pre-pregnancy BMI and type of congenital heart disease (CHD) in offspring.
Materials and Methods: This retrospective cross-sectional study involved all mothers of children with CHD who visited Pediatric Outpatient Unit at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, from January to December 2019. The maternal data were obtained from the KIA's (Maternal and Child Health) book or through anamnesis by telephone, while the offspring's data were collected from medical records. The data were analyzed using the Chi-Square test. Significance was determined at a 5% level ($p < 0.05$).
Results: We studied 117 mothers of children with CHD. The most frequent maternal pre-pregnancy body mass index (BMI) was normal (BMI 17-23 kg/m^2) accounting for 56.4% of the study population. The most common CHD was atrial septal defect (33.3%) among acyanotic patients and Tetralogy of Fallot (8.5%) among cyanotic patients. The Chi-Square test showed p=0.958 for the association between maternal pre-pregnancy BMI and type of CHD in offspring.
Conclusion: There was no association between maternal pre-pregnancy BMI and type of CHD in offspring.

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Highlights:

1. The most common CHD was atrial septal defect for acyanotic CHD and Tetralogy of Fallot for cyanotic CHD.
2. There was no association between maternal pre-pregnancy BMI and type of CHD in offspring.

INTRODUCTION

Congenital heart disease is the most common type of congenital disease, affecting 8.89 per 1000 live births and being the main cause of death in children with congenital abnormalities.[1] The cause of CHD remains unknown. In most cases, CHD is multifactorial and involves the combination of genetic and environmental factors. As many as 2-4% of CHD cases are associated with environmental factors such as pre-pregnancy obesity, diabetes mellitus, hypertension, phenyl-ketonuria, rubella, and cigarette smoking.[2]

The prevalence of overweight and obesity, measured from the Body Mass Index (BMI), has been a national health problem for several years. The latest data in 2018 from the Ministry of Health of the Republic of Indonesia showed that the prevalence of obesity in adults in Indonesia is 21.8%, whereas the prevalence of overweight is 13.6%.[3] Obesity and overweight have been associated with adverse pregnancy complications and outcomes, especially congenital heart disease.[4]

Previous studies have reported inconsistent results. Several studies have reported that mothers who are overweight or obese are at an increased risk of giving birth to a child with septal and conotruncal heart defect.[5,6] However, other studies reported that there might not be an association between maternal BMI and the likelihood of having a child with CHD.[7,8] Unfortunately, the association between maternal pre-pregnancy BMI and type of CHD in offspring among Indonesian pregnant women has not been studied. Hence, this study aims to determine the association between maternal pre-pregnancy BMI and type of CHD in offspring in Indonesia, so that appropriate changes in preventive health policies can be implemented.

MATERIALS AND METHODS

This was a retrospective cross-sectional study, conducted by collecting data from the medical record of the patients. The ethical approval for this study was obtained from the Regional Ethics Committee of Dr. Soetomo General Academic Hospital Surabaya, Indonesia (No.0103/KEPK/XI/2020). The population included all mothers of patients with congenital heart disease who visited the Pediatric Outpatient Unit, Dr. Soetomo Hospital, Surabaya, from January to December 2019. The sampling technique used in this study was a total sampling with inclusion and exclusion criteria. The inclusion criteria were mothers of patients with congenital heart disease who were recorded visiting the Pediatric Outpatient Unit, Dr. Soetomo General Hospital within the period of January to December 2019 and agreed to be a research subject by signing an informed consent. The exclusion criteria were the mothers of patients with congenital heart disease who have a family history of congenital heart disease and patients with incomplete medical record data. There were 326 patients who met the criteria.

The mothers were contacted via the telephone number listed in their medical records. Following an explanation of the study details, they were asked to provide consent and to confirm their agreement by signing an informed consent form. Some of the mothers did not agree to be the subject of the study due to several things, such as the patient had died, the telephone number was wrong, and they did not respond. So, 117 mothers agreed to be research subjects.

Mothers' data, such as weight, height, age, parity, history of abortion, pre-pregnancy diabetes, pre-pregnancy hypertension, were gathered from KIA's book or anamnesis through telephone, and offspring data such as sex, age, and type of CHD were gathered from medical records. Maternal pre-pregnancy BMI was calculated by weight and height recorded in the KIA book, usually measured in the first trimester. Weight gain in early pregnancy is generally very limited, with an average weight gain of 0.8-1.2 kg in the first trimester.[9] Thus, it can be said that maternal BMI in the first trimester represents pre-pregnancy BMI. In this study, we categorized BMI as underweight (BMI <17 kg/m^2), normal (BMI 17-23 kg/m^2), overweight (BMI 23-27 kg/m^2), and obesity (BMI >27 kg/m^2).[10] Data analysis used univariate analysis to describe the profile of pre-pregnancy mothers and children with CHD and bivariate analysis used SPSS software version 25 through the Chi-Square test. Statistical significance was defined as $p<0.05$.

RESULTS AND DISCUSSION

From January to December 2019, a total of 117 patients were studied. Table 1 shows the characteristics of the study sample. The most frequent maternal pre-pregnancy BMI was normal (66 mothers, 56.4%), the most frequent maternal pre-pregnancy age group was the age of 20-35 (83 patients, 70.9%), multipara (83 mothers, 70.9%) was more common than primipara, most mothers have never had a history of abortion (104 mothers, 88.9%) and the majority of mothers did not have pre-pregnancy diabetes mellitus (108 patients, 92.3%) and pre-pregnancy hypertension (114 patients, 97.4%). The dominant sex in congenital heart disease patients was male (63 patients, 53.8%), and the age group of patients was mostly 0-<5 years old (95 patients, 81.2%).

Table 1. Characteristics of the study sample

Characteristics	(n = 117)	%
Maternal Pre-Pregnancy BMI		
Underweight	5	4.3
Normal	66	56.4
Overweight	27	23.1
Obesity	19	16.2
Maternal Pre-Pregnancy Age (years)		
<20	3	2.6
20-35	83	70.9
>35	31	26.5
Parity		
Primipara	34	29.1
Multipara	83	70.9
History of Abortion		
Yes	13	11.1
No	104	88.9
Pre-Pregnancy Diabetes		
Yes	9	7.7
No	108	92.3
Pre-Pregnancy Hypertension		
Yes	3	2.6
No	114	97.4
Offspring Sex		
Male	63	53.8
Female	54	46.2
Offspring Age (years)		
0-<5	95	81.2
6-<11	15	12.8
11-18	7	6.0

Table 2. CHD's type of the patients

Type of CHD	n	%
Acyanotic	98	83.8
VSD	28	23.9
ASD	39	33.3
AVSD	7	6.0
PDA	17	14.5
PS	7	6.0
Cyanotic	19	16.2
ToF	10	8.5
TGA	2	1.7
Tricuspid atresia	1	1.0
PTA	2	1.7
EA	2	1.7
DORV	2	1.7
Total	117	100

Abbreviations: VSD: ventricular septal defect, ASD: atrial septal defect, AVSD: atrioventricular septal defect, PDA: patent ductus arteriosus, PS: pulmonary stenosis, ToF: Tetralogy of Fallot, TGA: transposition of the great arteries, PTA: persistent truncus arteriosus, EA: Ebstein's anomaly, DORV: double-outlet right ventricle

Table 2 shows the frequency of CHD type. Acyanotic CHD was more common (98 patients, 83.8%) than cyanotic CHD (19 patients, 16.2%). The most common acyanotic CHD's type was ASD (33.3%), VSD (23.9%), and PDA (14.5%), while the most common cyanotic CHD's type was ToF (8.5%).

Table 3. Characteristics by maternal pre-pregnancy BMI

Characteristics	Maternal Pre-Pregnancy BMI								p
	Underweight		Normal		Overweight		Obesity		
	n	%	n	%	n	%	n	%	
Maternal Pre-Pregnancy Age (years)									0.412
<20	0	0	3	2.6	0	0	0	0	
20-35	5	4.3	48	41.1	18	15.4	12	10.2	
>35	0	0	15	12.8	9	7.7	7	6.0	
Parity									0.060
Primipara	2	1.7	25	21.4	5	4.3	2	1.7	
Multipara	3	2.6	41	35.0	22	18.8	17	14.5	
History of Abortion									0.000
Yes	1	1.0	1	1.0	3	2.6	8	6.8	
No	4	3.4	65	55.4	24	20.5	11	9.4	
Pre-Pregnancy Diabetes									0.106
Yes	0	0	3	2.6	2	1.7	4	3.4	
No	5	4.3	63	53.8	25	21.4	15	12.8	
Pre-Pregnancy Hypertension									0.773
Yes	0	0	1	1.0	1	1.0	1	1.0	
No	5	4.3	65	55.4	26	22.2	18	15.4	
Offspring Sex									0.617
Male	2	1.7	39	33.3	13	11.1	9	7.7	
Female	3	2.6	27	23.1	14	11.9	10	8.5	
Offspring Age (years)									0.962
0-<5	4	3.4	53	45.3	23	19.6	15	12.8	
5-<11	1	1.0	9	7.7	2	1.7	3	2.6	
11-18	0	0	4	3.4	2	1.7	1	1.0	
Type of CHD									0.958
Acyanotic	5	4.3	56	47.7	17	14.5	16	13.7	
VSD	1	1.0	17	14.5	6	5.1	1	1.0	
ASD	3	2.6	24	20.5	8	6.8	7	6.0	
AVSD	0	0	4	3.4	1	1.0	2	1.7	
PDA	1	1.0	9	7.7	4	3.4	3	2.6	
PS	0	0	2	1.7	2	1.7	3	2.6	
Cyanotic	0	0	10	8.5	6	5.1	3	2.6	
ToF	0	0	5	4.3	2	1.7	3	2.6	
TGA	0	0	1	1.0	1	1.0	0	0	
Tricuspid atresia	0	0	1	1.0	0	0	0	0	
PTA	0	0	1	1.0	1	1.0	0	0	
EA	0	0	1	1.0	1	1.0	0	0	
DORV	0	0	1	1.0	1	1.0	0	0	

