Editorial

Screening of Preeclampsia for the Reduction of Maternal Morbidity and Mortality in Indonesia

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Hypertensive disorders of pregnancy including preeclampsia (PE) and eclampsia are the most common causes of maternal and perinatal morbidity and mortality. They are responsible for 16% of maternal deaths in high-income countries and approximately 25% in low and middle-income countries.[1] In Indonesia, they contribute to approximately 33.07 %, followed by hemorrhages 27.03, non-obstetric complications 15.7% and others.[2]

Screening in terms of accurate prediction by identifying women at high risk of developing PE is one of the pivotal steps to prevent its occurrence, allowing antenatal preventive measures to anticipate the onset of clinical syndrome and manage it promptly.

It is well established that a number of maternal risk factors are associated with the development of PE. These risk factors have been described by various professional organizations for the identification of women at risk of PE. Women should be considered to be at high risk of developing PE if they have any one high-risk factor (hypertensive disease in previous pregnancy, chronic hypertension, chronic renal disease, diabetes mellitus, or autoimmune disease) or any two moderate-risk factors (nulliparity, age ≥40 years, BMI ≥35 kg/m^2, family history of PE, or interpregnancy interval >10 years).[3]

An alternative approach to screening for PE is to use Bayes theorem to combine the a *priori* risk from maternal characteristics and medical history with the results of various combinations of biophysical and biochemical measurements. The four potentially useful biomarkers at 11-13 weeks of gestation are mean arterial pressure (MAP), uterine artery pulsatility index (UTPI), serum pregnancy associated plasma protein-A (PAPP-A) and serum placental growth factor (PLGF).[3]

The Fetal Medicine Foundation (FMF), has been developed the first trimester screening for PE which has been endorsed by the FIGO. Based on this approach, a competing risk model treats the gestational age at delivery with PE as an event in time by a survival-time model, that can be picked up freely from https://fetalmedicine.org/research/assess/pre-eclampsia/first-trimester

Recent advancements in preeclampsia research have led to the identification of novel markers that not only are helpful in detecting the disease earlier but also hold promise in enhancing our understanding of it. These emerging markers include a range of biological molecules, specific proteins, micro-RNAs, and metabolites such as elevated levels of visfatin, which is also known as nicotinamide phosphoribosyltransferase (NAMPT), uric acid, and allopurinol.[4]

By the advancements of technology on softwares and AI (artificial intelligence) methods that are most helpful in the prediction of the risk of preeclampsia, this way allowing physicians closer surveillance and to intervene earlier. In these softwares, physicians can type in the data of the mothers, biophysical and biomarkers measurements and automatically the program gives the approximate risk for the development of preeclampsia later during the pregnancy. Some of these programs are also available in the form of a mobile phone application, this way being more accessible to professionals.[4]

Finally, I would bring forward an eight-year work (2015-2022) of my colleagues in Bandung West Java who developed the so called 'ZerO mOther Mortality preeclampsia (ZOOM) program' aimed at reducing maternal mortality due to preeclampsia and hypertension in pregnancy (HIP) in dr. Hasan Sadikin Hospital Bandung. This is a community intervention study implementing four types of intervention i.e. re-education (identification of risk factors, early detection using uterine artery pulsatility index (UTPI); prevention (calcium 1000 mg/d and low dose aspirin 80 mg/d); timely referral system (all HIP mothers should be delivered in hospital), and updated protocol (active management at $\geq$ 34 weeks gestation, MgSO4, and antihypertension). They analysed 19,176 deliveries and associated maternal deaths due to HIP. As the result, there was a significant reduced of MMR from 61% to 10%, and significant reduced of case fatality rate from 2.6 to 0.2. [5] Indonesia scenario, by identifying maternal risk factors of PE combined with early detection of abnormal UTPI, followed by administration of calcium and low dose aspirin, timely referral, and prompt management could reduce maternal morbidity and mortality due to eclampsia and HIP significantly.

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Research Article

Effectiveness of Long Bean Leaf Green Noodles in Enhancing Prolactin Levels in Breastfeeding Mothers

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Abstract

Breastfeeding plays an important role in meeting the nutritional needs of infants and is useful in preventing malnutrition in children. However, insufficient breast milk is one of the obstacles in this process. Interventions that usually used for increasing breast milk can be done pharmacologically using Domperidone. On the other hand, the drug can trigger side effects, then the use of herbs is recommended. Long bean leaves (*Vigna sinensis L.*) are plants that are rich in nutrients and can stimulate prolactin through the phytocemichal contents[1-3].

Objectives: The aims of the research to be carried out is to formulate and analyze the effectiveness of Green Noodles based on long bean leaves (*Vigna sinensis L.*) to help increase prolactin of breasfeeding mother.

Methods: The research method used is a quasi-experimental with a Nonrandomized Control Group Pretest-Postest Design consisting of an experimental group (given green noodles) and a control group (given plain Noodles) using 10 respondents for each group. The intervention was carried out for 14 days by giving green noodles 2 times a day for 14 days.

Results: Green noodles contain 4 times higher levels of polyphenols than white noodles with amounts of 384.55 mg/kg and 85.39 mg/kg respectively. Based on the results of pre and post interventions in both intervention and control groups, it was found that breastfeeding mothers who consumed Green Noodles experienced an increase in prolactin levels (p value 0.004) and mothers who consumed plain noodles did not experience a significant increase in prolactin levels (p value 0.283). The lack of respondents and previous research that directly discusses the benefits of the longbean leaves requires further research to strengthen the research results to be implemented for breastfeeding mothers.

Conclusion: Consuming green noodles can help increasing prolactin hormone on breastfeeding mother in Jatinegara Health Center.

Keywords: Breastmilk; Long Bean Leaves; Breastfeeding; Prolactin; *Vigna sinensis L.*

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INTRODUCTION

Breastfeeding plays an important role in the growth and development of children to prevent various types of malnutrition such as wasting, stunting, obesity and micronutrient deficiencies. In addition, breastfeeding contributes to providing protection against infectious diseases[4] Exclusive breastfeeding for infants aged 0-6 months is very important because the nutrition in breast milk can improve the growth and development of children[5]. Inadequate breastfeeding causes 16% of children to die each year. Based on survey data from 2016-2022, 46% of newborns start breastfeeding within one hour of birth. Meanwhile, 71% of women continue to breastfeed their babies for at least one year, at the age of two years[6]. In Indonesia, in 2023, the percentage of infants under 6 months who receive exclusive breastfeeding is 72.99% for male infants and 75.02% for female infants and 76.39% in DKI Jakarta[7]. In 2022, East Jakarta is one of the cities with the second lowest rate of breastfeeding for infants under 6 months of age, namely 15.6% with an average duration of breastfeeding of 11.19 months[8]. Several obstacles such as sore or painful nipples, insufficient breast milk production, and breast swelling can cause the breastfeeding process to be less than optimal.[9] Nutrition is a need that must be met in the breastfeeding process because it determines the quality and quantity of breast milk production, then lack of nutrition or fluids will correlate with inhibited breast milk production.[10-12] This will then have an impact on the health, growth and development of children.[4] Breast milk production can be increased pharmacologically and non-pharmacologically. Interventions to increase breast milk pharmacologically can be done by administering Domperidone. The results of a study on 355 breastfeeding mothers who consumed Domperidone at

a dose of 20mg to more than 61mg per day were quite effective. However, almost half of the respondents experienced side effects such as weight gain and dry mouth and use with higher doses triggered more severe side effects. In this study, 9% of respondents stopped taking Domperidone due to side effects.[13] On the other hand, non-pharmacological interventions can be done by using herbal plants that have been proven to provide positive benefits with minimal side effects, one of which is katuk and lembayung or long bean leaves.[14] This is also supported by previous research in 1875 breastfeeding mothers stating that giving Domperidone caused 23% of respondents to experience side effects compared to herbal galactogogues, namely 3%.[15] Long beans (*Vigna sinensis L*.) as a vegetable that is very popular with the public, contain very high vitamins and minerals, and have great potential to be developed (1). Long bean leaves or lembayung are plants that are already known to the public, easy to get and economical. These leaves have a lactogogum effect that is useful to stimulate the hormones oxytocin and prolactin through alkaloids, saponins, polyphenols, steroids, and flavonoids that can overcome the problem of breast milk deficiency.[16,3]

In previous studies, consuming 200 grams of long bean leaf per day for 7 days can increase the amount of breast milk.[17] The benefits of these in increasing breast milk production can be seen from the characteristics of fulfilling the needs for breast milk in infants, namely the frequency of defecation, urination, weight and frequency of sleep in infants and prolactin level.[18-20]

The use of long bean leaf as vegetables or juice has begun to be used by the community to increase breast milk production, but this food is a product that can only be consumed at one time because it does not last long. While instant noodles are fast food that is very dominant and in demand by the Indonesian people. In 2020, instant noodle consumption was 12.6 billion servings, an increase of 120 million servings or 0.96% compared to the previous year.[21] Based on this, the urgency of conducting research is the development of long bean leaf products to increase the value and durability of the product. Utilizing these leaves in the form of noodles is a good thing and a unique innovation because in addition to increasing interest in consuming vegetables, it has an impact on increasing breast milk production by prolactin level and can increase the economic value of the community. So that research will be conducted on the Formulation and Analysis of the Effectiveness of Green Noodles Based on long bean Leaves (*Vigna sinensis L*.) to Increase prolactin

METHODS

This study was a quasi-experimental study with Nonrandomized Control Group Pretest-Postest Design consisting of two groups, namely the experimental and control groups. The inclusion criteria were breastfeeding mothers who had baby on age 0-6 months, having insufficient breastmilk, babies given exclusive breastfeeding, not career women, did not experience problems in the breastfeeding process such as mastitis or abscesses and were committed to following the study. The exclusion criteria included babies given food or drinks other than breast milk, and mothers consuming breastmilk Booster. The interfering variables in this study were the daily meal consumed by the mothers, maternal compliance and hormonal conditions which could vary among respondents. Then to avoid this, researchers conducted observations and documentation every day on WhattApps group to monitor eating activities and document 2 times a day for the consumption of green noodles and plain noodles for each respondent. on the other hand, researchers also always provide motivation and encouragement to respondents to always provide exclusive breastfeeding and provide counseling about breast milk and the benefits of longbean leaves in between studies to increase respondents' knowledge and interest in completing this study.

The study was conducted on 2 groups, namely breastfeeding mothers who were given Green Noodles (intervention group) and plain noodles (control group) with each group consisting of 10 respondents. Noodles as much as 100 grams were given twice a day for 14 days. The polyphenol content in green noodles was analyzed quantitatively in the SGI Laboratory (Saraswanti Genomic Institute) Bogor laboratory using spectrophotometry by analysts. Then prolactin levels were checked before and after the intervention, using the Rayto Type RT-2100C Elisa Analyzer with PRL reagent.

Ethical clearance approval for this study was obtained from Health Research Ethics Committee Binawan University with the following number 160/KEPK-UBN/VI/2024.

RESULTS

In this research, phytochemical tests were carried out on green noodles and plain noodles (without long bean content) to detect the polyphenol compound which is a substance that is useful in stimulating the hormone

prolactin in breastfeeding mothers. The process was carried out using spectrophotometry at the Saraswanti Genomic Institute (SIG) laboratory. Based on the test results, it was found that the polyphenol content in green noodles and plain noodles was 384.42mg/kg and 85.85 respectively. These results (Table 1) show that green noodles contain 4 times more polyphenols than plain noodles.

Table 1. Polyphenols of Green Noodle Composition

Type of Noodles	Parameter	Unit	Simplo	Duplo	Limit Of Detection	Method
Green Noodles	Polyphenols	mg / kg	384.55	384.42	-	18-9-20/MU/SMM-SIG (spektrofotometry)
Plain Noodles	Polyphenols	mg / kg	85.39	85.38	-	18-9-20/MU/SMM-SIG (spektrofotometry)

After conducting research on respondents in the intervention and control group for 14 days, Data analysis was carried out using the Paired t Test. Based on the results showed that there was a significant difference (p value 0.004) in the intervention group before and after being given green noodles. Meanwhile for the control group there was no significant difference (p value 0.283).

Table 2. The Differences of The Amount of Prolactin in Breastfeeding Mothers after Giving Green Noodles

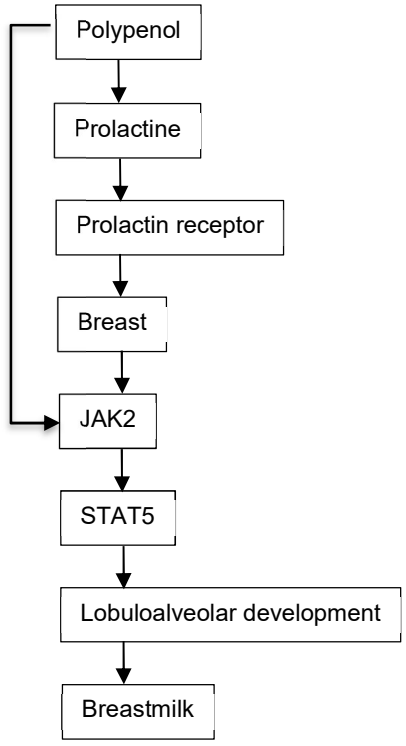
Intervention Group				Control Group			
n	**Mean**	**SD**	**P**	**n**	**Mean**	**SD**	P
10	-19.00240	15.55437	0,004	10	-2.21300	6.13129	0,283

DISCUSSION

In the breastfeeding process, there are two important hormones are needed, namely oxytocin and prolactin.[22] The oxytocin hormone functions to flow breast milk while prolactin produces breast milk. Prolactin (PRL) is a pleiotropic hormone released from anterior lactotrophic cells. The pituitary gland also originates from an extrapituitary source and plays an important role in regulation lactation in mammals.[23] Prolactin is secreted by the anterior pituitary, nervous system, uterus, ovaries, and glands in the breasts. Prolactin binds to the PRL receptor, which is expressed in many cells and tissues, including the pituitary, mammary glands, placenta, and ovaries. In the lactogenesis process, PRL concentrations increase as a result of stimulation of the baby's sucking at the breast. This increase in PRL concentration prevents ovulation (anoestrus) and stops implantation (diapause).[24] Prolactin is needed for the process of breast milk secretion. Production and volume of breast milk is determined by several factors, namely local factors and the process of emptying breast milk regularly. in addition, oxytocin has a role in stimulating neuroendocrine reflexes that produce stimulation of myoepithelial cells surrounding the alveoli and breast milk ducts. Prolactin secretion occurs periodically, with peaks lasting up to 75 minutes occurring 7 to 20 times daily. During pregnancy, serum prolactin continue to increase from 10 ng/mL before pregnancy to 100-200 ng/mL at term.[25] After giving birth, basal prolactin levels decrease, but in breastfeeding mothers, baby sucking on the nipple, intensity and frequency of breastfeeding can increase prolactin secretion.

On the other hand, prolactin levels cannot be used to determine milk volume.[26] Apart from being stimulated by the baby's sucking, increasing prolactin levels can also be supported by providing foods that are high in antioxidants such as polyphenols. Based on the results of laboratory tests, green noodles contain 384.42 mg/kg of polyphenols. This is certainly very beneficial and contributes to increasing breast milk production by increasing prolactin levels. This is also proven by previous research which states that eating foods containing polyphenols such as long beans can increase breast milk production.[18-20,27] Polyphenols can help form glands in the breasts and act as galactagogues.[28].The mechanism by which polyphenols help increase maternal prolactin levels is through a complex mechanism with prolactin receptors.

Polyphenols can stimulate galactagogues by maintaining prolactin. Prolactin binds to its receptor, namely the prolactin receptor (Prlr) to signal through the binding of endocrine and prolactin to the hypothalamus-pituitary-gonad (HPG). Binding to PRLR results in stimulation of JAK2 tyrosine kinase activity and subsequent phosphorylation of multiple tyrosine residues and activation of signal transducer and activator of transcription (STAT) proteins, in particular STAT5 (JAK2/STAT5 signaling) which is required for lobuloalveolar development and transcriptional regulation of breast milk protein genes in mammary glands, then breast milk production can be secreted properly.[23,29-31] In addition to stimulation through the prolactin receptor pathway, polyphenol compounds can stimulate the JAK-STAT pathway directly.[32] On the other hand, polyphenols triggered upregulation of breast tissue-specific genes, fatty acid bioavailability, lipogenesis, and adiponectin pathways. Regulation of adipokines and PPAR determines lipid homeostasis and inflammatory responses to maintain breast milk quality. Based on this, it also shows that lipids in breast milk can be modulated by foods containing polyphenols.[33]



Picture. 1 The mechanism of polyphenols stimulates prolactin to increase breast milk production.

Based on the results of research that has been carried out it can be concluded that giving green noodles based on *Vigna sinensis L*. which are rich in polyphenols can help stimulate prolactin production and sufficient prolactin production can support successful breastfeeding in breastfeeding mothers in Jatinegara Health Care. Further studies are needed in larger populations and the use of other parameters in the breastfeeding process to strengthen these findings.

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CONFLICT OF INTEREST

Reseachers declare that there is no conflict of interests in the research.

CONCLUSION

Based on the research, 5% Green noodles based on *Vigna sinensis L.* contain 384.42 mg/kg polyphenols which can help increase prolactin level in breastfeeding mother with p value 0,004 in Jatinegara Health Care.

This study produced the same results as the previous study using longbean leaves,[19,27] but in this study there was an increase in the quality of the shape of the vegetables, Noodles, that could increase the storage time and interest in using natural ingredients to support the breastfeeding process.

The limitations of this study is the small number of breastfeeding mothers that was only conducted in the Jatinegara Health Center work area, the respondents were not housed in one place during the intervention and the lack of related research on the benefits of longbean leaves on prolactin levels as a reference source.

Further research is needed to with a larger population, improve the taste and texture of green noodles, the effects on the maternal kidney system and baby digestion and other variables to strengthen the benefits and downstreaming of nutritious food for breastfeeding mothers.

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Research Article

Comparison of Pulsatility Index and Notching of Uterine Artery Doppler on Normotensive Pregnancy and Established Pre-eclampsia

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Abstract

Objective: The aim is to assess the pulsatility index of the uterine artery (UtA-PI) and the presence of notching, then compare them between normotensive pregnancy and pre-eclampsia.

Methods: This cross-sectional study was conducted at dr. Sardjito Hospital and Harapan Kita Maternal Children Hospital as a tertiary referral hospital. The study involved 220 women, this includes pregnant women who are at risk of illness and mortality during pregnancy, parturition, and postpartum periods, specifically those with chronic hypertension and a history of pre-eclampsia. The inclusion criteria comprised of women aged ≥18years, gestational age 28-40 weeks, singleton pregnancy, normotensive pregnant women, and pregnant women diagnosed with pre-eclampsia. The exclusion criteria included women with intrauterine fetal death, pregnant women with heart disease, acute fatty liver of pregnancy, chronic kidney disease, autoimmune disorders like systemic lupus erythematosus or antiphospholipid, and type 1 or type 2 diabetes. STATA 14.2 program was used for statistical analysis.

Result: There were 188 pregnant women normotensive pregnancy (85.5%) and 32 pre-eclampsia cases (14.5%). Body mass index, blood pressure, mean arterial pressure, chronic hypertension, history of pre-eclampsia, birth weight, UtA-PI and notching showed an significant association with pre-eclampsia. The receiver operating characteristic curve (ROC) analysis was used. The ROC analysis result of UtA-PI was found as sensitivity 87.50% and specificity 98,94% (AUC: 0.9963, 95% CI: 0.99-1) with cutoff 1,22. and notching was found as sensitivity 46,88% and specificity 87,23% (AUC: 0.6705, 95% CI: 0.57-0.76).

Conclusion: There are differences in the accuracy between UtA-PI and notching. UtA-PI has better performance the notching.

Keywords: Pulsatility index, notching, normotensive, pre-eclampsia

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INTRODUCTION

Hypertension in pregnancy remains the major cause of maternal death. Pre-eclampsia results in the deaths of 76,000 women and 500,000 infants annually, affecting 3-5% of pregnancies worldwide[1]. In Indonesia, the maternal mortality rate due to pre-eclampsia is approximately 2.2%, and at Cipto Mangunkusumo Hospital, it remains a significant cause of maternal deaths. To address this issue, quality antenatal care services are essential[2,3].

Pre-eclampsia is caused by abnormal uteroplacental circulation, which is a result of imperfect remodeling of the spiral arteries during trophoblast invasion[4]. This condition can be assessed using a

non-invasive method, namely, Doppler ultrasonography, which examines the UtA-PI and notching[5]. The UtA-PI is the difference between systolic and diastolic flow velocities divided by the average velocity, providing information about the impedance index[6]. Notching is associated with endothelial damage in the mother, resulting in increased vascular resistance[7]. The objectives of this study are to assess the UtA-PI and the presence of notching, then compare them between normotensive pregnancy and pre-eclampsia.

METHODS

A cross sectional study was conducted between March to August 2024. The inclusion criteria comprised of women aged ≥18years, gestational age 28-40 weeks, singleton pregnancy, normotensive pregnant women, and pregnant women diagnosed with pre-eclampsia. The exclusion criteria included women with intrauterine fetal death, pregnant women with comorbidities, such as heart disease, acute fatty liver of pregnancy, chronic kidney disease, autoimmune disorders like systemic lupus erythematosus or antiphospholipid, type 1 or type 2 diabetes and those unable to provide informed consent. This research used a consecutive sampling method.

The study was conducted in dr. Sardjito Hospital and Harapan Kita Maternal Children Hospital. The study had 227 participants and 7 of them were excluded, that only 220 research samples were analyzed, this includes pregnant women who are at risk of illness and mortality during pregnancy, parturition, and postpartum periods, specifically those with chronic hypertension and a history of pre-eclampsia. Pre-eclampsia is defined as a hypertensive condition that appears after 20 weeks of pregnancy, accompanied by end-organ damage, including proteinuria[8]. Chronic hypertension refers to hypertension that exists prior to pregnancy. A history of preeclampsia indicates that the pregnant woman experienced pre-eclampsia in a previous pregnancy. Superimposed pre-eclampsia refers to women with chronic hypertension accompanied by proteinuria after 20 weeks of gestation represents a significant complication[9]. Diagnosing pre-eclampsia using the guidelines of the International Society for the Study of Hypertension in Pregnancy (ISSHP)[8]**.** Superimposed pre-eclampsia is not included in analysis. Data analyzed using STATA version 14.2.

The pregnant woman undergoes an interview covering her previous pregnancy and medical history. The physical examination includes vital signs and an obstetric examination. An ultrasound examination is performed using a Voluson S8 ultrasound machine produced by General Electric Healthcare in Milwaukee, United States. The machine is equipped with a convex transducer probe operating at 1-5MHz for transabdominal scanning.

The operator of this study was two sonographers certified by the Fetal Medicine Foundation. Inter-Observer Agreement were also conducted to assess the reliability between two observers using intraclass correlations. The uterine artery examination and assessment of the notching were carried out according to the guidelines of the International Society of Ultrasound in Obstetrics and Gynaecology (ISUOG)[10].

RESULT

In Table 1, the total number of women who completed the study was 220 of these, 188 (85,5%) had normotensive pregnancy, while 32 (14,5%) of them developed pre-eclampsia. The analysis was carried out using t test and chi-square test. The table shows a significant association between pre-eclampsia and several variables are body mass index, blood pressure, mean arterial pressure, chronic hypertension, history of pre-eclampsia, birth weight, UtA-PI and notching. In contrast, other variables are age and parity showed no significant correlation.

Tabel 1. Distribution of pre-eclampsia cases based on characteristics and chi-square test

Variables	Total (N=220)			*P value*
	Normotensive(n=188)	Pre-eclampsia(n=32)	ALL	
Age, years*	32.088 (4.939)	32.035 (5.479)	32.080 (5.008)	0.956
Age				
<35 years old	134 (71.3%)	23 (71.9%)	157 (71.4%)	0.945
35+ years old	54 (28.7%)	9 (28.1%)	63 (28.6%)	
Body Mass Index, Kg/M^2	27.138 (4.529)	31.317 (4.585)	27.746 (4.761)	<0.001
Blood Pressure, mmHg				
Systolic	113.287 (10.610)	159.719 (19.069)	120.041 (20.415)	<0.001
Diastolic	69.963 (7.701)	97.125 (11.316)	73.914 (12.684)	<0.001
Mean Arterial Pressure, mmHg	84.404 (6.834)	117.990 (13.176)	89.289 (14.328)	<0.001
<90	146 (77.7%)	3 (9.4%)	149 (67.7%)	<0.001
90+	42 (22.3%)	29 (90.6%)	71 (32.3%)	
Parity				
Nulli/Primigravida	150 (79.8%)	24 (75.0%)	174 (79.1%)	0.538
Multigravida	38 (20.2%)	8 (25.0%)	46 (20.9%)	
Chronic Hypertension				
No	185 (98.4%)	23 (71.9%)	208 (94.5%)	<0.001
Yes	3 (1.6%)	9 (28.1%)	12 (5.5%)	
History of Pre-eclampsia				
No	188 (100.0%)	21 (65.6%)	209 (95.0%)	<0.001
Yes	0 (0.0%)	11 (34.4%)	11 (5.0%)	
Birth Weight, gram	2,900.005(564.238)	2,421.625 (693.284)	2,830.423(607.006)	<0.001
<2500	32 (17.0%)	17 (53.1%)	49 (22.3%)	<0.001
2500+	156 (83.0%)	15 (46.9%)	171 (77.7%)	
UtA-PI, score*	0.670 (0.141)	1.376 (0.178)	0.773 (0.289)	<0.001
Notching			181 (82.3%)	
Absent	164 (87.2%)	17 (53.1%)		<0.001
Presents	24 (12.8	15 (46.9%)	39 (17.7%)	

*) t test , all other using chi-square

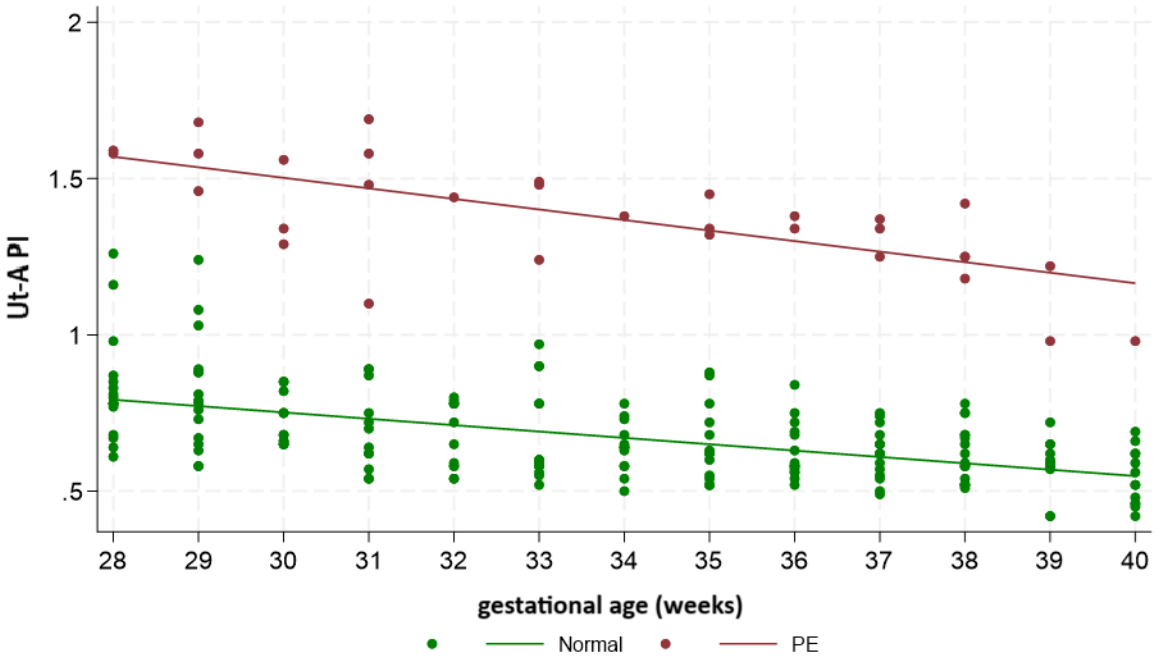


Figure 1. Uterine Artery Pulsatility Index on normotensive pregnancy (normal) and pre-eclampsia (PE)

Figure 1, they analysis was carried out using regression test, showed higher baseline UtA-PI values in pre-eclampsia compared to normotensive pregnancy. In another study, an increase in the UtA-PI ratio >95th percentile was reported in women with pre-eclampsia compared to normotensive pregnancy [11].

