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Editorial

The Existing Facts Regarding the Level of Vitamin D in Pregnant Women in Indonesia

Noroyono Wibowo

Vitamin D serves not only to control and maintain the regulation of essential minerals like calcium and phosphorous in bones but also plays a crucial role in various functions throughout the human body. It is involved in regulating inflammation, free radicals, the immune system, cell proliferation, differentiation, and the prevention of various diseases such as infections, autoimmune disorders, cancer, and metabolic conditions like diabetes and thyroid issues.

Within the field of obstetrics and gynecology, vitamin D is known to play a significant role in conditions like PCO (polycystic ovary), Endometriosis, Ovarian Cancer, Cervical Cancer, Preterm birth, preeclampsia, Gestational Diabetes Mellitus (GDM), and Intrauterine Growth Restriction (IUGR). In essence, vitamin D is a key player in reproductive health. Unfortunately, existing research shows that both pregnant and non-pregnant women in Indonesia generally have insufficient levels of vitamin D, even though comprehensive studies like riskedas have not been conducted yet.

In pregnant women with early-onset preeclampsia, fetal growth delays, or preterm births (both early and late onset), their vitamin D levels are lower compared to those of normal pregnant women.

The human body can naturally produce vitamin D with the help of sunlight, and Indonesia, being located near the equator, receives abundant sunlight. If low vitamin D levels are detected, the possible reasons could include; Pregnant women having insufficient exposure to sunlight at specific times, inadequate intake of pro-vitamin D nutrients, the presence of genetic variations in enzymes responsible for providing active vitamin D, or Vitamin D requirements surpassing intake and production. Research needs to be conducted on these four conditions. However, given Indonesia's vast geographical area, sampling from various regions is necessary, requiring significant efforts and funding.

The initial step involves collecting and reviewing all existing research on vitamin D during pregnancy in Indonesia. Subsequently, a research framework focusing on vitamin D (and nutrients in general) during pregnancy, including preparations up to BioBank level, should be developed. This research framework can then be proposed to Bapenas (National Development Planning Agency).

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Research Article

The Role of Vitamin D in Pregnant Women in Birth Weight of Neonates

Peran Vitamin D pada Ibu Hamil terhadap Berat Badan Lahir Neonatus

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Abstract

Objective: To determine the relationship between serum vitamin D levels in third trimester mothers and newborn birthttweight.

Method: The study was conducted at the maternity ward of Dr. Zainoel Abidin General Hospital in Banda Aceh, Indonesia. Maternal and infant serum vitamin D levels were measured using the Automatic Chemiluminescence Immunoassay Analyzer (CLIA) method. Blood samples were collected from mothers in the third trimester and from infants after delivery. Spearman's correlation rank test was employed with a confidence level of 95%. Vitamin D levels were categorized as sufficient, insufficient, and deficient.

Results: A total of 39 pregnant women with an average age of 30.38 ± 6.21 years participated in the study, with a predominance of 38-39 weeks of gestation (35.9%). The mean vitamin D levels in mothers and neonates were 17.4 ng/mL and 17.6 ng/mL, respectively (p = 0.003, R = 0.462). The average birth weight of the babies was 3,100 grams, ranging from 2,100 grams to 4,200 grams (p = 0.185, R = 0.217). Both variables showed a positive correlation with varying strength of the relationship.

Conclusion: Maternal serum vitamin D levels in the third trimester exhibited a positive correlation with serum vitamin D levels in neonates with moderate strength, but there was no correlation with birth weight. The evaluation of maternal third-trimester serum vitamin D levels can serve as a predictor of neonatal vitamin D levels.

Keywords: birth weight, neonates, pregnancy, vitamin D.

Abstrak

Tujuan: *Untuk menilai pengaruh hubungan kadar vitamin D serum ibu trimester ketiga terhadap kadar vitamin D dan berat badan neonatus yang dilahirkan.*

Metode: *Penelitian ini studi observasional korelatif dengan desain potong lintang yang dilakukan pada kamar bersalin RSUD dr. Zainoel Abidin Banda Aceh. Pengukuran kadar vitamin D serum ibu dan bayi dilakukan dengan metode Automatic Chemiluminescence Immunoassay Analyzer (CLIA). Analisis data dengan melakukan Uji Spearman's correlation rank test untuk menilai kekuatan hubungan dua variabel.*

Hasil: *Sebanyak 39 ibu hamil usia 30,38 ± 6,21 tahun terlibat dalam penelitian ini dengan dominasi usia kehamilan 38–39 minggu (35,9%). Rerata kadar vitamin D ibu dan bayi secara berurutan adalah 17,4 ng/mL dan 17,6 ng/mL (p = 0,003, R = 0,462). Rerata berat badan bayi yang dilahirkan adalah sebesar 3.100 gram dengan rentang 2.100 gram hingga 4.200 gram (p = 0,185, R = 0,217). Kedua variabel didapatkan korelasi positif dengan kekuatan hubungan bervariasi.*

Kesimpulan: *Kadar vitamin D serum ibu trimester ketiga berkorelasi positif terhadap kadar vitamin D serum neonatus yang dilahirkan dengan kekuatan sedang namun tidak berkorelasi terhadap berat badan lahir bayi. Kadar vitamin D serum ibu pada trimester ketiga dapat dijadikan prediktor kadar vitamin D neonatus saat dilahirkan.*

Kata kunci: *berat badan lahir, kehamilan, neonatus, vitamin D.*

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INTRODUCTION

Vitamin D is an active metabolite that takes a major responsibility in the body mainly in maintaining hemostasis of calcium, phosphate and bone metabolism.[1] During pregnancy, maternal metabolism undergoes various physiological changes to support fetal development.[2] However, the causes of vitamin D deficiency during pregnancy aren't fully comprehended. In recent decades, several observational studies have found a link between maternal and neonatal vitamin D levels. A systematic review and meta-analysis study concluded that over 50% of pregnant women and neonates are deficient in vitamin D globally.[3]

Pregnancy complications, such as pre-eclampsia, caesarean section (C-section) delivery, and gestational diabetes have all been linked to vitamin D deficiency.[4] In addition to affecting the mother, vitamin D deficiency can also have adverse effects on the fetus. Fetal bone development relies heavily on maternal 25(OH)D and calcium stores. Skeletal mineralization is significantly dependent on calcium, which is actively transported through the fetal bloodstream. Severe calcium deficiency in the mother can lead to skeletal defects, hypocalcemia, and rickets in the neonate. This condition arises when vitamin D deficiency goes undetected during pregnancy or is detected after delivery.[5-7] Another consequence of maternal vitamin D deficiency during pregnancy is the possibility of preterm labor and giving birth to small neonates not suitable for gestational age. Various research studies have shown a correlation between vitamin D levels and birth weight.[8]

In clinical application, examination of 25(OH)2D levels is not commonly performed because it has a short half-life and does not provide an overview of long-term vitamin D status.[4] Maternal 25(OH) D concentrations will cross the placenta and serve as the primary source of vitamin D in fetus. Fetal serum concentrations of 25(OH)D (cord blood) were reduced by an average of 25% compared to maternal serum concentrations of 25(OH)D.[9] Several studies have found a link between serum vitamin D deficiency and poor pregnancy outcomes. Based on the background above, researchers are interested in investigating the relationship between maternal and newborn vitamin D levels. The findings of this study are expected to serve as a scientific reference source to form the basis for vitamin D supplementation in pregnant women and thereby prevent various pregnancy complications caused by vitamin D deficiency.[10]

METHODS

This is a cross-sectional study with a correlational design conducted in the delivery room at the Regional General Hospital Dr. Zainoel Abidin Banda Aceh (RSUDZA). Ethical approval was obtained from the Health Research Ethics Committee (KEPK) of the Faculty of Medicine, Universitas Syiah Kuala - RSUDZA. The study was carried out during the period from March to June 2022.

The sample for this research consisted of pregnant women and neonates who gave birth at RSUDZA Banda Aceh. The inclusion criteria were third-trimester pregnant women with a single live fetus. However, those with fetal distress, fetal anomalies, and mothers suffering from chronic hypertension, pre-eclampsia, kidney disease, and pregestational diabetes were excluded. The subjects for this study were selected using a correlative analytic study sampling formula, resulting in a sample size of 39 individuals.

Upon receiving an explanation regarding the purpose and benefits of the research, the subjects were asked for approval to become research samples. Covariate data collected included maternal age, gestational age, gestational status (GPA), history of vitamin supplementation, body mass index (BMI), blood routine, blood sugar during pregnancy (GDS), and levels of Ur, Cr, SGOT, and SGPT. Subsequently, 3 cc of venous blood was drawn to check the levels of 25(OH)D3 using the CLIA method. Additionally, after delivery, 3 cc of blood was taken from the umbilical cord to examine 25(OH)D, which represents the level of vitamin D in the neonate.

The bivariate analysis used in this research using the Spearman alternative test with a 95% confidence level. The ethical approval from the Ethic Committee of the Faculty of Medicine, Syiah Kuala University no 365/EA/FK-RSUDZA/2021.

RESULTS

The inclusion and exclusion criteria were met by 39 pregnant women and their unborn children who were used as research subjects. The following are the characteristics of the study participants:

Tablei 1. Research Characteristics Data

Characteristics	n	%	Mean	*P-value*
Age, mean± SD			30.38± 6.21	0.104
BMI (kg/m2), mean ± SD			26.82 ± 2.94	0.105
Occupation,				
Housewife	29	74.4		
Government Employee	8	20.5		
Self employee	2	5.1		
Parity, n (%)				0.322
P0	12	30.8		
P1	11	28.2		
P2	11	28.2		
P3	4	10.3		
P6	1	2.6		
Gestasional Age, n (%)				
34 – 35	1	2.6		
37 – 38	8	20.5		
38 – 39	14	35.9		
39 – 40	6	15.4		
40 – 41	7	17.9		
41 – 42	3	7.7		

The table above presents data on the characteristics of the research subjects involved. The average age of the mothers was 30.38 years, and their body mass index was 26.82, which falls under the overweight category. The subjects' occupation was predominantly housewives. Most of the subjects came from Aceh Besar and Banda Aceh. The predominant pregnancy status in this study was G1, P1, and A0, with a predominance of caesarean delivery. There were 10.3% of subjects with a history of vitamin D supplementation.

Table 2. Maternal and Neonatal Vitamin D Status

Vitamin D level	Mother	Neonates
Sufficiency	7 (17.7)	14 (35.9)
Insufficiency	29 (74.4)	15 (38.5)
Deficiency	3 (7.7)	10 (25.6)

Table 2 above present the distribution of maternal and fetal vitamin D status. Known as much as 7.7%. Vitamin D deficiency affects pregnant women in their third trimester.