Table 3 illustrates that the mothers aged <20 years had normal pre-pregnancy BMI, while mothers aged 20-35 years tended to have normal pre-pregnancy BMI. Conversely, mothers aged >35 years were more likely to demonstrate pre-pregnancy overweight and obesity as defined by their BMI. Multiparas were more frequently found in all categories of BMI of pre-pregnancy mothers. Most of the mothers had no history of abortion in all categories of pre-pregnancy BMI. The majority of mothers had neither pre-pregnancy diabetes mellitus nor pre-pregnancy hypertension in all categories of pre-pregnancy BMI. The predominant sex of the child was male in each pre-pregnancy BMI category. The age of children was mostly found at the age of 0-<5 years in all categories of pre-pregnancy BMI. The most common defects found in all categories of BMI of pre-pregnancy mothers were ASD for acyanotic CHD and ToF for cyanotic CHD. There was no significant association between type of CHD (p=0.958), maternal age (p=0.412), parity (p=0.060), pre-pregnancy diabetes (p=0.106), pre-pregnancy hypertension (p=0.773), offspring sex (p=0.617), offspring age (p=0.962) and maternal pre-pregnancy BMI. However, we found a significant association between history of abortion and maternal pre-pregnancy BMI (p=0.000).

Congenital heart disease is the most common type of congenital disease and the main cause of death in children with congenital abnormalities. Obesity and overweight have been associated with adverse pregnancy complications and outcomes, especially congenital heart disease. However, this study did not find a significant association (p=0.958) between maternal pre-pregnancy BMI and type of CHD in offspring. Studies by Ghaderian et al. and Warrick et al. showed that maternal pre-pregnancy BMI had no significant association with the type of CHD in offspring.[7,8] Meanwhile, a study by Persson et al. showed a significant association between pre-pregnancy BMI level and aortic branch defect, ASD, and PDA in offspring.[5] Brite et al. demonstrated that maternal obesity levels were significantly associated with an increased risk of conotruncal defect, VSD, and ASD.[6] Zhang et al. also reported that maternal obesity tended to increase the risk of ASD and outflow tract defect in offspring.[11]

The mechanism for the association between maternal pre-pregnancy BMI and CHD remains unknown. However, several theories regarding the mechanism of higher risk of giving birth to a baby with congenital heart disease with increased BMI of pre-pregnancy mothers have been proposed. Increased fat mass, especially visceral fat mass, is associated with lipotoxicity and oxidative stress. Oxidative stress can arise from the intracellular accumulation of triacylglycerols (triglycerides), which impact mitochondrial efficiency, resulting in the accumulation of electrons in the electron transport chain that reacts with oxygen to form superoxide radicals. The combination of high lipid levels and oxidative stress leads to the production of three types of oxidized lipid products with harmful effects, namely lipid peroxides, oxidized lipoproteins (OxLDL), and oxysterols. Oxysterol can be toxic to cells which induces inflammation, oxidative stress, and apoptosis.[12] Oxidative stress stimulates Dnmt3b activity, which inhibits chromatin changes required for inducing Pax3 gene expression in the neuroepithelium. Inadequate expression of the Pax3 gene causes an increase in p53 protein levels resulting in increased apoptosis along the cardiac neural crest migration pathway, which results in disruption of cardiac neural crest migration, increases apoptosis along the cardiac neural crest migration pathway, and results in septal defects, outflow tract defects, and defects in cardiac arteries.[13,14]

Another possible theory is maternal diabetes. Diabetes is more common in overweight and obese individuals.[15] A recent meta-analysis by Najafi et al. reported a linear relationship between the risk of gestational diabetes mellitus (GDM) and an increase in maternal BMI.[16] Maternal diabetes inhibits the expression of the Pax3 gene in the neuroepithelium through hyperglycemia-induced oxidative stress. Inadequate expression of the Pax3 gene causes an increase in p53 protein levels resulting in increased apoptosis along the cardiac neural crest migration pathway.[13,14]

In addition to hyperglycemia, maternal malnutrition can also negatively affect embryogenesis. Mothers who are overweight or obese are more likely to be on a diet or have a poor diet. This can result in a lack of essential micronutrients such as folic acid and vitamin B12.[17] British guidelines suggested taking 5 mg folic acid supplementation per day for obese women.[18] Inadequate serum folate levels and vitamin B12 deficiency inhibit the re-methylation of 5-methyl-tetrahydrofolate, leading to an increase in homocysteine.[19] Excessive accumulation of homocysteine will result in disturbances in the migration, differentiation, and development of the cardiac neural crest, which is responsible for remodeling the great arteries, outflow septation, valvulogenesis, and development of the cardiac conduction system.[20,21]

Previous studies have identified that about 10% of CHD cases are associated with pathogenic mutations.[22,23] Meanwhile, epigenetic changes may be involved in the remaining cases. Catalano and Shankar also stated that maternal obesity could cause epigenetic changes in the embryo with an increased risk of cardiac malformations.[24] Epigenetic regulation can occur

through 3 mechanisms, the DNA methylation aberrations, histone modifications, and miRNA expression. These epigenetic changes have been found in several types of CHD in humans, the ASD, VSD, ToF, aortic stenosis, HLHS, and DORV. Epigenetic changes influence several processes in the formation and development of the heart, including differentiation and proliferation of cardiomyocytes, chamber morphogenesis, valve formation, and septation.[25]

The limitation of this study was that we could not examine the mothers directly, and our data were obtained from KIA's book and medical records. These may be inaccurate partly in measuring or recording data. Another limitation was that many missing patients were not included in our study, and we had no data of them and their mothers.

CONCLUSION

There is no association between maternal pre-pregnancy BMI and type of CHD in offspring from this study. We suggest that future studies consider a prospective study design to ensure more comprehensive data collection.

DISCLOSURES

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Conflict of interest

The author declares no conflict of interest

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Author Contribution

All authors have contributed to all processes in this research, including preparation, data gathering and analysis, drafting and approval for publication of this manuscript.

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ORIGINAL RESEARCH

Testosterone and sexual function in menopausal women based on the Female Sexual Function Index (FSFI) score

Muhamad Agung Khoiri[1], Muhammad Fidel Ganis Siregar[1], Sarma Nursani Lumbanraja[1], Iman Helmi Effendi[1], Yudha Sudewo[1], Edy Ardiansyah[1]*, Putri Eyanoer[2]

[1]Department of Obstetrics & Gynecology, Faculty of Medicine, University of Sumatra Utara, H. Adam Malik General Hospital, Medan, Indonesia.
[2]Department of Community and Preventive Medicine, Faculty of Medicine, University of Sumatra Utara, Medan, Indonesia.

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***Corresponding author:**
Edy Ardiansyah
easa_dy@yahoo.com

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ABSTRACT

Objective: This research aimed to analyze the correlation between testosterone levels and sexual function in postmenopausal women.

Materials and Methods: This research was a descriptive observational study with a case series approach conducted at Aras Kabu Health Center Outpatient Polyclinic from May to August 2022. The normality test was carried out using the Shapiro-Wilk test. If the data were not normally distributed, data would be analyzed using the Spearman correlation test. If the data were normally distributed, the data analysis would use the Pearson correlation test.

Results: There was a significant relationship between Female Sexual Function Index (FSFI) score with testosterone levels and duration of menopause with $p<0.05$. The degree of correlation found was 0.619 between testosterone levels and FSFI scores, indicating a moderate and significant positive correlation. A correlation degree of 0.482 was found between FSFI and length of menopause which indicated a significant moderate positive correlation, while the degree of correlation between testosterone levels and length of menopause was found to be 0.711, showing a strong and significant positive correlation.

Conclusion: There is a significant relationship between FSFI scores with testosterone levels and duration of menopause as well. There was also a significant relationship between testosterone levels and the duration of menopause.

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Highlights:

1. Testosterone level correlates with FSFI score, showing that sexual function correlates with hormonal physiology.
2. FSFI is a valid and useful tool in measuring sexual function.