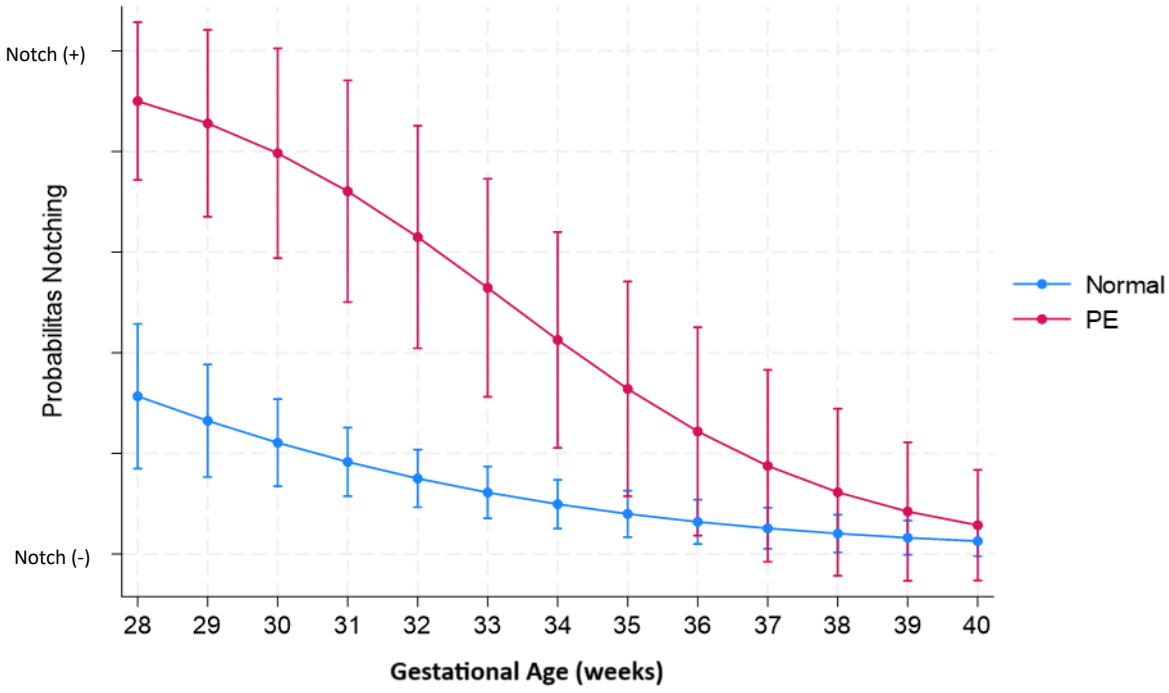
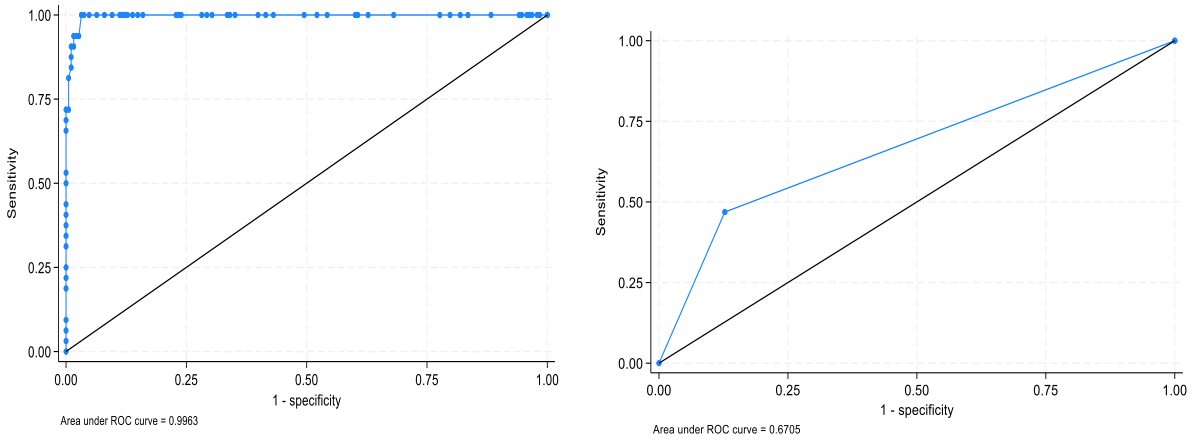


Figure 2. Notching in Normotensive Pregnancy and Pre-eclampsia

Figure 2, they analysis was carried out using regression test, showing notching is more often present in pregnant women with pre eclampsia compared to pregnant women with normotensive. Whereas other research, notching appears more often in pre eclampsia compared to pregnant women with normotensive [12].



a **b**

Figure 3. Receiving Operator Curve (ROC) Pulsatility Index Analysis (a) and ROC for notching (b)

Figure 3a shows the logistic model analysis, performed with a Receiver Operating Characteristic (ROC) curve value of 0.99 to evaluate the screening method's performance. Figure 3b shows the logistic model analysis for the notching yielding under the ROC curve value of 0,67.

Table 2. Sensitivity and Specificity Notching and UtA-PI

Variable	Sensitivity (%)	Specificity (%)	Cut off
Notching	46,88	87,23	-
UtA-PI	87.50	98.94	1.22

Table 2 compares the sensitivity and specificity of the UtA-PI and notching. The logistic regression model for the pulsatility index shows an area under the ROC curve (AUC) of 0.99, with a chosen cut-off 1,22 yielding 87.50% sensitivity and 98.94% specificity. The notching model has an AUC of 0.67, with 46.88% sensitivity and 87.23% specificity. After performing a one-way analysis using F-tests, the notching shows a power of 0,98 (α = 0,05), while the UtA-PI demonstrates a power of 1 (α = 0,05). Whereas other research the UtA-PI has defined the cut-off value as 2.51 AUC of 0,93 in the 1st trimester, 1,32 AUC of 0,93 in the 2nd trimester and 1,91 AUC of 0,96 in the 1st and 2nd trimesters[13].

DISCUSSION

This research identified 14,5% pre-eclampsia cases. The high rate of pre-eclampsia is consistent with previous report from Indonesia[14]. Globally, the incidence ranges from 2-8% and is increasing in developing countries[15]. Therefore, early screening of pre-eclampsia are essential. Given this, ultrasonography is a viable approach that can be implemented in Indonesia, even with limited resources.

Cytotrophoblasts invade the spiral arteries that supply blood to the basal decidua, establishing contact between the fetus and mother. The placenta functions to regulate oxygen and nutrients for the fetus. Disruptions in

perfusion and oxygen flow can lead to placental insufficiency. This condition is believed to be associated with the failure of spiral arteries to undergo vascular remodeling. The spiral arterial invasion, which should normally penetrate the medial elastic, muscular, and neural tissues and replace the endothelial layer, only penetrates superficially, resulting in blood vessels with high resistance. This leads to increased vascular resistance, which results in notching and causes increased blood flow, ultimately leading to elevated pulsatility index. In normotensive pregnancy, perfect spiral artery remodeling leads to decreased vascular resistance and reduced blood flow[4,16,17]**.** This explains why in this study, there was an increased UtA-PI in pregnant women with pre-eclampsia compared to normotensive pregnant women, and notching was more frequently observed in women with pre-eclampsia compared to women with normotensive pregnancies. These findings are supported by previous research: the presence of bilateral notching in pregnancy is associated with the occurrence of pre-eclampsia[18]**,** bilateral notching has a significant relationship with increased risk of pre-eclampsia in the 2nd and 3rd trimesters and increased mean UtA-PI occurs in pregnant women with preeclampsia[7], there is a difference in the average value of UtA-PI in pregnant women with preeclampsia compared to normotensive pregnant women[19].

In this study, The UtA-PI has a sensitivity of 87.50% and a specificity of 98.94% with a cutoff of 1.22. While the notching had a sensitivity of 46.88% and a specificity of 87.25%. A previous study found that the UtA-PI has a sensitivity of 65% and a specificity of 88%, while notching has a sensitivity of 54% and a specificity of 89%.[20] This is due to UtA-PI over notching is that UtA-PI provides information about vascular impedance, which is related to vascular resistance, preload, heart rate, and cardiac contractility throughout the cardiac cycle. Meanwhile, notching only indicates the occurrence of high vascular resistance[6].

CONCLUSION

The mean UtA-PI increases in pregnant women with pre-eclampsia. Notching is more commonly found in pregnant women with pre-eclampsia compared to normotensive pregnant women. The sensitivity of the UtA-PI is higher than that of notching, while the specificity of the UtA-PI is comparable to notching.

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Ethical clearance: This research followed a protocol approved by the Medical and Health Research Ethics Committee of the Faculty of Medicine, Public Health, and Nursing at Universitas Gadjah Mada – Dr. Sardjito General Hospital, with reference protocol number: KE/FK/0374/EC/2024. The study design adheres to all ethical principles to protect participants' rights, maintain confidentiality, and minimize risks. This aligns with both international and national human research procedures.

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Research Article

Accuracy of Transperineal Ultrasound Examination in Predicting Vaginal Delivery

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Abstract

Objective: To determine the accuracy of transperineal ultrasonography (HPD and AoP) in predicting vaginal delivery.

Methods: A cohort study was conducted using a consecutive sampling method on pregnant women in the active phase of labor at Fatimah Maternity Hospital, Pertiwi Maternity Hospital, and Syekh Yusuf Gowa Hospital.

Results: Out of 150 participants, 95 underwent vaginal delivery, 55 cesarean section. AoP and HPD parameters were found to be significantly different in both groups. The study found that an AoP value greater than 110.45 had a sensitivity of 90.53%, specificity of 70.91%, PPV of 84.31, NPV of 81.25, and P <0.001. In contrast, the HPD value of less than 3.54 predicted vaginal success with a sensitivity of 94.54%, specificity of 83.16%, PPV of 85.87, NPV of 89.66, and P <0.001.

Conclusion: AoP and HPD parameters on transperineal ultrasound can be considered to predict successful vaginal delivery.

Keywords: angle of progression, head perineum distance, transperineal ultrasound.

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INTRODUCTION

Vaginal delivery is a physiological and natural process. Between 1990 and 2018, the average cesarean section rate increased by 19 percentage points globally, including poor labor progress.[1] In Indonesia, the alternative of cesarean delivery compared to vaginal delivery increased from 12% in 2012 to 17% in 2017.[2] Maternal and neonatal morbidity rates are higher in cases of delayed labor. Hence, strategies to reduce the risk of complications for both the mother and the fetus include early prediction and decision-making about the mode of delivery in cases of delayed or arrested first or second stages of labor.[3] Detection of the mode of delivery preceding labor onset is beneficial since the emergency cesarean section during active labor leads to both maternal and fetal complications.[4] Transperineal ultrasound can be applied in real-time monitoring of labor progress, helping predict the possibility of vaginal delivery during labor, and further research in this area is warranted.[5]

Non-invasive transperineal ultrasonography has been utilized to detect fetal head descent by measuring the Head-Perineum Distance (HPD). The HPD is defined as the shortest distance from the fetal head to the perineum. Additionally, the Angle of Progression (AoP) is the angle between a line through the midline of the pubic symphysis and a line from the inferior crest of the symphysis to the front of the fetal skull.[6]

It has been demonstrated in multiple studies that in women with prolonged first stage, measurements of the Angle of Progression and Head-Perineum Distance are more reliable predictors of vaginal delivery. Researchers looked at 150 women in a multicenter trial that was carried out in 2012 in Cambridge and Norway. According to the study, there was a 7% chance of a cesarean section if the

head-perineal distance was less than 40 mm and an 82% chance if the distance was greater than 50 mm. According to the same study, the likelihood of a cesarean section is 12% if the angle of descent is greater than 110° and rises to 62% if the angle of descent is less than 100°.[7]

This research aimed to assess the predictive usefulness of transperineal ultrasound, using Head-Perineum Distance and Angle of Progression, in predicting the delivery method during the first stage of the active phase of labor.

METHODS

This study was conducted using a cohort research design. It was conducted for six months, from November 2022 to April 2023, at Fatimah Maternity Hospital, Pertiwi Maternity Hospital, and Syekh Yusuf Gowa Hospital. Researchers obtained Ethical Clearance with recommendation number 154/UN4.6.4.5.31/PP36/ 2022.

The inclusion criteria were Pregnant women in the first stage of labor in the active phase, gestational age from 37 - 42 weeks, and vertex presentation. The exclusion criteria were Malpresentation, pelvic organ disorders, macrosomia, and pregnant women with comorbidities.

The ultrasound examination was performed by one examiner, supervised and confirmed by two ultrasound professionals from the Maternal-Fetal Medicine Consultant, each with over 20 years of expertise. The ultrasound scans were conducted with 2 type Ultrasounds (Mindray DP-10 portable ultrasound and Mindray DC-8 ultrasound), which standardization is considered to have been equated by the same manufacturer.

A hundred fifty subjects of pregnant women in the active phase of labor were obtained through consecutive sampling. Data collection in this study utilized primary data obtained through a questionnaire and transperineal ultrasound examination to measure the size of AoP and HPD. An experienced Obstetrician Gynecologist conducted a transperineal ultrasound. To obtain the progression angle, the transducer should be placed in the sagittal plane translabially. Anatomic landmarks, such as pubic symphysis and the outer edge of the fetal skull, are used in this plane. Imaginary lines are drawn from the pubic symphysis long axis through the point of infra pubic, then end at the outer edge of the fetal skull. Head Perineum Distance is then achieved by placing the transducer transperineally with the transverse plane. Slight pressure is applied to display the fetal skull's perineal skin edge and outer edge (Figure 1). The measurements between the two calipers are then recorded (Figure 2) [8].

All data in this study were processed using IBM SPSS 24.0 with Mann-Whitney and chi-square analysis. The ROC (Receiver-Operating Characteristic) curve was used in this study to assess the predictive value of the Angle of Progression and Head Perineum Distance concerning the sensitivity and specificity of variables in predicting successful vaginal delivery.

RESULTS

This study was conducted on pregnant women in active phase 1 who underwent labor at the Teaching Hospital Network Hospital of Department of Obstetrics and Gynecology, Universitas Hasanuddin Faculty of Medicine, with 73 samples from Fatimah Maternity Hospital, 56 samples from Syekh Yusuf Gowa Hospital, and 21 samples from Pertiwi Maternity Hospital. The sample comprised 150 individuals who satisfied the inclusion criteria.

Table 1 displays the characteristics of the study subjects. Most study subjects were 20-35 years old, multigravida, high school education, and normal BMI. In this study, 95 (63.33%) participants had vaginal delivery, while 55 (36.67%) had Caesarean Section.

Table 2 shows that the parameters of age and BMI had a significant relationship ($p<0.05$). In terms of AoP, there was a significant difference between patients who had a vaginal delivery and the control group. The average AoP for patients with vaginal delivery was 122.02º (±15.86), while the control group had an average AoP of 107.27º (±7.23). HPD parameters were also found to be significantly different. In

the sample of vaginal deliveries, the mean HPD was 3.05 cm (±0.49), whereas in the control group, the mean HPD was 4.07 cm (±0.46).

The results of this study's sensitivity and specificity tests were based on tranperineal ultrasound parameters. Cut-off points for the Head-Perineum Distance and Angle of Progression were found, which have diagnostic value for vaginal delivery success, as demonstrated by the ROC (Receiver Operating Characteristic) Curve.

The Area Under Curve (AUC) value for the Angle of Progression was 0.881, and the Head-Perineum Distance was 0.955. This test obtained a cut-off point of ≥110.45o for the Angle of Progression, with a specificity of 70.91%, a sensitivity of 84.09%, PPV of 84.31, NPV of 81.25, and P < 0.001. The Head-Perineum Distance value obtained a cut-off point of <3.53 cm, with a specificity of 85.87%, a sensitivity of 83.16%, PPV of 85.87, NPV of 89.66 and P < 0.001.

DISCUSSION

The transperineal ultrasound technique can predict the success of vaginal delivery by measuring AoP and HPD. In this study, the cut-off value of AoP was ≥110.45, with a specificity of 70.91% and a sensitivity of 84.09%. Ultrasound techniques are more reliable than vaginal touche assessment for predicting whether spontaneous vaginal delivery is successful or requires a cesarean section. In previous study One hundred ten and one hundred fifty pregnant nulliparous women participated. The results showed 87% and 58% VD rates were noted in AoP ≥110°. It can be concluded that a higher vaginal delivery success rate is positively correlated with an increase in the AoP.[9] A study carried out in Indonesia discovered that a vaginal birth can be predicted with an AoP value of 107° with a sensitivity of 80% and specificity of 97%.[10]

Based on the ROC curve analysis, the AoP measurement in this study can predict vaginal delivery with an accuracy of 88.1%. Another study found that the optimal value of the angle of progression (AoP) is 116°, as this value optimizes the curve. No patient had a cesarean section with an AoP greater than 116°; instead, all patients had vaginal births. The 116° AoP demonstrated a sensitivity of 96.49% and specificity of 96.43% for a cut-off value of 116° in vaginally delivered cases, a value that was greater than that of cesarean section cases. With an AUC of 0.989, this difference had high statistical significance.[11]

In addition to assessing AoP, it was demonstrated in this study that the Head-Perineum Distance parameter, with a cut-off point value of <3.53 cm, could also accurately predict the success of vaginal birth, with a specificity of 85.87% and a sensitivity of 83.16%. The head-perineum distance is 4.2 cm as a cut-off value, 84% delivered vaginally (sensitivity 80%, specificity 84%, PPV 85%, NPV 78%, positive LR 5.2, and negative LR 0.24).[6]

The advantage of this research is that one person carried out the ultrasound assessment to avoid interobserver bias. This research was also the first to be conducted with a population of pregnant women in Makassar, with a reasonably balanced comparison between primiparas and multiparas by incorporating multiple parameters that evaluate both the head-perineum distance and the angle of development. This study provides more comprehensive evidence of the capacity for the prediction of transperineal ultrasonography to vaginal delivery.

The limitation of this study is that we employed two distinct Ultrasound devices to evaluate the Angle of Progression and Head-Perineum Distance. This approach potentially introduces reporting bias. Nevertheless, employing standardized machines sourced from the same factory helps reduce variability and uphold reliability. The limited sample size used in this study only partially guarantees the accuracy of this method in predicting successful delivery. Therefore, more research on a larger scale with more robust methods is still necessary.

CONCLUSION

The Angle of Progression and Head-Perineum Distance in transperineal

ultrasound have the potential to serve as additional modalities for predicting the likelihood of successful vaginal birth, and researchers should conduct further studies to develop these methods.

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CONFLICT OF INTERESTS

The authors declare that they have no competing interests.

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Figure 1. Transperineal Ultrasound. Measurement of Angle of Progression

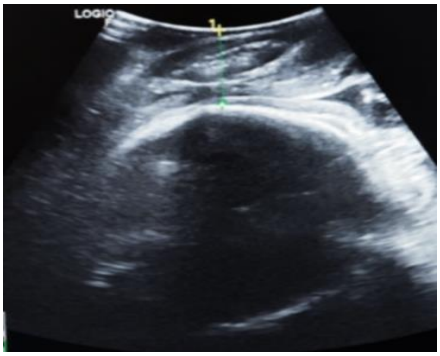

Figure 2. Transperineal Ultrasound. Measurement of Head-Perineum Distance

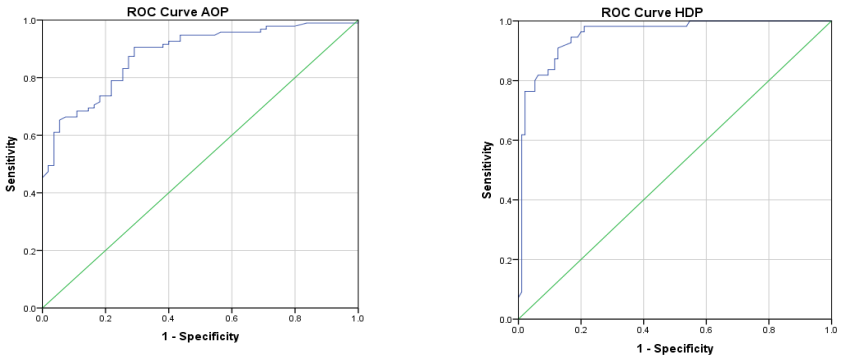

Figure 3. Receiver Operating Characteristic Curve

Table 1. Frequency Distribution of Respondent Characteristics by Group

Category	Frequency	(%)
Age (y o)		
< 20	13	8.67
20-35	121	80.66
> 35	16	10.67
Parity		
Primigravida	71	47.33
Multigravida	79	52.67
Education		
Junior High School	19	12.67
Senior High School	101	67.33
College	30	20.00
Pre-pregnancy Body Mass Index		
Normal	116	77.33
Overweight	33	22.00
Obesity	1	0.67
Labor Methods		
Vaginal Delivery	95	63.33
Cesarean Section	55	36.67

*Chi-square test

Table 2. Subject Characteristics Based on Delivery Method

Parameters		*P-value*	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC*
AoP	≥ 110.45 < 110.45	<0.001	90.53	70.91	84.31	81.25	83.33	0.881
HPD	< 3.53 ≥ 3.53	<0.001	94.54	83.16	85.87	89.66	87.33	0.955

*Mann-whitney test

Table 3. Sensitivity and Specificity of Angle of Progression (AoP) and Head-perineum Distance (HPD)

Category	Labor				*P-value*
	Vaginal		Cesarean Section		
	n	%	n	%	
Age					
Low risk	82	86.32	39	70.91	0.021
High risk	13	13.68	16	29.09	
Parity					
Primigravida	42	44.21	29	52.73	0.695
Multigravida	53	55.79	26	47.27	
Education					
Low education	11	11.58	8	14.55	0.599
Higher education	84	88.42	47	85.45	
Pre-pregnancy Body Mass Index					
Normal	80	84.21	36	65.45	0.008
Abnormal	15	15.79	19	34.55	
AoP (Mean ± SE)	122.02 ± 15.86		107.27 ± 7.23		< 0.001
HPD (Mean ± SE)	3.05 ± 0.49		4.07 ± 0.46		< 0.001

*From ROC Curve

Research Article

Midwifery Students' Experiences in Learning Pelvic Anatomy and Childbirth Mechanisms: A Phenomenological Study

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Abstract
Objective: To explore students learning experiences toward pelvic anatomy and the mechanism of labor.
Methods: The research design is qualitative with a descriptive phenomenological approach, utilizing the framework of the *Standards for Reporting Qualitative Research: A Synthesis of Recommendations.* The study involved 10 participants, including 8 midwifery students and 2 lecturers in charge. Informant recruitment was conducted by using purposive sampling. Data analysis was conducted using Collaizi's framework, which involves familiarization, identifying relevant statements, formulating meanings, clustering themes, developing detailed descriptions, constructing the fundamental structure of statements, and final validation.
Results: The analysis identified two main themes: the components of the pelvic bones and the labor process. Informants reported that the learning process provided them with an understanding of labor, which facilitated their clinical practice.
Conclusion: Students faced several challenges during the learning process, particularly in comprehending pelvic anatomy and the mechanism of labor. They made significant efforts to seek additional learning resources and expressed a desire for a digital learning application featuring animations, images, and detailed explanations of pelvic anatomy and the labor mechanism.
Keywords: learning media, mechanism of labor, pelvic anatomy, student experience

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INTRODUCTION

Anatomy is a visual science considered essential in the field of health. The primary goal of studying anatomy is to enable students to identify body structures and understand their functions. However, students often struggle to grasp three-dimensional (3D) anatomy from graphic representations such as textbooks and PowerPoint presentations [1]. Anatomists are now facing a new generation of learners who will study and work in technology-rich environments[2]. Digital technology skills are fundamental to education, serving as a means to enhance students' ability to identify and apply contemporary scientific and technological knowledge relevant to their disciplines [3].

Pelvic anatomy is crucial for understanding reproductive and sexual health, particularly for general practitioners and specialists in fields such as midwifery, gynecology, and urology [4]. Collaboration between pelvic anatomy and multimedia can facilitate a shift from passive, teacher-centered, lecture-based learning to an interactive, student-centered, and exploratory approach. This transition emphasizes the experiential nature of anatomy learning and allows more students to engage in collaborative, active, and team-based learning environments [5].

The mechanism of labor is a critical aspect of obstetric practice. During labor, both the mother and the fetus are regularly evaluated to assess their well-being and monitor the progress of labor[6]. Normal labor is a complex process involving the

interplay of hormonal, biochemical, and mechanical factors. Labor consists of four stages: quiescence, activation, stimulation, and involution. These stages include the transition from myometrial contractility and cervical structural changes to progressive uterine contractions, cervical effacement and dilation, the delivery of the fetus and placenta, and the return to a non-pregnant state. Labor management is divided into three phases: cervical dilation up to 4 cm, fetal delivery, and placental delivery. Midwives with a strong understanding of the mechanisms and management of labor are essential for performing clinical interventions and reducing maternal and fetal morbidity and mortality [7].

Higher education in health sciences (Universities or Institute of health science) is a key institution capable of implementing technology-based learning methods in line with current transformations. Midwifery students gain competence through classroom learning, practical training at midwifery clinics, hospital internships, and laboratory skills practice, including the study of pelvic anatomy and the mechanisms of labor, where the human is the primary client. Mother-centered education and information are crucial for ensuring the safety of both mother and fetus. Students often face difficulties in understanding pelvic anatomy and the mechanisms of labor through graphic images, as it is challenging to comprehend these anatomical structures and processes. Multimedia-based learning is one method aimed at enhancing midwifery students' understanding of pelvic anatomy and the mechanisms of labor.

This study aims to explore the learning experiences of students toward pelvic anatomy and the mechanism of labor at Universitas Hang Tuah Pekanbaru and Helvetia Institute of Health Pekanbaru. This research is considered important and highly beneficial for both the participants, namely the students, and the health education institutions involved. Understanding the teaching of pelvic anatomy can help students become knowledgeable and safety-conscious practitioners. As health students are the future healthcare providers on the front line of delivering care to clients. They are expected to master foundational knowledge in all areas of their competencies, including the recognition and understanding of pelvic anatomy in every client. Therefore, students' comprehension and knowledge will facilitate the achievement of their competencies in pelvic anatomy and the mechanisms of labor.