Table 3. Correlation Analysis between Vitamin D Levels of Third Trimester Mothers and Neonates

Characteristic (n=39)	Median (min-max)	R	*P-value**
Vitamin D level (mother)	17.4 (8.6-38.9)	0.462	0.003
Vitamin D level (neonate)	17.6 (6.2-45.8)		

**Spearman's correlation rank test*

Furthermore, it is known that 25.6% of neonates born have vitamin D deficiency.

The results of the Spearman's correlation rank test on the correlation between maternal vitamin D levels in the third trimester and neonatal vitamin D levels are shown in Table 3. The average maternal vitamin D value was 17.4 ng/mL, and that of the neonates was 17.6 ng/mL. Statistically, maternal vitamin D levels were found to be significantly correlated with neonatal vitamin D levels with a moderate correlation strength (p = 0.003, R = 0.462).

Table 4. Correlation Analysis between Third Trimester Maternal Vitamin D Levels and Fetal Birth Weight

Characteristic (n=39)	Median (min – max)	R	*P-value*
Mother Vit. D level	17.4 (8.6 – 38.9)	0.217	0.185
Neonates Vit. D level	3.100 (2.100 – 4.200)		

** Spearman's correlation rank test*

Correlation analysis between third trimester maternalivitamin Dilevels and neonates birth weight is presented in table 4 above. The average birth weight of babies is 3,100 grams with a range of 2,100 grams to 4,200 grams.

DISCUSSION

According to this study, the consumption of vitamin D supplementation during pregnancy is low. Research by Pratumvinit et al. in Bangkok, which examined maternal vitamin D status and the factors influencing it, found that the consumption rate for vitamin D supplementation tends to be low, at only 10.2%.[11] This low supplement consumption rate is thought to be related to the incidence of vitamin D deficiency in pregnant women. Vitamin D dosages that are considered safe for pregnant women have not been clearly defined. The World Health Organization (WHO) recommends a daily intake of 200 IU of vitamin D.[12-14]

The average maternal vitamin D level in this study was 17.4 ng/mL, and the fetal vitamin D

level was 17.6 ng/mL. A serum 25(OH)D level of less than 20 ng/mL (50 nmol/L) indicates vitamin D deficiency. If it is adjusted to the definition of vitamin D deficiency, it is known that the average sample of the study has this condition. The statistical correlation between maternal vitamin D levels and neonatal vitamin D levels was moderate (p = 0.004, R = 0.462). These results are consistent with several studies that have been previously conducted in various countries.

The results of a study in Nepal found that the average vitamin D level in pregnant women was 14.6 ng/mL and 25.7 ng/mL in neonates. Linear regression analysis revealed a linear relationship between maternal vitamin D levels and neonatal vitamin D levels (p 0.001).[15] A study in Turkey discovered that the mean serum vitamin Dllevels in pregnant women were 14.82 ng/mL and 13.16 ng/mL in neonates.[16] Another, the average serum vitamin D in pregnant women was 68.11 mol/L and 28% of the samples hadi vitamin D deficiency.17

Prenatal complications such as gestational diabetes, preeclampsia, preterm delivery, and low birth weight have been linked to low vitamin Di levels.[18] The lack of vitamin D in pregnant women can also be found in their neonates and can affect the development of these neonates. Complications that can occur in children include rickets disease, susceptibility to respiratory tract disorders, and autoimmune diseases such as Crohn's disease or type I diabetes mellitus. The most severe complication that may occur is cancer.19 Various risks of this disease can occur due to the function and role of vitamin D in the body. The placenta is an organ that has the ability to convert 25(OH)D into its active form, 1,25-dihydroxyvitamin D. This active form of vitamin D has the ability to modify histones, leading to immunomodulation.[20]

The various complications that can arise are an important point in studying vitamin D levels in pregnant women and neonates. The correlation between maternal serum vitamin D levels and neonatal vitamin D levels was established in this study. These outcomes are consistent with another study that determines the serum vitamin D level of the neonate, which is known to correlate with that of the mother in the first 8 months, and endogenous synthesis only starts to play a role afterwards.[15] The study found that a deficiency of vitamin D in the mother increases the risk of vitamin D deficiency in placental blood by 2.765 times higher compared to mothers with normal vitamin D levels.[21] Several studies have also found that pregnant women's 25(OH) D levels are positively correlated with serum vitamin D levels in the placenta. For that reason pregnant women must have sufficient vitamin D levels so that they can supply the vitamin D needed by the fetus.[22,23]

A study looking at maternal and neonatal vitamin D status in South Africa found that mean maternal and cord vitamin D levels were 29.7 ng/mL and 21.0 ng/mL. Predictors of vitamin D deficiency in neonates include maternal age (OR 16.5 95% CI 1.82-149), birth in winter (OR 3.68 95% CI 2.05-6.61), birth by section cesarean delivery (OR 4.92 95% CI 1.56-15.57) and low birth weight (OR 1.99 95% CI 1.13-3.50).[24] Another study in Southeast Asia found mean maternal vitamin D levels and umbilical cord of 25.42 ng/mL and 14.85 ng/mL and there is a positive correlation between the two (r=0.86 and p<0.001). Vitamin D deficiency is thought to be caused by low maternal vitamin D levels and vitamin D supplementation, which also affects umbilical cord vitamin D levels.[25]

Additionally, this study also obtained the result that the average birth weight of the fetus was 3,100 grams, where the vitamin D levels of third trimester mothers did not correlate with the birth weight of the fetus (p > 0.05). The results of this study have similarities with the study by Lee et al. in 2022, assessing the relationship between maternal and neonatal vitamin D deficiency on neonatal anthropometry. The study found an average fetal birth weight of 3,064 grams and found no association between maternal vitamin D deficiency and infant birth weight.[26] Studies in China investigating the association between maternal vitamin D levels, pregnancy conditions, and infant growth found no correlation between maternal vitamin D deficiency and preterm labor, low or small birth weight for gestational age, as well as neonatal anthropometry (weight, length, and BMI) at ages 0 to 3 years. The studies concluded that there was no relationship between maternal vitamin D levels and infant growth.[27]

The findings of this study differ from several previous researches. In another study, samples with maternal vitamin D deficiency had lower neonatal anthropometric measurements. Vitamin D insufficiency, defined as levels below 50 nmol/L, was associated with the risk of small babies for gestational age and preterm labor. [28] Another study by Shakeri found a significant relationship between vitamin D deficiency or insufficiency and

low birth weight babies. The study suggested that this link may be due to the role of vitamin D in bone mineralization, leading to decreased fetal bone growth. [29] A systematic review study also obtained different results, showing a positive correlation between vitamin D deficiency and low birth weight (OR=2.45; 95% CI=1.91-3.13).[30]

CONCLUSION

The study revealed an average maternal vitamin D level of 17.4 ng/mL in the third trimester, and neonates had an average vitamin D level of 17.6 ng/mL. The findings indicate a moderate positive correlation between maternal and neonatal vitamin D levels. However, maternal vitamin D levels in the last trimester did not show any correlation with the baby's birth weight. Maintaining sufficient levels of vitamin D during pregnancy is essential to ensure an adequate supply for the developing fetus.

SUGGESTION

Further research is warranted to investigate the changes in maternal serum vitamin D levels throughout each trimester of pregnancy. Additionally, more studies are needed to explore the relationship between maternal vitamin D levels and other markers of fetal growth and development during pregnancy, as well as its impact on fetal physiology during childbirth. Maintaining adequate vitamin D levels in pregnant women is crucial for providing sufficient vitamin D to the developing fetus. One major limitation of our study is the inability to monitor sun exposure in the participating mothers. As the cultural practice of wearing cloth in Aceh may limit sun exposure, all mothers included in our study were likely vitamin D deficient, and their lifestyles may not have changed during the study period.

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CONFLICT of INTEREST

There are no conflicts of interest in this report..

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Research Article

The Effect of Mannihot Esculenta on Prolactin Hormone Levels and Breast Milk Production in Breastfeeding Mothers

Efek Mannihot Esculenta pada Tingkat Hormon Prolaktin dan Produksi Susu Ibu pada Ibu Menyusui

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Abstract

Objective: To prove the effect of cassava leaves jerky (Mannihot Esculennta) on prolactin hormone levels and breast milk production in breastfeeding mothers in the Working Area of the Rejosari Health Center of Pekanbaru City.

Methods: This study used True Experiment Design with a pretest and posttest design with the control group, using a simple random sampling with a total of 28 breastfeeding mothers, 14 intervention group respondents, and 14 control group respondents. The intervention group was given cassava leaves jerky 60 gr/day, and the control group was given jerky without cassava leaves 20 gr/day for 2 weeks. Both groups were observed 3 times by weighing the baby's weight and checking the level of the hormone prolactin after administering the intervention using the ELISA method. Data analysis using Mann-Whitney, TIndependent, Repeated ANOVA test.

Results: There was a difference in the average difference of prolactin hormone levels in the intervention group and control group with a p-value of 0.000 (<0.05)

Conclusion: Giving jerky cassava leaves breast milk booster affects the hormone prolactin and breast milk production in breastfeeding mothers.

Keywords: breast milk production, cassava leaves, mannihot esculenta, prolactin.

Abstrak

Tujuan: *Untuk Membuktikan dendeng daun singkong (Mannihot Esculennta) terhadap kadar hormon prolaktin dan produksi ASI pada ibu menyusui di Wilayah Kerja Puskesmas Rejosari Kota Pekanbaru.*

Metode: *Penelitian ini menggunakan rancangan percobaan yang sebenarnya dengan desain pretest and posttest only with control group, sampling menggunakan sampel acak sederhana dengan jumlah 28 responden ibu menyusui, 14 responden kelompok intervensi, dan 14 responden kelompok kontrol. Kelompok intervensi diberi dendeng daun singkong 60 gr/hari, dan kelompok kontrol diberi dendeng tanpa daun singkong 20 gr/hari selama 2 minggu. Kedua kelompok diamati sebanyak 3 kali dengan menimbang berat badan bayi dan pemeriksaan kadar hormon prolaktin setelah pemberian intervensi dengan metode ELISA. Analisis data menggunakan uji Mann-Whitney, TIndependent, Repeated ANOVA.*

Hasil: *Terdapat perbedaan rata-rata selisih kadar hormon prolaktin pada kelompok intervensi 376,5 ng/ml, kelompok kontrol 103,5 ng/ml dengan p-value 0,000 (<0,05)*

Kesimpulan: *Pemberian dendeng penambah ASI daun singkong berpengaruh terhadap hormon prolaktin dan produksi ASI pada ibu menyusui.*

Kata kunci: *daun singkong, mannihot esculenta, produksi ASI, prolaktin.*

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INTRODUCTION

Breast milk is the best natural food, easily digested, and containing the energy and nutrients that babies need in the first six months of life.[1] Breast milk contains complex nutrients that are perfectly complemented by immune substances and most nutrients have an optimal composition according to the baby's needs.[2]

Not only does breast milk contain nutrients, antioxidants, hormones, and suitable antibodies a child needs, such as fat, carbohydrates, protein, minerals, and vitamins but also protective substances, namely IgA, IgE, IgM, lactobacillus biidus, lactoferi, lysozyme, cellular immunity that does not cause allergies so that it can neutralize bacteria, fungi, viruses, and parasites.[3,4] Breast milk provides all the essential components a baby needs, improves neurodevelopment, and protects babies from Sudden Infant Death Syndrome (SIDS).[5-6]

Data from the Indonesian Ministry of Health Performance Report in 2020, the achievement of exclusive breastfeeding during 0-6 months of life is 66.1% and this has not reached the Ministry of Health's Minimum Service Standard (SPM) target. Riau Province is one of the provinces that have relatively low exclusive breastfeeding coverage. Complete breastfeeding coverage in Riau Province based on Riau Province Health Profile Data in 2020 is 65.17%, and only 46.8% in Pekanbaru City which is still under the targe number.