INTRODUCTION

Menopause is a natural phase in a woman's life which is marked by the end of the menstrual cycle and the fertile period, which occurs because the ovaries do not produce estrogen. The cessation of menstruation is caused by estrogen deficiency and is not related to pathological conditions.[1] It is predicted that by 2030, there will be 1.2 billion women aged 50 years and over and of these, 76% will live in developing countries. More than 50% of middle-aged women often experience symptoms associated with menopause.[2]

Decreased libido refers to a reduced desire to have sex. Apart from decreased libido, other symptoms, such as vaginal dryness, hot flushes, and urinary incontinence can also occur in postmenopausal women. Low libido is the most common sexual problem found in women. Hormones are rarely the only factor involved in this problem. Other factors, such as physiological, social and environmental factors are thought to play a role in the occurrence of the disorder.[3,4] These may include relationship problems, psychological factors, side effects of common drugs, such as antidepressants, or a health problem such as diabetes. Decreased libido or sexual desire can be found throughout a woman's reproductive life and is a response to a number of complex stimuli, including psychological, psychosocial, relationship and physical health.[5]

Heidari et al. tried to see the relationship between menopause and libido assessed in a systematic review. The results found that there was an influence between menopause and decreased libido with figures starting from 21-70% from various related studies.[6] One of the hormones known to involve in sexual function is testosterone. Testosterone production in premenopausal women is estimated to be around 0.2-0.25 mg/day. In a European study, decreased libido becomes more common as women age, with a prevalence of 11% in women aged 20-29 years and 53% in women aged 60-70 years. Hypoactive sexual desire disorder, which is defined as reduced sexual desire, is more or less equal across age categories (6-13% of women aged 20-70 years).[7] There are no clear indications for testosterone therapy for postmenopausal women. Nonetheless, some clinicians have administered testosterone for decades, with the goal of reducing a variety of symptoms, with uncertain benefits and risks. However, previous research has shown an improvement in symptoms and sexual satisfaction with the use of testosterone over a 24-week study period.[8] Although there are some data for the use of physiologic doses of testosterone in the postmenopausal population for the treatment of hypoactive sexual desire disorder, in practice Dunsmoor et al. noted a lack of basic understanding of the physiology of testosterone in women, a lack of diagnostic tests for low libido, and a lack of a research base to support safe practice in the benefit of giving testosterone in menopausal women.[5]

Research into the relationship between serum testosterone levels and sexual desire and function is now important and should be preceded by careful evaluation of sexual pain, psychological distress, altered body image, relationship factors, as well as sleep and fatigue problems, all of which can increase in the menopausal transition period.[5] Therefore, through this study, the authors attempted to assess sexual function by considering external factors and assess the relationship between testosterone hormone levels and sexual function in menopausal women.

The Female Sexual Function Index (FSFI) is a brief multidimensional scale for assessing sexual function in women. The scale has received initial psychometric evaluation, including studies of reliability, convergent validity, and discriminant validity. In principle, FSFI consist of several domains such as desire, arousal, lubrication, orgasm, satisfaction, and pain. Research to acknowledge its validity has been performed and its validity can be concluded to have been proven by multitude of research. In Indonesia, the translation of FSFI has been deemed sufficient, valid and reliable.[21]

MATERIALS AND METHODS

This was a descriptive observational study using a case series approach to analyze the correlation between testosterone levels and sexual function in postmenopausal women. The ethical clearance of this study had been issued by Ethical Committee of Medical Research, Faculty of Medicine, University of Sumatra Utara in a letter number 946/KEPK/USU/2022. The process of filling out the questionnaire carried out at the UPT Aras Kabu Polyclinic Outpatient Installation, while blood tests were carried out at the Prodia S. Parman Medan Clinic Laboratory from May to October 2022. The research sample was menopausal women who came for treatment at the UPT Puskesmas Aras Kabu who met the inclusion and exclusion criteria and had signed the consent forms. To facilitate analysis, this study recruited at least 20 patients.

The inclusion criteria in this study were age over 51 years, have stopped menstruating permanently for at least 12 months, married or still having sexual partners, no history of using hormonal contraception, and no history of gynecological surgery. In addition, the exclusion criteria in this study were sudden refusal to participate, taking drugs that can interact directly or

indirectly with androgen hormones, having severe systemic diseases, such as kidney failure, type 2 diabetes mellitus, heart failure, hepatitis, etc. and having psychological disorders.

Respondents were collected and explained about the procedure for filling out the FSFI scoring form that had been used by previous researchers and had been validated. The respondents immediately filled out the scoring form once they understood how to fill it. Then, the blood sample was taken from the respondents for free testosterone levels by using the methods of liquid chromatography (LC) and mass spectrometry (LC-MS/MS) tests.

The normality test results used the Shapiro-Wilk test, indicating that the data were not normally distributed, so the data were analyzed using the Spearman correlation test. This study used a 95% confidence level, and a $p < 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

This research involved 20 menopausal women of over 51 years old and met the inclusion criteria. The mean age of the sample at menopause was 48.9 ± 2.713 years, with duration of menopause up to the time of the study was 3.8 ± 2.764 years. After completing the FSFI questionnaire, it was found that the average FSFI score in the sample was 22.86 (5.19). In addition, after examining free testosterone levels in the laboratory, it was seen that the average testosterone level in the study sample was 1.05 pg/ml ± 0.67.

Table 1. Characteristics of research subjects

Characteristics	Mean ± SD
Age (years)	52.65 ± 1.755
Age at menopause (years)	48.9 ± 2.713
Duration of menopause (years)	3.8 ± 2.764
Coitus frequency (every month)	3.45 ± 2.743
Height (cm)	153.25 ± 9.635
Body weight (kg)	61.35 ± 9.377

Table 2. Average FSFI score and free testosterone levels in the sample

	Mean ± SD	Md (min-max)
Female Sexual Function Index	22.86 ± 5.19	22.895 (10.7 – 34.1)
Testosterone levels	1.05 ± 0.67	1.695 (0.16 – 3.23)

After the Shapiro-Wilk test was carried out, it was found that the value of testosterone levels had an abnormal distribution along with the duration of menopause. However, the total FSFI scores were found to be normally distributed. Because the two independent variables were not normal, the Spearman correlation test was carried out.

Table 3. Correlation between Female Sexual Function Index with testosterone levels, menopause and duration of menopause.

	r value	p value
Testosterone vs FSFI	0.619	0.004
FSFI score vs menopause duration	0.482	0.031
Testosterone vs menopause duration	0.711	0.000

Those data showed significant relationship between testosterone levels, FSFI scores and menopausal duration ($p < 0.05$). The degree of correlation of 0.619 was found between testosterone levels and FSFI scores, indicating a moderate and significant positive correlation. The degree of correlation of 0.482 was found between FSFI and length of menopause, indicating moderate and significant positive correlation. The degree of correlation between testosterone levels and length of menopause was found to be 0.711, showing a strong and significant positive correlation.

The demographic characteristics of the patients in this study based on age were 52.65 ± 1.75 with age at menopause being 48.9 ± 2.713. The menopausal age range of the Indonesian population found in this study was almost similar to that of the population study conducted by Yang et al. in 2017 in China with a total of 134,010 female subjects having the age at menopause at the age of 48.6 years [SD = 4.0] and the total reproductive years was 32.7 years.[9] Another study conducted in India also identified that the age of 46 .2 ± 4.9 years is the age of natural menopause in India. Indian women started the perimenopausal stage, characterized by irregular menstruation, at the age of 44.69 ± 3.79 years.[10]

In this study, the mean score of FSFI in postmenopausal women was 22.86. A previous cross-sectional study conducted at Assiut University Hospital, with a sample of 500 women who took part in a survey of the Arabic version of the Female Sexual Function Index (FSFI), it was found that 67.8% of the women participating in the study suffered from sexual dysfunction, indicating a high prevalence.[11] Another study in Indonesia conducted at the Geriatric Clinic, Dr. Soetomo Hospital, Surabaya, in May 2016 used the Female Sexual Function Index (FSFI) questionnaire which indicated

sexual dysfunction if the score was <26.55 for the total aggregate score for each question in sexual domain. It was found that the prevalence of sexual dysfunction was present in 29 patients (78.4%) and 8 patients (21.6%) did not show sexual dysfunction from a total sample of 37 patients.[12]

The range of testosterone levels found in this study was 1.05 ± 0.67. A study conducted by Jones et al. in 2013 obtained similar results in a sample of general population women selected from a British cohort study. The sample comprised 177 postmenopausal women over 45 years of age and blood samples, obtained by consent at recruitment, revealed a testosterone level of 1.3 nmol/L.[13] A previous study conducted by Randolph et al. in 2003 to 2930 participants aged 42-52 years, with sample characteristics of African-American (27.6%), Caucasian (47.1%), Chinese (7.4%), Hispanic (8.8%), or Japanese (9.0%) at 7 clinical sites, found higher testosterone levels of 5.22.[14] After menopause, serum estradiol levels decrease by 90%, while testosterone continues to decline by age 25.[15] In a Norwegian population-based survey of sexual habits, 41% of women between the ages of 50 and 59 reported lack of sexual desire as a real problem due to decreased testosterone levels during menopause.[16]

This study showed that testosterone levels, FSFI scores and menopausal duration all had a significant relationship with a p <0.05. Female sexual dysfunction is common, affecting 25-43% of women, a percentage that has increased markedly over the years. It is one of the major health problems concerning postmenopausal women, and the frequency of these sexual problems increases as menopause approaches, reaching a peak in the postmenopausal years. Although 33–50% of middle-aged women exhibit some degree of sexual dysfunction related to aging and hormonal status, this percentage may vary according to factors such as the population analyzed, the study design, or the approach used.[17] Ovarian steroids (estradiol, testosterone, and progesterone) modulate sexual desire, or libido, in women. The gradual, age-related cessation of ovarian function associated with natural menopause reduces ovarian steroid levels, accompanied by reduced sexual desire in most postmenopausal women.[18,19] Other than menopause, there are many factor that may predict sexual dysfunction such as age, estrogen deficiency, type of menopause, chronic medical problems, partner's sex problems, severity of menopause symptoms, dystocia history, and health status. All of these are the physical factors influencing sexual function of menopausal women. In the mental–emotional area, all studies confirmed the impact of depression and anxiety. Social factors, including smoking, alcohol consumption, the quality of relationship with husband, partner's loyalty, sexual knowledge, access to health care, a history of divorce or the death of a husband, living apart from a spouse, and a negative understanding of women's health were found to affect sexual function.[22]