METHODS

This study employs a qualitative research design. Qualitative research is concerned with participants' experiences of life events, aiming to understand what participants express and to explain why they express it[8]. The approach used in this study is descriptive phenomenology, which seeks to capture the essence of experiences and understand their fundamental structures[9]. A qualitative research approach is deemed more appropriate for gaining in-depth insights into pelvic anatomy and the mechanism of labor at Universitas Hang Tuah Pekanbaru and Helvetia Institute of Health Pekanbaru. Qualitative research is often challenging to evaluate due to incomplete reporting; therefore, the Standards for Reporting Qualitative Research: A Synthesis of Recommendations (SRQR) framework is employed to enhance the completeness of the reporting [10].

The method used in this qualitative research was conducted offline, allowing the researcher to deeply explore midwifery students' experiences in learning pelvic anatomy and the mechanism of labor at Universitas Hang Tuah Pekanbaru and Helvetia Institute of Health Pekanbaru. The interviews in this study were conducted in person, using offline interviews. The selection of informants was also carried out offline, employing purposive sampling techniques. The total number of informants is ten. The primary informants consist of eight students, while two lecturer have been included as supplementary informants due to the point of data saturation being reached.

In purposive sampling, the researcher deliberately selects individuals and research locations that can provide meaningful insights into the research problem and the phenomenon under study [11]. The researcher determines the informants and research sites, ensuring

that the decision aligns with the inclusion criteria relevant to the study. The informants for this study included students and lecturers in charge who consented to participate by signing informed consent forms. Ethical clearance for the study was obtained under the number 466/KEPK/UHTP/VIII/2024.

The primary tool or instrument for data collection in qualitative research is the researcher themselves, who can observe, ask questions, listen, inquire, and collect data for further analysis. As a human instrument, the researcher plays a critical role in qualitative studies. The researcher must ensure the validity of the data by selecting appropriate interview sources. Additionally, the conditions of the informants must meet the data needs of the study to ensure the accuracy and credibility of the data collected [12].

To enhance the quality assurance of this research, the researcher must deepen their understanding of qualitative methods and the experiences of midwifery students regarding pelvic anatomy and the mechanism of labor. This can be achieved by conducting a literature review, refining the research site, and revisiting the informants previously identified by the researcher to facilitate the research process. The researcher's connection with the informants in the field, as well as the collection of preliminary data, can be strengthened through more frequent field visits, organized as part of a preliminary study.

The instrument for this research includes an interview guide to assist the researcher in the data collection process. The key questions outlined in the in-depth interview guide aim to enhance quality assurance and have been verified by an expert, in this case, a lecturer specializing in pregnancy and childbirth.

The structure provided framework allows for data transparency [9]. The clarity and ease of implementation within this structured framework indicate that this study uses a method that offers credible insights. Its ease of use, transparency, reliability, and dependability further contribute to the credibility of the research. This is crucial as qualitative research has historically been criticized for being less thorough and objectivity [13]. The primary informants in this study are students from Universitas Hang Tuah Pekanbaru and Helvetia Institute of Health Pekanbaru. The characteristics of the informants are presented in the table 1.

Table 1. Characteristic of Informants

The interviews with students highlighted the importance of learning pelvic anatomy and the mechanism of labor. Pelvic anatomy is divided into two key aspects: the structure of the pelvic bones and the labor process. Informants expressed that learning the stages of labor facilitated their ability to apply this knowledge in practical fieldwork.

Pelvic Bone Structure

The interviews revealed insights into the structure of the pelvic bones and the labor process.

Pelvis

The students' responses indicated that the pelvis consists of the pelvic bones, femur, upper boundary, pelvic plane, the upper pelvic inlet, and the Hodge plane. Below are the students' statements regarding pelvic anatomy learning from informants A1, A2, A4, A5, A6, A7, and A8:

"The hard parts are formed by bones, and the soft parts are formed by muscles" (A1)
"The hard parts are formed by bones, and the soft parts are formed by ligaments" (A2)
"The hard parts are formed by bones" (A4)
"The soft parts are formed by muscles" (A5)
"The hard parts are formed by bones, and the soft parts are formed by muscles" (A6)
"The soft parts are formed by bones, and the soft parts are formed by ligaments" (A7)
"The soft parts are formed by ligaments" (A8)

Pelvic Bones

Interviews revealed the following subtheme: informants explained that the pelvic bones consist of the femur, sacrum, and coccyx. Below are the statements regarding the pelvic bones provided by informants A1, A2, A5, A7, B1, and B2.

"2 femurs, 1 sacrum, and 1 coccyx" (A1)
"2 femurs, 1 sacrum, and 1 coccyx" (A2)
"2 femurs (os coxae), 1 sacrum (os sacrum), and 1 coccyx (os coccygis)" (A5)
"2 femurs, 1 sacrum, and 1 coccyx" (A7)

"2 femurs (os coxae), 1 sacrum (os sacrum), and 1 coccyx (os coccygis)" (B1)
"2 femurs (os coxae), 1 sacrum (os sacrum), and 1 coccyx (os coccygis)" (B2)

Mechanism of Labor

This subtheme from the interviews highlighted the labor mechanism, with informants explaining that it involves occiput presentation, engagement, and internal rotation. Below are the statements provided by informants A1, A2, A5, A7, B1, and B2:

"*Engagement, descent, flexion, internal rotation, extension, external rotation, and expulsion" (A1). "Engagement, synclitism, descent, flexion, internal rotation, extension, external rotation, and expulsion" (A5). "Engagement, synclitism, descent, flexion, internal rotation, external rotation, and expulsion" (A7)*

DISCUSSION

The study of pelvic anatomy and the mechanism of labor is essential for students, as it facilitates their understanding of the labor process for practical fieldwork and can be accessed outside of classroom learning.

Learning Pelvic Anatomy and the Mechanism of Labor

Anatomically, the pelvis is a complex and functionally informative structure that directly influences human movement and midwifery. In midwifery, the pelvis plays a crucial role, as it is one of the most sexually dimorphic skeletal elements in the human body [14]. The pelvis serves two primary functions in humans: providing a relatively rigid support for muscles involved in movement and acting as the birth canal[15]. According to Desilva, the pelvis has three main functions. Movement; The pelvis transfers body weight to the lower limbs through the pelvic girdle. Childbirth: Neonates must pass through the birth canal, which is located within the pelvic girdle, during delivery. Support of Abdominal Organs: The pelvic floor muscles and the pelvis itself support the abdominal organs.

Pelvis

The basic structure of the human pelvis is inherited from our quadrupedal ancestors, but the development of bipedalism (approximately 6-7 million years ago) brought about changes in the shape of muscles and the pelvic girdle. Additionally, an increase in brain size in adults and newborns (about 2 million years ago) contributed to more recent studies on the pelvis. The terms "os coxae" and "pelvic bone" are derived from the word *innominata* (literally meaning "unnamed," as it did not originally have a specific meaning)[14].

Pelvic Bones

The human pelvis comprises the sacrum, coccyx, and two os coxae. Each os coxae is further divided into three parts: the ischium, ilium, and pubis. The ilium, positioned laterally, runs parallel to the spine, while the ischium extends dorsally. The three sacral bones fuse and are situated high above the pubic symphysis, allowing the baby's head to pass through the sacrum before entering the pelvic inlet during delivery [15]. The ischial spine serves as the point of reference for evaluating the descent of the fetus's presenting part [7].

The pelvis features a notably long pubic bone, and the ischium is also quite elongated. The superior pubic ramus has a sharply defined pectineal peak, and its superior surface is concave in the mediolateral direction [16]. The pelvic structure includes the sacrum, coccyx, and two os coxae, with each os coxae consisting of the ischium, ilium, and pubis [16].

The lower part of the pelvis is formed by the joint between the sacrum and coccyx (sacrococcygeal symphysis), the posterior connection between the sacrum and each ilium (sacroiliac joints), and the anterior junction at the pubic body (pubic symphysis). The sacroiliac joints allow for limited movement during childhood but transition into synarthrodial joints that permit little to no movement in adulthood [17].

The pubic symphysis is a synarthrodial joint characterized by a fibrocartilaginous interpubic disc [17]. This joint allows for minimal translational and rotational movement. The pelvic ring forms a closed chain; thus, movement at the pubic symphysis requires simultaneous

movement at the sacroiliac joints and vice versa [15].

Mechanism of Labor

On occasion, the process of labour is described as the cardinal movement, whereby the fetal head is displaced as it progresses through the birth canal. For the fetus to successfully pass through the birth canal, a degree of rotation is required, given the asymmetrical shape of the fetal head and the mother's pelvic bone [18].

The mechanism of labor requires the fetal head and shoulders to pass through the birth canal, which presents a size disproportion between the fetal head and the maternal pelvis, especially when compared to the fetal-maternal proportions of other primates[19]. The birth canal mechanism primarily involves the anterior-posterior (AP) dimensions at both the pelvic inlet and outlet. In the bipedal pelvis, the ilium is shorter, larger, and broader from front to back. The ilium part of the pronunciation with the sacrum is larger, thus providing better ability and support [20].

The upper boundary of the pelvis is called the iliac crest, where the anterior superior iliac spine deviates medially. The thick and robust iliac base measures approximately (left: 31.9mm, right: 27.1mm), with a prominent lateral iliac spine. The anterior inferior iliac spine is strong and sigmoid-shaped, while the acetabular roof is shelf-like, and the supra-acetabular groove is well-developed [21].

The diameters of the pelvic inlet and outlet, as well as the dimensions of the broad and narrow planes of the pelvis, are substantial. The pubic symphysis is quite large, measuring approximately 24.8 mm, and convex dorsally (similar to the pubic promontory)[16]. The superior pubic ramus is longer, positioning the pubis directly in front of the hip joint. The acetabulum is not closer to the sacroiliac joint in females, as the lower iliac height remains significant [22].

A full-term fetus can pass through the birth canal with ease, as the biparietal diameter is approximately 9.3–11 mm, and the suboccipitobregmatic diameter is about 9.4–12 mm. The pelvic diameter is reduced by 5 mm due to the soft tissue covering the inner pelvis. The narrowest diameter of the female birth canal is the bispinal diameter, which defines the obstetric plane and limits the descent of the fetus through the pelvis during labor[15]

Regardless of the phase or stage, the fundamental signs of labor are regular uterine contractions or cervical dilation. The uterine muscle's alterations due to contractions will be increased by physiological mechanisms as the time for delivery near. As the cervix dilates, the mother must push her own and maintain her respiration for a minimum of 10 seconds [23]. Prolonged pressure on the pelvic floor during the second stage of labor may cause injury to the nerve plexus and pelvic tissue. Outflow blockage and "detrusor neuropraxia" may result from this injury [24]. Assert that the cardinal motions in the presentation of the occiput include[18]

Engagement, the pivotal phase in labor development, which confirms that the pelvic dimensions are sufficient for the passage of the infant's head. The presenting section can be palpated on the abdomen (when only two-fifths of the head are palpable) or vaginally (when positioned at or below the ischial spine) to confirm engagement. When the fetus's maximal diameter reaches a location below the pelvic inlet plane, it descends. In cephalic presentation with the head suitably flexed, the biparietal diameter (9.5 cm) is the fetus head's largest transverse diameter.

Descent is the term used to describe the descent of the presenting part through the pelvic. Fetal descent is not a continuous and stable procedure. The deceleration phase of the first and second stages of labor is when the rate of decline is at its maximum. Flexion is the process by which the embryonic head descends passively as a result of the resistance of the soft tissue of the pelvic floor and the shape of the pelvic bones. Flexion of the fetal head to the thorax is a common occurrence in the majority of fetuses prior to delivery; however, complete flexibility typically occurs during labor. The fetus's diameter is at its smallest (suboccipito-bregmatic diameter) when the cranium is entirely flexed, enabling it to transit through the pelvis effectively.

Internal rotation is the process by which the presenting part is rotated from its initial position (which is typically transverse to the birth canal) to an anteroposterior position as it traverses the pelvis. This

alteration typically results in the fetus occiput rotating toward the symphysis pubis as it descends, causing the widest axis of the fetal head to align with the widest axis of the pelvic canal. Internal rotation is a passive movement that is the consequence of the pelvic floor muscles' resistance and the configuration of the pelvis.

Extension takes place after the fetus reaches the introitus level. This descent results in the base of the occiput coming into contact with the lower border of the pubic symphysis. The birth canal curves upward at this juncture. Extension delivers the fetal head, which subsequently rotates around the pubic symphysis. The pelvic floor muscles exert an upward force to expel the embryo, while the fetus experiences a downward force from uterine contractions. As the infant's head approaches the birth canal and delivery becomes imminent, the obstetrician's hands apply pressure to ensure the infant's head remains flexed and to aid in the childbirth process. The prevention of abrupt amniotic fluid release is correlated with a decrease in perineal lacerations and intracranial injuries. External rotation (restitution). Upon deflection (extension), the fetal head rotates into the appropriate anatomical position in relation to the fetal body. Rotation to the left or right is contingent upon the fetus's orientation. Restitution's passive movements are the consequence of the maternal pelvic bones and muscles' discharge of forces on the fetal cranium, which is facilitated by the basal tone of the fetal muscles. If the cord wraps around the neck, it should be wrapped around the head or, if it cannot be reduced, double clamped and cut crosswise. The use of suctioning to clear secretions from the fetal mouth, oropharynx and nostrils has not been shown to reduce the incidence of meconium aspiration syndrome.

Expulsion is the term used to describe the procedure is the process of expelling the fetal body. A health worker's hand is placed on each parietal eminence and the anterior shoulder of the fetus is delivered with subsequent contractions with downward traction towards the mother's sacrum, together with an attempt to expel the baby. The posterior shoulder is then delivered with upward traction. The baby should be held securely and dried with a sterile towel.

The Augmented Reality based learning application to recognize the anatomy of the human body is a solution for teachers and students to create an innovative and interactive learning medium. The first stage of creating an application is to design the application design that will be built based on the results of the analysis of the existing problems. The designed display must be user-friendly so that all people can easily use the application, especially users in the field of education. [25]

The majority of students felt confident in performing the pelvic examination. Mentoring by clinical tutors and the use of professional patients are important factors in planning pelvic examination training, and this knowledge can be used when teaching other intimate examinations during medical school. [26]

CONCLUSION

The study of pelvic anatomy and the mechanisms of labor is a critical component of the curriculum in midwifery care for labor. This material is essential for midwifery students to understand the processes involved in the mechanism of labor and the signs indicating fetal descent through the birth canal. Students can access this learning material not only during classroom instruction but also outside the classroom or in the field. Students who have a thorough understanding of this subject will find it easier to apply their knowledge in practical settings, thereby assisting in physiological deliveries and contributing to the reduction of maternal and infant mortality rates. The problems faced by students are the low literacy levels in higher education environments, which are closely linked to technology, the habit of consuming fast and unclear information, and the lack of motivation to learn deeply. The solution to this problem is an approach that combines technology with learning methods that encourage critical analysis, contextual understanding and active participation.

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CONFLICT of INTEREST

The authors declare that they have no conflict of interest

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Code	Year	University	Profession
A1	19	Hangtuah	Student
A2	20	Hangtuah	Student
A3	19	Hangtuah	Student
A4	20	Hangtuah	Student
A5	19	Helvetia	Student
A6	20	Helvetia	Student
A7	20	Helvetia	Student
A8	19	Helvetia	Student
B1	30	Hangtuah	Lecturer
B2	37	Helvetia	Lecturer

Research Article

Impact of Attending Prenatal Yoga Classes on Prepartum Maternal Mental Health: A Quasi-Experimental Study

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ABSTRACT

Introduction Anxiety from the imagination of childbirth pain and fear of childbirth in pregnant mothers. Fear of childbirth has been associated with prolonged labor, childbirth complications that increased postpartum depression.

Objective: This study aimed to analyze the impact of attending Prenatal Yoga Classes on Prepartum Maternal Mental Health.

Methods The research design was a quasi-experiment of two groups with pre-test and post-test design. The sample was pregnant women who met the inclusion and exclusion criteria. A total of 106 participants were divided into two groups: intervention, and control group. The research instrument was Mental health questionnaire based on the World Health Organization-5 Well Being Index (WHO-5). The ANOVA test was used to analyze the data.

Result The average mental health score of the intervention group was higher (84.04) than that of the control group (67.32), with a p-value <0.001.

Conclusions This study concludes that Attending Prenatal Yoga Classes on Prepartum can improve maternal mental health. This research suggest that prenatal yoga can be alternative for physical pregnancy to improve mental health and have positive impact on labor process.

Keywords: Pregnant Women; Yoga Prenatal Class; Mental Health

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INTRODUCTION

Pregnancy is both an exciting and scary event for women leading to psychological changes that can develop into depression and anxiety.[1] The incidence of antenatal and postpartum depression reached 43%.[2]. Maternal perinatal mental health have a significant impact on the health of the baby, impacting their physical and mental disorders in the future and brain development in the newborn.[3] The presence of sympathetic nerve stimulation increases the secretion of the hormone catecholamine, which increases cases of premature birth, complications of childbirth, anxiety symptoms during pregnancy were related to intrauterine growth restriction (IUGR) of the child,[4] and prolonged labor,

leading to cesarean section. Anxiety is commonly caused by pain during labor and scared of labor process. This condition was associated with prolonged labor, triggering severe pain that increased the section cesarean rate and postpartum depression.[5] Complementary antenatal classes, including Yoga can be utilized to reduce anxiety and scared of childbirth.[6,7] An increase in heart rate, blood pressure and increased secretion of catecholamine and cortisol hormones accompanies stress and fear of childbirth.[8]

Physical exercise during pregnancy is one way to reduce childbirth complications such as insomnia, stress, overweight, back pain, constipation, hypertension, diabetes in pregnancy, and anxiety during pregnancy. In addition, physical activity also increases the individual's ability to adapt to the baby.[9] Several physical activities are considered complementary therapy such as yoga, gymnastics, Pilates and, Kegel exercise. One everyday physical activity pregnant women practice is Yoga.[6] Previous studies stated that yoga exercise increases pregnancy outcomes and reduces the impact of high-risk pregnancy.[10] Yoga is a combination of physical activity and psychological relaxation. Yoga improves muscle strength, memory, and sleep quality and lowers pain and stress.[11] Yoga is considered an optimal form of exercise during pregnancy, offering numerous physical and psychological health benefits for expectant mothers. During pregnancy, yoga allows communication of the mind, body, soul, and fetus.[12] Prenatal Yoga decreases anxiety, depression, back pain and pelvic pain, affecting a term childbirth and maintaining infant weight in normal conditions. Yoga is usually a combination of mental exercises, meditation, breathing exercises, stretching, and relaxation. Meditation is a specific practice for the body, soul, and mind.[13,14] Another research project reported there was the influence of pregnancy yoga exercise on the level of anxiety in pregnant women in trimester III. There was the difference in the level of anxiety in pregnant women with the age of pregnancy more than 32 weeks in the pre and post yoga exercise.[15] Attending antenatal classes gives pregnant mothers the opportunity to meet with other mothers who have experiences in childbirth, to think and focus on personal needs and goals, to be less afraid and more confident, and to learn how to adapt to the stages of childbirth.[2]

Recently implementation of prenatal yoga class in Riau Province Indonesia has popular in community. Many Hospital and clinics have active prenatal yoga class program for pregnant women. Most previous studies have discussed the level of anxiety of pregnant women but have not been followed up until a term pregnancy who attended routine antenatal and yoga class, another control group without prenatal yoga. Furthermore, the purpose of this study was to analyze the impact of attending Prenatal Yoga Classes on Prepartum Maternal Mental Health.

METHODS

Study Design and Setting, ethical procedures

This study was a quasi-experiment with pre-test and post-test design. The study was conducted in Bakti Clinic and four community health centers (called as *Puskesmas)* in Riau Province, Indonesia. The Community health were *Puskesmas* Rumbai Timur, Payung Sekaki, Kuala Cenamu, and Pulau Kijang. The study was started after obtaining approval from the Research Ethics Committee of Abdurrab University, under approval number 313/KEP-UNIVRAB/VII/2024. All participants first filled out the informed consent, before becoming a sample of this study. Their Addresses and phone numbers were taken for follow-up of pregnancy development until postpartum period. Pregnant women in the intervention group were assisted by professional facilitators/midwives who had obtained prenatal yoga certificates. In this study, the intervention group participated in prenatal yoga accompanied by brief education about pregnancy, childbirth and postpartum.

Study Participants and sampling

Technique sampling using consecutive sampling, the sample consisted of 106 pregnant women divided into an intervention group and control group (53 pregnant women in each group). The intervention

group consisted of pregnant women who participated in prenatal classes, while the control group comprised those who did not attend the classes. The inclusion criteria for both the intervention and control groups were as follows: women in their third trimester of pregnancy, no chronic illnesses, no history of mental disorders within the past year, no consumption of psychotropic substances, non-smokers, no alcohol consumption, no childbirth complications such as preeclampsia, bleeding, IUFD, or premature labor, having communication abilities, and willing to participate as respondents. The exclusion criteria for the intervention group was missing prenatal classes for more than three weeks.

Procedures

The intervention group (prenatal yoga class) received antenatal care, education, addition 1 hour of yoga class, once a week starting from the third trimester until 37 weeks of pregnancy (minimum 7-10 sessions) in a yoga studio. The control group received routine antenatal care without attending yoga classes, pregnant women were free to practice independently. Before the prenatal yoga class began, they first filled out a mental health questionnaire for a pre-test. Then continued with the prenatal yoga class. The stages of yoga are breathing exercises, yoga (physical movements such as triangle exercises, angled exercises, archery position, pelvic rotation in a standing position, joyful jumps, rotation and release, pelvic floor stretches, strengthening the pelvic floor muscles, gentle perineal traction, upward pelvic rotation, pink panther steps, hip release, knee rotation, active traction in the kneeling position, knee movements, hip and knee cycles, and knee sitting), meditation Self Hypnosis dan self-awareness. Furthermore, filling out the questionnaire for the mental health follow-up was carried out after 4 weeks of the prenatal yoga class, and the mental health post-test was carried out at the last of the 37th week of pregnancy.

Measurement

The data collection tool was a questionnaire consisted of three parts:

1. The questionnaire consisted of several questions related to obstetric information, including age, gestation week, education level, occupation, this completed when the mother has agreed to become participant.
2. Mental health questionnaire based on the World Health Organization-5 Well Being Index (WHO-5). The mental health questionnaire consisted of five positive statements about the feelings of participants intervention and control group in 3 times measurements pre test, follow up dan post test. The five statements used in the assessment were: 1) “I feel cheerful and enthusiastic,” 2) “I feel happy and relaxed,” 3) “I am active and energetic,” 4) “I wake up feeling fresh and open-minded,” and 5) “My daily life is filled with things that interest me.” Each item was rated on a 0-5 scale, with 0 indicating a lack of positive feelings and 5 indicating strong positive emotions. The scale ranged from 0 (never) to 5 (always), where 0 = never, 1 = very rarely, 2 = rarely, 3 = sometimes, 4 = often, and 5 = all the time. The scores were transformed into a range of 0 to 100, with a score of ≤ 50 indicating emotional instability. Mental health well-being was measured during four weeks: pre-test, follow-up, and post-test

Statistical analysis

Data were analyzed using SPSS 22, descriptive statistics including frequency, relative frequency, mean, and standard deviation were used to describe the samples. The Kolmogorov–Smirnov test was used to evaluate the normality of the variables. ANOVA tests for mental health,

RESULT

The participant’ characteristic in Table 1 indicates that the age average and standar deviation of the participant in the intervention group and the control group were 27,55 ±3,98 and 29,09 ± 5,70,

respectively. The majority of education level was from elementary school counted 73,6% for the intervention group, and 83% for the control group. In addition, most of the participants were not employed (84.9 % for the intervention group, 92.5% for the control group) and were multigravida (66% for the intervention group and 47% for the control group).

The average and standard deviation pre-test mental health scores for the intervention and control groups were 74.26±9,33 and 68.30±9,53, respectively. The average scores for the second measurement were 76.00±9,79 and 67.55±9,83, while the third measurement
yielded average scores 84.04±11,53 for the intervention group and 67.32±7,71 for the control group (Table 2). The intervention group demonstrated significantly higher scores than the control group, with a p-value of less than 0.01

The outcomes of pregnancy and neonatal results comparing the intervention and control groups are presented in Table 3. A total of 88.7% of pregnant women who attended prenatal classes had spontaneous deliveries, compared to 52.8% of those who did not attend the classes. Women who participated in prenatal class were significantly less likely to undergo cesarean section (OR = 0.143, 95% CI = 0.052-0.391, $p < 0.005$). Prenatal classes also had a significant impact on birth weight ($p = 0.023$), with the average birth weight being higher among those who attended the classes compared to those who did not, at 3023.58 g (SD = 339.555) versus 3017.92 g (SD = 338.351), respectively.

DISCUSSION

Study in the control group revealed that despite the decreasing of mental well-being of pregnant women in the second measurement until before childbirth, this opposite with attending prenatal yoga class affected significant difference in positive mental health during and until aterm pregnancy period, in addition pregnant women more confident to preparation childbirth. In the intervention group, participants received pregnancy education, including antenatal care, childbirth preparation, postpartum care, and newborn care. Furthermore, the participants were divided into several groups and performed yoga and prenatal exercise under the Yoga facilitator's guidance. On the other hand, the control group was encouraged to independently learning through books and other accessible media.

Based on other study prenatal education affected developing positive behavior of pregnant mothers toward healthcare providers as well as increasing mother self-confidence.[16,17] Antenatal education is integral to positive pregnancy outcomes, improve women's ability to take control of their pregnancy by undertaking self-management at home.[18] Physical activity need family support,[19] a recent study implementing interventions aimed to boost maternal well-being through stress management education, effectively reduced anxiety and improved overall mental well-being.[20] Another study conducted among infertile women demonstrated that relaxation techniques and breath training enhanced the well-being by reducing anxiety and decreasing sympathetic system activities.[21]

This study contradicts previous research, which suggested that telephone counseling conducted by midwives to pregnant women between 24 – 34 weeks did not affect postpartum depression.[22] Prenatal classes were more effective in improving mental health compared to only telephone counselling. Providing training for pregnant women has been shown to significantly stabilize mental well-being, which in turn promotes improved postpartum mental health. Another benefit of prenatal classes is that they provide an opportunity for pregnant to have direct interaction and peer support, leading to enhanced psychological and mental well-being. This study supported previous findings mentioned that Yoga not only improved the psychological well-being but also enhanced childbirth preparedness of pregnant women.[23]

Complementary based prenatal class, including prenatal yoga classes provide guidance on stretching training, relaxation training, and breathing technique training.[24] This class is deemed to improve positive behavior on the normal delivery.[25] A study revealed that childbirth education and yoga prenatal training enhanced their physical preparedness and breathing control during the delivery process[26]

Despite the lack of comprehensive explanation regarding yoga mechanism, the benefits of yoga on the muscular and nervous are sufficiently evident. Yoga strengthens and improves the flexibility of the muscles involved in the childbirth process, especially back muscles and pelvic floor muscles.[27] Yoga training effects on endocrine system and the autonomy nervous system of pregnant women, contributing to hormone secretion and reducing stress.[28,29] Furthermore, relaxation technique involving breathing training during Yoga enables pregnant women to maintain a calm and relaxed state during childbirth, thereby increasing the oxygen supply for expectant babies.[30] To conclude, prenatal Yoga is significant for building strength, enhancing muscle flexibility, boosting energy, to eventually promoting relaxation of mind and body. Previous study indicates that Yoga improves maternal and child health, decreases pain levels during childbirth, and decrease other discomfort related to pregnancy.[31,32].