The low coverage of exclusive breastfeeding may play a role in more than one million child deaths yearly. It affects growth and development of infants, hence the quality of life of the nation's next generation.[7] Babies who do not get exclusive breastfeeding will are at risk in developing nutritional problems that could inhibit their growth and development, such as stunting. Stunting can lower children's intelligence. Stunted children are more susceptible to disease and at risk in having lower productivity levels in the future.[8,9] A researcge stated that babies who are not exclusively breastfed are at 61 times greater risk of stunting compared to babies who are fully breastfed for 6 whole months.[10]

Many efforts have been made to facilitate breast milk production, both pharmacological and non-pharmacological. Pharmacological therapies such as administering domperidone and metoclopramide are considered optimal as laktagogums. However, they are expensive and have side effects such as headache, diarrhea, dry mouth, stomach cramps, and even skin redness.[11] Thus people prefer non-pharmacological efforts to increase milk production. Non-pharmacological approach may become an alternative for breastfeeding mothers and are relatively easy to do. This could be done by utilizing existing natural resources obtained from plants or plants. [12]

Food containing lactagogum increases breast milk production. Indonesia is rich in traditional plants that have a laktagogum effect. indonesian prefer to use plants to increase milk production, including katuk leaves, fenugreek seeds, gotu kola leaves, and torbangun leaves. Research revealed the benefits of consuming certain plants such as papaya leaves, moringa leaves, mulberry leaves, green beans, thorn spinach, cassava leaves, black cumin, jackfruit, temulawak and turi to increase breastmilk production. [13]

Indonesia is rich in natural resources thought to increase breast milk, one of it by consuming cassava leaves. The people of Pekanbaru City believe that consuming cassava leaves can increase breast milk and could also be used as a natural therapy. Cassava leaves, commonly called Manihot Esculenta Cranzt are daily food source for the people of Indonesia because they are easy to find and containing good nutrition for the body.

Cassava leaves contain lipid elements and hormonal structures with active compounds, namely flavonoids and saponins, which have an anti-inflammatory role and a laktagogum effect essential in increasing prolactin hormone levels and breast milk production[14]. Flavonoid compounds in cassava leaves can stimulate the release of prolactin hormone (PRL) and growth hormone (GH), up-regulated prolactin hormone (PRLR), and encourage breast development.[15]

The results of laboratory tests conducted at Unika Soegijapranata Semarang in 100 grams of cassava leaves contain high flavonoids, namely 3.502 grams. Cassava leaves also contain high levels of vitamin A and minerals; calcium, iron, protein, carbohydrates, phosphorus, vitamins B and C, which have many benefits for the body.[16] Cassava leaves are very easy to find and familiar to the people of Indonesia because they easily disseminated and suitable in environmental conditions in all regions in Indonesia, especially in Pekanbaru City. Researchers have received ethical approval or ethical clearance from Research Ethics Commission (KEPK) of the Health

Polytechnic of the Ministry of Health Semarang No. 0146/EA/KEPK/2022.

Jerky is one of the processed food products made from dried meat which is the result of a drying process and is in the form of a thin sheet then added with salt, and spices such as coriander and garlic.[17] The people of Pekanbaru City are no strangers and like to consume beef jerky, which usually made from beef, but not all can consume it every day because it has a relatively high price.

Processed cassava leaves jerky could be the better alternative and healthier choice from the beef jerky as it tastes almost like beef-based one and has good nutritional component for breastfeeding mothers. Laboratory finding of phytochemical compounds in 100 grams of cassava leaves jerky carried out independently in the Unika Semarang Laboratory found that flavonoid content of cassava leaves jerky is 1.988 grams higher than tin the katuk leaves which was proven to affect breast milk production, which was 0.8371 grams.18 So cassava leaves jerky can be an alternative choice for breastfeeding mothers.

In this study we intended to evaluate the effect ofcassava leaves jerky (Manihot Esculenta consumption in increasing prolactin hormone levels and breast milk production in Rejosari Health Center Pekanbaru City by measuring the baby's weight in breastfeeding mothers?

The difference in the existing research found in the dependent variable, namely the absence of research on cassava leaves on the hormone prolactin and breast milk production in breastfeeding mothers. This research used quantitative approach with a true experimental type, which is different from previous study with a qualitative research design that only dealt with interviews related to people's habits in increasing breast milk production.

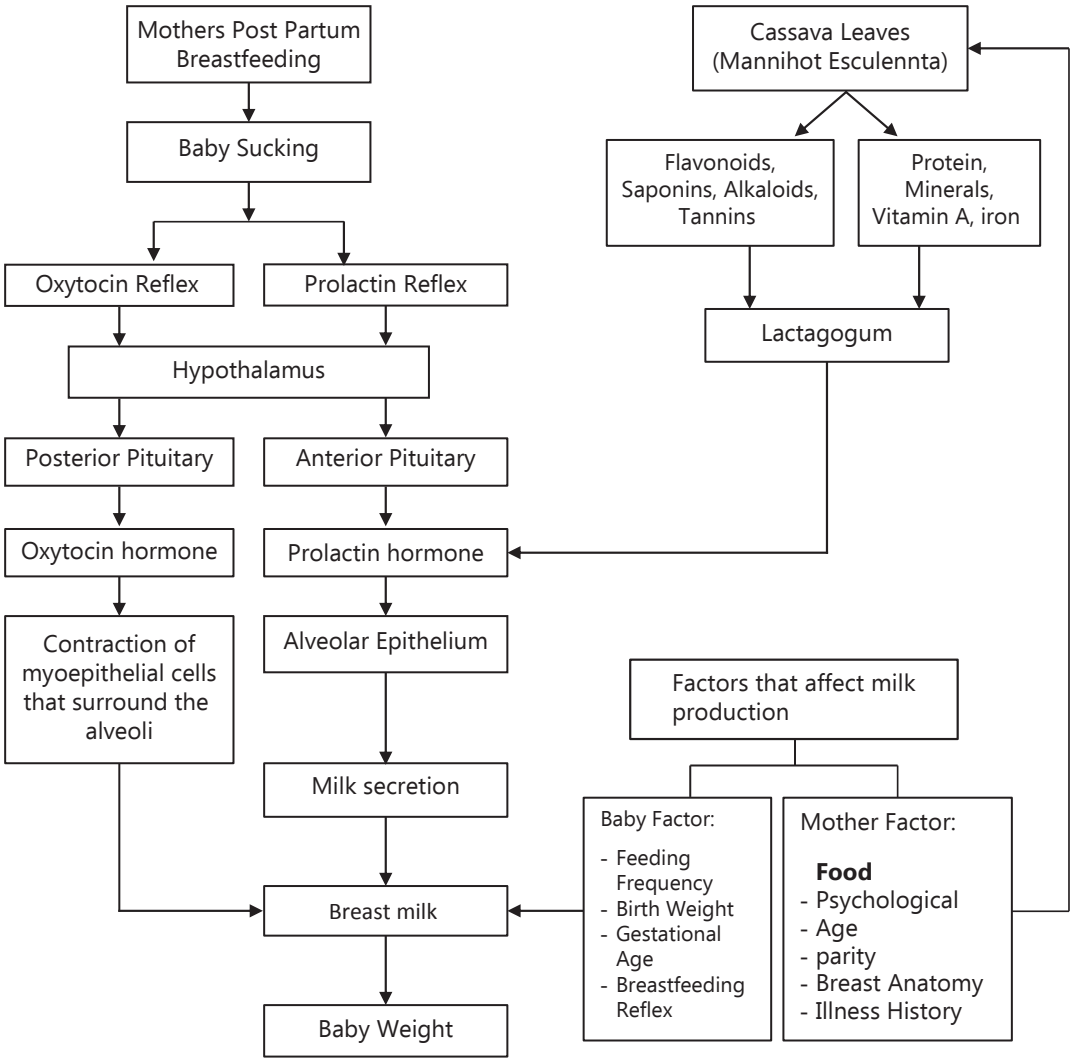

Figure 1. Theoretical Framework
(Pratiwi, et al., 2018; Bahekar, S., and Kale, R., 2013)

METHODS

This study used true experimental design withpre test and post test only with the control group, using sampling simple random sampling with a total of 28 breastfeeding mothers, 14 intervention group respondents and 14 control group respondents. Firstly, iIntervention group was given cassava leaves jerky 60 gr/day and the control group was given beef jerky without cassava leaves 20 gr/day for 2 weeks. Secondly, observations were done 3 times by weighing the baby's weight and to check prolactin hormone levels after the intervention using the ELISA method. Data was analyzed using Mann-Whitney test, T- Independent, repeated ANOVA.

The population in this study were all mothers in their 14th post partum day around the working area of the Pekanbaru City Rejosari Health Center, and the study sample is 28 respondents who had met the requirements. They were divided into 2 groups (14 respondents in the intervention group and 14 respondents in the control group). The sample were selected from 5 private midwives around Rejosari Health Center Pekanbaru City. Determination of the number of samples was based on the minimum number of samples in a simple experimental study that is 20 respondents, with the number of samples in each group being 10 respondents.19 The sample of this study was obtained by randomization with the draw lottery method from 9 private midwives' practices with the highest number of patients in the working area of the Rejosari Health Center. It was found that 5 private midwives' practices had enough respondents according to the inclusion and exclusion criteria. The total of 28 respondents consisted of 8, 6, 4, 4, 4 respondents from Y, M, D, TS and S private midwives's practice respectively.