A previous study by Turna et al. found significant differences between women with low libido levels and controls in the level of total testosterone, free testosterone and DHEA-S and full-scale FSFI scores for pre- and postmenopausal women (p <0.05). Reductions in total testosterone, free testosterone, and DHEA-S levels positively correlated with full-scale FSFI score and FSFI desire, FSFI arousal, FSFI lubrication, and FSFI orgasm scores (p <0.05). These data show that women with low libido have lower androgen levels compared to the age-matched normal control group and the decrease in their androgen levels is positively correlated with the female sexual function index domain. Several studies have found that adding testosterone to hormonal therapy can improve sexual function and general well-being among women during climacteric. Significant improvement was seen by several variable studies when surgical menopausal women were given 40 mg of oral testosterone undecanoate daily along with their comparable estrogen therapy to estrogen alone. Twice weekly addition of testosterone undecanoate to daily oral estrogen is associated with a significant improvement in sexual function among postmenopausal women than use of estrogen alone.[20] Our study was also consistent with those published by Nathorst-Böös in 2006 which included 53 sample. This was in range with our sample size and indeed it showed that testosterone may have effect towards sexual function, thus, therapy with testosterone may help in improving the patient’s sexual function.[23]

CONCLUSION

Female Sexual Function Index (FSFI) scores have significant correlation with testosterone levels, as well as with duration of menopause, while the testosterone levels also correlate significantly with the duration of menopause. This proves that sexual function correlates with hormonal physiology.

DISCLOSURES

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Conflict of interest

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Author Contribution

All authors have contributed to all processes in this research, including preparation, data gathering and analysis, drafting and approval for publication of this manuscript.

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META-ANALYSIS

The effect of micronutrients on postpartum pelvic organ prolapse patients

Rahajeng*, Mukhamad Nooryanto, Muhammad Dzikrifishofa
Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia

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***Corresponding author:**
Rahajeng
rahajeng.fk@ub.ac.id

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ABSTRACT

Objective: Pelvic Organ Prolapse (POP) is when pelvic tissues sink into the vagina due to weakened ligaments or muscles. POP is common globally. Adequate nutrition, including Vitamin D, is vital for prevention. Vitamin D maintains bone and muscle health, regulates MMP-9 to control collagen, essential for pelvic support. Increased MMPs lead to collagen breakdown and POP. Recognizing vitamin D's role in collagen and POP is crucial for prevention. This study aimed to determine definitive association between vitamin D, collagen type I and MMP-1 in POP patients.

Materials and Methods: Our search yielded 1375 studies, of which 7 were included in the present investigation. Two studies addressed the micronutrient status of vitamin D, four investigated the micronutrient status of type 1 collagen, and two studied the micronutrient status of MMP-1 in postpartum POP patients.

Results: The results showed that the mean of vitamin D levels from POP group was substantially decreased compared to a those of healthy women in the control group (95% confidence interval (CI), -3.64; -3.44 and $p < 0.05$). There was a decrease of collagen I protein in POP (95% CI, -3.26; -2.45. $p < 0.05$). Additionally, MMP-1 expression increased in POP patient (95% CI. 1.48-2.23, $p < 0.05$)

Conclusion: Micronutrient status was severely compromised in POP group compared to control subjects.

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Highlights:

1. Serum vitamin D levels were significantly different between POP and in healthy women.
2. Micronutrient MMP-1 expression is increased in POP patients.

INTRODUCTION

Pelvic organ prolapse (POP), known as a common gynecologic disorder, is defined as the descent of the pelvic structures into the vagina due to the loss of ligament or muscle support.[1] It is one of a disease that remarkably affects women's quality of life.[2] Pelvic organ prolapse is highly prevalence disease with unknown primary cause which affects up to 50% of parous women in both developing and developed countries.[3] POPs are also subcategorized by descending compartment. Cystocele is described as anterior wall herniation, rectocele means a descent of the posterior vaginal wall and vaginal vault prolapse is described as descent of the uterus, cervix, or apex of vagina.[4] Nutrition require in POP disease is an important topic to discuss. Baseline characteristics of the average daily intake of energy and nutrients are considered as the percentage of the recommended postpartum intake. ECLIPSES study in Spain recommended adequate intake (above 80% of the RDA) during postpartum is about 82.6% for energy component, 80.6% for protein,

99.5% for carbohydrate, 88,7 for vitamin C, 95.1% for vitamin B2 and 170.8% for vitamin B12, while the intake is far from RDA recommendation which about below 35% is vitamin D, iron and folate.[5]

Vitamin D is important micronutrient for skeletal integrity and muscle function. In postmenopausal women, vitamin D deficiency and POP are often found together.[6,7] Vitamin D downregulates matrix metalloproteinase-9 (MMP-9), reduces collagen breakdown and improves organization of collagen.[8] Collagen, especially collagen type I, helps maintain supportive function of the pelvic floor. Abnormality in collagen anabolic activity that cause changes in collagen content and structure may be involved in the pathogenesis or development of POP.[9] Expression of MMP-1, MMP-2 and MMP-9 was found to be associated in more collagen breakdown, losing collagen integrity and increase in POP patients.[10] This study aims to determine definitive association between vitamin D, collagen type I and MMP-1 in POP patients.

MATERIALS AND METHODS

Articles were searched using three electronic databases: PubMed, Google Scholar, and Cochrane. Searches were performed using keywords appropriate to the clinical question and the Boolean operators 'AND' and 'OR' were used to search for items in three databases.

Articles identified by the search were further excluded based on inclusion and exclusion criteria. The inclusion criteria for this article search were articles in English, interventional meta-analytical studies, proportion of micronutrient requirements in POPs, and study subjects. The exclusion criteria were observational studies, studies without meta-analytical data, repeatedly published literature sources, data extracted from reviews or abstracts, and reported results only in mean ± standard deviation of score coloring. Seven relevant articles were obtained after sorting using the above inclusion and exclusion criteria.

All authors participated in summarizing and systematically evaluating the evidence using standard abstraction forms. The team tested the screening and abstract forms on several articles before starting the abstract and review process. Screening and data collection forms were revised by the team. Data were entered from the included studies and analyzed for data heterogeneity using Review Manager 5.4. We concluded that the data showed heterogeneity when the p-value was less than 1. 0.05 at high I2. A forest plot showing the mean difference for each included study, which was used to ascertain the overall effect of the included studies, with a CI of 95%. This study had been granted ethical clearance issued by the Health Research Ethical Committee Faculty of Medicine Universitas Brawijaya, Malang, Indonesia. No. 04/UN10.F08/PN/2023.

RESULTS AND DISCUSSION

Our search yielded 1375 studies and 7 of which were included in our study. Two studies discussed the micronutrient status of vitamin D, four studies discussed the micronutrient status of type 1 collagen and seven studies addressed the micronutrient status of MMP-1 in postpartum POP patients. The flowchart literature through the assessment process for this review update is shown in Figure 1.

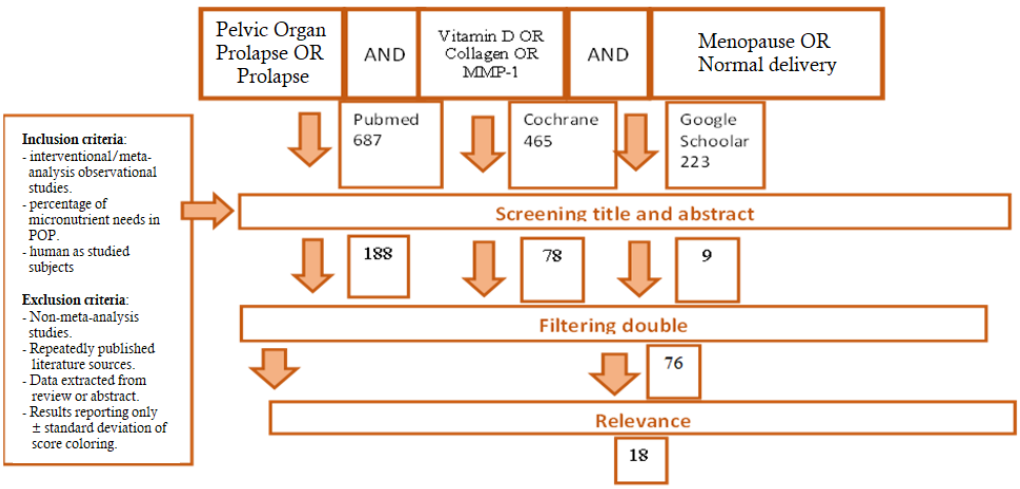

Figure 1. Flowchart of included studies.

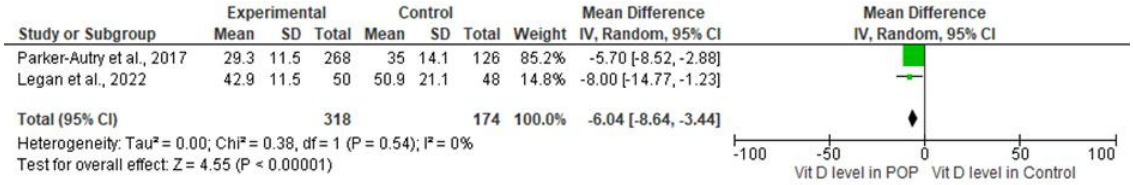

Figure 2. Vitamin D status and pelvic floor disease in forest plot analysis.