Yoga was also effective for mothers with high risk pregnancy. Beside that Yoga alleviates pregnancy complications related to hypertension.[5,33] Yoga has an essential role in decreasing blood glucose levels, which may provide significant benefits for both diabetes-pregnant mother and their infants.[34] Yoga is not considered dangerous for infant. A physical activity guidance states that prenatal Yoga improves the physical and mental health of pregnant mothers, decreases pregnancy complications, and increases childbirth outcomes.[35] Thus, promoting prenatal class and physical activities is essential for enhancing both emotional and physical well-being.

CONCLUSION

Attending Prenatal Yoga Classes on Prepartum can improve maternal mental health. This research suggest that prenatal yoga can be differentiator of physical activity during pregnancy that can improve mental health and have positive impact on labor process, therefore healthcare providers can incorporate yoga into antenatal classes to promote relaxation, improve maternal mental health and reduce anxiety.

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Table 1. Characteristics of pregnant women in the intervention and control groups

Variable		Intervention group (Participated in Prenatal class)	Control Group (not participated in prenatal class)
		N (%)	N (%)
Education level	Elementary school	39 (73.6)	44 (83)
	University	14 (26.4)	9 (17)
Occupation	Employed	8 (15.1)	4 (7.5)
	Unemployed	45 (84.9)	49 (92.5)
Parity	Primigravida	18 (34)	6 (11.3)
	Multigravida	35 (66)	47 (88.7)
		Mean (SD)	**Mean (SD)**
Age		27.55 (3.98)	29.09 (5.70)

Table 2. The distribution of the mean scores of maternal mental well-being in the intervention and control groups

Variable	Group	Pre-test		Follow up		Post Test		Group Effect	Time Effect
		M	SE	M	SE	M	SE	F/P	F/P
Mental Health Score	Intervention group	74.26	1.28	76	1.34	84.04	1.58	1.736	9.77
	Control group	68.30	1.31	67.55	1.02	67.32	1.25	0.755	0.981
	Mauchly's W = 0.852; P<0.01								

Research Article

Current Trends in Contraceptive Use and Fertility Concerns among Women of Reproductive Age in Indonesia

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Abstract

Objective: To investigate the most recent trends in contraceptive use in Indonesia as well as evaluate fertility concerns and access to reproductive healthcare service.

Methods: Women of reproductive age in Indonesia were asked to fill in an online questionnaire. They were asked about sociodemographic characteristics, marital status, pregnancy history, perception towards fertility, and access to healthcare service and information. Descriptive statistics and independent t-test were performed.

Results: Of 370 women, more than half (57.8%) had used some form of contraception. The most frequently used contraceptive method was natural family planning (30.3%), followed by condom (20%). Women with no prior sexual history, had never been pregnant before, and had not been married cared more about having a child in the future. Internet and social media represented the most popular information source for family planning.

Conclusions: Many Indonesian women still prefer traditional contraceptive methods over the more effective modern contraceptive methods. Numerous socio-cultural factors are likely to influence the behaviour of reproductive-age women regarding contraceptive use and childbearing in the future. More effort should be put into raising awareness about modern contraceptive methods and addressing fertility concerns.

Keywords: awareness, contraception, family planning, fertility, reproduction.

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INTRODUCTION

Family planning is crucial in promoting the well-being of individuals, families, and societies by enabling informed reproductive choices, thus reducing maternal mortality and enhancing pregnancy health outcomes. The term family planning covers methods of contraception, procedures, and behaviors that empower individuals to control the number of children they want and the intervals between pregnancies.[1] One metric to monitor the performance of family planning programs in a country is by assessing the unmet need for family planning. Women with an unmet need for family planning are those who want to stop or delay childbearing but are not using any method of contraception. The unmet need for family planning in Indonesia has relatively stagnated, ranging from 10% to 12% for the past 20 years.[2]

Since the concept was first introduced, family planning and contraception have substantially lowered maternal mortality rates by reducing the number of unplanned pregnancies and unsafe abortions. The use of contraceptives has also improved perinatal outcomes by increasing the

interval between pregnancies.[3,4] According to a multi-country analysis family planning prevented approximately 272,000 maternal deaths worldwide annually, with the potential to avert another 104,000 deaths every year if the unmet need for family planning was addressed. In Indonesia, contraceptive use prevented up to 70.5% of maternal deaths in 2008.[5] Altogether, substantial evidence has cemented family planning as a highly cost-effective public health intervention for reducing maternal and child mortality.[2]

In contrast, while family planning programs have focused on limiting the number of pregnancies, little emphasis has been given to the declining global total fertility rate (TFR) which is now below replacement level fertility (2.1 births per woman) in many countries.[1,6] Indonesia has seen a gradual decrease in TFR, which currently sits at 2.204 births per woman, with significant regional disparities.[7] Several factors influence contraceptive practices and fertility decisions among women, including the desire to delay childbirth for career and educational pursuits, as well as religious and cultural beliefs that shape attitudes toward family planning.[8] Worryingly, discovered that up to 69% of young women also worried that contraception might negatively affect their ability to conceive in the future.[9] This concern, if not properly addressed, may cause some individuals to end up using less effective contraceptive methods or avoid using contraception altogether. This study aimed to investigate the most recent trends in contraceptive use in Indonesia as well as evaluate fertility concerns and access to reproductive healthcare services.

METHODS

This study used an observational, cross-sectional study design aimed at investigating trends in contraceptive use and attitude towards fertility among Indonesian women of reproductive age. Data were collected using a self-developed online questionnaire distributed to the target population. The study was conducted from January 2024 until May 2024. Eligibility criteria for the study's participants were; willing to provide informed consent before participating; women between the age of 18 and 40 years old; 3) able to access the Internet to fill in the online questionnaire; 4) residents of Indonesia. The study has obtained ethical clearance from the Ethics Committee of the Faculty of Medicine, Universitas Indonesia – Dr. Cipto Mangunkusumo Hospital.

Study Questionnaire

The questionnaire was developed by the research team after searching the literature and consulting experts in reproductive immunoendocrinology. It was designed to capture comprehensive information on several key areas: sociodemographic characteristics (age, education, marital status, pregnancy history), use or nonuse of contraceptives, attitude towards current and future fertility, and access to reproductive healthcare services and information about family planning. The questionnaire was designed in Indonesian language to cater to the target population. After finalization of the question items, the questionnaire was uploaded to Google Form and made available online. The questionnaire items can be found in Supplementary Material 1, which has been translated into English language.

Data Collection

The questionnaire link was distributed using convenience and snowball sampling methods through popular social media platforms in Indonesia such as Facebook, Twitter, Instagram, WhatsApp, and LINE. Participation was entirely voluntary with no incentives offered. On the first page of the questionnaire, participants had the option to contact the research team in case they did not fully understand any of the questions. All responses were then automatically compiled in Google Forms and downloaded as encrypted Microsoft Excel files accessible only by the research team, ensuring data security and privacy for all participants.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics 27.0. Descriptive statistics were used to summarize the data regarding sociodemographic characteristics, prevalence of contraceptive use and nonuse, attitude towards fertility, access to reproductive healthcare services, and preferred sources of information regarding fertility and family planning. Independent t-test was utilized to compare the means of attitude towards current and future fertility between groups.

RESULTS

A total of 370 women of reproductive age participated in this study. Details on the sociodemographic characteristics of the respondents can be seen in Table 1.

Of 370 responses, 156 women claimed to never have sexual intercourse before (42.2%, almost half), while the rest had previously used some form of contraception for sex. The least commonly used contraceptive methods were permanent birth control such as tubectomy or vasectomy (1,6%) and abstinence (5.4%). The most popular contraceptive method was natural family planning (withdrawal, calendar method, lactational amenorrhea, also known as traditional methods) with usage rate reaching up to 30.3%, followed by barrier method/condom (20%). The use of hormonal contraception and intrauterine device (IUD) was similar (12.2% and 14.3%, respectively). For those who had previously relied on hormonal contraception, the most commonly used was pill followed by injectable.

Women with no prior sexual history appeared to value their future fertility significantly more than sexually active women with prior contraceptive use. Similarly, fertility status in the future mattered significantly more for nulligravid women as well as unmarried women. Regarding perceived importance of current fertility status, no significant differences were found between the groups compared.

Most respondents (74.6%) believed that they could access reproductive healthcare service conveniently (Figure 3). Regarding sources of health information concerning fertility and family planning, the Internet and social media represented the most popular platform (78.6%), followed by obstetricians and gynecologists (64.6%) and period tracking mobile application (50.8%). Meanwhile, general practitioner (21.9%), nurse and/or midwife (31.6%), and family and/or friend (32.4%) showed comparable popularity.

DISCUSSION

Data from 2017 Indonesia Demographic and Health Survey (IDHS) showed that many women of childbearing age preferred modern contraceptive methods (41.4%) over traditional contraceptive methods (4.6%). The most frequently chosen modern methods were injectables (20.9%), pills (8.7%), IUD (3.5%), and implants (3.4%). In contrast, our more recent study revealed that there were more respondents who used traditional methods than modern methods. Condom was the most popular modern method, followed by IUD, pills, and injectables. However, these differences may not be entirely justifiable due to the relatively smaller number of samples in our study compared to IDHS which was conducted by the National Population and Family Planning Board, Statistics Indonesia, and the Ministry of Health. Nevertheless, it remains important to take these different trends into account since changes in sexual activity and contraception preference evolve over time. Trends in contraception are heavily influenced by rapid demographic and socio-cultural changes, especially in this digital era. Globally, many women of childbearing age nowadays are more sexually active, favor a smaller family, and tend to postpone parenthood after marriage. These behaviors not only affect contraceptive use but also the declining fertility rate.[10]Moreover, easier access to the Internet has allowed virtually people

from all ages to research about contraceptives and fertility on their own.

Some of the probable explanations for underutilization of modern contraceptive methods may be related to lack of knowledge on contraceptive usage, fear of side effects, socio-cultural barriers, financial constraints, and limited access to reproductive healthcare service.[3,11] Such objection to using modern methods is unfortunate because they have already been proven to be significantly more effective than traditional methods.[12] Fear of side effects may be partially responsible for the increasing popularity of traditional methods among Indonesian women living in urban areas with higher education.[2,13] In the United States and Europe, a large percentage of women remain opposed to using hormonal contraception due to fear of side effects and concerns about future fertility. Many of them have also shared these concerns, colloquially known as "hormonophobia", on social media platforms which further propagate misinformation.[14] Thus,counseling on modern contraceptives should cover both the effectiveness of each contraceptive and how to manage any accompanying side effects. This study revealed that reproductive healthcare service was accessible for most respondents, and the most influential source of information was the Internet and social media. Obstetricians and gynecologists, general practitioners, and other health professionals need to be more involved in regulating information online to prevent any circulating misinformation.

In Indonesia, the role of a woman's partner or spouse is also crucial in determining whether or not she uses contraceptives.[15] An Indonesian study found that women with lower spouse's education were more likely to have an unmet need for family planning.[3] This pattern can also be found in other countries with strong patriarchal societies.[16,17] Hence, efforts to engage men in family planning must be initiated by educating them on the socioeconomic and health benefits of using contraceptives for couples as well as debunking common misconceptions surrounding modern methods.[2,16] Regardless of their initial opinions on family planning, many men were found to be open to learning more about it and discussing it with health professionals.[16]

Regarding financial barriers, it appears that many women in Indonesia are not fully aware that the country's national health insurance program, *Jaminan Kesehatan Nasional (JKN)*, provides family planning services for free. As a result, many women obtain their contraceptives from pharmacies or private practices and therefore pay out of pocket. Increasing public awareness of the JKN family planning services can help encourage more women to use modern methods of contraception.[18]

Another important misconception that must be addressed is the fear that using contraceptives might negatively affect future fertility.[9] Multiple studies have shown that the use of contraceptives, regardless of the type and duration, does not negatively affect a woman's chance of conceiving and does not significantly delay the return of fertility.[19,20] An Indonesian study also produced similar findings, in which no significant relationship was found between the length of time using contraceptives and the return of fertility after family planning.[21] In this study, it was found that future fertility was perceived differently depending on whether a woman has been sexually active and used contraception, has been pregnant, or has been married before. These findings are likely to be influenced by country-specific cultural and social factors, such as fear of social insecurity, family income, number of siblings, type of residence, religious beliefs, and ethnic affiliations. Altogether, these factors are an important determinant of fertility rate in a country.[22-24] Future research is needed to elucidate the relationship between these variables and attitude towards fertility whilst considering the varying socio-cultural factors among countries.

CONCLUSION

In conclusion, modern contraceptive methods remain underutilized among women of reproductive age in Indonesia, which further increase the unmet need for

family planning. Women in Indonesia should be counseled on the types of modern contraceptives available, effectiveness, how to manage accompanying side effects, and the available family planning services provided for free by national health insurance. Several socio-cultural factors such as prior sexual history and contraceptive use, history of pregnancy, and marriage may influence women's views on having a child in the future. These behaviors must be analyzed to seek solutions for managing the declining fertility rate.

AUTHORSHIP CONTRIBUTIONS

RM, ECY, and ANI conceived the study idea, formulated the study design, obtained ethical approval and consent from participants, carried out data collection and analysis, and wrote the original draft of the paper. KS, AKH, GP, MM, and RHK contributed to data analysis, data interpretation, and comments for revision of the paper. BW and AH supervised the study and data collection process and helped with revision of the paper. All authors read and approved the final manuscript.

DECLARATION of COMPETING INTEREST

The authors have no conflicts of interest relevant to this article.

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Table 1. Sociodemographic Characteristics of Respondents

Variable	N (%)
Age group	
18-30	208 (56.2)
31-40+	162 (43.8)
Education	
Middle school	1 (0.3)
High school	24 (6.5)
Diploma	56 (15.1)
Bachelor's degree	218 (58.9)
Postgraduate	71 (19.2)
Marital status	
Not married	172 (46.5)
Married	198 (53.5)
Pregnancy history	
Nulligravid women	211 (57.0)
Parous women	159 (43.0)

Table 2. Attitude towards fertility according to prior sexual history and contraceptive use

Variable	Women with no prior sexual history	Sexually active women with prior contraceptive use	95% CI	*p-value*
Importance of fertility at present	4.33 ± 1.02	4.34 ± 1.05	-0.23 – 0.20	0.917
Importance of fertility in the future	4.68 ± 0.74	4.33 ± 1.10	0.17 – 0.54	<0.001*

Values are presented as mean ± SD except otherwise noted.
*P-value < 0.05. Independent t-test was used.
Attitude scores were evaluated using 5-point Likert scale (1 = very not important; 5 = very important)

Table 3. Attitude towards fertility according to pregnancy history

Variable	Nulligravid	Gravid	95% CI	*p-value*
Importance of fertility at present	4.39 ± 0.97	4.27 ± 1.13	-0.10 – 0.33	0.280
Importance of fertility in the future	4.70 ± 0.68	4.18 ± 1.22	0.31 – 0.74	<0.001*

Nulligravid refers to women who have never been pregnant before. Gravid refers to women who have been pregnant before. Values are presented as mean ± SD except otherwise noted.
*P-value < 0.05. Independent t-test was used. Attitude scores were evaluated using 5-point Likert scale (1 = very not important; 5 = very important)

Table 4. Attitude towards fertility according to marital status

Variable	Not married	Married	95% CI	*p-value*
Importance of fertility at present	4.28 ± 1.03	4.39 ± 1.05	-0.32 – 0.10	0.311
Importance of fertility in the future	4.65 ± 0.76	4.33 ± 1.13	0.12 – 0.51	0.001*

Values are presented as mean ± SD except otherwise noted. *P-value < 0.05. Independent t-test was used.
Attitude scores were evaluated using 5-point Likert scale (1 = very not important; 5 = very important)

Research Article

Unraveling of Urinary Disorders to Adenomyosis and Dysmenorrhea

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Abstract

Objective: To explore the links between micturition disorders, adenomyosis, and dysmenorrhea and provide insight into the factors associated with the severity of LUTS symptoms in these conditions.

Methods: This study was a descriptive qualitative study. We retrospectively collected medical record data from the Obstetrics Gynecology Outpatient Ward of Dr. Moewardi Surakarta General Hospital from January 2021 to May 2023. This study used The Modified International Prostate Symptom (IPSS) Score questionnaire to assess urinary complaints. The results of this study were analyzed using the Pearson correlation or Mann-Whitney test.

Results: There is a significant relationship between adenomyosis and dysmenorrhea in urinary disorders (p-value of 0.016), where urinary disorders are found to be more severe in adenomyosis patients with dysmenorrhea.

Conclusion: Lower urinary tract phenomena often occur symptomatically in adenomyosis patients and impact the quality of life of sufferers. Dysmenorrhea can be the most acute risk factor that increases the appearance of moderate to severe LUTS.

Keywords: adenomyosis; dysmenorrhea; urinary disturbance.

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INTRODUCTION

Adenomyosis is characterized by endometrial tissue invading the myometrium, leading to the diffuse enlargement of the uterus. Microscopic examination shows non-neoplastic ectopic endometrial glands, stromal hyperplasia, and hypertrophy in myometrial tissue. The basic phenomena of female adenomyosis patients are severe pain during menstruation (dysmenorrhea), heavy bleeding, infertility, and miscarriage.[1,2] Dysmenorrhea, derived from Greek, refers to periodic painful bleeding.[3] Dysmenorrhea is categorized as primary and secondary. The primary type manifests as lower abdominal pain related to menstruation, independent of any other medical conditions. Meanwhile, secondary dysmenorrhea is frequently associated with problems in the uterus and nearby areas, such as adenomyosis. Dysmenorrhea has considerable psychological and functional health effects.[5,6] Causes of dysmenorrhea from the 1960s include many factors, such as anatomical, biochemical, and psychological.[7] Abnormalities of uterus position, shape, and cervix length are anatomical aspects. An elongated and thick cervix might present a mechanical obstruction which leads to more uterine contractions and ultimately dysmenorrhea. This is one potential mechanism explaining how the length of the uterine corpus and cervix affects the severity of dysmenorrhea.[8] Increased contractions in the muscle of the uterus may cause pain

during menstruation and sexual intercourse in the pubic region. This is indicated by higher levels of oxytocin receptor (OTR) and more muscular contractions in the uterine muscle cells in the adenomyotic uterus.[9,10]

Lower urinary tract phenomena (LUTS) include both urinary and obstructive phenomena, persistent urge to urinate, intermittent urination, a feeling of incomplete bladder emptying, storage phenomena or irritation such as frequency, urgency of urination, urge to urinate, incontinence, and nocturia. LUTS's severity level is best assessed using a quantitative phenomenon index. The instrument often accepted for evaluating the severity of a phenomenon is a phenomenon index compiled by the American Urological Association (AUA).[11] The most common LUTS is a sense of urinary urgency for women aged over 40 years. The most important factors for developing LUTS are recurrent urinary tract infections, followed by chronic illness, persistent constipation, higher body mass index (BMI), and parity.[12]

Lower urinary tract issues frequently occur in women who have uterine fibroids. Research indicates that greater fibroid size and increased uterine mass are linked to more severe LUTS symptoms and pelvic floor disorder symptoms. Urinary tract phenomena often appear in people with adenomyosis and affect their quality of life (QOL). Adenomyosis should indeed be considered when evaluating lower urinary tract symptoms (LUTS) in women with uterine fibroids, as there is a significant association between these conditions.[13] Prior research indicates a greater prevalence of micturition irritation symptoms associated with overactive bladder in patients diagnosed with adenomyosis in comparison to control subjects. However, the incidence of LUTS The phenomenon of adenomyosis in women is still uncertain.[14,15] This research examined this condition and the association of micturition disorders with adenomyosis and dysmenorrhea.

METHODS

This descriptive qualitative study uses a retrospective approach using secondary data from medical records taken at Dr. Moewardi Regional General Hospital, Surakarta. This study obtained ethical clearance from Dr. Moewardi Hospital. The population of this study was adenomyosis patients at Dr. Moewardi Surakarta Regional General Hospital from January 2021 to May 2023. The sample of this study was adenomyosis patients with complaints of urinary disorders at Dr. Moewardi Regional General Hospital Surakarta from January 2021 to May 2023, which fulfills the research inclusion and exclusion categories.

The independent variable of this study is the diagnosis of adenomyosis obtained from medical records, and the dependent variable is complaints of urinary disorders. Adenomyosis is a non-neoplastic condition characterized by the benign invasion of endometrial tissue into the myometrium, resulting in diffuse enlargement of the uterus. Microscopically, non-neoplastic ectopic endometrial glands and stroma are observed, surrounded by hyperplastic and hypertrophic myometrial tissue. Lower urinary tract phenomena include urinary and obstructive phenomena, including a constant urge to urinate, intermittent bladder emptying, and a sensation of incomplete bladder emptying. Additionally, storage and irritation phenomena such as increased frequency of urination, urgency, incontinence, and nocturia.

The modified International Prostate Symptom (IPSS) Score questionnaire was used to assess complaints of urinary disturbances in patients with adenomyosis and dysmenorrhea. The findings will be evaluated using Pearson correlation analysis under the condition of a normal distribution and Mann-Whitney analysis if that is not the case. The normality of the data will be assessed using the Kolmogorov-Smirnoff test. Data were analyzed using SPSS software.

RESULTS

This study included 47 female patients with adenomyosis, 29 patients with dysmenorrhea, and 18 patients without dysmenorrhea. The characteristics of the subjects are shown in Table 1. There was no significant difference in age between the two groups (20-30 years and 31-40 years, respectively, $p = 0.062$).

Urinary disorders had the same proportion between the dysmenorrhea and non-dysmenorrhea groups, specifically mild urinary disorders (73% and 100%, respectively). There was a significant difference in the level of urinary disorder between the two groups (p=0.022).

Table 3 shows that the correlation between age and urinary disorders was not statistically significant (p = 0.920). A significant correlation identified between adenomyosis and dysmenorrhea related urinary disorders (p = 0.016, Table 4).

DISCUSSION

Symptoms of LUTS often appear in patients with symptomatic adenomyosis and significantly impact the patient's QOL. Dysmenorrhea can be the most significant risk factor contributing to the development of LUTS of moderate to severe intensity.[16] In this study, there is a significant comparison of urinary disorders, including dysmenorrhea and the absence of dysmenorrhea (p=0.022). The group with dysmenorrhea had a higher chance of moderate and severe micturition, according to the theory. This study also found that adenomyosis and dysmenorrhea were significantly associated with micturition (p=0.016). These results show that the patient who has adenomyosis and dysmenorrhea has a greater chance of voiding than the same patient with no adenomyosis and dysmenorrhea and show that sufferers of adenomyosis and dysmenorrhea experience severe urinary problems. This study's findings are consistent with a previous study, which showed similar results in that lower urinary tract phenomena are prevalent in adenomyosis patients[16]. Another previous study also showed that urinary tract phenomena are common in adenomyosis patients and impact the patient's quality of life (QOL).[14]

Adenomyosis is a gynecological condition that causes the uterus to enlarge and the myometrial walls to thicken asymmetrically.[1,17] The larger uterus can increase pressure on the bladder, affecting its capacity and causing the sensation of needing to urinate at lower volumes.[17] Storage symptoms in LUTS are often due to the pressure exerted by an enlarged uterus on the bladder, reducing its capacity and increasing urinary frequency.[15] Also, adenomyotic nodules have been demonstrated to produce inflammatory and neurogenic substances like interleukin-1β, corticotropin-releasing hormone, neurodevelopmental factors, and synaptic proteins. These substances can impact the pelvic plexus neurons that supply the lower urinary tract layers, leading to urinary tract dysfunction. Abnormal contractility of uterine muscle in adenomyosis also indirectly contributes to LUTS or micturition disorders.[18]

Pelvic pain, abnormal uterine bleeding (AUB), pelvic pain, and infertility are common experiences for women with adenomyosis, and these symptoms significantly affect the patient's QOL. [5,14] Menstrual bleeding is generally caused by increased endometrial surface area, heightened vascularization, abnormal uterine contractions, and increased signaling molecules such as prostaglandins, eicosanoids, and estrogens.[5] In addition, dysmenorrhea and dyspareunia (pain that appears in the pubic region) can be explained by myometrial hypercontractility, which is indicated by higher oxytocin receptor (OTR) expression and increased uterine smooth muscle cell contractility.[9,10]

The LUTS phenomenon in women is categorized into storage phenomena, urinary phenomena, and post-urinary phenomena. The typical storage phenomena are frequency and urgency of urination, incontinence, and nocturia. Hesitation, reduced flow, interruption or spurting, intermittency, and effort are all urinary phenomena. Post-urination, it is common to experience sensations of incomplete emptying and drooling.[19] Due to the anatomy and physiology of the female urogenital system, women are more prone to developing certain lower urinary tract symptoms (LUTS) compared to men. Epidemiological studies have suggested a 40 to 70% prevalence of LUTS in women. Urinary symptoms may worsen due to hypertonicity or dysfunction of the pelvic floor muscles caused by the persistent pain associated with dysmenorrhea in adenomyosis. Storage symptoms like urgency and increased daytime frequency,

as well as voiding symptoms, are common in adenomyosis patients.[15] These urinary symptoms are associated with severe dysmenorrhea and significantly impact patients' quality of life.

CONCLUSIONS

This study showed a correlation between adenomyosis, dysmenorrhea, and LUTS. Uterine enlargement from adenomyosis may compress the bladder and surrounding tissues and frequently results in LUTS symptoms, which negatively affects the patient's quality of life. In cases of moderate to severe LUTS, dysmenorrhea may be one of the significant factors. Dysmenorrheic adenomyosis patients might be screened for LUTS symptoms to facilitate early diagnosis and prompt treatment.

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Table 1. Characteristic of the Study

Basic Characteristics	Group		*P-value*
	Dysmenorrhea (n=29) %	No Dysmenorrhea (n=18) %	
Age (y o)			0.062
20-30	16 (55)	4(25)	
31-40	11 (38)	10 (50)	
41-50	1 (4)	4 (25)	
>50	1 (4)	0	
Education			0.593
Elementary school or equivalent	1 (4)	1 (5)	
Junior high school or equivalent	4(14)	3(15)	
High school or equivalent	16(55)	10(55)	
College	8(27)	4(25)	
Urinary Disorder			0.022
Mild	21(73)	18(100)	
Moderate	6(21)	0	
Severe	2(6)	0	

Table 2. The Correlation between Age and Urinary Disorders

Variable	*P-value*
Age	0.920
Urinary disorders	

Table 3. The Correlation between adenomyosis and dysmenorrhea on Urinary Disorders

Variable	*P-value*
Adenomyosis and dysmenorrhea	0.016
Urinary disorders	

Research Article

Precision of Ultrasound During Peripartum for Predicting and Diagnosing Obstetric Anal Sphincter injuries

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Abstract

Background: Early detection of obstetric anal sphincter injuries (OASIs) following vaginal delivery is essential for effective care and management.Obstetric anal sphincter injury (OASI) is the most common cause of anal incontinence in women and can have a devastating effect on a woman's mental and physical health as well as their social wellbeing. Other long-term effects after OASIS are perineal pain, dyspareuniaand more unusual abscess formation and anovaginal fistulas. This study aimed to assess the accuracy of transperineal ultrasound (TPUS) in diagnosing OASIs in primiparous women between 37 and 41 weeks of gestation.