The inclusion criteria were mothers with productive age of 20-35 years, normal maternal breast anatomy, not taking breast milk booster, healthy mother and baby, full breats-fed babies without any additional food, birth weight >2500 grams, baby's weight on day 14 remains the same as the birth weight (reagent), good baby sucking reflex. Exclusion criteria were mothers allergic to cassava leaves, abnormal nipple anatomy/diseases throughout the study, sick babies for 3 days, addition of nutrition to the babies other than breastmilk. The Operational Definition refers to measurement of the variables in questionniarre and measuring instruments/ instruments. The variables in this study were as follows:

Independent Variable : Cassava Leaves Jerky
Dependent Variable : Prolactin hormone and breast milk production
Confounding Variables : Frequency of breastfeeding, food intake and mother's psychological condition

RESULTS

Table 1. Frequency distribution of Respondents' Characteristics by Age, Education, Occupation and Parity of Breastfeeding Mothers

Variable	Intervention (n=14)		Control (n=14)	
	N	%	N	%
Age				
20-30	12	85.7	10	71.4
31-35	2	14.3	4	28.6
Total	14	100.0	14	100.0
Education				
Basic elementary/junior high)	6	42.9	2	14.3
SMA/SMK	6	42.9	7	50.0
College	2	14.2	5	35.7
Total	14	100.0	14	100.0
Occupation				
Unemployed	11	78.6	10	71.4
Employed	3	21.4	4	28.6
Total	14	100.0	14	100.0
Parity				
Primipara	6	28.6	3	21.4
Multipara	8	71.4	13	78.6
Total	14	100.0	14	100.0

Table 2. Homogeneity Test Results and Differences in Confounding Variables

Variable	Intervention (n=14)		Control (n=14)		*pa*	*pb*
	mean	SD	mean	SD		
Psychological Status	4,787	2,359	4,714	2,091	0.387	0.933
Breastfeeding Frequency	12.93	1,730	12.71	1.541	0.727	0.732
Nutritional status	7,599	9,355	7,126	12,329	0.097	0.265

[a] Levene, s[b]Independent T-Test

The study found that the psychological status, breastfeeding frequency, and nutritional status of the intervention and the control group were homogeneous (p = > 0.05).

Table 3. Normality of Data on Increased Breast Milk Production with Indicators of Baby Weight

Variable	Treatment	Group	*P-value*
Data on Increased Breast Milk Production with Baby Weight Indicators	BB Pre Day-1 (before intervention)	Cassava Leaves Jerky	0.991
		Jerky without cassava leaves	0.342
	BB Day 7	Cassava Leaves Jerky	0.196
		Jerky without cassava leaves	0.311
	BB Post Day-15	Cassava Leaves Jerky	0.936
		Jerky without cassava leaves	0.475

Table 3 shows that prolactine hormone have normal distribution on the Cassava leaves Jerky group, while the data in the jerky group without cassava leaves is not normally distributed. Therefore, non-parametric statistical analysis should be done.

Table 4. Differences in Infant Weight Gain by Group

Treatment	Group (Mean ± SD)						*Pa*
	Cassava Leaves Jerky			Jerky Without Cassava Leaves			
	Mean	SD	Min – Max	Mean	SD	Min – Max	
BB Day-1 Intervention	3310.7	403.9	2500- 4100	3357.1	425.6	2700 – 4200	0.770
BB Day 7 of intervention Post 1	3810.7	393.3	3000- 4700	3557.1	428.7	2900- 4200	0.115
BB Day-15 intervention (Post 2)	4092.9	365.2	3500- 4800	3725.0	456.0	2950 -4500	0.026
Pb	0.000			0.096			

*[a]*n *Independent T-Test[b]One Way ANOVA*

Table 4 shows that weight gain in infants in cassava leaves jerky group has normal distribution and the jerky without cassava leaves group has p values >0.05. Therefore, non-parametric statistical analysis should be done.

DISCUSSION

Breastfeeding mothers have different levels of the hormone prolactin from normal women. The normal prolactin hormone levels in breastfeeding mothers is around 100 ng/ml.[20] The average level of prolactin hormone in the intervention group was 376.5 ng/ml while in the control group was 103.5 ng/ml. This is in line with the theory regarding the value of prolactin hormone levels in breastfeeding mothers. The prolactin hormone levels in the first week after giving birth will increase compare to normal prolactin levels in women. The process of breastfeeding affects the level of the mother's prolactin hormone. This is due by several factors one of it being the mother's food intake.[21]

This study alters mother's food intake by adding cassava leaves which contain galactogogue, as an effort to increase breast milk, which is still rarely done, especially in Indonesia. Galactogogue is a substance found in herbal plants that are considered helpful in producing, maintaining, and increasing breast milk in breastfeeding mothers in African countries.[22] Galactogogue derived from various plants and have been widely studied and proven to increase milk production. Most of them are very safe for breastfeeding mothers.[23,9] The average increase in prolactin hormone levels in the group that was given cassava leaves jerky was higher than that in the control group that was only given flour jerky. It was proven that the flavonoid content in plants helped increase prolactin and breast milk production up to 10-20 times.[18] A study showed a significant difference in prolactin levels in breastfeeding Wistar rats after being given processed foods containing galactogogue with a p-value of 0.000.[24]

Flavonoids in 100 grams of processed cassava leaves jerky are somewhat higher, namely 1.988 grams compared to 0.8371 grams of katuk leaves. This was because flavonoids, components of phytochemical compounds in cassava leaves, are chemical messengers delivered by the bloodstream to the tissues to stimulate or inhibit a process. So, the presence of phytochemical compounds in cassava leaves was thought to have a relationship with stimulating the effect of increasing prolactin levels and milk production for breastfeeding mothers.[25]

Cassava leaves jerky affects prolactin hormone levels in breastfeeding mothers with a significant effect (effect size) 1.3 > 0.8, so it can be concluded that the of cassava jerky significantly affects the increase in prolactin hormone levels in breastfeeding mothers.

Based on the results of statistical analysis, it can be concluded that consumsing cassava leaves jerky affects infant weight, namely, in this study, breast milk production. Its consumption increased infant weight significantly on the 15th day after the intervention with p-value = 0.026 <0.05. In addition to that, the study showed that giving cassava leaves jerky had a very significant effect on the baby's weight starting from day 1 to day 15 (p-value = 0.000), meaning that there was an effect of giving cassava leaves jerky to breast milk production. At the same time, the consumption of beef jerky in the form of flour without cassava leaves did not affect the baby's weight from day 1 to day 15 (p-value = 0.096).

Consuming cassava leaves jerky was proven to increase milk production looking at the increase in weight gain. This was in line with a study by Riski, et al. (2020), and it was found that there was a significant difference in the provision of processed papaya leaves stir fry on the baby's weight (p = 0.000).[26]

The effect size of cassava leaves beef jerky compared to flour alone was 1.6 > 0.8. The difference in the average increase in breast milk production in the group given cassava leaves jerky was higher than that in the flour jerky group. Therefore, consumption of cassava leaves jerky to increase breast milk production has a significant effect compared to giving flour jerky without cassava leaves.

CONCLUSION

Based on the results of the study it can be concluded that jerky leaves Cassava has been shown to be effective in increasing prolactin hormone levels based on the baby's weight indicator. Consuming cassava leaves jerky for 14 days was proven to increase prolactin hormone levels in breastfeeding mothers with p value = 0.000 and milk production as seen from the increase in baby weight with value sig. p value = 0.026 (<0.05).

SUGGESTION

Further study is needed to examine the prolactin hormone levels before and after the intervention with different grams of cassava leaves. Not only does this research has proven the consumption of cassava leaves jerky as an alternative to increase breast milk production but also this could be developed further as an effort to improve the community's economy so that training can be held for the community, especially in Micro, Small and Medium Enterprises (MSMEs).

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Research Article

Friedman Curve Positively Correlates with Cesarean Section and Oxytocin Augmentation in Active Phase Delivery as Compared to Partograph

Kurva Friedman Berkorelasi Positif dengan Seksio Sesarea dan Augmentasi Oksitosin pada Fase Aktif Persalinan dibandingkan Partograf

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Abstract

Objective: To investigate the correlation between cesarean section and oxytocin augmentation in childbirth monitored with the Friedman curve compared to the World Health Organization (WHO) partographs.

Methods: An analytic cross-sectional study was conducted from March to May 2021, involving mothers giving birth whose delivery process was monitored using either the Friedman curve or the WHO partograph (n=28 for each group) at Wangaya Hospital in Denpasar City. The duration of the active phase until delivery, occurrence of cesarean section, and administration of oxytocin augmentation were assessed using the Friedman curve and the WHO partograph. The normality of the data was tested using the Kolmogorov-Smirnov test, and the Spearman correlation test was employed to measure the direction and strength of the correlation.

Results: There was no significant difference between the groups in terms of monitoring the active phase until delivery using the Friedman curve compared to the WHO partograph (p=1.000 > 0.05). Maternal monitoring with the Friedman curve showed a positive correlation with the occurrence of cesarean section compared to the WHO partograph (r=0.296, p=0.027). Additionally, monitoring childbirth with the Friedman curve exhibited a positive correlation with the administration of oxytocin augmentation compared to the WHO partograph (r=0.298, p=0.026).

Conclusion: The findings suggest a stronger positive correlation between the incidence of cesarean section and the administration of oxytocin augmentation in childbirth monitored with the Friedman curve compared to the WHO partograph.

Keywords: cesarean section, Friedman curve, oxytocin augmentation, WHO partograph.

Abstrak

Tujuan: *Untuk menentukan korelasi antara operasi sesar dan augmentasi oksitosin pada persalinan yang dipantau dengan kurva Friedman dibandingkan dengan partograf Organisasi Kesehatan Dunia (WHO).*

Metode: *Desain penelitian analitik potong lintang dilakukan pada Maret-Mei 2021, dengan melibatkan ibu bersalin yang proses persalinannya dipantau menggunakan kurva Friedman atau Partograf WHO (n=28 untuk setiap kelompok) di ruang bersalin di Rumah Sakit Wangaya, Kota Denpasar. Waktu fase aktif hingga kelahiran bayi, persalinan seksio sesarea, dan augmentasi oksitosin dinilai dengan menggunakan kurva Friedman dan Partograf WHO. Uji normalitas dilakukan dengan uji Kolmogorov-Smirnov, dilanjutkan dengan uji korelasi Spearman untuk mengukur arah dan kekuatan korelasi.*

Hasil: *Pemantauan ibu bersalin dengan kurva Friedman dibandingkan dengan Partograf WHO dalam hal fase aktif-persalinan bayi menunjukkan tidak ada perbedaan yang signifikan di antara kedua kelompok (p = 0,000 > 0,05). Pemantauan ibu dengan kurva Friedman berkorelasi positif dengan kejadian bedah sesar dibandingkan dengan Partograf WHO (r = 0,296, p = 0,027). Selain itu, pemantauan persalinan dengan kurva Friedman berkorelasi positif dengan pemberian oksitosin dibandingkan dengan partograf WHO (r = 0,298, p = 0,026).*