The effect of micronutrient vitamin D on Pelvic Organ Prolapse

The heterogeneity among the included studies was found in low level (I2=0%, p >0.05). The findings showed that mean serum vitamin D levels were significantly different between POP and in healthy women in control group (95% confidence interval (CI), (-8.64; -3.44) and p <0.05) (Figure 2).[11,12]

Legan et al., (2022), in a cross-sectional study, found that vitamin D levels in POP patient had decreased as compared to control or normal patient. In this study, 66% of POP patients were found with vitamin D deficient of lower than 25-30 nmol/L. Based on prolapse stages, the participants did not significantly differ in the incidence of vitamin D deficiency. But in bivariate analyses, there was relationship between POP grade (0 to 4) and vitamin D levels, with the relationship showing a significant, moderately high negative correlation.[12]

In a retrospective cohort study by Parker-Autry et al. (2017), POP patients had reduced vitamin D level compared to healthy women. Among women in the pelvic floor dysfunction group, 48% had adequate amount of vitamin D levels and 52% had vitamin D deficiency. Mean serum 25(OH)D levels in the adequate and deficient group were 38.4 ± 7.6 ng/ml and 18.6 ± 7.1 ng/ml, respectively. Women with inadequate/ deficient vitamin D levels were more likely to be younger, had a higher BMI and African American ethnicity.[11] Kaur et al. (2017) found that mean modified vaginal health index (MVHI) improved as vitamin D levels increased.[13] While Rahajeng et al., (2021) suggested that vitamin D has a significant positive effect on extracellular matrix expression.[7]

The effect of micronutrient collagen type I on Pelvic Organ Prolapse

Collagen type I alpha 1 is an important structural component of the vaginal epithelium and endopelvic fascia. The results showed that the expression of collagen type I was significantly different between POPs and healthy women in control group (95% confidence interval (CI), (-3.24; -2.45) and p <0.05) (Figure 3). [9,14–16]

Han et al. (2014) hypothesized that collagen expression has an important function in POP angiogenesis. Collagen type I has been found to decrease in POP patients and causing POP. When examined micros-copically, the collagen fibers showed a disordered arrangement within the tissue.[9]

Hu et al. (2017) also observed that the metabolic network of tissue collagen is highly dependent on in vivo synthesis and degradation of collagens. The decreased collagen content in POP patients may have occurred due to increased collagen degradation explained by increased of MMP components.[14]

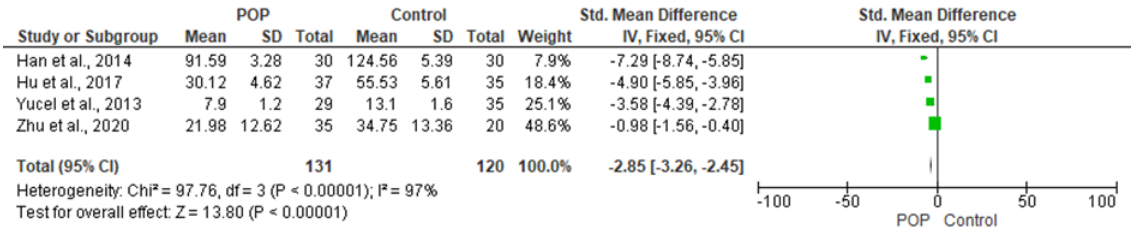

Figure 3. Collagen type I and pelvic floor disease in forest plot analysis.

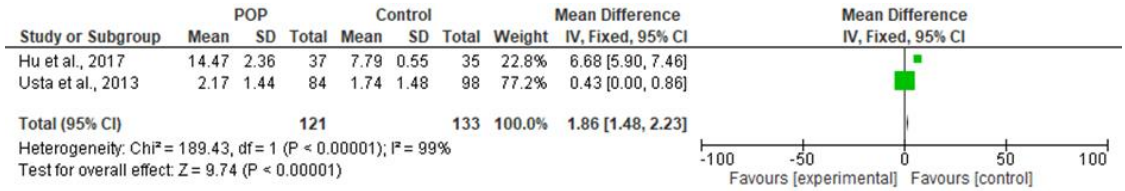

Figure 4. Relationship between MMPI status and pelvic disorder.

Yucel et al. (2013) stated that collagen is a major component of connective tissue produced by fibroblasts and plays a role in tendon resistance. In particular, collagen type I is known to impart strong mechanical forces to connective tissue compared to other collagen families. Yucel et al. (2013) also found that there was decreased expression of collagen type I in uterosacral tissue in women with POP. Tissues from POP women had significantly reduced vascular subarea of the uterosacral ligament.[15]

A study by Zhu et al. (2020) showed no significant change in MMP1 levels between POP and control patients, but increased expression of MMP2 and MMP9. Also, compared with those in the control group, TIMP1 and TIMP2 mRNA levels were found decreased in POP group, but without difference in the protein levels statistically. Collagen I protein expression levels were found to be decreased by histopathological examination, which explains the aberrant collagen expression involvement in POP pathophysiology.[16]

All studies included in this study reported that there was lower collage type I expression in patient with POP compared to control. Because of few numbers of included study, we could not exclude the publication bias. Another publication like that of Gong and Xia (2019) also had similar findings as in our research. They observed that collagen fibril structure in POP patients was loose, disordered, discontinued and stiffer than that in control group.[17] Saputra et al. (2022) had shown odds ratio having POP are 3.23 times more frequent in patients with lower collagen type I expression compared to control.[18]

The effect of Micronutrient Matrix Metalloproteinase (MMP-1) on Pelvic Organ Prolapse

Collagen type I, II, III and IV are major substrates for MMP-1, an interstitial collagenase enzyme that contributes to collagen degradation process.[19] Hu et al. (2017) had revealed differences between MMP-1 expression in women with POP compared to women without POP. However, Usta et al. (2013) was not in agreement with Hu et al.'s study results. When the included studies' data were analyzed further, there was a remarkable difference in MMP-1 expression level in POP women compared to control.[14,20]

Possible explanations include age differences, environmental condition, lifestyle difference, and menopausal status that may correlate with MMP-1 expression. As shown in Figure 3, the included studies showed statistical significance, with associations varying from 1.48 to 2.23 across sub-studies. However, heterogeneity of the data was found very high (I2 = 99%, p <0.05). This was due to the limited number of studies included in this meta-analysis.[14,20]

We hereby applied meticulous exclusion criteria in order to obtain the very finest selection of articles. However, due to a fine selection process, we may only include a limited number of studies in this systematic review. We suggest that there will be more studies in the future discussing about role of vitamin D and MMP-1 in POP.

CONCLUSION

This meta-analysis discussed the relationship between vitamin D, collagen type 1 and MMP-1 status with pelvic floor disease, revealing that micronutrient status in POP women was severely impaired compared to that in healthy women.

DISCLOSURES

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Author Contribution

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REVIEW ARTICLE

Impact of COVID-19 on the histopathological aspect of the placenta during pregnancy

Anak Agung Ngurah Jaya Kusuma*
[1]Department of Obstetrics and Gynecology, Prof. Dr. I.G.N.G. Ngoerah Hospital, Faculty of Medicine, Universitas Udayana, Bali, Indonesia

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***Corresponding author:**
Anak Agung Ngurah Jaya Kusuma
jayakusumakars@gmail.com

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ABSTRACT

The coronavirus disease 2019 (COVID-19) is still classified as a world pandemic. This disease can affect numerous systems of the human body. Pregnant women are classified as a vulnerable group since COVID-19 can cause high morbidity and mortality. Angiotensin-converting enzyme-2 (ACE-2) acts as a COVID-19 receptor, and this receptor is also present in the placenta. The placenta plays a significant part in the fetus, especially protecting it from harmful conditions. Since only a few studies are available, COVID-19's influence on the placenta in pregnancy needs to be discussed further. The SARS-CoV-2-infected pregnant woman's placenta showed histopathological alterations. Viral particles were detected on syncytiotrophoblast and chorionic villi vascular endothelial cells. Some studies show inflammatory conditions are not prominent in SARS-CoV-2 positive infection. This, perhaps due to the placenta's immunological reaction, plays a significant role. The SARS-CoV-2 disorder tends to cause abnormalities within the placental tissue. Fetal vascular malperfusion (FVM) and maternal vascular malperfusion (MVM) are the most frequent findings from the studies included.

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Highlights:

1. Pregnant women with positive SARS-CoV-2' placenta showed histopathological alterations.
2. SARS-CoV-2 tends to cause abnormalities within the placental tissue.

INTRODUCTION

COVID-19 is a disease that attacks the breathing system. SARS-CoV-2 causes this disease, initially reported in December 2019 in Wuhan, China. This disease had been declared a global pandemic, resulting in more than six million deaths. Existing research shows the spread of this disease through respiratory droplets, especially those close to a COVID-19 patient.[1,2]

In addition to affecting the respiratory system, it is known that this disease can attack by various other techniques. Its symptoms resemble viral infections, i.e., fever, shortness of breath, cough, and runny nose. The condition is divided into mild, moderate, and severe degrees. This disease can affect all age groups, from infants to the elderly. Pregnant mothers are the vulnerable groups, which may cause high morbidity or mortality if attacked by this disease.[3]

Existing research indicates that COVID-19 infection can occur via ACE-2 receptor, which is found in various bodies, including the placenta. During pregnancy, the placenta is critical in the mother-delivery. In addition, the placenta is essential in protecting the unborn baby from harmful infections or toxins from the mother. Based on several existing studies, SARS-CoV-2-infected pregnant women's placenta showed histo-pathological alterations. SARS-CoV-2 can pass through the placenta, resulting in various adverse effects.[4–6]

Presently, there remains a requirement for numerous additional studies to thoroughly explore the effect of COVID-19 on placental function. In this review, the author's focus is directed towards the disclosing of the influence of COVID-19 on the histopathological dimension of the placenta in pregnancy.