Methods: A cohort observational study was performed on 697 nulliparous women with singleton pregnancies at 37-41 weeks' gestation. The study involved prenatal ultrasound measurement of ano-vaginal distance (AVD) and postnatal evaluation of anal sphincter contraction.

Results: Significant differences were observed between women with and without OASIs in terms of BMI, fetal parameters (BPD, HC, gestational age by US), and AVD. The area under the receiver operating characteristic curve (AUC) for AVD was 0.659 (95% CI: 0.583-0.735), indicating moderate predictive ability for OASIs. Multivariate analysis revealed significant correlations among BMI, AVD, duration of the second stage of labor, and fetal occiput position at delivery. The strongest correlation was between AVD and the duration of the second stage, while the weakest was between BMI and fetal occiput position.

Conclusion: TPUS could serve as a valuable complement to clinical examination for identifying women at risk of OASIs, potentially lowering the incidence of undiagnosed or occult injuries. Enhanced training and competency assessment are crucial for improving OASIs detection by healthcare professionals.

Keywords: Ano-Vaginal Distance (AVD), Obstetric Anal Sphincter Injuries (OASIs), Primiparous Women, Transperineal Ultrasound (TPUS), Vaginal Delivery.

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Introduction

Injury of anal sphincter during delivery (OASI) is a significant cause of anal incontinence in women, impacting their physical, mental, and social well-being. In the UK, the incidence of OASI among first-time mothers is 6.1%, with a threefold increase from 2000 to 2012.[1] Overall, studies looking at the incidence of OASIS based on the WHO's International Classification of Diseases (WHO,2015). Report an incidence of 4% to 6.6% of all vaginal birth, with higher rates in assisted deliveries (6%) than in spontaneous vaginal deliveries (5.7%), However, the prevalence is dependent on variations in obstetric practice, including rates and type of episiotomy, which vary not only between one country and the next but also at a national level between delivery units and individual practitioners .OASI can range from minor tears to severe injuries involving the perineal body, pelvic floor muscles, and anal sphincters. These injuries can lead to short-term issues like hemorrhage and perineal pain, as well as long-term complications, including rectovaginal fistulae and anal incontinence.[2] Prompt diagnosis of OASI after vaginal delivery is critical for appropriate care. Perineal lacerations should be examined immediately postpartum, with diagnosis established before primary suturing.[3]. The examination typically involves inspecting and palpating the vagina and perineum, often under adequate anesthesia, to determine sphincter involvement. Accurate differentiation between isolated lacerations and sphincter injuries is essential to prevent long-term consequences. Research indicates that undiagnosed sphincter injuries may result from misidentification or inadequate repair.[4] Enhancing clinical awareness and documentation of anal sphincter injuries is vital for improving diagnostic accuracy. Endoanal ultrasonography (EAUS) has advanced the evaluation of the anal sphincter complex but is limited by cost, the need for specialized training, and discomfort compared to other imaging modalities like transperineal ultrasound (TPUS). TPUS, increasingly used over the past decade, is widely accessible, allows multiplanar imaging, and supports 3D volume storage for offline review.[5,6] This study aims to assess the accuracy and diagnostic value of peripartum ultrasound in detecting obstetric anal sphincter injuries in primiparous women between 37 and 41 weeks + 6 days of gestation.

Methods

This cohort observational study was carried out at the Kasr Alainy Hospital for Obstetrics and Gynecology, Cairo University, from January 2021 to May 2023. A total of 697 nulliparous women who presented to the Labor and Delivery Unit with a singleton, living fetus at a gestational age between 37 weeks and 41 weeks + 6 days were included. All participants were fully informed about the study's purpose and procedures and provided written consent before participating. The study received approval from the Ethical Committee. The study included nulliparous women at term with a singleton, vertex presentation, and aged between 18 and 40 years. All participants were in labor, and none had a history of medical conditions. Women with the following conditions were excluded: congenital fetal anomalies, maternal age below 18 or above 40 years, non-vertex presentation, multifetal pregnancies, and those with medical disorders such as diabetes mellitus or hypertensive

conditions. Comprehensive patient history was obtained, including age, confirmed gestational age (based on the first day of the first trimester), gravidity, parity, and medical history. A thorough physical examination was performed, which included vital signs, weight, height, and a full obstetric examination. All ultrasound assessments were conducted using the SONOACE R3 (Samsung Medison Company Ltd, Seoul, South Korea) ultrasound machine, equipped with a convex 3.5-5 MHz transducer for transabdominal scans. To minimize interobserver variability, a single examiner (Dr. Niven) performed all ultrasounds. Routine ultrasonography was performed to confirm fetal viability, gestational age, and to rule out multiple pregnancies and major congenital anomalies. Detailed ultrasound examinations were carried out in the emergency room and during labor, measuring parameters such as head circumference, biparietal diameter, and estimated fetal weight. Additionally, transperineal ultrasound was employed to assess anal sphincter contraction and ano-vaginal distance (AVD)using the standard convex 5-9 MHz probe of the same ultrasound machine used for trans abdominal probe. Fetal biometry followed established guidelines, and the fetal occiput position was determined using a clock-face method. The transperineal ultrasound was conducted by placing a sterile, glove-covered transducer between the labia majora and moving it cranially along the anal canal to measure the internal anal sphincter distance in millimeters. The AVD was measured using the standardized procedure.[7] (Figure 1-a,b).

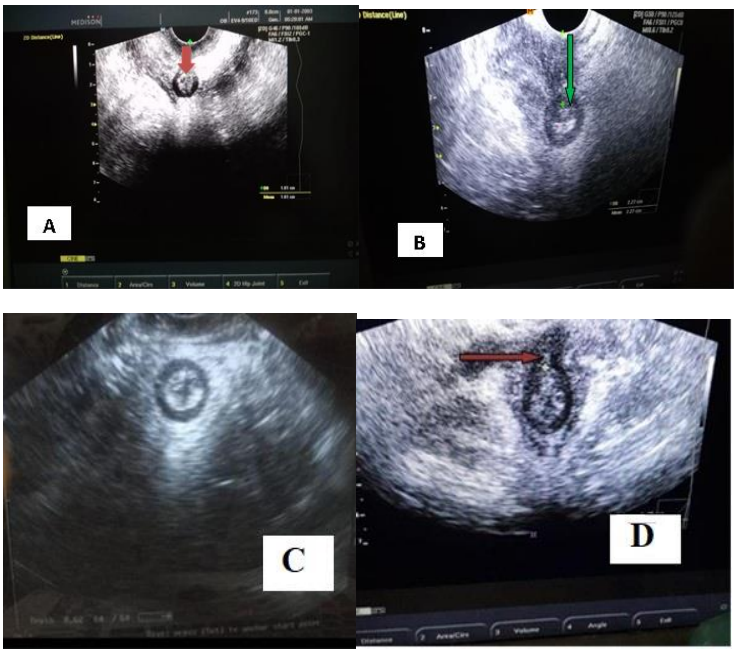

Figure (1): (A)Anovaginal distance in women with OASIs, (B): Anovaginal distance in women without OASIs. Postpartum ultrasound EAS assessment (C): An intact external anal sphincter, (D): A torn external anal sphincter (site of tear shown at the cursor).

The examination was done with the woman in the lithotomy position. The probe was placed at a right angle to the posterior vaginal distal wall and in a transverse scanning plane. The probe was then moved cranially in the vagina from the distal to middle level anal canal until the internal anal sphincter could be seen as a low-echogenic ring. The distance between the anal edge of the internal sphincter and the probe was measured in millimeters (Figure 2). Standard obstetric care was provided by the labor ward team, independently of the specialist conducting the ultrasounds. After delivery, obstetric anal sphincter injuries (OASIs) were initially identified by the attending birth assistant and then confirmed by the study specialist. The specialist assessed the

thickness of the anal sphincter without sharing the diagnosis with the labor ward team, and the birth assistant repaired the sphincter independently, without interference from the study group.Postnatally, the women underwent a perineal examination in the lithotomy position to check for OASIs. A "pill-rolling" technique was used for palpation, with the dominant index finger placed in the anus and the thumb in the vagina. A cavity was palpated along the sphincter muscle if the external sphincter was torn. Following delivery, a dynamic 2D transperineal ultrasound was conducted in a supine position with an empty bladder to assess the anal sphincters at rest and during contraction.[8] Patients were instructed to voluntarily contract their anal sphincter prior to the examination. The ultrasound probe was positioned between the vaginal fourchette and the perineal body to visualize the sphincters (Figure 1-b, c). The primary outcome was the prediction of the risk of OASIs, as determined by clinical examination and supported by transperineal ultrasound findings. Secondary outcomes included other degrees of perineal trauma and the duration of the second stage of labor.

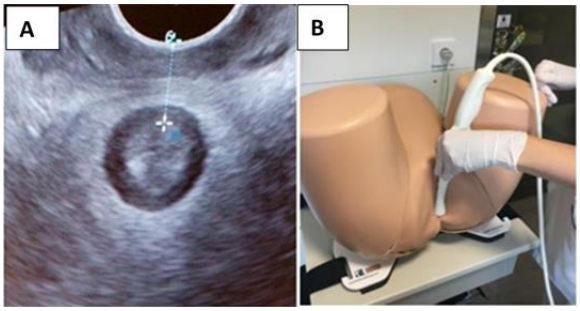

Figure (2):
A Transperineal ultrasound image of the anovaginal distance measured from the anal mucosa to the posterior vaginal wall.
B Transperineal ultrasound method to determine the anovaginal distance.

Sample Size

Given that we have five candidate predictors, our cohort will require at least 50 women who experience the primary outcome of interest, which is obstetric anal sphincter injuries (OASIs). Based on the reported OASIs rate of 4% in primiparous women,[9] we estimate the need to recruit 1,250 women to observe the required number of OASIs cases. Consequently, we plan to continue enrollment until we either achieve 50 confirmed cases of third- or fourth-degree tears or reach a total of 1,250 participants, whichever occurs first. For candidate predictors that do not follow a normal distribution, log transformation will be applied to enhance model fit. Missing data will be handled using multiple imputation methods to address any absent predictor values. The backward selection method will be employed to determine which predictors should be included in the final models. The model's performance will be assessed by its capacity to differentiate between those who do and do not develop the outcome. Prior to conducting any analysis, a detailed Statistical Analysis Plan will be developed and reviewed by an independent Data Monitoring Committee (DMC).

Statistical Analysis

Data were analyzed using IBM SPSS Statistics version 25. Descriptive statistics, including mean and standard deviation (SD), were used for quantitative variables, while frequency and percentages were employed for qualitative variables. Comparisons between qualitative variables were made using the chi-squared or Fisher's exact tests, and the Mann-Whitney test was applied to skewed quantitative variables. The discriminatory power of AVD for OASIs was assessed using Receiver Operating Characteristics (ROC) curve analysis. Multivariate logistic

regression was used to identify predictors of clinical OASIs, employing the ENTER method, with significance set at $p \leq 0.05$.

Results

This cohort study included 697 pregnant women who presented to the emergency department, all of whom underwent antenatal ultrasound evaluations, except for the assessment of external anal sphincter (EAS) contraction, which was performed postpartum. Out of these participants, obstetric anal sphincter injuries (OASIs) were identified in 50 women.

Table 1 outlines the baseline characteristics of the study population, revealing that the participants were relatively young, with a mean age of 23.6 years and an age range of 18-40 years.

The majority of pregnancies were at term, with gestational ages ranging from 37 to 42 weeks and a mean of 38.9 weeks. A significant finding was the high prevalence of obesity, with 58.2% of participants classified as obese, which could potentially influence the study's outcomes, particularly concerning BMI-related pregnancy complications.

Table 1 also highlights a significant association between BMI and the occurrence of OASIs, where women with OASIs had a significantly higher mean BMI (33.8±5.2) compared to those without OASIs (31.2±4.5), with a highly significant p-value of 0.000. Notably, 84% of women who sustained OASIs were categorized as obese, suggesting that obesity may be a critical risk factor for these injuries during childbirth.

*Values for continuous quantitative data are given as mean ± SD.
**Values for categorical data are presented as numbers (percentage).
Kolmogorov–Smirnov test was used to examine the normal data distributional characteristics of all study cases.
***The t-test was used for normally distributed continuous quantitative data.
#The chi-square test was used for categorical data.
A P-value of <0.05 is considered significant

Table (1) Demographic and baseline characteristics of the participants, with a comparison of BMI between women with and without obstetric anal sphincter injuries (OASIs):

	Description (n=697)	**OASIs Clinically Yes (n=50)**	**OASIs Clinically No (n=647)**	**P-value**
Age*		-	-	-
Range	18–40			
Mean± SD	23.6±4.6			
Gestational age*		-	-	-
Range	37–42			
Mean± SD	38.9±1.2			
BMI*				
Range	20.3–46	20.5-44.9	20.3–46	
Mean± SD	31.4±4.6	33.8 ± 5.2	31.2 ± 4.5	<0.001***
BMI**				
Normal weight	50(7.2%)	3 (6%)	47 (7.3%)	<0.001#
Overweight	241(34.6%)	5 (10%)	236 (36.5%)	
Obese	406(58.2%)	42 (84%)	364(56.2%)	

Table (2): Comparison Between Women With and Without OASIs Regarding Ultrasound (US) and Postpartum Data:

	OASIs clinically		P value
	Yes(n=50)	**No(n=647)**	
conventional US			
Occiput position*			
Anterior	18(36%)	335(51.8%)	0.097##
Posterior	22(44%)	210(32.5%)	
Transverse	10(20%)	102(15.8%)	
GA**			
Range	36.7-40.7	36-41	
Mean± SD	38.5±1.1	37.9±1	0.000#
BPD**			
Range	85–103	67-101	0.000#
Mean± SD	94.5±3.7	92.4±3.4	
HC**			
Range	312–355	290-357	0.000#
Mean± SD	331.1±10.8	324±9.1	
Fetal weight**			
Range	3033-4390	2013-4340	0.000#
Mean± SD	3539.6±319.3	3200.4±294.9	
AVD(mm)**			
Range	10–26	11-35	0.000#
Mean± SD	19.4±4.2	22.1±4.2	
External anal sphincter contraction*			
Yes	12(24%)	457(70.6%)	0.000##
No	38(76%)	190(29.4%)	
Postpartum Data			
Occiput Position*			**0.000**##
- Anterior	33 (66%)	560 (86.6%)	
- Posterior	17 (34%)	87 (13.4%)	
Duration of Second Stage (mins) **			**0.000#**
- Range	25–120	15–120	
- Mean ± SD	87.9 ± 25.0	57 ± 27.5	
Episiotomy**			0.713##
- Yes	49 (98%)	620 (95.8%)	
- No	1 (2%)	27 (4.2%)	
Fetal Weight (Postpartum) (g) **			**0.000#**
- Range	2800–4000	1900–4000	
- Mean ± SD	3415.6 ± 272.4	3110.9 ± 251.2	
Spontaneous Perineal Tears*			0.092##
- 1st Degree	0 (0%)	11 (40.7%)	
- 2nd Degree	1 (100%)	4 (14.8%)	
- No Tears	0 (0%)	12 (44.4%)	

*Values Qualitative (categorical) data are given as numbers (percentage).
**Values (continuous quantitative data) are given as mean± SD and range while Kolmogorov–Smirnov test was used to examine the normal data distributional characteristics of all study cases.
#t-test was used for normally distributed continuous quantitative data
##Chi-square test was used for qualitative (categorical) data
P value <0.05 significant

Table 2 compares various obstetric ultrasound parameters between women with and without OASIs. The data shows that women with OASIs had significantly higher mean gestational ages (38.5 weeks vs. 37.9 weeks, p=0.000) and larger fetal head measurements, including biparietal diameter (BPD) and head circumference (HC), both with p-values of 0.000.
Additionally, the mean fetal weight was significantly higher in the OASIs group (3539.6 g vs. 3200.4 g, p=0.000).

Interestingly, the mean Ano-vaginal diameter (AVD) was notably smaller in women with OASIs (19.4 mm vs. 22.1 mm, p=0.000), and the absence of EAS contraction was significantly more common in women with OASIs (24% vs. 70.6%, p=0.000). These findings suggest that larger fetal size and the absence of EAS contraction are associated with an increased risk of OASIs.

Table 2 also presents postpartum data, showing significant differences in several key areas between women with and without OASIs. Women with OASIs were more likely to have a posterior occiput position at delivery (34% vs. 13.4%, p=0.000) and a longer second stage of labor (87.9 minutes vs. 57 minutes, p=0.000). They also had significantly higher mean fetal birth weights (3415.6 g vs. 3110.9 g, p=0.000). Although episiotomy rates were high in both groups, no significant difference was found (p=0.713), but there was a trend towards fewer spontaneous perineal tears in the OASIs group, although not statistically significant (p=0.092).

Table (3): Multivariate analysis to explore the independent predictors of OASIS.

	P-value	OR	95% CI for OR		
Age	0.537	0.972	0.887	-	1.065
Gestational age by date	0.940	1.019	0.625	-	1.660
BMI	0.042	1.086	1.003	-	1.175
Occiput position by US (posterior or Transverses VS Anterior)	0.553	1.277	0.569	-	2.862
Gestational age by US	0.708	1.115	0.631	-	1.969
BPD	0.429	0.953	0.846	-	1.074
HC	0.209	1.030	0.984	-	1.077
Fetal weight	0.709	1.001	0.998	-	1.003
AVD(mm)	0.000	0.785	0.713	-	0.864
Occiput position by at delivery (posterior VS Anterior)	0.032	2.627	1.087	-	6.353
Duration of the 2nd stage in mins	0.000	1.027	1.013	-	1.041
Episiotomy	0.995	0.992	0.079	-	12.469
Fetal weight (PP)	0.085	1.003	1.000	-	1.006

Table 3 identifies independent predictors of OASIs through multivariate analysis. Significant predictors included BMI (p=0.042, OR=1.086), AVD (p=0.000, OR=0.785), occiput position at delivery (p=0.032, OR=2.627), and the duration of the second stage of labor (p=0.000, OR=1.027). These findings emphasize the importance of monitoring these factors to reduce the risk of OASIs during childbirth.

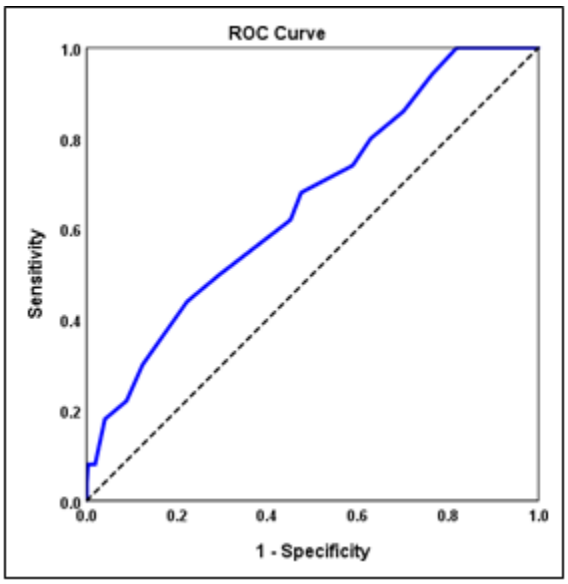

Figure (3): ROC curve for AVD values

Finally, **Figure 3** provides ROC curve analysis for AVD in predicting OASIs, with an AUC of 0.659, indicating moderate discriminatory power. The cut-off point of ≤21.5 mm yielded a sensitivity of 68.0% and a specificity of 52.6%, highlighting a balance between sensitivity and specificity but also suggesting a relatively higher rate of false positives. This indicates that while AVD measurements can be a useful predictor of OASIs, their application in clinical practice should be carefully considered to ensure reliability in prediction (Figure 3).

Discussion

Injury of anal sphincter during delivery (OASI) is a leading cause of anal leakage in women, adversely affecting their mental, physical, and social well-being. In the UK, the incidence of OASI in primiparous women is 6.1%, with a threefold increase from 2000 to 2012.[1] Women with undiagnosed OASIs are more likely to develop anal incontinence.[10] To enhance the detection of OASIs during delivery, endoanal ultrasound (EAUS) has been evaluated. A previous study revealed that 58% of OASIs were missed by doctors and midwives but were identified using EAUS, though it had a 2% false-positive rate.[11] Endoanal ultrasound is considered the golden standard when diagnosing issues with the anatomy of the perineum and anal sphincters when examining women with anal incontinence. The use of endoanal ultrasound before or immediately after primary repair postpartum improved the diagnosis of anal sphincter tears and reduced the risk of severe fecal incontinence postpartum. It has been suggested to routinely use endoanal ultrasound of the perineal tissues and anal sphincters immediately after childbirth. However, EAUS is costly, requires specialized training, and is not widely available. Moreover, it causes more discomfort compared to other imaging methods like transperineal ultrasound (TPUS).[5] In recent years, TPUS has gained attention for imaging the anal sphincter, as it is less invasive, widely accessible, and allows for visualization without disrupting the anatomy.[5] Given the poor outcomes associated with injury of anal sphincter during delivery and repair,[12] identifying antepartum clinical risk factors is crucial. This study evaluated anovaginal distance

(AVD) as a predictor of anal sphincter tears during the first vaginal delivery, finding it to be a safe, non-invasive, and cost-effective assessment tool.In this prospective cohort study, primiparous women with confirmed external sphincter injury had a shorter AVD compared to those with perineal lacerations without sphincter injury. The palpatory thickness of the anal sphincter, as measured by the specialist, correlated well with the AVD measured using TPUS. Previous research has not explored antenatal anovaginal distance or perineal tissue assessment in full-term pregnancies using TPUS. Typically, the perineal area is evaluated during pregnancy or postpartum, with EAUS considered the gold standard for assessing perineal tissues, including the anal sphincter complex.[13] Our findings align with another researcher, who reported a higher incidence of third- and fourth-degree perineal lacerations when the perineal body was ≤2.5 cm.[14] Another research suggested a 20 mm AVD threshold for predicting external sphincter injury,[15] with our study identifying an AVD of 21.5 mm as a cutoff for EAS injuries. However, comparing these findings to another study., who assessed the perineal body and anal sphincter complex antenatally using EAUS, is challenging due to differences in techniques. EAUS impacts perineal tissues differently than TPUS, and no comparative studies between TPUS and EAUS during term pregnancy are available.[16] Transperineal ultrasound (TPUS), in both two-dimensional and three-dimensional formats, has been utilized in the postpartum period to evaluate anal sphincter injuries and their repairs.[17] Applied TPUS using a vaginal ultrasound probe prior to hospital discharge following vaginal birth, observing a notable difference in the average perineal body distance among mothers, with thinner perineums linked to cases involving obstetric anal sphincter injuries (OASIs).[17] Additionally, a strong correlation was reported between the bidigital assessment of external sphincter thickness and TPUS measurements of perineal length immediately following the primary repair of an external anal sphincter tear. These findings align with our own study, conducted shortly after childbirth.[18]

In our study, the gold standard was the inspection and palpation of perineal lacerations, with TPUS compared to these methods. However, as TPUS is not yet widely used in clinical practice, standard examination served as a logical comparison.To our knowledge, this is the first study to evaluate the anal sphincter immediately after delivery in a postpartum ward using 2D TPUS and anal sphincter contraction. We found that 76% of clinically visible anal sphincter defects were confirmed on ultrasound by the absence of anal sphincter contractions, and 70.6% of clinically intact sphincters exhibited good contractions on 2D TPUS. TPUS demonstrated a low positive predictive value (16.7%) for diagnosing sphincter defects, a high negative predictive value (97.4%) for detecting intact sphincters, and an overall accuracy of 71%. While most patients showed no contraction effect on ultrasound three days postpartum, contractions were observed in all patients after six months, likely due to healing.[19] The most robust study to date comparing TPUS, TVUS, and EAUS noted that their training standards were exceptionally high, potentially limiting generalizability. TPUS has additionally been applied in the early postpartum period to assess the anal sphincter complex.[5] In another study

among 146 women who had TPUS within 48 hours postpartum, 12 clinically detected OASIs were confirmed through TPUS.[6] However, due to the small sample size and insufficient power, these results should be interpreted with caution.

In our study, two anal sphincter defects (4%) observed on ultrasound were classified as third-degree tears clinically but were missed during the clinical examination. These might represent occult sphincter injuries, which are defects visible only on ultrasound and not clinically detectable. Previously thought to be "occult," these injuries are now recognized as clinically missed OASIs. Our findings align with an observational study, where 1% of OASIs were visible on ultrasound but not detected clinically.[11] In a similar study, it was reported that three anal sphincter defects (2%) went undetected during the clinical examination but were identified in later ultrasound imaging.[6] However, findings across studies are contradictory. Numerous extensive population-based cohort studies have pinpointed independent risk factors for both primary and recurrent OASIs, which include factors such as nulliparity, higher birth weight, operative vaginal delivery, and a persistent occipito-posterior fetal position.[20-22] In our study, maternal BMI was a significant factor, consistent with recent UK data indicating that higher BMI is protective against minor perineal trauma but not OASIs.[23] However, other studies suggest that higher BMI is protective against OASIs.[24,25] Consistent with other studies, we found that high birth weight is a significant risk factor for OASIs. Although the risk was higher when birth weight exceeded 4000 g, the use of episiotomy did not significantly reduce the risk.[26] In contrast to our findings, another study reported that mediolateral episiotomy strongly protects against third-degree perineal ruptures and may serve as a primary method for preventing fecal incontinence.[27] A thorough knowledge of perineal and anal sphincter anatomy is crucial for accurately diagnosing obstetric anal sphincter injuries (OASIS). Reconstructive surgery aims to reestablish continuity of both the internal and external anal sphincters, ideally performed promptly after the injury occurs. Key factors in reducing complications following chronic perineal rupture repair include accurate anatomical identification of the anal sphincter complex, careful surgical technique, and attentive postoperative care.[28,29] Our study did not observe a significant difference in the performance of mediolateral episiotomy between women with and without OASIs, with p-values >0.05.

Conclusion

This study concludes that transperineal ultrasound (TPUS) is a valuable tool for diagnosing pelvic floor injuries and dysfunction, offering significant potential for improving women's health through early detection of risk factors and encouraging timely pelvic floor rehabilitation. The anovaginal distance (AVD) measured via ultrasound is closely associated with perineal laceration outcomes, with a shorter AVD indicating a higher risk of external sphincter injury. An AVD cutoff of 21.5 mm could be used as a clinical warning sign in the delivery room, prompting careful examination of perineal lacerations before suturing but it is not a perfect tool alone for detection of OASIs as it had low sensitivity and specificity.

Strength and limitation of the study

Strengths:

1. **Novelty:** The study explores the accuracy of transperineal ultrasound (TPUS) in diagnosing obstetric anal sphincter injuries (OASIs), a relatively underexplored area.
2. **Large Sample Size:** Involving 697 participants, the study ensures robust statistical analysis.
3. **Comprehensive Analysis:** The study evaluates multiple variables, including BMI, gestational age, fetal parameters, and AVD, providing a thorough understanding of risk factors.
4. **Real-world Application:** The findings suggest TPUS can complement clinical examinations, potentially improving OASI diagnosis and management.