Kesimpulan: *Terdapat korelasi positif yang lebih tinggi antara kejadian bedah sesar dan pemberian augmentasi oksitosin pada proses persalinan yang dipantau dengan kurva Friedman dibandingkan dengan partograf WHO.*

Kata kunci: *augmentasi oksitosin, kurva friedman, partograf WHO, seksio sesarea*

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INTRODUCTION

The maternal mortality rate is an indicator of women's health status and a component of Indonesia's development and quality of life index.[1] The occurrence of labor and delivery complications worldwide ranges from 15% to 20%. Based on these statistics, it has been found that only 5% to 10% of deliveries necessitate a cesarean section. According to the International Conference on Indonesia Family Planning and Reproductive Health, Indonesia's maternal mortality rate remained high at 305 per 100,000 live births as of 2019. The Sustainable Development Goals aim to achieve a maternal mortality rate of 70 per 100,000 live births by 2030.[2] Problems associated with pregnancy and childbirth, including the elevated maternal mortality rate, cannot be isolated from the various influencing factors.Delivery methods and immediate post-delivery care are among the factors contributing to the high maternal mortality rate.[3]

The Friedman curve and the World Health Organization (WHO) partograph are widely utilized for delivery monitoring and guiding clinical decision-making. The Friedman curve demonstrates moderate sensitivity in predicting the progress of the first stage of delivery. It accurately detects cervical dilatation progress in the latent phase with a 72% correctness rate, in the accelerated phase with 79%, in the maximum slope phase with 78%, and in the deceleration phase with the highest sensitivity of 85%.[4] The partograph, a simple and cost-effective tool, employs visual aids to monitor labor progress for healthcare providers. The WHO partograph is a synthesis and implementation of various partograph models from around the world. In 2000, the WHO Partograph underwent modifications to enhance simplicity and ease of use. The modified partograph eliminated the latent phase and started from the active phase when the cervix is open at 4 cm. Partographs are utilized to assess labor progress and identify the need for interventions.

There is a debate over whether the Friedman curve, which examines the duration of delivery, increases the likelihood of interventions such as cesarean sections and oxytocin augmentation. Generally, the examination principles of the Friedman curve differ from those of the WHO partograph. Attempts to establish normal limits for delivery duration have yielded varying results due to the limited number of tests that can be performed based solely on periodic cervical dilatation examinations. Compared with the WHO partograph, the Friedman curve does not include other clinical information that influences decisions on delivery management.[5] The use of partographs has been previously evaluated in a multicenter trial involving 35,484 parturient women. The results showed that the use of a partograph reduced prolonged labor by about half (from 6.4% to 3.4% of labors) and decreased the proportion of labors requiring stimulation from 20.7% to 9.1%. Emergency cesarean sections were also reduced from 9.9% to 8.3%, and intrapartum stillbirths decreased from 0.5% to 0.3%. This is further supported by research conducted by Walss Rodriguez, where cesarean rates were lower in the group observed with a partograph than in the group that did not use one (RR 0.38, 95% CI 0.24 to 0.61).[6]

To evaluate the role of the Friedman curve, this study aims to assess the correlation between the duration of the active phase of delivery until the birth of the baby, the increased rate of cesarean section deliveries, and the use of oxytocin augmentation, comparing the Friedman curve with the WHO partograph.

METHODS

An analytical observational study with a cross-sectional design was conducted from March to May 2021 in the delivery room of the Emergency Unit at Wangaya Regional General Hospital, located in Denpasar City, Bali Province, Indonesia. The study aimed to examine pregnant women who underwent delivery in the delivery room. The participants were divided into two groups based on the monitoring tools used: the Friedman curve group and the WHO partograph group. Participant selection was performed using a simple random sampling technique. The inclusion criteria consisted of pregnant women with cervical dilatation ranging from 1 to 4 cm and fetuses in the cephalic presentation. Exclusion criteria included pregnant women with a height less than 140 cm, a history of antepartum bleeding, medical abnormalities, malpresentation, fetal emergencies, intrauterine fetal death, previous cesarean section deliveries, grand multiparity, twin pregnancies, and premature rupture of membranes. The minimum sample size was calculated using the study formula for testing the hypothesis of two independent proportions,[7]

(α = 0.05 and β = 0.2). It was determined that a minimum sample size of 28 patients was required for each group. Informed consent was obtained from each participant. Ethical clearance for this study was granted by the Ethical Review Board of Wangaya Regional General Hospital with letter number 017/11.3/KEP/RSW/2022. Additionally, research permission was obtained from the Education and Research Unit with letter number 070/1080/RSUDW.

The study identified the dependent variables as the duration of the active phase (reported in minutes) and the decision to perform cesarean section delivery and oxytocin augmentation. The independent variables examined were the use of the Friedman curve and the WHO partograph. To account for potential confounding factors, the statistical analysis included the following variables: maternal age, gestational age, maternal body mass index, estimated fetal weight, and cervical effacement.

During the monitoring of the active phase, the duration of the active phase and decisions regarding cesarean section delivery and oxytocin augmentation were recorded. Interviews were conducted to gather information on parity, maternal age, history of previous cesarean section delivery, twin pregnancy, and premature rupture of membranes. The interview data were then cross-referenced with the available medical records. Gestational age, maternal body mass index, cervical effacement, and estimated fetal weight were measured directly through physical examinations and ultrasonography. Gestational age was determined using the Naegle rule based on uterine fundal height, and it was categorized as preterm (<37 weeks) or at term (≥37 weeks). Parity was further classified as grand multiparity (≥5 births at ≥37 weeks of gestation) or not grand multiparity. Data collected for variables listed in the exclusion criteria were used to exclude participants accordingly.

Statistical analysis was conducted using IBM Statistical Package Software for Social Sciences version 22. The Kolmogorov-Smirnov test was employed to assess the normality of numerical scale data. If the p-value was less than 0.05, the data were considered non-normally distributed. Normally distributed numerical data were reported as mean (standard deviation), while non-normally distributed data were reported as median (minimum-maximum value). Categorical scale data were presented as frequency distributions and proportions. The Spearman correlation test was utilized to evaluate the correlation between the independent and dependent variables due to the non-normal distribution of the data. A correlation was deemed significant if the p-value was less than 0.05. Additionally, the correlation coefficient (r) indicating the direction and strength of the correlation was reported.

RESULTS

Table 1 presents the correlation of participant characteristics between the groups. The results indicate that there were no significant differences in the characteristics of pregnant women monitored by the Friedman curve and WHO partograph.

Table 1. Participant's Characteristics between Groups

Variable	Median (IQR) between Groups		*P-value*
	Friedman Curve	**WHO Partograph**	
Maternal age (years)	26.50 (12)	26 (8)	0.313
Parity	2 (3)	1 (2)	0.202
Gestational age (weeks)	39 (2)	39 (2)	0.553
Cervical effacement (%)	25 (0)	25 (19)	0.752
Body mass index (kg/m^2)	27.50 (3)	27 (3)	0.920
Estimated fetal weight (grams)	3186.50 (508)	3118 (597)	0.553

Table 2 presents the results of the correlation test comparing maternal monitoring using the Friedman curve to the WHO partograph in terms of the duration of the active phase until the birth of the baby, cesarean section, and oxytocin augmentation.

Table 2. Correlation Test Results

Variable	Delivery Monitoring				*r*	*P-value*
	Friedman Curve		WHO Partograph			
	n=28	%	n=28	%		
Duration of active phase until the birth of baby (hours)					0.000	1.000
< 4.5	16	57.1	16	57.1		
≥ 4.5	12	42.9	12	42.9		
Cesarean Section						
Yes	10	35.7	3	10.7	0.296	0.027*
No	18	64.3	25	89.3		
Oxytocin Augmentation						
Yes	14	50	6	21.4	0.298	0.026*
No	14	50	22	78.6		

*significant correlation, p-value<0.05

The correlation test revealed a weak positive correlation between the Friedman curve and the incidence of delivery by cesarean section when compared to the WHO partograph. Additionally, there was a weak positive correlation observed between the Friedman curve and oxytocin augmentation, indicating that the administration of oxytocin augmentation increased following maternal monitoring using the Friedman curve.

DISCUSSION

This study demonstrates that monitoring using the Friedman curve is associated with an increased incidence of cesarean section and oxytocin augmentation. The findings reveal a positive correlation, indicating that maternal monitoring using the Friedman curve leads to a 29.6 times higher likelihood of deliveries by cesarean section compared to the WHO partograph. Specifically, when delivery was monitored using the Friedman curve, 35.7% of participants underwent cesarean section, while monitoring with the WHO partograph resulted in only 10.7% of participants having a cesarean section. Previous research has shown that the use of the WHO partograph effectively reduces the rate of cesarean section, surgical interventions, and complications associated with prolonged delivery.[8]

The Friedman curve is a labor monitoring device that relies on simple measurements obtained through periodic physical examinations during labor after the onset of labor has been determined. The monitoring primarily focuses on cervical dilation, which marks the onset of active labor and influences the decision-making process for appropriate interventions that impact the clinical outcomes of both the mother and the child. Friedman divided the active phase into three stages: the acceleration phase, the maximum slope phase, and the deceleration phase, during which labor progress is evaluated through vaginal examinations conducted every 2 hours. Furthermore, distinctions are made between childbirth in nulliparous (first-time mothers) and multiparous (women who have given birth before) women. According to Friedman, problems that arise during the active phase can be categorized as protraction disorders or arrest disorders. Protraction is characterized by a slow rate of cervical opening or descent, with a cervical dilatation of less than 1.2 cm/hour for nulliparous women and less than 1.5 cm/hour for multiparous women. Arrest of dilatation refers to the absence of cervical changes within 2 hours, while arrest of descent indicates the absence of fetal descent within 1 hour. Recommended therapies for prolonged labor include a waiting approach, administration of oxytocin for obstructed labor without cephalopelvic disproportion, and cesarean section in cases of cephalopelvic disproportion.

The American College of Obstetricians and Gynecologists (ACOG) has recently issued new guidelines that are grounded in evidence-based data provided by the Consortium of Safe Labor. As part of these guidelines, a new curve has been developed, building upon the findings of the study.[9] The new recommendation differs significantly from Friedman's curve, particularly in terms of the slower cervical dilation observed, especially before reaching six centimeters of dilation. Additionally, Zhang's curve lacks the distinct deflection observed in Friedman's curve between nine and ten centimeters. These findings suggest that the diagnostic standards for labor dystocia based on Friedman's curve may be excessively stringent.[10] Thus, this study result reflected the higher cesarean section delivery in mothers monitored with the Friedman curve.