SARS-COV-2 INFECTION IN PREGNANT WOMAN

The pregnant woman is regarded as one of the most prone clusters in the population. Changes in physiological and immunological function during pregnancy might raise the risk of severe sickness and the danger of vertical transmission to the infant or fetus. The first and second trimesters are essential for the fetus during vertical transmission because they account for most complications associated with viral infections. Even though the placental wall defends the fetus from intrauterine infections, certain viruses have been linked to congenital abnormalities or syndromes. They have an impact on the health of newborns. SARS-CoV-2 in pregnancy is expected to increase the risk of fetal and maternal health issues progressing to severe pneumonia, necessitating hospitalization in critical care units. In placental tissue, several virulent, polytrophic strains of the coronavirus have been shown to transmit and are said to harm both the fetus and the mother.[7]

Many new types of research suggest some intrauterine transmission, despite several prior studies that do not support the SARS-CoV-2 transmission vertically in humans. As a result, SARS-CoV-2 in prenatal is constantly a contentious subject since there is a lack of relevant data and because finding viral particles in the placental tissue is the most reliable technique to confirm this infection. Some reports stated there is a chance of SARS-CoV-2 transplacental infections with positive virions in amnion fluid, nasopharyngeal swabs, placental, and positive serology of neonatal. However, verifying maternal-fetal contagion validity constantly needs to be determined. Pathogens can transverse the placenta and infect the fetus in several ways, such as transvaginal ascending infection, placental, and breastfeeding transmission.[8]

ACE-2 and transmembrane protease serine-2 are primarily expressed in exact cell types of the maternal–fetal interface. Viruses enter the innate immune system of the mother and the placental trophoblastic host when the maternal-fetal interface barrier breaks. Some studies found that SARS-CoV-2 may contaminate monocytes and macrophages via the antibody-dependent enhancement pathway and macrophages and monocytes via the ACE-2 pathway. Specifically, the SARS-CoV-2' S protein attaches to the monocytes and macrophages ACE-2, allowing the cell to be invaded by the viruses.[9,10]

Jing et al. reported that there is ACE-2 expression and activity during pregnancy, and it was discovered that ACE-2 is found to be expressed in numerous parts, including the placenta. ACE-2 is mainly expressed in placental villi syncytiotrophoblast, cytotrophoblast, endothelium, and vascular smooth muscle. The ACE-2 expression in the placenta is higher than in the lung, signifying a viral infection of the placenta. ACE-2 expression was found in invasive and intravascular trophoblast and decidual cells of the maternal stroma. ACE-2 is also present in the umbilical cord's endothelium and smooth muscle.[11,12]

Another study stated that a SARS-CoV-2-infected woman who had a miscarriage at 13 weeks of pregnancy. This study recommends the opportunity of straight-up transmission via the monocytes and macrophages of the infected mother and maybe also by contaminating the fetus via the disease-ridden macrophages during pregnancy. Few studies have linked COVID-19 during pregnancy to issues, i.e., membranes' early rupture or preterm labor.[13–17]

IMPACT OF COVID-19 ON HISTOPATHOLOGICAL ASPECT OF PLACENTA

The SARS-CoV-2-infected mother's placentas show considerable histopathological alterations. Bertero et al. observed the histopathological deviations in the placenta in chronic villitis. In 66.67% of cases, there was CD8+ T cell decidual infiltration and thrombo-hemorrhagic regions with laminar fibrin precipitation inside the intervillous area. Thrombo-hemorrhagic and inflamma-tory changes were the majority, and unusual pathological abnormalities were observed. However, only chronic villitis and rapid villous maturation preserved statistical significance after limiting the study to placentas delivered before a cesarean section.[18]

Another study found that placentas in the third trimester tended to contain at least one MVM characteristic, specifically aberrant or damaged maternal blood vasculatures, and intervillous thrombi. In intrauterine fetal death patient' placenta, villous edema, and retroplacental bruises were discovered. COVID-19 placentas had a higher incidence of decidual arteriopathy and other MVM characteristics, an illustration of placental damage defined by anomalies in intervillous space oxygenation and associated with poor perinatal outcomes.[19]

Another study performed a pathological examination of a 3rd-trimester pregnant woman infected with COVID-19 and showed features of MVM, i.e., an increasing number of syncytial knots. The cases showed higher focal perilous fibrin depositions.[20] There were rises in intervillous or subchorionic fibrin in pregnant women in the acute stage of severe acute respiratory syndrome placentas, which could be linked to troubles in the mother's placenta blood flow caused by respiratory hypoxia.[21]

Khong et al. reported that the most prevalent results in the histological examination were intramural fibrin accumulation and FVM. Villous stromal-vascular karyorrhexis was seen in two instances. Additionally, intramural nonocclusive thrombi, meconium, macrophages, lesions of MVM, and perilous fibrin deposits were caught in the particular placenta. Placental tissue showed acute chorioamnionitis and acute funisitis in patients with pneumonia and acute hypoxia. Other individuals were found to have chronic villitis and obliterative vasculopathy. Increased incidence of a hypercoagulable state was also seen in COVID-19-infected mothers.[22]

Smithgall et al. also reported about MVM and FVM changes in COVID-19 cases during pregnancy. Histopathological examination found that the SARS-CoV-2-infected woman's placentas were found to have subchorionic thrombi and villous agglutination.[23] In women with COVID-19, placental pathology revealed a more considerable prevalence of FVM, indicating thrombi in fetal blood vasculatures.[24] Similar previous studies also reported that COVID-19 patients tended to demonstrate FVM evidence, such as avascular villi and mural fibrin precipitation and villitis of the unclear source.[25]

Another study that analyzed the placenta showed the presence of MVM and FVM. The finding of FVM in two cases indicated thrombus development in the fetus and caused the late villous effect. Another mother's placenta with mild respiratory symptoms had lymphohistiocytic villitis and intervillositis, with CD8-positive T-cells being the most prevalent cell population. There were also a few CD68-positive macrophages, CD4-positive T-cells, a small number of plasma cells, and no neutrophil rise. The authors used ISH to show the virus particles in the identical placenta's decidual and umbilical cords. Other authors also noticed a similar discovery of persistent villitis, which they labeled villitis of unknown etiology (VUE).[26–29]

Villous chorangiosis and acute chorioamnionitis are two additional frequent findings in several investigations. Some case reports also noted the existence of chronic and massive histiocytic intervillositis, perilous fibrin precipitation linked with virus spike glycoprotein, primarily in the trophoblast coat. In a 13-week twin pregnancy in which COVID-19 was positive, N-protein and RNA, as well as viral duplication, were discovered in the fetal kidneys, plumes, and placentas. Diffuse infarction, chronic histiocytic intervillositis, and subcortical inflammation were seen in the placental tissue.[13,30–33]

A clinical pathology study by Debelenko et al., which examined 75 placentas from mothers with confirmed COVID-19, showed cell damage characterized by cytoplasm clearing, karyorrhexis, pyknosis, lack of nuclear basophilia, and darkish nuclei with homogenized chromatin. Besides that, it can also be accompanied by an inflammatory infiltrate dominated by monocytes/macrophages, neutrophils, and some lymphocytes such as CD3, CD15, and CD68. Activation of fibroblasts and reactive vascular proliferation were visible in the villous stroma.[34]

Another recent study reported that maternal-fetal malperfusion (MFM), hypoxic placental, decidual arteriopathy, and uteroplacental inadequacy in the intervillous region were all more common in COVID-19 placentas. The COVID-19-induced inflammatory or hypercoagulable state could be to blame. The majority of prevalent pathological discoveries of the COVID-19-infected patient' placenta are signs of MFM. These conditions, however, had little effect on mother outcomes in near-delivery patients, although FVM caused fetal discomfort.[35] SARS-CoV-2-infected pregnant women's placenta and umbilical cord also show substantial pathological changes in another recent study. These data demonstrated that the virus could produce immune responses in the placenta, and the disease is probably associated with a greater likelihood of unfavorable newborn outcomes and mother ICU hospitalization.[36] Table 1 summarizes several histopathological findings of the SARS-CoV-2-infected pregnant woman's placenta.

Table 1. Impact of COVID-19 on the histopathological aspect of placenta

Author (Year)	Research Type	Finding
Al-Rawaf (2022)[36]	Case-control	Pregnant women's placenta and umbilical cord with COVID-19 show substantial pathological changes.
Bertero (2021)[18]	Case series	The most common and unusual pathological abnormalities described were inflammatory and thrombo-hemorrhagic changes.
Gao (2021)[20]	Cohort	Features of MVM were presented in the 3rd trimester of COVID-19-infected pregnant women.
Garg (2022)[35]	Case-control	Signs of MFM are the majority type of pathological discoveries.
Patberg (2021)[25]	Cohort	Patients were found to have an increased risk of placental histopathologic abnormalities.
Prabhu (2020)[24]	Cohort	According to placental pathology, women with COVID-19 had a higher prevalence of FVM, indicating thrombi in fetal vasculature.
Shanes (2020)[19]	Case-control	Placentas in the 3rd trimester tended to exhibit at least an MVM characteristic.
Smithgall (2020)[23]	Case-control	SARS-CoV-2-infected 3rd-trimester women's placentas tended to display indications of MFM.