Limitations:

1. **Moderate Predictive Power:** The AVD's area under the curve (AUC) was 0.659, indicating only moderate accuracy in predicting OASIs.
2. **Single-Center Study:** Conducted at one hospital, the results may not be generalizable to other settings.
3. **Observer Bias:** A single examiner performed all ultrasounds, which could introduce observer bias.
4. **Limited Follow-Up:** The study focuses on immediate postpartum outcomes, lacking long-term follow-up data on the effectiveness of TPUS in preventing complications from OASIs.

Ethical approval statement

This research has received ethical approval from faculty of medicine of Cairo University's Ethical Research Committee approved the study protocol. under protocol number (MD-21-2021). The study adheres to all ethical principles, ensuring the protection, rights, and well-being of participants. Consent has been obtained, and confidentiality measures are in place to safeguard sensitive information. The research design aligns with established ethical guidelines, and any potential risks have been minimized to ensure the ethical integrity of the study.

Patient and public involvement

This study was conducted at Kasr Alainy Hospital, Cairo University, with 697 nulliparous women. Although patients were fully informed and provided consent, they were not involved in the study's design, conduct, selection of outcome measures, or dissemination planning. The research questions and methods were formulated by the clinical team based on existing knowledge, with the goal of improving maternal health outcomes. The study's findings will be disseminated through academic channels to advance clinical practice, indirectly benefiting the patient community. Future research could be strengthened by incorporating more direct involvement from patients and the public.

Consent to Participate:

Informed consent was obtained from all participants. They were provided with detailed information about the study objectives, procedures, potential risks and benefits, confidentiality measures, and their right to withdraw at any time without consequences. Written consent was obtained from each participant before their inclusion. Participants' confidentiality was strictly maintained throughout the research process, and all data were anonymized.

Authors Contributions

The authors contributed to the study as follows: Dalia Samir ZoElfakar contributed to the conception and design of the study,

data collection, and interpretation of the results. Niven Abu Al-Foutouh Shaban was involved in the acquisition of data, drafting the manuscript, and critical revision for important intellectual content. Ahmed Nagy Shaker wrote and edited the manuscript, revised the statistical plan and analysis, and contributed to the interpretation of the results. Sherif Mohamed Negm contributed to data analysis, interpretation, and assisted in drafting and revising the manuscript. Mohamed Fikry Kasem participated in the study design, data collection, and provided critical revisions to the manuscript.

Guarantor Statement

Dr. Ahmed Nagy Shaker, is the guarantor for this manuscript. As the corresponding author, Dr. Shaker takes full responsibility for the integrity of the research, including the data, analysis, and conclusions presented. Dr. Shaker is accountable for ensuring that all aspects of the study, including its design, execution, and reporting, adhere to ethical standards and journal guidelines. Any potential conflicts of interest have been disclosed, and all authors have contributed significantly to the research and manuscript preparation. Dr. Shaker is also responsible for addressing any queries or concerns that arise during the review process.

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Conflict of interest

The authors have no conflicts of interest.

Data Availability Statemen

The data supporting this research is available upon request. Please contact corresponding Author at ahmedafifi38527@postgrad.kasralainy.edu.eg for access to the relevant datasets. We are committed to transparency and facilitating the reproducibility of our findings, and we welcome inquiries regarding the data used in this study.

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Consent for publication.

The manuscript does not contain any individual person's data in any form (including any individual details, images, or videos). Not applicable.

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Research Article

The Age as a Risk Factor for Advanced Stage in Cervical Cancer Patients: A Retrospective Multivariate Study

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Abstract

Objectives: To evaluate the relationship between age and the occurrence of advanced-stage cervical cancer in a national referral hospital setting as a step towards effective prevention, early detection, and management.

Methods: This research adopts a retrospective study design based on the Cancer Registration database of Dr. Cipto Mangunkusumo General Hospital focusing on cervical cancer patients from 2019 to 2022. Multivariate analysis was conducted with age as the primary independent variable, considering parity and employment status in the analysis. The FIGO classification of cervical cancer stages was used to categorize patients into early and advanced stages.

Results: Out of 512 cervical cancer cases, 492 were included in this study. The distribution of cervical cancer stages shows Ninety-one subjects (18.4%) were classified as having early-stage cervical cancer, while 401 other subjects (81.6%) were classified as having advanced-stage cervical cancer. The age distribution of patients is 273 cases (55.4%) in the 18-54 years old group and 219 cases (44.6%) in the >54 years old group. The multivariate analysis of the relationship between cervical cancer stage and age shows an increased risk towards the occurrence of higher cervical cancer stages, and is statistically significant ($p<0.05$) with an odds ratio of 2.13, particularly in individuals aged >54 years.

Conclusion: Age over 54 years is a significant risk factor for advanced-stage cervical cancer. Although there is no significant association with parity and employment history, these findings support preventive and early detection efforts in the older population. Increased screening programs and education are expected to reduce cases of advanced-stage cervical cancer in the future.

Keywords: age, cervical cancer, FIGO staging, multivariate analysis, risk factor.

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INTRODUCTION

In 2020, cervical cancer ranked as the fourth most common cancer in women globally, with an incidence of 604,000 cases. In Indonesia, cervical cancer holds the second position among the most prevalent cancers in women, with a total of 36,663 cases and 21,003 deaths, accounting for 19.1%; this information is based on the health profile data (2021) of all cancer-related deaths.[1] Approximately 70% of cervical cancer cases in Indonesia are diagnosed at an advanced stage.[2] Known risk factors contributing to cervical cancer include age, histological findings, smoking habits, race, and the initial cancer stage at diagnosis.[3] Several studies conclude that old age is an independent risk factor for the increased occurrence of advanced-stage cervical cancer cases.[3] Cervical cancer is known to be predominantly caused by persistent Human Papilloma Virus (HPV) infections. Among 200 different HPV serotypes, 12 have been deemed carcinogenic, and two of which, HPV-16 and HPV-18 are known as high risk serotypes which accounts for 50% and 10% of cervical cancer cases, respectively.[4] It is known that an infection of the two strains increases risk of cervical cancer by 435-fold and 248-fold respectively.[5] Persistent cervical infections of high-risk HPV serotypes are known to be detected among 99.7% of cervical cancer patients globally, and it is estimated that

roughly 80% of women would be infected by HPV through sexual contact by the age of 45.[5-7] HPV infection that occurs during early adulthood or adolescence, are known to remain asymptomatic for the next 10-15 years, however such infection are known to cause micro damage of the cervical epithelium, allowing pathogens and other HPV serotypes to inflict multiple infections. It has been demonstrated that increasing age is a risk factor for developing multiple HPV infection, which is speculated to be the result of decreased immunity, and the longer duration of time which allowed for the infection to manifest into symptoms of cervical cancer.[8] According to the National Cancer Institute (2013-207), there is a surge in the incidence of advanced-stage cancer cases in the population aged >=55 years compared to those <55 years.[9] Therefore, exploring the connection between age and cervical cancer becomes crucial for prevention, early detection, and effective management. This study aims to investigate the relationship between old age and the occurrence of advanced-stage cervical cancer in cervical cancer patients at Dr. Cipto Mangunkusumo General Hospital from 2019 to 2022.

METHODS

The research design employed in this study is a retrospective study based on the Cancer Registration database of Dr. Cipto Mangunkusumo General Hospital for cervical cancer patients from 2019 to 2022. Ethical approval for this study was obtained from the Health Research Ethics Committee of FKUI-RSCM with the approval number KET-1291/UN2.F1/ETIK/PPM.00.02/2023 on October 2, 2023. We conducted multivariate analysis with age as the primary independent variable, considering parity and employment status as other variables in the analysis. Age was categorized into two groups: 18-54 years and >54 years. Parity was divided into two groups: parity history 0-2 and >2. Employment history was also divided into two groups: employed and unemployed. The classification of cervical cancer stages by the Fédération Internationale de Gynecologie et d'Obstetrique (FIGO) was used, where stages IA1-IIA were classified as early-stage, and stages IIB-IVB were classified as advanced-stage. The inclusion criteria for this study were cervical cancer patients registered in the Cancer Registration database of Dr. Cipto Mangunkusumo General Hospital from 2019 to 2022 with complete clinical and demographic data, while patients with missing data (e.g., age, parity, employment status, or cancer stage) were excluded. Employment status was classified as "employed" for patients with a recorded profession or job and "unemployed" for those listed as homemakers, retirees, or without employment. Age was categorized into 18-54 years and >54 years, based on evidence from the National Cancer Institute (2013-2017) showing a significant increase in advanced-stage cancer incidence in individuals aged ≥55 years compared to those <55 years.[9] Variables with a P-value <0.25 in bivariate analysis were included in the multivariate logistic regression to analyze associations between age (primary variable), parity, employment status, and cervical cancer stages. The results were expressed as adjusted odds ratios (aORs) with 95% confidence intervals, considering a P-value <0.05 as statistically significant.

RESULTS

Based on medical records, the total number of cervical cancer cases at Dr. Cipto Mangunkusumo from 2019 to 2022 was 512; however, due to data incompleteness, the total cases used in this study amounted to 492. Out of 512 cervical cancer cases recorded at Dr. Cipto Mangunkusumo from 2019 to 2022, 20 cases were excluded due to incomplete sociodemographic data: 8 patients lacked parity information, 7 were missing age data, and 5 did not have employment status recorded. This resulted in a total of 492 cases included in the analysis.

The distribution of age, parity, occupation and cervical cancer stages among patients can be observed in Table 1. Ninety-one subjects were classified as having early-stage cervical cancer, while 401 other subjects were classified as having advanced-stage cervical cancer. The relationship between cervical cancer stage and sociodemographic factors can be seen in Table 2.

The table presents the sociodemographic profile and stages of cervical cancer. In terms of age, there were 273 cases in the 18-54 years old group and 219 cases in the >54 years old group, with a significant association ($p<0.05$) and an adjusted odds ratio (aOR) of 2.13 (95% CI: 1.28-3.53). Regarding parity, 262 cases were in the 0-2 parity group and 230 cases were in the >2 parity group, with no significant association ($p=0.59$) and an aOR of 1.13 (95% CI: 0.70-1.84). Regarding occupation, there were 69 cases among the employed and 423 cases among the unemployed, with no significant association ($p=0.58$) and an aOR of 1.20 (95% CI: 0.61-2.38).

The non-significant findings for parity and employment status may reflect the complex interplay of sociodemographic and clinical factors that were not fully captured in this study, such as broader socioeconomic conditions or health-seeking behaviors. Study limitations include the retrospective design, reliance on secondary data prone to missing information, and the inability to explore other potential confounders not recorded in the dataset, which may influence the associations observed.

DISCUSSION

According to data from the Indonesian Ministry of Health, the incidence of cervical cancer cases in Indonesia continues to increase each year, with the discovery of 40,000 new cases annually and approximately 7,000 deaths each year.[2] About 70% of new cases are diagnosed at an advanced stage.[2] In this study, approximately 81.5% of cervical cancer cases were found at an advanced stage (IIB-IVB). Similar findings were obtained in another study, where 64.1% of cases were diagnosed at an advanced stage (IIIB), with the highest incidence in the age group of 51–60 years.[3] In Table 2, an increase in advanced-stage cases was observed in the age group of 18-54 by twofold, while in the age group >54 years, advanced-stage cases increased sevenfold. Another study states that 63% of advanced-stage cervical cancer cases were found in patients aged ≥65 years.[10] Several factors that may support this include a decline in the immune system function in elderly patients, affecting the growth and spread of cancer cells.2 Other factors may be influenced by a lack of early detection or screening coverage, leading to most cases being diagnosed at an advanced stage.[11] Age itself can affect cervical tissue changes; long-term exposure to estrogen and progesterone hormones can lead to changes in the transformation zone of the cervix, increasing the risk of pre-cancerous lesions and cervical cancer itself.[11] The possibility of infection by certain HPV types also has the potential to progress to an advanced stage in patients. In this study, old age was found to be statistically significant ($p<0.05$).[11]

In examining the correlation between age and the increased risk of advanced-stage cervical cancer in individuals aged above 54, an intriguing aspect emerges, suggesting a potential link between the progression of the disease and the historical lack of screening practices, particularly during the early stages of adulthood or before the age of 30. The discussion revolves around the assumption that individuals in this older age group may not have undergone comprehensive screening measures during their formative years, a critical period for the early detection of cervical abnormalities.[12] Currently, various methods are available for cervical cancer screening. Screening for high-risk HPV (hr-HPV) is now considered the gold standard for preventing cervical cancer and other HPV-related diseases. In high-resource countries, current screening strategies include cytological evaluation (Pap smear), nucleic acid HPV testing, or a combination of both. Visual inspection with acetic acid (VIA) is another method commonly performed in developing countries, aiming to detect pre-cancer and early cancer lesions in apparently normal and asymptomatic women. Additionally, urine-based HPV-DNA testing using CerviScan has been studied in Indonesia and has demonstrated reliability in detecting high-risk HPV subtypes. This test could serve as an alternative method for HPV-DNA testing to expand cervical cancer screening programs.[13] This assumption draws attention to the possibility that, without

regular screenings and proactive healthcare initiatives at a younger age, there might be missed opportunities for identifying precancerous lesions or early-stage cervical cancer. Consequently, the disease may evolve unnoticed, gaining momentum and reaching advanced stages before clinical intervention. While this hypothesis underscores the importance of early and consistent screening practices, it's essential to emphasize that it is speculative in nature and warrants empirical investigation to substantiate the claim definitively. Addressing this assumption through further research could shed light on the effectiveness of current screening programs and potentially inform the development of targeted interventions for specific age groups, ultimately contributing to more tailored and impactful cervical cancer prevention strategies. Implementing a mandatory HPV vaccination program for elementary school children by the Indonesian government could be a key strategy for cervical cancer prevention in Indonesia. This program has the potential to protect both younger and older individuals in the future from HPV infections, including high-risk types, thereby reducing the likelihood of developing cervical cancer.[14]

Cases of advanced-stage cervical cancer were also found to be higher in populations with parity history 0-2 (79.3%) and in populations with parity history >2 (83.9%). My previous study also compared parity with cervical cancer stages. The results showed no significant difference in cervical cancer stages at diagnosis between the parity groups ($p = 0.058$).[15] Another meta-analysis states a similar finding. This can be explained by the high levels of estrogen and progesterone hormones during pregnancy, especially in the late stages.[16] In the third trimester, metaplasia of the transformation zone also significantly increases, contributing to the occurrence of uterine cancer.[16] However, in this study, no significant statistical difference was found between the two groups ($p=0.59$).

A total of 81.3% of advanced-stage cases were found in patients who were unemployed. Another study links employment status to cervical cancer incidence, where 39.4% of cervical cancer cases are unemployed patients. Employment status is indirectly related to cervical cancer incidence. Employment status, especially in the unemployed population, correlates with low socioeconomic status. In this study, socioeconomic status is said to affect patient knowledge. The population with stable employment is likely to have better access to education and information about cervical cancer, while the population with low socioeconomic status is assumed to have less awareness of cervical cancer and its prevention methods, leading to less effective screening and advanced gynecological examinations.[17] However, no significant statistical relationship was found in this study ($p=0.58$).

CONCLUSIONS

Based on the results of this study, it can be concluded that age is a significant risk factor for the occurrence of advanced-stage cervical cancer in patients with cervical cancer at Dr. Cipto Mangunkusumo General Hospital during the period 2019-2022. Age over 54 years has a statistically significant relationship with an increased risk of advanced-stage cases. Although there is no significant relationship between the patients' parity history and employment status with cervical cancer stage, these findings provide important insights into efforts for prevention, early detection, and effective management of cervical cancer, especially in the elderly population. These findings can ultimately be applied as soon as possible through rigorous screening for elderly women by not only gynecologists, but as early as possible from general practitioners, and emphasizing the need for national-scale programs for cervical cancer screening in the elderly. Besides that, future research can be directed to see whether any additional modifiable and unmodifiable risk factors add to the prevalence of advanced stage cervical cancers, and see whether added effects from the risk factors increase the likelihood of said cancers.

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CONFLICT of INTEREST

None.

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Tabel 1. Profile of Patient Characteristics in Cervical Cancer Patients at Dr. Cipto Mangunkusumo General Hospital in the Years 2019–2022 (n=492)

Category	N	%
Age (y o)		
18-54	273	55.50
>54	219	44.50
Parity		
0-2	262	53.20
>2	230	46.80
Occupation		
Employed	69	14.00
Unemployed	423	86.00
Cervical Cancer Stage		
Early	91	18.50
Late	401	81.50

Table 2. Relationship between Cervical Cancer Stage and Demographic Factors in Cervical Cancer patients at Dr. Cipto Mangunkusumo General Hospital in the Years 2019–2022 (n=492)

Sociodemographic	Cervical Cancer Stages			*P-value*	aOR
Age (y o)	**Early**	**Late**	**Total**		**95% CI**
18-54	64	209	273	<0.05	2.13 (1.28-3.53)
>54	27	192	219		
Parity					
0-2	54	208	262	00.59	1.13 (0.70-1.84)
>2	37	193	230		
Occupation					
Employed	12	57	69	00.58	1.20 (0.61-2.38)
Unemployed	79	344	423		

Leptin Expression in High-Grade Serous Ovarian Carcinoma: The Controversy of Leptin Paradox in Ovarian Cancer

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Abstract

Objectives: To analyse the characteristics and expression patterns of Leptin in High-grade serous epithelial ovarian carcinoma (HGSC), the most prevalent subtype of ovarian carcinoma, and to compare them with overall serous ovarian carcinoma population.

Methods: A cross-sectional study was performed on a total of 77 paraffin-embedded HGSC tissue samples from patients over a period of 3 years. Immunohistochemical analysis was performed using a polyclonal Leptin antibody to samples. Data were analyzed using SPSS version 22.0.

Results: Among HGSC patients, the majority (64.3%) were over 50 years old, and a significant portion (39.3%) were obese. Leptin showed a strong cytoplasmic expression in 69.6% of HGSC tumor cells and in 100% of LGSC tumor cells (p-value = 0.004). There was no correlation between lymphovascular space invasion and leptin expression. Interestingly, leptin expression in overall serous ovarian carcinoma patients exhibited a protective effect against metastasis (p-value = 0.047), suggesting a leptin paradox exists in this type of cancer**.** However, this association was no longer significant when the analysis excluded the LGSC group (p-value = 0.193).

Conclusion: This study suggest that leptin expression is not a significant prognostic factor in HGSC. Comparison of HGSC with the overall serous ovarian carcinoma population reveals that the results of several previous studies were likely confounded by the inclusion of heterogeneous tumor morphologies within their samples. The presence of low-grade serous carcinoma within the population may have inadvertently led to the observation of a seemingly protective effect of leptin, a phenomenon sometimes referred to as the 'leptin paradox'.

Keywords: high-grade serous carcinoma, leptin paradox, immunohistochemistry, leptin, obesity

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INTRODUCTION

Ovarian cancer is still the most cancer among all gynecological malignancies.[1] Ovarian cancer is a heterogeneous group of tumors. These tumors can originate from epithelial cells, germ cells, or stromal/sex cord cells. Around 90% of ovarian cancers originate from ovarian surface epithelium.[2-4] The American Cancer Society ranks ovarian cancer as the 5th leading cause of death in women due to malignancy. Data from 2018 in Indonesia also shows a high mortality rate from ovarian cancer: 3.8% of all diagnosed cases.[3,5,6]

Serous type ovarian neoplasm is the most common type of ovarian epithelial cancer. Based on their histopathological characteristics, serous ovarian cancers are further divided into low-grade type (LGSC) and high-grade type (HGSC). This division also reflects the differences in the carcinogenesis process, mutation patterns, and prognosis between the two types of serous ovarian cancer. Thus, high-grade serous carcinoma does not develop from low-grade serous carcinoma. Instead, both types arise through their own distinct developmental pathways.[2,7,8]

Previous research focused on conventional risk factors for ovarian cancer, such as family history, genetic predisposition, and reproductive factors including nulliparity, early menarche, and late menopause.[9] However, despite this focus, ovarian cancer incidence has remained high in recent decades. Obesity, a growing global health concern, has emerged as a significant metabolic risk factor linked to ovarian cancer.[10]

There are many studies linking body mass index (BMI) parameters to an increased risk of cancer.[11-13] The results of these studies remain mixed. Therefore, there is a need for more specific variables that better represent the obese population and can reveal more meaningful correlations than clinical parameters alone.

There are some efforts to identify correlations between the pathophysiological pathways of obesity and ovarian cancer.[14] Adipose tissue in obese conditions influences the microenvironment of cancer cells by providing fatty acids as an energy source, activating pro-inflammatory cytokines and protease enzymes, creating an imbalance in the overproduction of the pro-inflammatory adipokine leptin compared to the reduced production of the anti-inflammatory adiponectin.[14,15] Interleukin-6, TNF-α, and leptin are a group of cytokines produced by adipocytes. Their levels increase as body fat mass increases.

In individuals with obesity, leptin often acts as a pro-inflammatory adipokine and can even be carcinogenic, promoting the invasion and migration of tumor cells (metastasis). Thus the combined presence of high leptin concentration and its receptor (Ob-R) expression in certain tumors is associated with a poor prognosis.[1,13,14,16-23] However, some studies suggest that high leptin expression in ovarian cancer patients can be associated with improved outcomes, such as increased disease-specific survival (DSS), disease-free survival (DFS), and reduced recurrence rates, as well as a lower incidence of lymphovascular space invasion (LVSI).[24-25]

This contrasting effect of leptin on cancer is known as the "obesity/leptin paradox".[25,26] This phenomenon has been observed in several types of cancer, including colorectal adenocarcinoma.[25,27] The exact mechanism behind this paradox remains unclear, but one hypothesis suggests that overweight and obese individuals may have larger energy reserves, allowing them to survive cancer for a longer period.

Considering leptin dualism which could be a poor prognostic factor in one study and a protective prognostic factor in another study, we investigate its effects in a more targeted population – women with serous type ovarian carcinoma. Previous studies have employed ovarian cancer samples without considering their heterogeneity, leading us to hypothesize that a more specific investigation focusing on samples with distinct morphologies, serous subtype, would yield more reliable results.

METHODS

Patients and specimens

This cross-sectional study was performed from January to June 2023 at Pathology Anatomy Laboratory, Faculty of Medicine, Hasanuddin University. This study analyzed resected ovarian tissue samples obtained from hysterectomy oophorectomy procedure at Wahidin Sudirohusodo General Hospital Makassar over the past 3 years. Samples were histopathologically diagnosed with High-Grade Serous Carcinoma or Low-Grade Serous Carcinoma using hematoxylin-eosin staining. Seventy-seven patients were included in this study, of whom 56 had high-grade serous carcinoma.

All accessible subjects meeting the inclusion criteria were consecutively enrolled from the Department of Anatomic Pathology, Wahidin Sudirohusodo General Hospital, Makassar, until the sample size of 49 subjects was reached. Inclusion criteria: Paraffin blocks with a pathology report diagnosing high-grade serous carcinoma or low-grade serous carcinoma; Availability of other medical records to confirm clinicopathological parameters such as age, body mass index, lymphovascular space invasion (LVSI), and metastasis. Exclusion criterion: Samples damaged during reprocessing for Leptin immunohistochemistry examination.

BMI was measured using the Asia-Pacific Body Mass Index Classification. A person is considered obese if their BMI is ≥25 kg/m² (table 2). This value is slightly lower than the World Health Organization (WHO)

standards due to adjustments for the posture of Asian populations.[10,28]

H&E and Immunohistochemical Staining

The collected tissue blocks were cooled again in the refrigerator before being cut into 3 µm sections using a microtome. These sections were then transferred to a 60°C water bath. A polysilane glass object was used to retrieve sections from the water bath, which were then dried and placed on an adhesive-coated slide warmer at 60°C for 15 minutes. A single tissue slide was deparaffinized with xylol three times, hydrated through a series of graded ethanols in water, stained with hematoxylin and eosin (H&E), dehydrated through graded ethanols, cleared, and finally mounted with a coverslip.

For immunohistochemical staining, sections were cut to 3 µm thickness and transferred to a water bath. They were then retrieved using a glass slide. TMA slides were deparaffinized with xylene and rehydrated through a series of graded ethanol washes (100%, 96%, and 70%) for 5 minutes each. The slides then underwent pre-treatment with Tris-EDTA solution at 95°C for 10 minutes. This was followed by sequential incubations with: peroxidase block containing 3% hydrogen peroxide for 10 minutes, Super Block for 5-10 minutes, primary antibody (primary polyclonal rabbit anti-leptin antibody, DF8583, Affinity Biosciences, Cincinnati, OH, USA) diluted 1:200 in goat serum for 45 minutes, UltraTek Anti-polyvalent for 10 minutes, UltraTek HRP for 10 minutes, and DAB solution for 1-5 minutes. After each incubation step, the slides were washed with PBS (pH 7.4) before proceeding to the next incubation.

The slides were then conterstained with hematoxyline, soaked in bluing reagen, and dehydrated according to a standard protocol and sealed with deck glass. Negative controls were prepared by omitting the leptin antibody during the primary antibody incubation. Positive controls consisted of liver tissues which showed positive for leptin expression.

Interpretation of Leptin Expression

Two pathologists and a researcher semiquantitatively evaluated the results of immunohistochemical staining using a light microscope. The IHC staining score was determined based on both color intensity and the proportion of positively stained areas within a visual field (24,27). The intensity scale ranged from 0 (no expression) to 3 (strong expression). Staining extent was similarly scored on a scale of 0 (10%), 1 (10-39%), 2 (40-90%), and 3 (>90%) based on the percentage of positively stained cells.

The final staining score was obtained by multiplying the intensity and extent scores. All cases were then classified into two expression groups based on their final score: low expression (0-3) and high expression (4-9).

Statistical Analysis

Statistical analysis was conducted using IBM SPSS Statistics (version 22.0). The chi-square test was employed to assess the association between ordinal variables in two or more unpaired groups. Specifically, Pearson's chi-square test was used to examine the relationships between body mass index (BMI) and both leptin expression and tumor morphology. A p-value of less than 0.05 was considered statistically significant.

RESULTS

The study included a total of 77 samples collected over the past 3 years. Among these samples, 56 were diagnosed with the high-grade serous ovarian carcinoma (HGSC) and 21 with the low-grade type (LGSC). The patients' ages ranged from 25 to 70 years old, with a median age of 51 and an average age of 50.43 years. Two age groups were identified: less than 50 years old (41.6%) and greater than 50 years old (58.4%). The HGSC group tended to have a higher proportion of patients in the older age group (>50 years).

Body mass index (BMI) were divided into three groups, the underweight group was 12 (15.5%), the optimal group was 31 (40.3%), the overweight/obesity group was 31 (40.3%). The results of the analysis did not show a correlation between serous carcinoma morphology and BMI (p-value 0.961).

There were 27 samples (35.1%) that showed lymphovascular space invasion, while 50 samples (64.9%) did not show lymphovascular space invasion (LVSI). The results of the analysis did not reveal a correlation between the morphology of serous carcinoma and LVSI (p-value 1.000).

The number of samples that experienced metastases was 46 (60%) while

the group that did not have metastases was 31 (40%). A total of 71.4% of the HGSC group experienced metastasis. On the other hand, in the LGSC group, the majority did not experience metastasis, 76.2%. Thus, the results of the analysis showed a correlation between the morphology of serous carcinoma and metastasis (p-value 0.000).