In this study, the proportion of pregnant women who received oxytocin augmentation was similar between those monitored using the Friedman curve and those who were not. However, in the case of delivery monitoring using the WHO partograph, the majority of women (78.6%) did not receive oxytocin augmentation. The administration of oxytocin augmentation is typically prioritized for mothers experiencing complications related to prolonged delivery (dystocia) caused by abnormalities in uterine contractions, such as uterine inertia. One characteristic of oxytocin is its rapid action, providing visible results quickly. Therefore, prolonged administration of oxytocin is unnecessary in most cases.[11] The ACOG and the Japanese Society of Obstetrics and Gynecology (JSOG) guidelines agree that the latent phase of labor is highly individualized; thus, interventions such as oxytocin augmentation are not always required.[12–14] This study result showed that maternal monitoring using the Friedman curve increased the administration of oxytocin augmentation 29.8 times greater than the WHO partograph. Overall, this study has shown no significant differences in the duration of active phase delivery until the birth of the baby between groups. Although the duration was comparable, monitoring with the Friedman curve was associated in a more aggressive delivery approach, including a higher likelihood of decisions for cesarean section and oxytocin augmentation.

The study has a number of limitations that need to be addressed. Firstly, due to the cross-sectional study design, it is challenging to establish clear cause-and-effect relationships. Although efforts were made to control potential confounding variables, the design itself does not allow for definitive causal conclusions. Secondly, the study was conducted at a single center and involved a relatively small sample size. To obtain more conclusive results, further research with a larger sample size and multiple centers is necessary.

CONCLUSION

Delivery monitoring with the Friedman curve positively correlates with increased incidence of cesarean section deliveries and oxytocin augmentation. Therefore, using the WHO partograph as a delivery monitoring tool is recommended.

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Research Article

Granisetron was more Effective than Ondansetron as Antiemetic in Ovarian Cancer Patients: a Randomized Controlled Trial

Granisetron Lebih Efektif Dibandingkan Ondansetron Sebagai Antiemetik Pada Pasien Kanker Ovarium: Penelitian Uji Acak Terkendali

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Abstract

Objective: To determine the effectiveness of intravenous injection of granisetron compared to ondansetron in preventing nausea and vomiting, we used the MASCC Antiemesis Tool (MAT) in ovarian cancer patients undergoing paclitaxel-carboplatin chemotherapy

Methods: This study was conducted as a double-blind, randomized controlled trial. The treatment group received 1 mg of granisetron, whereas the control group received 8 mg of ondansetron intravenously. Nausea and vomiting were assessed using the MAT scale at 12 hours, 24 hours, and 48 hours after chemotherapy. The differences in MAT scores between the groups were analyzed using the Mann-Whitney test.

Results: A total of 60 participants were enrolled in this study. The results indicated that the MAT score at the 12-hour mark significantly differed from the 24-hour and 48-hour MAT scores (p = 0.00, p = 0.00). The MAT scores in the granisetron group at 12 hours, 24 hours, and 48 hours were statistically lower compared to the ondansetron group (p = 0.00, p = 0.00, p = 0.00).

Conclusions: In conclusion, intravenous granisetron proved to be more effective than intravenous ondansetron in preventing nausea and vomiting among patients with ovarian cancer undergoing paclitaxel-carboplatin chemotherapy.

Keywords: chemotherapy, granisetron, MAT score, ondansetron, ovarian cancer.

Abstrak

Tujuan: *Mengetahui efektivitas perbandingan pemberian injeksi intravena antara granisetron dan ondansetron dalam mencegah mual dan muntah dengan menggunakan MAT pada pasien dengan kanker ovarium yang mendapat kemoterapi dengan regimen paclitaxel-carboplatin.*

Metode: *Penelitian ini merupakan double blind randomized controlled trial dengan kelompok perlakuan diberikan granisetron 1 mg dan kelompok kontrol yang diberikan injeksi ondansetron 8mg. Kemudian dilakukan penilaian terhadap mual dan muntah dengan menggunakan skor MAT pada 12 jam, 24 jam, dan 48 jam setelah diberikan kemoterapi dengan menggunakan Mann-Whitney test karena distribusi data tidak normal.*

Hasil: *Total sampel pada penelitian ini adalah 60 subjek. Hasil skor MAT pada 12 jam berbeda bermakna dengan skor MAT 24 jam dan skor MAT 48 jam (p= 0,00, p= 0,00. Terdapat perbedaan bermakna secara statistik pada pengaruh terapi granisetron dan ondansetron terhadap skor MAT 12 jam, 24 jam, dan 48 jam (p= 0,00, p= 0,00, p= 0,00).*

Kesimpulan: *Pemberian injeksi granisetron intravena lebih efektif mencegah mual dan muntah dengan menggunakan MAT dibandingkan dengan injeksi ondansetron intravena pada pasien dengan kanker ovarium yang mendapat kemoterapi paclitaxel-carboplatin.*

Kata kunci: *kemoterapi, granisetron, kanker ovarium, ondansetron, skor MAT.*

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INTRODUCTION

Globally, in 2018, more than 295,000 women were diagnosed with ovarian cancer[1]. Data from the International Society of Gynecologic Oncology reveals that ovarian cancer is the second most common cancer following cervical cancer. The most prevalent type of ovarian cancer is the epithelial type, accounting for 90% of primary ovarian tumors[2]. Chemotherapy, particularly for stage IC or IIIC epithelial ovarian cancer, involves platinum-based combinations like carboplatin and paclitaxel every 3 weeks for 6 cycles[3].

Nausea and vomiting occurring after chemotherapy is known as chemotherapy-induced nausea and vomiting (CINV). Chemotherapy's side effects affect patients' quality of life[34] Nausea and vomiting top the list of chemotherapy-related side effects affecting daily life and causing anxiety [4]. The severity of these symptoms can lead to dose adjustments, potentially reducing chemotherapy dosage. Uncontrolled nausea and vomiting might even prompt patients to refuse further chemotherapy, underscoring their significance in cancer treatment [5].

Ondansetron and granisetron, both anti-vomiting 5-HT3 antagonists, are often used to mitigate chemotherapy-induced nausea. These drugs have different pharmacodynamics and pharmacokinetics mechanisms for reducing nausea and vomiting. Ondansetron has a half-life of 6 hours, with 70% protein binding, hepatic metabolism, and 5% elimination through feces and urine. Granisetron, on the other hand, has a half-life of 9½ hours, 65% protein binding, hepatic metabolism, and elimination via urine and feces [6]. In terms of pharmacodynamics, granisetron selectively binds to 5-HT3 receptors, while ondansetron also binds to 5-HT1b, 5-HT1C, 1-adrenergic, and -opioid receptors. Both drugs are cost-effective [7].

The MASCC Antiemesis Tool (MAT) was developed to assist patients and oncologists in preventing and controlling chemotherapy-induced nausea and vomiting. MAT is an easy-to-use tool applicable in individual patient care [8]. There is still controversy regarding the effectiveness of granisetron compared to ondansetron in preventing nausea and vomiting. Hence, this study aims to compare the anti-emetic effects of granisetron and ondansetron using the MASCC Antiemesis Tool (MAT) in ovarian cancer patients who recently received paclitaxel-carboplatin chemotherapy.

METHODS

Globally, in 2018, more than 295,000 women were diagnosed with ovarian cancer [1]. Data from the International Society of Gynecologic Oncology reveals that ovarian cancer is the second most common cancer following cervical cancer. The most prevalent type of ovarian cancer is the epithelial type, accounting for 90% of primary ovarian tumors [2]. Chemotherapy, particularly for stage IC or IIIC epithelial ovarian cancer, involves platinum-based combinations like carboplatin and paclitaxel every 3 weeks for 6 cycles [3].

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emetic effects of granisetron and ondansetron using the MASCC Antiemesis Tool (MAT) in ovarian cancer patients who recently received paclitaxel-carboplatin chemotherapy.

RESULTS

This study was performed at Dr. Sardjito Hospital from July 2020 to March 2021. The number of study participants was 60 patients divided into two groups: 30 patients in the control group received 8 mg intravenous ondansetron injection, and 30 patients in the treatment group received intravenous granisetron (Granon®) 1 mg (Figure 1).

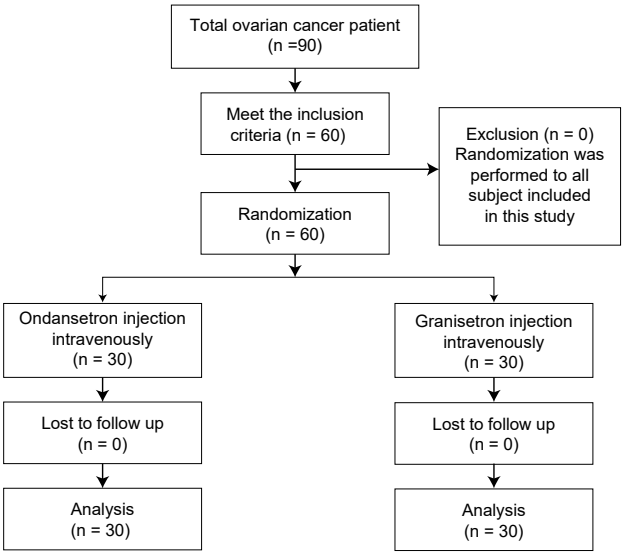

Figure 1. CONSORT Diagram

Table 1. Subject Characteristics

Variabel	Treatment				n		*P-value*
	Granisetron		Ondansentron				
Age (y o)							
< 50	18	(56.2)	14	43.8	32	53.3	0.31
> 50	12	(42.8)	16	57.2	28	46.7	
BMI (kg/m²)							
< 27.5	27	(50)	27	50	54	90	1.00
> 27.5	3	(50)	3	50	6	10	
History of nausea and vomiting							
Yes	5	(62.5)	3	37.5	8	13.3	0.70
No	25	(48)	27	52	52	86.7	
Cancer stage							
Early	16	(47)	18	53	34	56.7	0.60
Late	14	(53.8)	12	46.2	26	43.3	
Residual tumour (cm)							
<2	28	(54.9)	23	45.1	51	85	0.14
>2	2	(22.2)	7	77.8	9	15	
Chemotherapy dose							
Paclitaxel		230		230			0.29
(Median (Min-Max)		(180-230)		(180-230)			
Carboplatin		450		450			0.30
(Median (Min-Max)		(450-600)		(450-600)			

Table 1 displays the subject characteristics of the two groups. In the age group < 50 years old, there were 32 cases (53.3%), while for the age group >50 years old, there were 28 cases (46.7%). For the BMI <27.5 kg/m2 group, there were 54 cases (90%), and BMI > 27.5 kg/m2 group had 6 cases (10%). Fifty-two subjects (86.7%) had a previous history of nausea and vomiting, with 26 subjects (43.3%) having advanced tumor stage, and 51 subjects (85%) having residual tumor < 2cm.