CONCLUSION

SARS-CoV-2-infected pregnant women may have substantial histopathological abnormalities in the placental. The majority of monsters are MFM and villitis with unclear causes. Careful research of the relationship between microscopic abnormalities and the obstetric outcome is required to better aid physicians in delivering obstetric therapy for their patients during the COVID-19 pandemic.

DISCLOSURES

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Author Contribution

The author contributed to all aspects of this study, including preparation, article searching, drafting, and manuscript approval for publication.

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CASE REPORT

The management of Monochorionic Monoamniotic (MCMA) twin pregnancy

Ernawati[1]*, Jihan Qonitatillah[2], Agus Sulistyono[1]
[1]Department of Obstetrics and Gynecology, Universitas Airlangga, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.
[2]Postgraduate Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.

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***Corresponding author:**
Ernawati
ernawati@fk.unair.ac.id

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ABSTRACT

Objectives: To present the management of monochorionic monoamniotic (MCMA) twin pregnancy.

Case Report: Advanced prenatal treatment has improved the prognosis for Monochorionic Monoamniotic (MCMA) pregnancies; however, there is still no agreement on how to handle MCMA twins. The authors report 2 cases of monoamniotic monochorionic twin pregnancies. In the first case, a 30-years-old primi pregnant woman detected MCMA at 14 weeks of gestation; no complications related to MCMA were found; she planned delivery at 32 weeks, but one of the babies died in the womb at 31/32 weeks pregnant, a live baby born by cesarean section. The second case was a 36-year-old pregnant woman, on her third pregnancy, diagnosed with MCMA after 12 weeks of pregnancy, no complications related to MCMA, the baby was born at 32 weeks pregnant, and both babies survived. The management was the same in both cases, but different outcomes were obtained; in case 1, the baby died allegedly due to cord entanglement, which could not be detected during pregnancy.

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Highlights:

1. Monochorionic monoamniotic (MCMA) twin pregnancy has a significant risk of perinatal morbidity and mortality, including intrauterine fetal death (IUFD).
2. The risk of prematurity, the risk of death due to MCMA complications, the availability of the NICU, also high costs on preterm care were factors in deciding to terminate the pregnancy.
3. The ideal time to deliver monochorionic twins in order to reduce the risks of cord entanglement, growth discrepancies, and intrauterine fetal death is still a point of controversy.
4. Early diagnosis, intensive antenatal monitoring, patient and family decision would contribute to antenatal mortality reduction.

INTRODUCTION

Monochorionic monoamniotic twin pregnancy shares the same amniotic sac with a single fertilized egg and embryo as a result of a single fertilization. Typically, it is diagnosed by the first trimester ultrasound, showing a single placenta and amniotic cavity that are shared.[1,2] After 8 to 12 days of fertilization and zygote division, MCMA twin pregnancies occur.[3] The incidence of MCMA twins is only about 5% among monochorionic pregnancies, or one in every 10,000 pregnancies.[4]

Assisted reproductive techniques, ethnicity, advanced maternal age, genetic and epigenetic mechanisms have been implicated as MCMA twin pregnancy risk factors.[3] Advanced prenatal treatment has improved the prenatal prognosis for MCMA pregnancies, however there is still no agreement on how to handle MCMA twins. Monochorionic monoamniotic (MCMA) twin pregnancy has a significant risk for poor pregnancy outcomes, increasing perinatal morbidity and mortality, including intrauterine fetal death (IUFD) correlated to double twin demise due to severe fetal hypovolemia and anemia caused by twin-to-twin transfusion syndrome and also a risk of cord entanglement compare to the risk of prematurity and their complications due to earlier delivery time.[5–9] Early diagnosis usually at early semester and proper management can reduce the risk of complications. It is a challenging decision to decide on a delivery time because there is less evidence regarding the optimal timing or method of delivery due to their rarity.[10]

There is no consensus regarding the timing of delivery in monochorionic monoamniotic pregnancies. This case report will present the management of MCMA twins pregnancy and reporting two cases of monochorionic monoamniotic twin with a single fetal loss in the 31st week of gestation and surviving both twins in second cases.

CASE REPORT

Case 1

Mrs. S, 26-year-old, primigravida, attended the Obstetrics and Gynecology Polyclinic type B Hospital with a one-month history of delayed menstruation. There was no family history of past medical illness or twin pregnancies. The physical assessment and vital signs were normal. According to 6 weeks gestation age, an abdominal ultrasound examination showed a gestational sac containing a yolk sac with no apparent fetal pole. The patient returned at 14 weeks of gestation; an ultrasound examination showed an intrauterine gestational sac with two fetuses in one sac and a positive fetal heart rate. There was no visible amniotic membrane, but the fetal growth was normal. The patient was given folic acid, iron, and calcium supplements and planned for pregnancy control a month later.

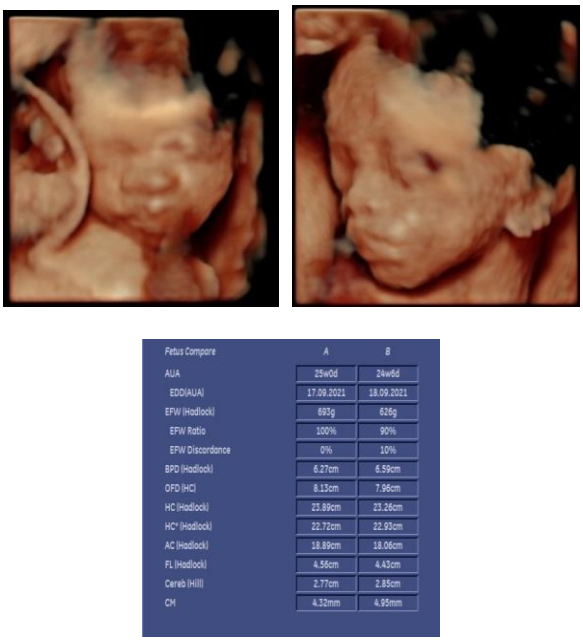

Figure 1. Case 1: Normal fetal biometry on both of the fetus. No sign of twin-to-twin transfusion syndrome (TTTS)

Second-trimester screening examination at 24 weeks gestation showed a normal general condition. Ultrasound obtained twin babies; the first fetus was in a transverse position, equal to 24 weeks and three days gestational age, and the second fetus was in a breech position, equal to 23 weeks and five days gestational age (Figure 1). The placenta was located in the front wall, grade 2, and the amniotic fluid index was sufficient. No dividing amniotic membrane was found, concluding a monochorionic monoamniotic twin pregnancy. The patient was planned for outpatient care, iron and calcium supplementation, and delivery at 30- or 31-weeks gestation. The patient was planned for control every two weeks and asked to monitor daily fetal movements. During antenatal care, fetal growth was normal, and there were no signs of discrepancies in the fetus.

The fetus was in the head/head position, there was no cord entanglement, the estimated fetal weight was 1100–1200g, and the fetal movement was active according to anamnesis at 30 weeks of gestation. We decided to delay delivery until 32 weeks due to the

fetus's all-head positioning, average fetal growth, and the possibility of preterm for small newborns. Patients were checked every week, and if they saw a change in the fetus' movements or experienced any contractions, they were urged to go back to the hospital right away.

A week later, the patient returned, uncomplaining and with frequent fetal movements. The second fetus, however, had no heartbeat, according to an ultrasound. As the first pregnancy reached 31 or 32 weeks, the fetus was still in good health. The patient was admitted to the hospital, got fetal lung maturation, and underwent cesarean delivery preparation. During the procedure, cord entanglements and red-black amniotic fluid were discovered. The first fetus, which weighed 1330 g, was still alive; the second, which weighed 1220 g, passed away. The infant was then given surfactant and put on a ventilator in the NICU for treatment. No neurological damaged detected. The infant was released in good health following a four-week stay in the hospital.

Case 2

A 36-year-old female, gravida 3, para 2, was attended to the hospital and diagnosed with an MCMA twin pregnancy at 12 weeks of gestation. She is from a mid to high-income family. No medical and pregnancy complications were recorded in her previous pregnancy and delivered by C-section. The two living children were normal—no history of assisted reproduction in this pregnancy. An abdominal ultrasound examination showed no signs of twin-to-twin transfusion syndrome (TTTS) and normal fetal growth during antenatal care. Maternal laboratory examination also showed a normal result. The patient was planned to undergo monthly monitoring until 24 weeks gestation, every two weeks until 30 weeks gestation, and weekly monitoring until delivery.

Considering the risk of umbilical cord entanglement and prematurity, patients were informed of the option to terminate pregnancies after 30 weeks. As a result of the evaluation showing normal fetal growth, the patient was encouraged to decide either delivering the baby at 30/31 weeks or expecting as of 31/32 weeks. The family decided to wait until 32 weeks, with fetal movement monitoring and weekly hospital monitoring after 30 weeks gestation.