Among the samples, 44 (57.1%) showed necrosis, while 33 (42.9%) did not. The HGSC group had a higher prevalence of necrosis, with 71.4% exhibiting large areas. Conversely, the LGSC group showed a much lower prevalence, with most samples (81%) lacking necrosis. This finding suggests a correlation between serous carcinoma morphology and tumor necrosis (p-value = 0.000).

Strong leptin expression was observed in 60 samples (77.9%), while only 17 (22.1%) showed weak staining intensity and proportion. The HGSC group had a high prevalence of strong leptin expression (69.6%). Interestingly, all LGSC samples (100%) appeared to express strong leptin. This suggests a correlation between serous carcinoma morphology and leptin expression. Leptin expression was significantly higher in the LGSC group (p-value = 0.004).

DISCUSSION

While morphologically similar, low-grade and high-grade serous ovarian carcinomas are distinct entities with differing pathogenesis and molecular profiles.[8] Our sample population's incidence aligns with epidemiological studies, which show that LGSC has a lower incidence and typically presents at an earlier age compared to HGSC (7). (Table 1)

Classified as a type I ovarian carcinoma with indolent behavior, low-grade serous carcinoma exhibits a significantly lower frequency of tumor invasion and metastasis.[29] LGSC arises from a spectrum of benign lesions, progressing from benign adenofibroma or serous cystadenoma to precursor serous borderline tumors, and finally to low-grade serous carcinoma. Mutations in KRAS, BRAF, and/or ERBB2 oncogenes activate the MAPK pathway, driving LGSC carcinogenesis. This process may be further enhanced by leptin binding to its receptor on tumor cells, which also activates the MAPK pathway.[1,2,7,8,25]

HGSC, a type II ovarian carcinoma, is an aggressive and invasive tumor. It can arise from the fimbria epithelium of the fallopian tube. Notably, HGSC develops from a non-cancerous (non-neoplastic) lesion in the tubal epithelium called secretory cell outgrowth (SCOUT), which lacks TP53 mutations and has low Ki67 proliferation rates. In contrast, the neoplastic lesions arise due to a TP53 mutation. This mutation gives rise to the first cancerous (neoplastic) entity, known as serous tubal intraepithelial lesions (STILs) or tubal dysplasia. STILs are characterized by positive p53 immunohistochemistry (IHC) or a Ki67 proliferation rate exceeding 10%. STILs can then progress to serous tubal intraepithelial carcinomas (STICs), a more severe form of dysplasia with positive for p53 immunohistochemistry and a Ki67 proliferation rate exceeding 10%.[2,7,8,30] Leptin is known to be a regulator of p53 expression. The anti-apoptotic effect of leptin comes from leptin's ability to suppress the p53 pathway (p53 downregulation). However, regardless of the p53 status in the tumor, leptin stimulation has the potential to trigger tumor cell proliferation.[21,31]

Leptin is a protein hormone composed of 167 amino acids (16 kDa) encoded by the Lep gene on chromosome 7. It is primarily synthesized by white adipose tissue alongside other hormones like resistin, adiponectin, visfatin, omentin, and vaspin. Interestingly, leptin expression is not limited to adipose tissue; it's also found in the gastrointestinal system, brain, and muscle. Under normal physiological conditions, leptin expression is regulated by cortisol and insulin. However, in inflammatory states, interleukin-1β (IL-1β) can influence leptin expression. [25,32-34]

A recent study found that leptin protein behaves differently in obese populations compared to those with ideal body weight. Physiologically, leptin plays a role in regulating energy homeostasis and body weight through the Central Anorexigenic Pathway.1,10,32,35

It is known that free leptin and serum leptin levels are consistently higher in people with a high BMI compared to the normal weight/BMI population.[33,35] This study also found a tendency for leptin expression in tumor cells to increase with increasing body mass index (p-value 0.059) (Table 2). Even though it

is not yet significant, the results of our research are quite representative compared to previous studies. The previous study found no significant correlation between BMI and leptin expression in tumors (p-value = 0.20).[24] These results could be caused by the sample size being insufficient or the sample population being too heterogeneous.[24,26,36]

Furthermore, our study demonstrated significantly higher rates of metastasis and tumor necrosis in high-grade serous carcinoma (p-values = 0.000 and 0.000, respectively) (Table 1). These findings suggest that our sample population reflects the characteristics of the actual tumor population, potentially leading to more representative results for leptin analysis.

We further attempted to formulate the role of leptin in the process of ovarian carcinogenesis by reviewing previous studies (see Figure 2). Leptin exerts anti-apoptotic effects in ovarian carcinoma cells by inhibiting components like TNFR1, Bad, caspase-6, and caspase-3. Additionally, activation of the PI3K/AKT pathway promotes cell survival and proliferation, alongside the JAK/STAT and MEK/ERK pathways. Leptin also binding to its receptor (Ob-R) on immune cells modifies the tumor microenvironment. This inhibits IFN-γ production in Natural Killer (NK) cells, reducing their cytotoxicity. Leptin also activates tumor-associated macrophages (TAMs), which secrete: MMPs (promoting invasion and migration) and growth factors (EGF, FGF, VEGF) for remodeling and angiogenesis. Furthermore, TAMs modulate T cells by recruiting regulatory T cells (Tregs). CCL22 secretion by TAMs attracts Tregs, which then secrete immunosuppressive factors like TGF-β and IL-10 (14). TAMs, stromal adipose tissue, and tumor cells themselves also secrete IL-6. This, along with TNF-α, induces aromatase expression. The resulting hyperestrogenic environment acts as a mitogenic agent on ovarian epithelial cells, and promoting their growth.[37,38] Additionally, elevated IL-6 levels are associated with increased chemotherapy resistance[14,23]

Leptin facilitates cell migration through several mechanisms. The first involves inducing the secretion of MMP-9, MMP-2, and MMP-14 by TAMs (tumor-associated macrophages). Matrix metalloproteinases (MMPs) are enzymes known to degrade extracellular matrix components, which is crucial for cancer cell invasion and metastasis.[14] Leptin also promotes cell migration by inducing increased expression of uPA (urokinase plasminogen activator) in cancer cells. This activation occurs through the RhoA/ROCK intracellular signaling pathway.[39] uPA is an extracellular proteolytic enzyme that activates a cascade of proteases upon binding to its receptor (uPAR).[40] This cascade ultimately leads to the degradation of the extracellular matrix, facilitating tumor metastasis.[39,40] Leptin induces invasion/migration of cancer cells by activating intracellular signaling such as RhoA/ROCK, PI3K/AKT and JAK/STAT3 pathways (see Figure 2).[9,39]

Recent studies have re-emphasized the potential role of leptin in promoting epithelial mesenchymal transition (EMT) in cancer cells, including epithelial ovarian cancer. EMT is a process of reprogramming epithelial carcinoma cells to acquire mesenchymal characteristics, which can be identified by changes in phenotype, transcription factors, miRNAs, lncRNAs, cell junctions, cytoskeletal proteins, and secreted factors. EMT enhances the malignancy of tumor cells because with mesenchymal phenotype, cancer cells can easily invade, migrate, evade the immune system, and ultimately lead to successful metastasis.[41]

Our study found that leptin antibodies stained positive in all low-grade serous ovarian carcinomas, while only 69.6% of high-grade tumors showed strong expression (p-value = 0.004) (Table 1). This is surprising because leptin is typically thought to be more abundant in the less aggressive form of serous cancer. Interestingly, leptin antibody expression was localized to tumor nests with well-differentiated tumor cell architecture and cytology. No previous studies have been able to explain this phenomenon. The authors hypothesize a role for estrogen in this case. It is known that LGSC tumor cells are more immunoreactive to hormonal receptors, particularly estrogen receptors (ER), compared to HGSC. Our hypothesis is that estrogen stimulates an increase in the number of leptin receptors on tumor cells. However, further studies are needed to investigate the relationship between

estrogen and leptin expression in ovarian tumor cells.

While no studies have directly investigated leptin's tendency towards specific EOC subtypes, research using body mass index (BMI) suggests a correlation between obesity and low-grade serous ovarian carcinoma. This type of cancer is generally considered indolent and well-differentiated, but also more resistant to chemotherapy.[11,12,42-44] In cases of endometrial carcinoma, the influence of obesity also predominates in type I carcinoma which has good tumor differentiation and a better prognosis.[20,26]

In summary, overexpression of leptin is linked to a poor prognosis in ovarian cancer. This is because leptin promotes several processes that enable cancer progression, including migration and metastasis of cancer cells, angiogenesis (the formation of new blood vessels that nourish tumors), epithelial-to-mesenchymal transition (a cellular shift that enhances invasiveness) (44), and degradation of the extracellular matrix (the network that provides structural support to tissues). However, several studies have found the leptin paradox phenomenon among various cancers. The obesity/leptin paradox is a phenomenon in which a cancer population has a significantly better prognosis when the body mass index is more than normal, when the opposite would be expected.[25,26] This phenomenon applies to several types of cancer, including ovarian cancer.[24]

The analysis of the entire serous carcinoma population revealed a significant correlation (p-value = 0.047) between leptin expression and metastasis incidence. Interestingly, 90.63% of ovarian carcinoma patients without metastases had strong leptin expression on tumor cells, compared to only 68.89% of those with metastases who had strong leptin expression (Table 4). This suggests a potential protective role of leptin, with an odds ratio (OR) of 0.23 for reduced metastasis risk. However, it's important to consider the heterogeneity of epithelial ovarian cancer (EOC) (7). High-grade and low-grade serous carcinomas are distinct entities with different biology and molecular characteristics. When analyzing the high-grade population specifically, no significant association was found between leptin expression and either protection from metastasis (p-value = 0.193) or lymphovascular space invasion (LVSI) (p-value = 0.341). This suggests a potential "pseudo-leptin paradox" effect in this study, likely influenced by the inclusion of low-grade serous carcinoma samples, which rarely metastasize.

Overexpression of leptin has been associated with a better prognosis in various cancers, including colorectal carcinoma,[27]hepatocellular carcinoma, pancreatic cancer,[25] and ovarian cancer.[24] Studies on nonmucinous colorectal adenocarcinoma have revealed that strong leptin expression in tumor cells is associated with a more favorable prognosis, characterized by lower depth of invasion, less frequent nodal metastasis, better tumor differentiation according to the American Joint Committee on Cancer (AJCC) and Dukes' staging systems, and significantly improved overall and disease-free survival rates.[27] Conversely, studies on ovarian carcinoma have yielded conflicting results. One previous study found that high leptin expression is associated with good prognosis, characterized by a lower chance of LVSI and significantly improved disease-specific survival (DSS) and disease-free survival (DFS) in ovarian cancer patients.[24] While other studies have demonstrated that leptin can activate intratumoral proliferation pathways such as the Janus kinase 2 (JAK2)[19] and RHOA/ROCK pathways,[39] stimulate migration and invasion,[18] and most critically, drive epithelial-mesenchymal transition (EMT).[44]

The results of the colorectal adenocarcinoma study are considered more reliable due to the more homogeneous characteristics of the sample population. In contrast, many ovarian cancer studies have overlooked the significant heterogeneity of epithelial ovarian cancer. For example, the study by other researchers included all types of ovarian cancer, encompassing both epithelial ovarian cancer (EOC) and non-epithelial ovarian cancer. Previous research has shown that only EOC is linked to obesity.[11,12,45] Furthermore, EOC itself has six different tumor types, each with unique molecular characteristics and behavior.[2,7,8] Notably, even serous carcinoma includes two distinct entities: HGSC and LGSC, which have opposite clinical courses. This reflects the heterogeneity of

ovarian cancers. Combining these entities, or including other ovarian tumor types, can introduce bias and potentially lead to misleading results. The results of leptin analysis in previous ovarian cancer studies may be confounded by the presence of several ovarian carcinoma subtypes with indolent characteristics that tend to be confined to the ovary.

Despite the heterogeneity of the sample, the underlying mechanism for this "leptin paradox" remains unclear. However, one hypothesis suggests that overweight or obese individuals might have larger energy reserves, leading to a longer survival even with cancer. Additionally, leptin might activate tumor-infiltrating lymphocytes (TILs), promoting anti-tumor immunity.[46] Our findings do not support the existence of a "leptin paradox" within the high-grade serous carcinoma population. Conversely, low-grade serous carcinomas exhibited unexpectedly strong leptin immunostaining. Based on these observations, we conclude that leptin expression correlates with well-differentiated serous ovarian carcinoma. Therefore, further studies are necessary to specifically investigate the role of leptin expression in low-grade serous carcinoma in order to evaluate the potential metastasis, invasion, prognosis and its impact on chemoresistancy .

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CONFLICT of INTEREST

The authors declare no conflicts of interest, financial or otherwise.

CONCLUSION

High-grade serous carcinoma shows no association between leptin expression and the occurrence of metastasis or lymphovascular space invasion. The conflicting findings on leptin in previous ovarian carcinoma studies (leptin paradox) might be due to the inclusion of samples with heterogeneous characteristics. Notably, leptin expression is higher in ovarian carcinomas with less aggressive features, such as low-grade serous carcinoma. Thus, including these two distinct tumor types (HGSC and LGSC) within the same study group can bias the results. Future research on leptin in ovarian carcinoma should utilize homogeneous samples to ensure reliable outcomes.

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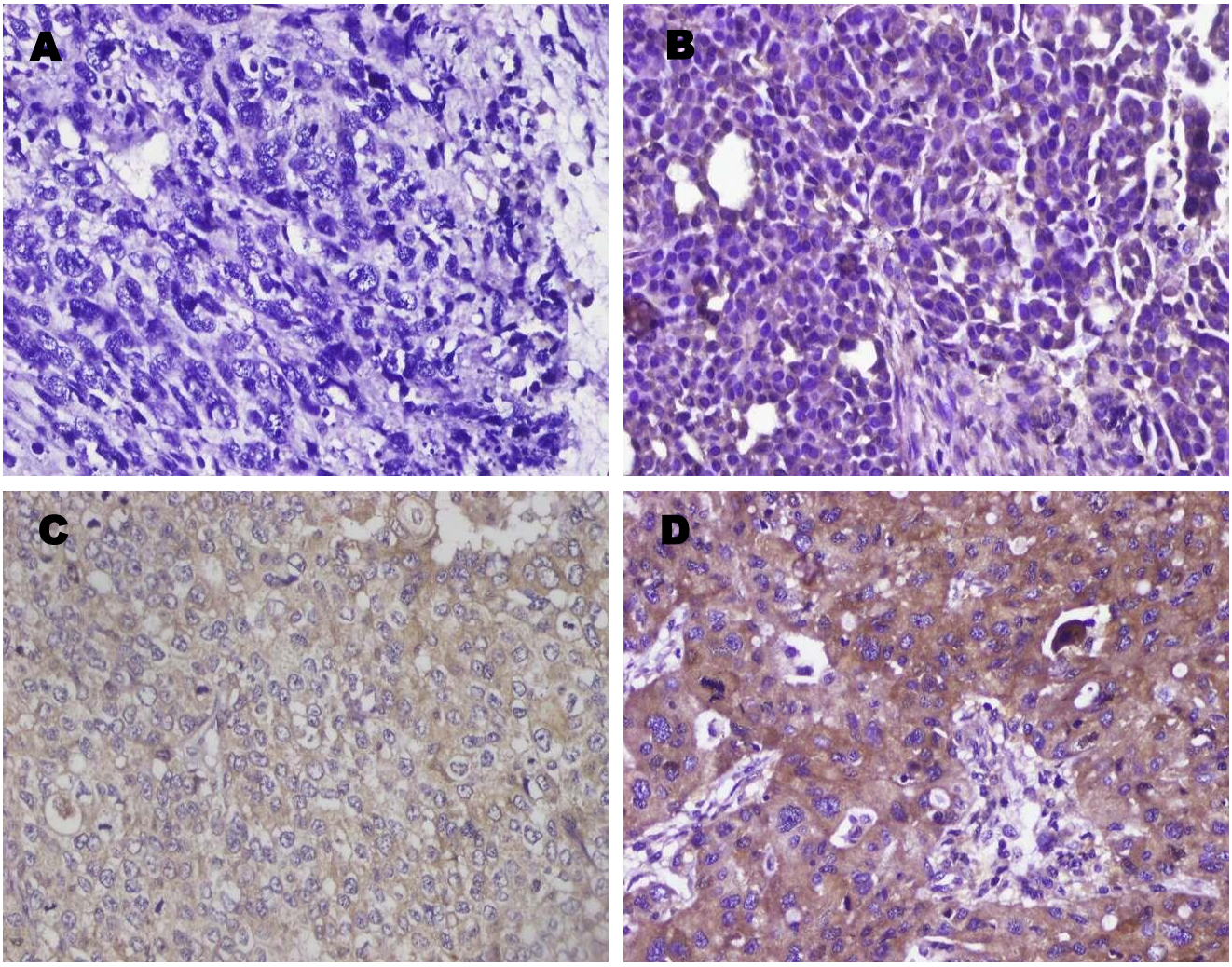

Figure 1. Leptin immunohistochemical staining in high-grade serous carcinoma. Leptin protein was expressed in the cytoplasm of tumor cells with varying intensity ranging from A Negative, B Weak, C Moderate, D Strong.

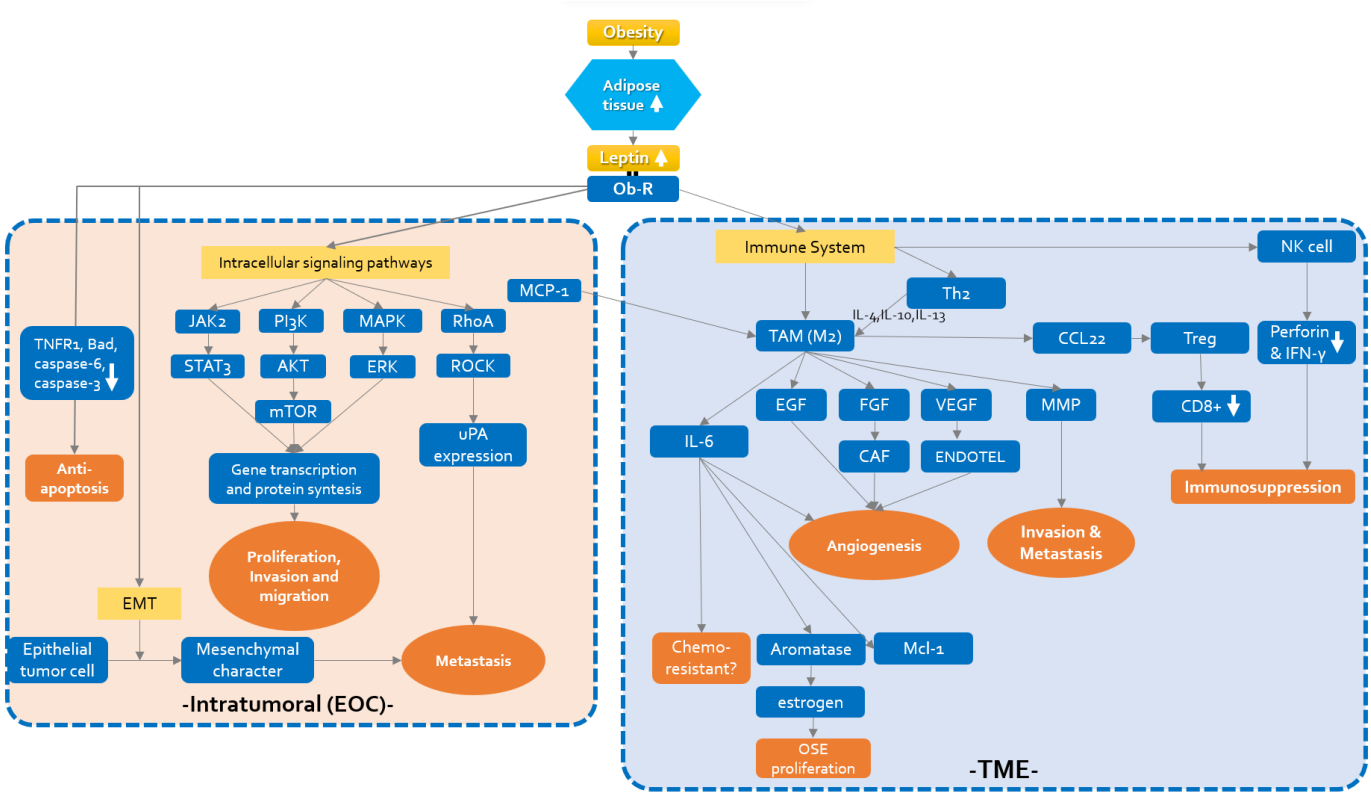

Figure 2. Role of leptin in the carcinogenesis of epithelial ovarian cancer.
CAF: Cancer-associated fibroblast, CCL22 : Chemokine (C-C Motif) Ligand 2, EGF: Epidermal growth factor, EMT: Epithelial–mesenchymal transition, IFN-γ : Interferon - Gamma MAPK/ERK: Mitogen Activated Protein Kinase/ Extracellular-Signal-Regulated Kinase Pathway, JAK2: Janus kinase 2, MCP1: Monocyte Chemoattractant Protein 1, MMP: Matrix metalloproteinase, NK cell: Natural Killer cell, Ob-R: Leptin receptor, PI3K: Phosphatidylinositol 3-kinase, Rhoa/ROCK : Ras Homolog Family Member A/ Rho-Associated, Coiled-Coil Containing Protein Kinase Pathway , STAT3: Signal transducer and activator of transcription 3, TME: Tumor microenvironment, TAM: Tumor-associated macrophages, uPA: Urokinase Plasminogen Activator , VEGF: Vascular endothelial growth factor

Table 1. Subject Characteristics

Variables	n(%)	HGSC (N=56)	LGSC (N=21)	P-value*
Age (Year)				
<50	32 (41.6)	20 (35.7)	**12 (57.1)**	0.150
>50	45 (58.4)	**36 (64.3)**	9 (42.9)	
IMT				
Underweight	12 (15.6)	9 (16.1)	3 (14.3)	0.961
Optimal	31 (40.3)	22 (39.3)	9 (42.8)	
Overweight/Obesity	31 (40.3)	**22 (39.3)**	**9 (42.8)**	
Missing	3 (3.9)	3 (5.4)		
LVSI				
Yes	27(35.1)	20 (35.7)	7 (33.3)	1.000
No	50 (64.9)	**36 (64.3)**	**14 (66.7)**	
Metastasis				
Yes	46(60)	**40 (71.4)**	5 (23.8)	**0.000**
No	31(40)	16 (28.6)	**16 (76.2)**	
Necrosis				
Yes	44 (57.1)	**40 (71.4)**	4 (19)	**0.000**
No	33 (42.9)	16 (28.6)	**17 (81)**	
Leptin Expression				
High	60 (77.9)	**39 (69.6)**	**21 (100)**	**0.004**
Low	17 (22.1)	17 (30.4)	0 (0)	

Chi-square test

Table 2. Analysis of the Relationship Between Body Mass Index and Leptin Protein Expression in Serous Ovarian Carcinoma

Leptin Expression	BMI			Total	P value*
	Underweight	Optimal	Overweight/ obesity		
	(%)	(%)	(%)		
Low	5 (41.7)	7 (24.1)	3 (9.7)	15	***0.059***
High	7 (58.3)	24 (75.9)	28 (90.3)	59	
Total (%)	12 (100.0)	31 (100.0)	31 (100.0)	74	

**** Pearson Chi-square***

Table 3. Leptin Expression and LVSI in Serous Ovarian Carcinoma: A Comparison Between Overall and High-Grade Serous Tumors

Leptin expression	Serous Ovarian Carcinoma				OR 95% CI	P-value*	High-grade Serous Carcinoma				OR 95% CI	P-value*
	No LVSI		LVSI				No LVSI		LVSI			
	n	%	n	%			n	%	n	%		
Low	13	26.00	4	14.81	2.020 (0.587-6.951)	0.4	13	36.11	4	20	2.261 (0.623-8.21)	0.341
High	37	74.00	23	85.19			23	63.89	16	80		
Total	50	100	27	100			36	100	20	100		

Chi-square test

Table 4. Leptin Expression and Metastasis in Serous Ovarian Carcinoma: A Comparison Between Overall and High-Grade SerousTumors

Leptin expression	Serous Ovarian Carcinoma				OR 95% CI	P-value *	High-grade Serous Carcinoma				OR 95% CI	P-value *
	No Metastasis		Metastasis				No Metastasis		Metastasis			
	n	%	n	%			n	%	n	%		
Low	3	9.38	14	31.11	0.229 (0.060-0.880)	**0.047**	3	18.75	14	35	0.429 (0.104-1.762)	0.193
High	29	90.63	31	68.89			13	81.25	26	65		
Total	32	100	45	100			16	100	40	100		

Chi-square test

Initial Management of Acute Pulmonary Edema in Pre-Eclampsia: A Case Report

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ABSTRACT

Objective: Describe the initial management for acute pulmonary edema in pre-eclampsia.
Methods: A case report.
Case: 41-year-old woman, G5P4A0, unknown gestational age, admitted with headache, dyspnea, and unconsciousness. The patient denied a history of past illness. Crisis hypertension, tachypnea, tachycardia, low oxygen saturation, audible lung crackles, pretibial edema, and 3+ proteinuria were found on examination, consistent with the diagnosis of pre-eclampsia with severe features. For initial management of acute pulmonary edema, the patient was given oxygen with Jackson-Rees bagging and furosemide injection, while nicardipine drip and MgSO4 injection were also given to treat pre-eclampsia. After the right initial management, patient was fully conscious, stable, then treated in the intensive care unit using non-invasive positive pressure ventilation. The patient underwent vaginal delivery and gave birth to male, BW 2900gram, BL 47cm, APGAR 3/8.
Discussion: Initial emergency management focuses on providing adequate oxygen is the main management of pulmonary edema in preeclampsia. A non-invasive positive pressure ventilation is required as the main flow of oxygen delivery because it's not invasive and is more convenient. Additional therapy such as diuretics, antihypertensive, and anticonvulsant are also needed. Close monitoring in the intensive care unit was also required for best results.
Conclusion: Initial management of acute pulmonary edema in pre-eclampsia patients should be done correctly, consequently decreasing maternal and perinatal morbidity and mortality.
Keywords: pregnancy, pre-eclampsia, pre-eclampsia with severe features, pulmonary edema.

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Introduction

Preeclampsia is one common complication in pregnancy and causes 10-15% of morbidity and mortality in pregnant women.[1] Based on the American College of Obstetricians and Gynecologists, severe preeclampsia or preeclampsia with severe features specifically defined as new hypertension presenting after 20 weeks with significant systolic blood pressure 160 mmHg or more or diastolic blood pressure 110 mmHg or more on two examinations at least 4 hours apart accompanied by massive or absence of proteinuria, or thrombocytopenia <100 x 10^9/L, or progressive renal insufficiency showed by serum creatinine >1.1mg/dL, or an impaired liver function showed by elevated in transaminases concentration, or the presence of pain in epigastric region or right upper

abdominal region, or the presence of pulmonary edema or neurological symptoms.[2]

One of the complications that occur in severe preeclampsia is acute pulmonary edema, with an incidence rate of only about 0.08%[3] and it's the leading cause of death in women with pre-eclampsia.[4] Pulmonary edema in patients with preeclampsia is a life-threatening condition, increasing mortality and morbidity in both maternal and perinatal, therefore the management of preeclampsia patients with pulmonary edema is important and must be carried out appropriately.[5]

Methods

This is a case report about 41-year-old woman with pulmonary edema as a severe feature of pre-eclampsia. The patient was initially treated in the emergency unit and after stabilized patient was transferred to the intensive care unit, patient then underwent vaginal delivery to a healthy baby. This case report is important because most publications on this topic only explain the maternal and perinatal outcomes without explaining the initial management that led to a good outcome.