There was no significant difference in the dose of paclitaxel and carboplatin in the granisetron and ondansetron groups. The Friedman test was then performed to assess the differences in MAT scores at 12-hour, 24-hour, and 48-hour intervals. Friedman test results showed that the highest average MAT score was at 48-hour (2.28), followed by 24-hour (2.19), and 12-hour (1.53). The p-value < 0.05 indicates differences in MAT scores across measurements at 12-hour, 24-hour, and 48-hour intervals. Wilcoxon test (post hoc analysis for Friedman test) was performed to evaluate the differences between MAT scores.

Table 2. Wilcoxon test results

MAT Score (hours)	Median (min-max)	*P-value*
12 – 24	0.00 (0-6)	0.001
12 – 48	2.00 (0-7)	0.001
24 – 48	2.00 (0-11)	0.211

Statistically, it can be concluded that the 12-hour MAT score was significantly different from the 24-hour MAT score and the 48-hour MAT score, but the 24-hour MAT score was not significantly different from the 48-hour MAT score.

Table 3. Effect of therapy on MAT scores at 12-hour, 24-hour, and 48-hour

MAT Score (hours)	Granisetron (n=30)	Ondansetron (n=30)	*P-value*
	Median (min-max)	Median (min-max)	
12	0.00 (0-5)	3.00 (0-6)	0.000
24	0.00 (0-4)	3.50 (0-7)	0.000
48	1.00 (0-4)	4.50 (0-11)	0.000

The Mann Whitney test was performed to determine the effect of therapy on 12-hour, 24-hour, and 48-hour MAT scores. The test results found that $p < 0.05$ and the difference in the median value between groups was 3, which means differences in MAT scores (12, 24, and 48 hours) between subjects receiving granisetron and ondansetron therapy. There is a relationship between MAT scores and treatment, both statistically and clinically. Granisetron is more effective in preventing nausea and vomiting (lower median value) than ondansetron.

Table 4. Multivariate Analysis between Therapy (granisetron and ondansetron) and Patient Age on MAT score.

	MAT Score (hours)	F	df	Error df	*P-value*
Antiemetic	12	17.806	1	56	0.000
	24	35.706	1	56	0.000
	48	24.853	1	56	0.000
Age	12	17.806	1	56	0.000
	24	35.706	1	56	0.000
	48	24.853	1	56	0.000

MANOVA (Multivariate Analysis of Variance) test was performed to determine the effect of therapy (granisetron and ondansetron) and age on 12-hour, 24-hour, and 48-hour MAT scores, respectively. The test results found that there were differences in MAT scores (12, 24, and 48 hours) based on the given therapy and age ($p < 0.05$).

DIISCUSSIION

Chemotherapy-induced nausea and vomiting (CINV) is a significant side effect experienced by cancer therapy patients. Inadequate control of CINV can reduce patients' quality of life, leading to additional complications, increased hospital costs, and decreased patient compliance with cancer therapy. Our study demonstrates both clinical and statistical differences between the 12-hour MAT score and the 24-hour MAT score, as well as the 48-hour MAT score. However, the 24-hour MAT score was not significantly different from the 48-hour MAT score. This finding is attributed to the pharmacodynamics of the antiemetic drugs. The relatively short half-life of ondansetron, ranging from 3 to 6 hours, results in declining levels in the body within 24 hours. Similarly, granisetron's half-life is 5 to 9 hours, causing a decrease in systemic concentration after 24 hours.

Our study also reveals differences in MAT scores (12, 24, and 48 hours) between subjects receiving granisetron and ondansetron therapy. Granisetron was more effective in preventing nausea and vomiting (lower median value) than ondansetron. This outcome contrasts with a previous study by Muhilrel et al., 2016, which found similar effectiveness between granisetron and ondansetron in controlling CINV, especially in the acute phase. These discrepancies may be attributed to variations in subject characteristics and the type of therapy administered.

Our results align with studies demonstrating that 1 mg of granisetron is more effective than 8 mg of ondansetron in preventing acute CINV. Administering granisetron with dexamethasone in gynecologic cancer patients who received carboplatin chemotherapy also yielded positive responses. Prophylactic single antiemetic therapy is suitable for patients undergoing minimally emetogenic chemotherapy (such as Paclitaxel). Furthermore, another cohort study found that granisetron effectively prevents CINV in low emetogenic potential chemotherapy. Patients receiving granisetron exhibited better clinical responses to nausea and vomiting during the acute phase.

One limitation of this study was that MAT score assessments were conducted through indirect communication methods (telephone). Some subjects were difficult to contact due to inactive or unreachable phone numbers, resulting in imprecise timing of MAT score assessments at 12-hour, 24-hour, and 48-hour intervals.

CONCLUSION

In conclusion, our study demonstrated that intravenous injection of granisetron was more effective in preventing nausea and vomiting at 12 hours, 24 hours, and 48 hours compared to intravenous ondansetron injection in ovarian cancer patients undergoing paclitaxel-carboplatin chemotherapy

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CONFLICT of INTEREST

There is no apparent conflict of interest for the authors to declare in this report.

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AUTHOR CONTRIBUTION

This case report was written with equal contributions from all authors.

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Research Article

Roma Index and Adnex Model: which is more Superior in Predicting Epithelial Ovarian Malignancy?

Index Roma dan Model Adnex: Manakah yang Lebih Unggul dalam Memprediksi Keganasan Ovarium Epitelial?

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Abstract

Objective: To compare the accuracy of ROMA index and ADNEX model in predicting the risk of malignancy in ovarian tumour.

Methods: This was a prospective analytic study. A total of 37 samples were acquired from women of all ages diagnosed with an ovarian cystic tumour in the Central General Hospital Prof. Dr. R. D. Kandou. A CA-125 marker, HE4 marker, menopausal status and ultrasonography (USG) examination were obtained, and subsequently compared with the final histopathological results. The data were analysed by using the SPSS statistics software.

Results: Thirty-seven women participated in this study. The mean age of participants was 43 years old. The Area Under Curve (AUC) of the ADNEX was 0.979 with a sensitivity of 90.0%, specificity of 88.2%, negative predictive value of 89.8%, and positive predictive value of 80.5%. The AUC of the ROMA model was 0.734 with the sensitivity, specificity, negative predictive value, and positive predictive value of 65.0%, 64.7%, 64.8%, and 64.8%, respectively. Both models showed AUC values > 0.50 (p-value < 0.05).

Conclusions: The IOTA ADNEX had better accuracy than the ROMA model in predicting ovarian epithelial malignancy. The ADNEX model had higher sensitivity and specificity than the ROMA model.

Keywords: ADNEX, CA-125, HE4, Ovarian tumour, ROMA.

Abstrak

Tujuan: *Untuk membandingkan akurasi indeks ROMA dan ADNEX model dalam memprediksi keganasan tumor ovarium*

Metode: *Penelitian ini merupakan studi analitik prospektif. Total 37 sampel penelitian didapatkan dari wanita yang didiagnosa tumor ovarium kistik di RSUP Prof. Dr. R. D. Kandou. CA-125, HE4, status menopause dan pemeriksaan USG dilakukan, dan dibandingkan dengan hasil histopatologi. Data kemudian dianalisa menggunakan program statistik SPSS.*

Hasil: *Tiga puluh tujuh perempuan yang berpartisipasi dalam penelitian ini. Dengan rerata usia 43 tahun. Total Area Under Curve (AUC) dari IOTA ADNEX adalah 0,979 dengan sensitivitas 90,0%, spesifisitas 88,2%, nilai prediksi negatif 89,8%, dan nilai prediksi positif 80,5%. AUC dari model ROMA adalah 0,734 dengan sensitivitas, spesifisitas, nilai prediktif negatif dan nilai predikitif positif 65.0%, 64.7%, 64.8%, dan 64.8% berturut-turut. Kedua model menunjukkan nilai AUC > 0,50 (nilai p <0,05).*

Kesimpulan: *IOTA ADNEX memiliki akurasi yang lebih baik dibandingkan model ROMA dalam memprediksi keganasan ovarium epithelial. ADNEX model memiliki sensitivitas dan spesifisitas lebih tinggi dibandingkan model ROMA*

Kata kunci: *ADNEX, CA-125, HE4, ROMA, Tumor Ovarium.*

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INTRODUCTION

Adnexal mass is a mass or tumour originating from the ovarium, fallopian tube, and other structures adjacent to the two organs. Ovarian tumour is considered a major and important adnexal mass. Ovarian tumour is an abnormal growth of mass from the ovarium, which varies from ovarian cyst to ovarian cancer. The prevalence of ovarian cancer is lower than breast cancer, but it is three times more lethal, and the mortality rate caused by ovarian cancer in 2040 is predicted to increase significantly.[1-3] Tumour marker is a vital component of early diagnosis in several types of malignancy. The Carbohydrate Antigen 125 (CA 125) is one of the widely used tumour markers; it increases in some physiological and pathological conditions, such as menstruation, pregnancy, endometriosis, and peritoneal inflammatory disease. However, CA 125 does not increase in approximately 50% of early-stage ovarian cancer cases. Therefore, the specificity of CA 125 is considered to be poor.[4,5]

Another tumour marker has been developed to obtain a better specificity. The Human Epididymis Protein 4 (HEP4) is widely used and investigated in ovarian cancer cases. It is abundantly produced in patients with ovarian cancer. Despite its high specificity, it has poor sensitivity, hence it is not recommended to use HE4 as a single diagnostic modality.[2,5]

In 2014, the International Ovarian Tumor Analysis (IOTA) published The Assessment of Different Neoplasias in the adnexa (ADNEX) model, consisting of three clinical and six ultrasonographic predictors. The ADNEX model was designed to estimate someone's risk of developing benign ovarian tumour, borderline ovarian tumour (BOT), stage I ovarian cancer, stage II-IV ovarian cancer, and metastatic tumour. Some preliminary studies showed excellent prediction performance based on a sensitivity of 96.5% and a specificity of 71.3%. The ADNEX model also can be used to differentiate benign ovarian tumours and ovarian cancer well.[6-8]

Considering the high mortality rate caused by ovarian cancer in Asia, particularly the epithelial one, and the possibility of different accuracy for different populations even by using the same ovarian cancer prediction model, it is essential to conduct a further study to estimate the accuracy of epithelial ovarian cancer prediction models in Asia – especially in Indonesia. Therefore, we conducted a study to analyse the difference in diagnostic accuracy between the ROMA and the ADNEX model in the Central General Hospital Prof. Dr. R. D. Kandou, Manado. This research aimed to compare the accuracy of two diagnostic methods (the ROMA and the ADNEX model) in predicting ovarian cancer preoperatively to histopathological results as the gold standard in ovarian tumour cases.