The baby was born at 32 weeks gestation after being given lung maturation for two days. Due to the patient's prior two caesarean sections, caesarean delivery was chosen as the delivery method. Infants born weighing 1900 g and 2000 g; despite the infant weighed more than 1500 g, respiratory distress syndrome (RDS) still occurred (Figure 2). The infants were discharged after three weeks of ventilator support.

DISCUSSION

Monoamniotic twin pregnancies are distinguished by a single shared placenta and amniotic cavity.[2] The absence of a dividing membrane, rather than the number of yolk sacs present, is used to diagnose an MCMA twin pregnancy.[11] If the membrane is less than 2 millimeters thick or there are only two layers visible, the pregnancy is monochorionic. It has been found that the number of membrane layers can accurately predict prenatal chorionicity with an accuracy of better than 98 percent.[12] Sometimes the transvaginal approach allowed for accurate representation of chorionicity and amnionicity.[2,7]

In the first case MCMA undetected on the 6th weeks of pregnancy, but detected when she was attend the second time at 14th weeks of pregnancy. During the first few weeks of pregnancy, when the membrane is almost undetectable, MCMA twins are frequently mis-diagnosed. It is recommended to determine amnionicity prior to 14 weeks of gestation and to repeat the ultrasound examination in cases where the dividing membrane cannot be identified.[6,13] It is advantageous to be able to predict amnionicity at an early stage since the diagnostic precision of recognizing monoamniotic twin pregnancies is crucial for management strategies. The aim of MCMA management is to reduce the mortality associated with undetected cases and minimize false-positive diagnosis that lead to improper interventions.[11]

After the first trimester, we typically perform ultrasounds every two weeks to check the viability of the fetuses and screen for growth restriction and TTTS. Cord entanglement is difficult to detect in cases of MCMA; no examination can predict it. Weakening of fetal movement after previously moving quickly is a subjective symptom that can be known but cannot be used as a reference. The presence of decelerations on cardiotocography examination during labor is one of the signs. However, seeing if the patient has yet to give birth will be difficult. When delivery and postnatal care become an option, often between 24 and 28 weeks of gestation, the frequency of follow-up visits is increased; from that point on, we are able to intervene in the event of findings indicating imminent fetal mortality.[2,14]

Figure 2. Case 2: Twisted umbilical cords at risk of cord entanglement to fetal death were found at surgery. Left: The first baby. Right: The second baby.

There is not enough evidence currently available to recommend which method of monitoring is the most effective; hence, the majority of professionals will use a combination of ultrasound surveillance and monitoring of the fetal heart rate.[2,14] In cases of monochorionic diamniotic twin pregnancy, it is recommended that ultrasonography be performed at least once every two weeks, with attention paid to discrepancies in amniotic fluid volume and fetal growth, in order to detect TTTS.[6] Regular ultrasound monitoring can help predict pregnancies with an increased risk of fetal growth restriction and growth discordance.[5,15] Observational studies show that once surveillance is implemented, the prospective risk of fetal death decreases by 5% compared to before surveillance was implemented. It is recommended to refer monoamniotic twin pregnancies to specialized centers for management and delivery.[2]

The ideal time to deliver monochorionic twins in order to reduce the risks of cord entanglement, growth discrepancies, and intrauterine fetal death is still a point of controversy. However, the number of previous studies indicates that the best timing for delivery of MCMA twins is between 32 and 34 weeks of gestation.[5,13] The crude perinatal mortality rate for women with monoamniotic twins at 22 weeks of gestation is approximately 15%.[6] Many researchers consider that inpatient management, thorough monitoring of monoamniotic twins, and early birth at 32 to 34 weeks of gestation may enhance outcomes,[6] although this has not yet been confirmed.

Despite the findings of cord entanglement, expectantly managed monoamniotic twins at 20 weeks have a very better prognosis. Expectant management was started during the late second or early third trimester, with a targeted delivery between 32 to 34 weeks. Perinatologists at the tertiary care facilities where the patients were transferred for confirmation and consultation prepared these strategies. Considering that the fetus in this case was less than 32 weeks, the patient was managed as an outpatient. Also, recent studies indicate that prolonged hospital stays have considerable economic, societal costs, and family disruption including psychiatric symptoms such as hopelessness and despair, which the inpatient group experienced more than the outpatient group did.[2]

Due to the larger placenta and greater uterine capacity in monochorionic monoamniotic twin pregnancies, monoamniotic twin pregnancies are associated with a higher risk of pregnancy problems compared to singleton pregnancies.[2] Studies stated between 28 to 47 percent of monochorionic monoamniotic twin pregnancies result in perinatal mortality.[7,9] Frequent and adversely severe problems are associated with a shared placental circulation. TTTS and TAPS are caused by imbalanced blood flow across the placental vascular anastomoses, while fetal growth restriction is mostly caused by unequal placental sharing.[16,17] Most fetal deaths occur during the first two trimesters of pregnancy, however, even after 24 weeks, the risk of fetal death in monoamniotic pregnancies is nine times greater than in dichorionic twin pregnancies. Cord entanglement or abrupt hemodynamic imbalances resulting from massive placental anastomoses commonly contribute to fetal deaths.[2]

In the Case 1, during follow-up to 31/32 weeks of gestational age, an ultrasound examination showed normal fetal growth and no signs of discrepancy in the fetus or umbilical cord, but we could not find the second fetal heart rate. In a monochorionic twin pregnancy, single IUFD is fatal for the surviving twin due to severe

fetal hypovolemia and anemia caused by blood transfusion from the surviving fetus to the deceased fetus.[7] In the case of a single fatality, 57% of the surviving twin is at risk of sustaining a serious brain injury. The presence of extensive placental artery-to-artery anastomoses allows the surviving fetus to exsanguinate into the dead fetus.[2]

Elective preterm delivery of monochorionic twin pregnancy is recommended when the possible risks of postponing delivery exceed the risk of delivery.[2,18] Premature newborns, particularly those delivered prior to 32 weeks of gestation, are susceptible to a variety of health complications. Cordero et al.[9] reported a high incidence of perinatal depression, respiratory distress, early and late onset sepsis, patent ductus arteriosus, necrotizing enterocolitis, intracranial hemorrhage, prolonged hospitalization, and poor neurological outcomes in premature newborns. Therefore, although elective very preterm delivery has a low fatality rate, it should be reevaluated due to its high morbidity rate.[7] Delivery of the baby should be considered while there are prolonged episodes of fetal tachycardia or repeated heart rate decelerations. Due to the lack of evidence on optimal delivery triggers and poor response to subtle indicators of fetal distress, physician experience plays an important role in preventing unnecessary early delivery.[2]

Delivery at 31/32 weeks of gestational age in both case were decided by cesarean section after receiving lung maturation. Considering monoamniotic twins, most centers would suggest a cesarean delivery to prevent cord prolapse or accidental clamping of the second twin's cord, which could be securely wrapped around the neck of the first twin.[7,15] A cesarean section is recommended to be done at 32 to 34 weeks of gestation age.[4] To reduce the risk of cord prolapse for the remaining fetus, fetoscopic cord transection of the deceased fetus may be considered on a case-by-case basis.[2,19] There is still no consensus in the evidence regarding the management and mode of delivery of these rare cases.

The risk of prematurity and the risk of death due to MCMA complications must be considered in MCMA pregnancy care, so parents must be involved in decision-making in order to comprehend the risks. In the two cases above, there were no complications associated with MCMA, such as TTTS. However, in case 1, there appeared to be a risk of cord entanglement, where this diagnosis was difficult to make due to the constant movement of the fetus. While the second case did not occur, we were able to manage to get both infants alive. It was difficult to predict the occurrence of these complications; therefore, a joint decision with the parents to consider the risks and benefits, as well as the availability of the NICU, was the factor in deciding whether to terminate the pregnancy. Basnet et al.[20] reported that 40.6% of preterm infants in tertiary care center had neonatal intensive care unit admissions, which may then improve preterm outcomes and significantly associated with lower mortality.[20,21] Other study reported NICU admission has increased from 6.4% in 2007 to 7.2% in 2018 as the number of newborns requiring intensive care has increased.[22] In the two cases above, all infants needed a NICU for treatment, hence in cases of twins and MCMA, a hospital with a NICU was required for care.

The strength of this case report is that it presents the management of a rare case of monoamniotic twins and the challenges of their management. Handling must be reviewed case by case because each type of case has its uniqueness. While the weakness in this case report is that the number of cases reported is only two because the types of cases are rare, so they cannot be presented in a case series. However, these two cases can provide an overview of the management of monoamniotic twin cases.

CONCLUSION

Monochorionic monoamniotic twin pregnancy is at a significant risk for poor pregnancy outcomes, and due to their rarity, there is less evidence regarding their management. Guiding expert opinions to the current best practice, risks can be avoided through close monitoring and following viability. Monitoring should include ultrasonography and monitoring of the fetal heart rate; however, the optimal frequency of monitoring, the optimal management, whether inpatient or outpatient, and the delivery triggers have not been determined. To improve outcomes, monoamniotic twins should be delivered by elective cesarean section between 32 and 34 weeks of gestation. Early diagnosis, intensive antenatal monitoring in the hospital beginning at the time of fetal viability, and elective delivery at 32 weeks would contribute to antenatal mortality reduction.

DISCLOSURES

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Conflict of interest

The authors report there are no competing interests to declare.

Patient consent for publication

The patient signed the informed consent form and agreed that this case report is published.

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Author Contribution

All authors have contributed to all processes in this research, including preparation, data gathering and analysis, drafting and approval for publication of this manuscript.

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