Case Report

Woman, 41-year-old, G5P4A0, unknown gestational age, presented to the emergency room (ER) with sudden onset of headache, difficulty of breathing, and unconsciousness. The patient had no other complaints, never had a pregnancy checked, denied a history of similar complaints in a previous pregnancy, and denied a history of past illness. Initial examination, the patient appeared somnolence ($E_3M_5V_2$) and dyspneic, blood pressure (BP) was 210/120mmHg, heart rate (HR) was 104 beats/minute, respiratory rate (RR) was 32 times/minute, oxygen saturation was 56% in room air, and had normal temperature 36.6°C. On physical examination, audible lung crackles, bilateral pretibial edema, and normal patellar reflexes were found, BMI was 27.7 kg/m2 before pregnancy marked an obesity grade I based on the Asia-Pacific category. On obstetric examination, no uterine contractions were found, fundal height was 34cm, Leopold's examination showed breech presentation and pelvic examination marked 1 cm dilatation without a bloody show. Fetal heart sound was detected at 110x/minute by Doppler, marked fetal bradycardia. On laboratory examination, routine blood tests, liver function (AST and ALT), BUN, and creatinine were found normal. Urine dipstick showed proteinuria (3+). The patient was suspected with acute pulmonary edema as a severe feature of pre-eclampsia and fetal distress.

Initial emergency management focuses on providing adequate oxygen to the patient. We first used a non-rebreathing mask with 15 l/m, but the oxygen saturation did not increase so it was replaced with a bag-valve-mask, the oxygen saturation increased to 69-70% but the patient's consciousness remained somnolence $E_3M_5V_2$, which we then replaced with Jackson-Rees bagging, oxygen saturation increased to 92-93%. While the patient was receiving adequate oxygenation, a Foley catheter placed, 250 ml of urine was collected and an intramuscular injection of 5 g $MgSO_4$ was administered into the right and left buttocks.

After intravenous (i.v.) access was obtained, furosemide 40 mg injection was administered to reduce fluid overload, maintenance of 6 g $MgSO_4$ in Ringer's lactate solution was administered to prevent convulsions, 6

mg of dexamethasone injection was given to fetal lung maturation, and nicardipine at a 5 mg/hour was also administered using a syringe pump to reduce the blood pressure.

Following 30 minutes of Jackson-Rees bagging and i.v. injection therapy, oxygen saturation stabilized at 93-94%, patient's level of consciousness was raised to apathetic $E_3M_6V_4$, and oxygen administration was replaced using a 15 m/l non-rebreathing mask. The patient was stabilized for another hour in the ER, the patient was then concious $E_4M_6V_5$, BP was 147/89mmHg, HR was 97x/m, RR was 30x/m, and O_2 saturation was 91%. Urine collected was approximately 700ml, which showed urine output was exceeded 0.5/hour. The patient was transferred to the intensive care unit (ICU) for further stabilization using non-invasive positive pressure ventilation (NPPV). After 30 minutes in the ICU, a cardiotocography (CTG) was performed and showed a non-reassuring category II result. The patient was then positioned on her left side and an emergency cesarean section was planned. CTG was not repeated after that.

Due to the limited number of obstetricians, the emergency cesarean section has been postponed. Seven hours later, the patient complained of strong and regular contractions with a discharge from the birth canal. Obstetric examination revealed an 8 cm dilatation, a non-intact amniotic membrane with clear amniotic fluid, and bloody mucus. She gave birth to a male, weighing 2900 grams, 47cm body length, APGAR 3/8/9, New Ballard Score equal to 36 weeks of physical maturity, and treated to level II special care nursery room.

One day after delivery, the patient underwent an echocardiography and chest X-ray. Her systolic ejection function was 52.6%, and she had moderate pulmonary edema. She was treated in the ICU using NIV for the next 2 days. While in the ICU, vital signs, fluid balance, and urine output were closely monitored. A negative fluid balance was established by restricting the patient's drinking and intravenous fluids to remove excess fluid while maintaining a urine output of > 0.5ml/hour. Treatment of furosemide intravenously was continued 20mg twice/day with additional administration of candesartan 8mg/day, amlodipine 10mg/day, cefadroxil 500mg 2x/day, mefenamic acid 3x/day, while the use of dexamethasone, $MgSO_4$, and nicardipine were stopped. Afterward, the patient was treated in the hospital ward for another 2 days, then in the outpatient care with a stable condition.

Discussion

Preeclampsia is a multi-system disorder in pregnancy characterized by new-onset hypertension and organ failure after 20 weeks of gestation. Until now the pathophysiology of pre-eclampsia is very complex and unknown. The main hypothesis for the cause of pre-eclampsia is the failure of re-modeling of the spiral arteries which was initiated due to impaired penetration of the cytotrophoblast into the spiral artery muscle layer, causing placental dysfunction that releases pro-inflammatory factors and angiogenic proteins in the maternal circulation and leads to systemic endothelial disturbance.[6] Several risk factors such as nulliparous patients, aged > 40 years, multiparas with a previous history of pre-eclampsia or a history of chronic disease, multiple pregnancies, obesity before pregnancy, or pregnancies > 10 years apart are often associated with pre-eclampsia.[7]

Preeclampsia is also characterized by an organ failure,

including the cardiovascular system. Complications in the cardiovascular system that can be found are heart failure, stroke, and pulmonary edema. Acute pulmonary edema is a rare complication in pre-eclampsia with an incidence rate of only 0.08%.[5] Some factors that increase the risk of pulmonary edema in preeclampsia include pregnancy at an advanced age, obesity, receiving tocolytic therapy, having a history of heart problems before pregnancy, and administering too much fluids in the treatment of pre-eclampsia.[3]

Acute pulmonary edema caused by preeclampsia is defined as acute respiratory distress that occurs during pregnancy or within the first 45 days after delivery, and more often occurs before birth compared to after birth. It is characterized by sudden shortness of breath, moist crackles, desaturation, and an X-ray examination that describes pulmonary edema. The pathophysiology underlying the development of acute pulmonary edema in preeclampsia is due to increased plasma volume or cardiac output and decreased plasma colloid osmolarity or osmolality during pregnancy.[8] There is also an increase in peripheral vascular permeability and peripheral vascular resistance in preeclampsia which increases after-load.[9] Diagnosis of acute pulmonary edema requires echocardiography which is later used to differentiate between cardiogenic and noncardiogenic causes. In noncardiogenic acute pulmonary edema, echocardiography results usually do not reveal any abnormalities and preeclampsia is usually the cause.[8]

The most important initial management of acute pulmonary edema caused by preeclampsia is giving adequate oxygen, fluid restriction, and lowering blood pressure with intravenous antihypertensive agents, such as beta-blockers (labetalol), diuretics (furosemide), vasodilators (nitroglycerin, hydralazine), or using calcium channel antagonists (nicardipine, nifedipine).[5,9] Additionally, fluid therapy in preeclampsia is still needed to maintain fluid and electrolyte balance or replace lost intravascular volume, but it should be restricted. The recommended administration is approximately 60-80 ml/hour, with urine output, stool, and insensible loss calculated and monitored based on clinical observations.[9]

According to ESC guidelines for acute pulmonary edema, three commendable treatments exist. First, oxygen should initially be administered as continuous positive airway pressure, non-invasive positive-pressure ventilation (NPPV), or high-flow nasal cannula (HFNC). Second, i.v. diuretics is needed. Last, if systolic BP is high, an i.v. vasodilators can be given.[10] NPPV (non-invasive positive pressure ventilation) is required as the main flow of oxygen delivery because it's not invasive, compared to HFNC, NPPV/NIV is more convenient because of its ability to heat and humidify the gas.[11] In several studies that have been conducted, administration of NPPV during pregnancy can prolong gestation with better neonatal outcomes and its use improves oxygenation and pH, decreases the work of breathing and partial pressure of carbon dioxide, and also prevents intubation.[12,13]

Giving MgSO4 in preeclampsia with acute pulmonary edema is still a debate. MgSO4 has benefits as anti-eclampsia and neuroprotective for the fetus, but the use of MgSO4 in pre-eclampsia patients increases the risk of acute pulmonary edema. However, if the administration of MgSO4 provides benefits outweigh the consequences,

then MgSO4 can be administered under close monitoring.[14]

Acute pulmonary edema causes acceleration of birth, which causes an increase in the rate of prematurity, neonatal morbidity and mortality, and neonatal asphyxia with the need for neonatal resuscitation.[8] Termination of pregnancy is the only treatment for preeclampsia. Patients with preeclampsia with severe features are delivered immediately to prevent maternal and fetal complications.[4] As per ACOG, preeclampsia with severe features at or beyond 34 0/7 weeks must undergo delivery after maternal stabilization and should not be delayed to allow steroid administration.[13] Although in the case of preeclampsia with severe features, labor induction can be performed using prostaglandin or an osmotic dilator. However, if vaginal delivery is not successful or attempts failed, then cesarean delivery is indicated.[4]

A retrospective case-control study found in a referred hospital in Indonesia concluded that pulmonary edema increased the morbidity and mortality for the maternal and perinatal, and major cases needed intensive care and even mechanical ventilation support[15]. Another literature review found also concluded that acute pulmonary edema is a medical emergency so an emergency response must be initiated[16]. NPPV should be tried as an initial treatment before tracheal intubation to maintain adequate oxygenation and ventilation. An i.v. furosemide (20-40 mg) is also used for venodilation and diuresis, and an i.v. antihypertensive agent such as nitroglycerin starting 5 μg/min is necessary to reduce high blood pressure. High-dependency care and close observation are essential and should be carried out by a multidisciplinary team.

Conclusion

Acute pulmonary edema as a severe feature of preeclampsia is quite rare but it's the leading cause of death in preeclampsia. It also has a high risk of maternal and neonatal morbidity and mortality. Giving an adequate oxygenation is the most important initial management, and additional treatment such as diuretics, anti-hypertensive, anti-convulsion, and fluid restriction can provide a good outcome which consequently reducing morbidity and risk of mortality on the patient and perinatal.

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Figure 1. Cardiotocography in the ICU showed a non-reassuring category II result

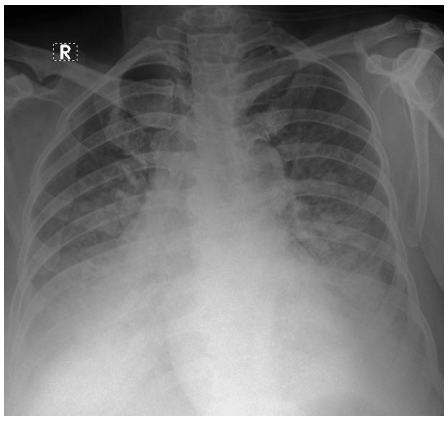

Figure 2. Postpartum Chest X-ray showed moderate pulmonary edema

Case Report

From Diagnosis to Management: A Rare Case of Disseminated Low-Grade Endometrial Stromal Sarcoma with Extensive Extrauterine Spread

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Abstract
Objective: To report a rare case of low-grade endometrial stromal sarcoma; which was found not only in the uterus but also in several extrauterine sites, such as the ovary, omentum, and jejuno-ileum. In this article, we provided the management performed, based on appropriate literatures.
Methods: Case report.
Case: A 44-year old para 2 complained of abdominal enlargement since 3 months. Patient also complained of pelvic pain. The patient has never received treatment before and has never been diagnosed with endometriosis. Abdominal examination revealed a 20-cm mass in the lower to umbilical region and positive shifting dullness. Bimanual pelvic examination revealed immobile and smooth masses in both sides of adnexa, with pain during palpation. Computerized tomography (CT) scan of the abdomen revealed complex cystic masses suspected for right and left ovaries-origin (±11 & 15 cm respectively) Surgical resection and staging, frozen section, cytology examination, and immunohistochemistry (IHC) test were performed, revealing consistent result of endometrioid stromal sarcoma, low grade. Five-months postoperative follow-up through abdominal CT-scan in the patient revealing no abnormalities.
Conclusion: We know that LG-ESS is one of the rare types of endometrial stromal sarcoma. Moreover in this case extrauterine manifestations make it more challenging in clinical management. Risk factors and history of endometriosis are important to explore when meeting ESS cases. Further research needs to be done regarding the exact mechanism and the association between endometriosis or other risk factors and the development of ESS, especially the EESS type to allow intervention.

Keywords: endometrial stromal sarcoma, management, uterine sarcoma

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INTRODUCTION

Endometrial stromal sarcoma (ESS) is a type of mesenchymal tumor, which accounts for about 0.2% of uterine malignancies and approximately 15% of uterine sarcomas.[1] ESS is studied to be the second most common type of uterine mesenchymal neoplasia, after uterine leiomyosarcoma. This type of sarcoma is typically found in the uterus, but also can be found in some extrauterine sites, including in the bowel wall, pelvic structures, peritoneum, vagina, and the ovary.[2,3] However, greater number of extra-uterine endometrial stromal sarcoma (EESS) cases presented are confined to the ovaries. Some references are also conventionally using the term “endometrioid stromal sarcoma” to define extrauterine endometrial stromal sarcoma.[3,4]

Patients with endometrial stromal sarcoma typically complain with enlargement of the abdomen, vaginal bleeding, or even pelvic pain.[3] The World Health Organization (WHO) simply classifies endometrial stromal neoplasms as benign endometrial stromal

nodule (ESN) and ESS. The main difference in this classification is that in ESN, there is no infiltration of myometrium, whereas in ESS it's the other way around. ESS itself is classified into low-grade endometrial stromal sarcoma (LG-ESS) or high-grade endometrial stromal sarcoma (HG-ESS) based on cell morphology and mitotic count.[5]

In the past decade, endometrial stromal sarcomas of the uterus are quite notable and some related guidelines have been made. However, clinical and scientific experience with ESS with primary lesions in the ovary is limited since they are quite rare. We report a case of a patient with low-grade endometrial stromal sarcoma that was found in both uterus and several extrauterine sites (primarily arising from both ovaries) managed with surgical resection.

CASE

A 44-year old Asian para 2 came to the obstetrics and gynecology outpatient clinic with the chief complaint of abdominal enlargement since 3 months prior to admission. The patient also complained of pelvic pain with numerical pain rating scale (NPRS) 5. The pain was felt both during and outside the menstrual cycle and had gotten worse in the last 2 weeks. The patient has never received treatment for this complaint and has never been diagnosed with endometriosis before. Weight loss, abnormal bleeding, abnormal vaginal discharge, dyschezia, painful urination, bloody stool, difficulty in defecating, and other complaints were all denied. History of hepatitis, hepatic cirrhosis, irritable bowel syndrome, malignancy, or other systemic diseases were also denied.

On physical examination, the general condition and vital signs were within normal range. The patient's anthropometric measurement was also considered to be normal. On abdominal examination, the percussion revealed dullness and a mass was palpable in the lower region up to the umbilical region, with positive shifting dullness and a diameter of approximately 20 cm. There was pain and tenderness during deep palpation of the mass. Enlargement of lymph nodes in the neck, axillary, or inguinal was not found in this patient. Clinical gynecologic examination revealed normal condition of vulvovaginal and portio. There was no fluor albus, blood or active bleeding, abnormal vaginal discharge, mass, inflammation, or erosion found during examination. Bimanual pelvic examination revealed masses in both sides of adnexa, immobile, with smooth surface, and pain on palpation

Laboratory examination parameters were all within the normal limit. Abdominal computerized tomography (CT) scan with contrast was performed, revealing complex cystic masses suspected for right and left ovaries-origin (±11 & 15 cm respectively) that extend into the abdominal cavity, pushing the intestinal cisterns cranially, and pressing the uterus inferiorly (highly suspicious of malignancy). Infiltration to the anterosuperior wall of the urinary bladder and left distal ureter was suspected. Ascites and multiple peritoneal seeding nodules were also found. CT scan also revealed some findings such as mild bilateral pleural effusion especially on the right, signs of adhesion, mesenteric mass and adenopathy (suspected of metastasis), mild hepatosplenomegaly, suspected intramural uterine myoma, and thickening of left aspect mesentery with fat stranding suspected of metastasis. No abnormality was found in the pancreas, aorta, bilateral kidney, psoas muscles, or rectum. Tumor marker CA-125 result on this patient was about 348.1 U/mL, highly increased from the normal limit of <35 U/mL.

Multidisciplinary surgical resection and staging were performed on this patient by gynecologic oncologist and digestive surgeon, with estimated operation duration for about 3 hours. Incision was performed in the midline up to approximately 2 cm above the umbilicus. Ascites as much as 1000 cc was found and about 20 cc was taken for cytological examination. A 20 cm cystic mass from the left ovary was found attached to the rectosigmoid; adhesiolysis was carried out. The cyst ruptured and came out as much as

700 cc of brown fluid; adhesiolysis was continued. Left salpingo-oophorectomy was performed and tissue specimen was sent for frozen section. The uterus enlarged to a size of 15 x10 x 10 cm and total hysterectomy and right salpingo oophorectomy were performed. During exploration, impression of an omental cake was found, so a total omentectomy was performed. No enlarged pelvic and paraaortic lymph nodes were found. The peritoneum, liver, and spleen are smooth. Further exploration revealed a mass in the mesentery and ileum. Digestive surgeons identified that the small intestine was occluded by a mass in the mesojejunoileal approximately 50 cm from the ligament of Treitz to the oral and 100 cm distal to the ileocecal valve. Resection was performed at 40 cm from the Treiz ligament and 90 cm from the ileocecal valve and then a side-to-side jejunoileal anastomosis was performed. Bleeding during the surgical procedure was approximately 400 cc.

Frozen section examination revealed the cyst was lined with granulation tissue (hemosiderophages). On the solid part, endometrial stroma and glands were partially separated by fibrotic connective tissue. Conclusion of the frozen section diagnosis in the form of endometrial cyst with stromal hyperplasia. Cytology examination from ascites specimens revealed reactive mesothelial cells, leukocytes, macrophages, and glandular structures lined with simple thoracic epithelium with minimal nuclear atypia. Conclusion of the cytology examination compatible with endometriosis.

Immunohistochemistry (IHC) examination was performed, revealing positive CD10, positive CD34 on connective tissue and vascular vessel walls, and 5% positive KI67. Estrogen receptors (ER) and progesterone receptors (PR) were also positive, while CD117 and DOG1 were both negative. IHC examination is consistent with an endometrioid stromal sarcoma, low grade.

Follow-up examination in this patient through abdominal CT scan was performed 5 months after surgery. No residual mass, pleural effusion, ascites, or enlarged lymph nodes were found. No mesenteric mass or ileus sign was seen anymore. Other structures were found to appear normal.

DISCUSSION

As mentioned above, uterine sarcoma is a diverse group of rare tumors in the uterine connective tissue and musculature. According to the current World Health Organization (WHO) classification, they are distinguished from malignant mixed epithelial-mesenchymal tumors and malignant mesenchymal tumors. It classified uterine sarcomas into leiomyosarcoma, low-grade endometrial stromal sarcoma (LG-ESS), high-grade endometrial stromal sarcoma (HG-ESS), undifferentiated uterine sarcoma (UUS), rhabdomyosarcoma, adenosarcoma, and malignant-type perivascular epithelioid cell tumor 6,7. In the latest WHO classification published in 2014, LG-ESS is classified as an endometrial stromal tumor along with benign endometrial stromal nodule (ESN), HG-ESS, and UUS. ESS is staged along with uterine leiomyosarcoma according to the FIGO and TNM classifications.[7,8]

Symptoms of a patient with ESS are unspecific, with abnormal uterine bleeding being one of the most common symptoms related. Other symptoms include abdominal or pelvic mass, pain, and gastrointestinal symptoms. Some of them may be asymptomatic.[9–11] Most frequent manifestations of EESS are abdominal or pelvic pain, mass, gastrointestinal symptoms and vaginal bleeding.[4] In this case, the patient only complained of abdominal enlargement and pelvic pain, while other symptoms were denied. ESS occurs primarily in premenopausal and perimenopausal women, ranging between 45 to 55 years of age. Compared to HG-ESS, the age group of LG-ESS is typically younger.[9] Our patient presented at 44 years, which is similar to the common age group. The exact pathogenesis of these tumors is yet to be determined, but some identified risk factors for ESS are long-term tamoxifen use, unopposed estrogen use, and past exposure

to pelvic radiation therapy. However, those were not found in this patient. But again, the patient is suspected to have a history of endometriosis based on the cytology examination, which has not been previously diagnosed. This condition could be related to her current condition, as 30 out of the 63 EESS cases in one series had endometriosis.[4] Extrauterine low-grade endometrial stromal sarcoma is supposed to derive from endometriosis, as most reported cases of EESS were associated with foci of endometriosis. [1,11]

In this patient, extreme and unexplained weight loss in the past months was not found. Ascites that were suspected from positive shifting dullness during physical examination, could also be confirmed from abdominal CT scan. CT findings showed that the masses were large enough, suspected for the ovaries-origin, extending into the abdominal cavity, and pushing other structures nearby. Metastasis was also suspected in this patient considering there was mesenteric mass and adenopathy, thickening of left aspect mesentery with fat stranding, and also multiple peritoneal seeding nodules. Regardless of these findings during abdominal CT scan examination, no gastrointestinal or EESS symptoms were found in this patient. In contrast to carcinomas of the endometrium, a diagnosis of LG-ESS cannot be securely determined using hysteroscopy and fractional curettage. Moreover, a clear distinction from benign ESN can only be reliably determined after histological analysis of the tumor's entire interface with the neighboring myometrium.[12,13] Analysis of the patient's specimens in this case was performed through frozen section, cytology, and IHC examination. Immunohistochemistry test results showed a matched and consistent findings of endometrioid stromal sarcoma, low grade. This can be seen on positive CD10, ER and PR, which is usually negative in high-grade ESS cases and is typically varied/heterogeneous in undifferentiated uterine sarcoma. Differences of the low-grade ESS, high-grade ESS, and undifferentiated uterine sarcoma can be seen in the figure below.[14]

Preoperative tumor marker CA-125 level in this patient was extremely high, which was 348.1 U/mL from the normal range of less than 35 U/mL. CA-125 is an antigenic tumor marker which is commonly expressed by the epithelial ovarian neoplasms and other tissues such as cells lining the endometrium, fallopian tubes, pleura, peritoneum, and pericardium. It is carried out when suspecting ovarian neoplasm and is also used in monitoring patients that have already been diagnosed with epithelial ovarian cancer. CA-125 level in this patient was markedly increased probably because the sites of the ESS involved the ovaries and other extrauterine sites that expressed this marker. It was not measured anymore after the surgery in this patient since it is not a specific marker for endometrioid stromal sarcoma. This test has limited utility in diagnosing the early stage of ovarian cancer, owing to its low sensitivity. The specificity is particularly low in premenopausal women; thus, it is most useful in postmenopausal women.[15,16]

Based on the recommendation of the German guideline Sarcoma of the Uterus (DGGG and OEGG, 2019), the treatment of choice for LG-ESS must consist of complete resection of the uterus (total hysterectomy) without morcellation but with complete bilateral resection of the adnexa.[14] In this patient, surgical resection and staging have been done, including total hysterectomy and complete removal of bilateral adnexa, which has been done in accordance with the latest guideline.

There is much evidence regarding the endocrine dependence of LG-ESS. A retrospective study of 153 patients with LG-ESS found a significantly increased rate of recurrence when the ovaries of premenopausal patients were not removed.[17–19] In this patient, bilateral adnexa

were removed considering the risk and higher probability of recurrence. About the oncological safety of hormone replacement therapy after previous primary treatment of a low-grade ESS, there are currently no data. Since the tumor biology of LG-ESS is highly estrogen-dependent, patients should be dissuaded from starting hormone replacement therapy.[20] Prognosis of the patient with LG-ESS is mainly based on the tumor stage. The disease-specific 5-year survival rate for LG-ESS is 80-90% and the 10-year survival rate is approximately 70%. If the tumor is limited only to the uterus at the time of diagnosis, thus the rates are even higher; about 100% and 90%, respectively. The rate drops to 40% for higher stage disease. Positive hormone receptors are a favorable prognostic factor with regard to overall survival. When compared to the high-grade ESS and undifferentiated uterine sarcoma (UES), low-grade ESS has a favorable prognosis. [4,21,22] In this case, tumor sites at the time of diagnosis were already located at several extrauterine sites. Nevertheless, 2 years and 6 months following the surgical procedure there was no complaint or relapse, and overall favorable outcomes could be seen in this patient. However, it is important to keep routine monitoring and follow-up on the patient if signs of recurrence or metastasis appear at any time.

Emerging evidence highlights that adjuvant hormonal therapy can play a pivotal role in preventing recurrence in LG-ESS cases, particularly in hormone receptor-positive tumors.[9, 20] Progestins, such as medroxyprogesterone acetate, and aromatase inhibitors like letrozole, have been shown to stabilize residual disease and improve outcomes.[23] Additionally, multidisciplinary approaches to managing extensive extrauterine involvement—such as combining cytoreductive surgery with targeted therapies—have demonstrated potential for improved survival rates.[24]

CONCLUSION

We know that LG-ESS is one of the rare types of endometrial stromal sarcoma. Moreover, in this case, extrauterine manifestations make it more challenging in clinical management. Risk factors and history of endometriosis are important to explore when meeting ESS cases. Further research needs to be done regarding the exact mechanism and the association between endometriosis or other risk factors and the development of ESS, especially the type of EESS to allow medical intervention. So far, guidelines on ESS management are available, but to the best of the author's knowledge there are no guidelines that specifically address specific management related to EESS, so the management principles are basically still the same. Early diagnosis and increased awareness are important because the patient's prognosis depends on the stage, or the extent to which the disease progresses. In addition, it is also important for clinicians to educate patients diagnosed with ESS about the possibilities that can occur if left untreated, complications, relapse rates, death and survival rates.

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Figure 1. FIGO and TNM stages for leiomyosarcomas and endometrial stromal sarcomas* of the uterus.[9]

FIGO/TNM stage		Definition
I/T1		Tumor limited to the uterus
	IA/T1a	Tumor 5 cm or less in greatest dimension
	IB/T1b	Tumor larger than 5 cm in greatest dimension
II/T2		Tumor extends beyond the uterus, within the pelvis
	IIA/T2a	Involvement of the adnexa (unilateral or bilateral)
	IIB/T2b	Tumor has spread to extrauterine pelvic tissue excluding the adnexa
III/T3		Tumor has infiltrated abdominal tissue
N1	IIIA/T3a	One site
	IIIB/T3b	More than one site
	IIIC	Metastasis of pelvic and/or para-aortic lymph nodes
IV/T4	IVA/T4	Tumor has infiltrated bladder and/or rectum
	IVB	Distant metastasis

*Tumors simultaneously present in the corpus uteri and the ovary/pelvis accompanied by ovarian/pelvic endometriosis must be classified as independent primary tumors.

Figure 2. Summary of the morphology, IHC, and molecular pathology of ESS and UES.[9]