METHODS

This prospective analytic study aimed to compare the accuracy of two diagnostic methods (the ROMA model and the ADNEX model). This study was conducted from December 2021 until March 2022. The samples were acquired from women of all ages diagnosed with ovarian cystic mass who visited the Department of Obstetrics and Gynecology of Central General Hospital Prof. Dr. R. D. Kandou. Sample size was calculated to represent the whole ovarian tumor population in Central General Hospital Prof. Dr. R. D. Kandou. The samples were obtained as primary data from women of all ages who visited the Department of Obstetrics and Gynecology of Central General Hospital Prof. Dr. R. D. Kandou as outpatients or inpatients with the diagnosis of ovarian cystic mass, met the inclusion and exclusion criteria of the study, and signed the informed consent.

The inclusion criteria in this study were women of all ages who visited the Department of Obstetrics and Gynecology of Central General Hospital Prof. Dr. R. D. Kandou as outpatients or inpatients diagnosed with an ovarian cystic mass from December 2021 until March 2022; have consented to be included in the study and have had histopathology examination carried out as the gold standard in the diagnosis of an ovarian mass. The exclusion criteria were patients who declined to be included in the study and with incomplete data.

The dependent variable in this study was histopathology examination results as the gold standard of adnexal mass diagnosis, and the independent variables were the ROMA model and the ADNEX model. The data were analyzed by using the SPSS statistics software.

RESULTS

There were 37 participants included in this study. Participants ranging from 16 years old to 75 years old. Nineteen of 37 participants has reached menopause, and 14 out of 37 participants

were nulliparous. The mean ages of participants with benign, borderline, and malignant tumours were 43, 55, and 49.5 years old, respectively. Participants' mean Body Mass Index was 25.50 kg/m^2 for benign tumour cases, 34.70 kg/m^2 for borderline tumour cases, and 24.85 kg/m^2 for malignant tumour cases. Ten malignant and one borderline tumour cases presented with more than ten locular cysts. The mean sizes of cysts for benign, borderline, and malignant tumour cases were 14.50 mm, 23.10 mm, and 24.00 mm, respectively. Furthermore, the mean sizes of the solid lesions for each benign, borderline, and malignant tumour case were 11.00 mm, 13.00 mm, and 16.20 mm. The mean laboratory CA 125 levels in benign, borderline, and malignant tumours were 83.09 U/mL, 88.46 U/mL, and 532.4 U/ml, respectively. The mean laboratory HE-4 levels for each benign, borderline, and malignant tumours were 107.86 U/mL, 126.10 U/mL, and 745.67 U/mL.

Table 1. Characteristics Distribution of Study Participants

	Benign		Borderline		Malignant	
	N	**x̄(s)/M(Range)**	**N**	**x̄(s)/M(Range)**	**N**	**x̄(s)/M(Range)**
Age (y o)						
<50	8	29 (16-47)	1	24	10	41.5 (32-49)
≥50	6	53 (51-74)	2	57.5 (55-60)	10	57 (50-75)
Total	14	43 (16-74)	3	55 (24-60)	20	49.5 (32-75)
Number of parity (s)						
0	3	-	1	-	4	-
1	2	-	0	-	4	-
>2	9	-	2	-	12	-
BMI (kg/m²)						
<18.5 (underweight)	0	-	0	-	1	18.0
18.5-24.9 (normoweight)	5	22.2 (20.3-23.6)	1	23.5	9	23.2 (19.0-24.7)
25-29.9 (overweight)	9	26.7 (25.3-29.1)	0	-	8	27.5 (25.0-29.8)
>30 (obese)	0	-	2	42.43 (34.7-50.2)	2	32.3 (31.6-32.9)
Total	14	25.50 (20.30-29.10)	3	34.70 (23.50-50.17)	20	24.85 (18.00-32.90)
Menopausal state						
Premenopausal	8	-	2	-	8	-
Postmenopausal	6	-	1	-	12	-
Diameter of lesion (mm)						
Size of the lesion	14	14.50 (7.60-26.80)	3	23.10 (19.00-31.00)	20	24.00 (12.10-34.40)
Size of the solid lesion	14	11.00 (3.00-23.40)	3	13.00 (11.00-27.00)	18*	16.20 (3.00-26.10)
Number of locules						
<10	14	-	2	-	10	-
>10	0	-	1	-	10	-
Number of papillary projection (s)						
1	5	-	1	-	0	-
2	4	-	0	-	2	-
3	4	-	1	-	6	-
>3	1	-	1	-	12	-
Acoustic Shadow						
Present	11	-	1	-	0	-
Not present	3	-	2	-	20	-
Ascites						
Present	0	-	2	-	20	-
Not present	14	-	1	-	0	-
CA 125						
Levels (U/mL)	14	83.09 (107.60)	3	88.46 (124.74)	20	532.48 (1072.70)
HE-4						
Levels (U/mL)	14	107.86(98.71)	3	126.10(76.60)	20	745.68(1409.84)

*x̄ = mean, s = deviation standard, M = median, *: 2 empty participants' data*

The histopathological examination revealed 20 samples of malignant tumours, 14 samples of benign tumours, and three samples of borderline tumours. Most of the tumour was the mucinous type, consisting of 14 malignant and six benign mucinous tumours.

The comparison of the ADNEX and the ROMA model prediction results were shown in Tables 2 and 3, respectively. The ADNEX showed excellent accuracy in predicting all malignant tumour cases, while the ROMA prediction model failed to predict four cases accurately. The ADNEX accurately predicted 11 out of 14 benign tumour cases, while the ROMA model predicted 6 out of 14 benign ones. The ADNEX predicted three borderline cases correctly, while the ROMA model detected two borderline cases as malignant tumours and one as a benign tumour. The Area Under Curve of ADNEX was 0.979 with a sensitivity of 90.0%, specificity of 88.2%, negative predictive value of 89.8%, and positive predictive value of 80.5%. The AUC of the ROMA model was 0.734 with the sensitivity, specificity, negative predictive value, and positive predictive value of 65.0%, 64.7%, 64.8%, and 64.8%, respectively.

Table 2. The Prediction Results of the IOTA ADNEX Compared to Histopathology Examination Results

		Histopathology Results			
		Malignant	**Benign**	**Borderline**	
IOTA ADNEX	Malignant	20	3	0	
	Benign	0	11	0	
	Borderline	0	0	3	
Total		20	14	3	37

Table 3. The Prediction Results of the ROMA Model Compared to Histopathology Examination Results

		Histopathology Results			
		Malignant	**Benign**	**Borderline**	
ROMA	Malignant	16	8	2	
	Benign	4	6	1	
Total		20	14	3	37

Furthermore, the comparison between the IOTA ADNEX and the ROMA prediction models in detecting malignant tumour cases was analysed in ROC curves by using SPSS analytic software, as shown in Figure 1.

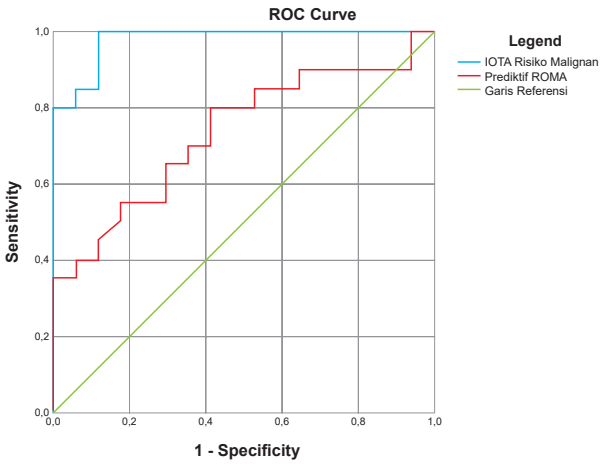

Figure 1. ROC Curves

Table 4. The Prediction Results of the ROMA and IOTA ADNEX Models

	AUC	**CI95%**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	***P-value***
ROMA	0.734	0,572-0,896	65.0	64.7	64.8	64.8	0.015
IOTA ADNEX	0.979	0,944-1,000	90.0	88.2	80.5	89.8	0.000

DISCUSSION

The comparison between the demographic characteristics of the participants, such as age, BMI, parity, and menopausal state, and their respective histopathological results showed less significant value. The age of diagnosis in benign cases was younger than in malignant ones, with an age difference of approximately ten years. This result concluded that old age is a predisposition factor to ovarian cancer incidence. However, our study results showed that participants with borderline cases had older mean age than those with benign and malignant cases. This result was probably due to scarce identification of borderline cases compared to benign and malignant cases, so the data was considered less representative due to a lack of sample numbers.[3]

Parity as a single indicator did not show a significant correlation in the incidence of benign or malignant ovarian tumour cases. This result was in contrast to the results reported that parity had a protective effect on the incidence of ovarian tumours. The difference could be caused by the different sampling techniques used. The study used the case-control method, while our study used the convenience sampling technique in which the samples were obtained from the patients who visited the hospital as outpatients or inpatients.[3,8]

Our study revealed that the subjects with benign cases had greater BMI than that of malignant cases, even though both group were found in the overweight criteria. This finding was similar with previous study that the correlation between obesity based on BMI and the incidence of ovarian cancer was controversial.[3]

The menopausal status in this study demonstrated that more cases of malignant tumours were found in postmenopausal patients compared to premenopausal patients, but it was an insignificant difference. It was in accordance with the result of a study there was a difference between the number of malignant cases in premenopausal and postmenopausal patients by two per cent.[9] It was in contrast to the findings however, the sample in the study was larger compared to our study.[3,10]

The diameter of the lesion tended to increase with the tumour progression into malignant cases. The same result was reported which the mean size of the tumour in stage I cancer is larger than in benign or borderline cases.8 Our study demonstrated a similar result with a ten millimetres difference in tumour mean size between benign and malignant cases.

The more locules in the tumour, the more likely it is to be malignant than benign. A study showed a resembling pattern; a tumour with more than ten locules had a higher probability of being malignant than benign cases.[8]

All subjects in this study had at least one papillary projection. In comparison with another study, the absence of papillary projection was suggestive of a benign case instead of a malignant one. If less papillary projection was present, the tumour would likely to be benign.[8]

The tendency to find an acoustic shadow in ultrasonographic parameters was likely higher in benign cases and less in malignant case. In contrast, the finding of ascites in cases of adnexal masses was more suggestive of malignant tumour conditions. A previous study conducted [11-13] also described the presence of acoustic shadow as a parameter indicating cases of benign tumours and not cases of malignant tumours which could also be found in various types of assessment models, such as the IOTA Simple Rules, IOTA LR, De Priest, and O-RADS. In contrast, the IOTA Simple Rules established the presence of ascites as an indicator parameter for malignant cases.[13,14] Ascites is caused by fluid outflow due to vasodilation which then accumulates in the peritoneal cavity but fails to be reabsorbed into the lymphatic system due to the inhibition of fluid backflow by tumour cells.[15] These findings were then established as excellent additional examination and indicator in predicting the incidence of adnexal tumours, such as ovarian tumours.[14]

The results of the CA 125 and HE 4 parameters in this study showed that an increase could indicate the incidence of malignant tumour cases. This result was in accordance with some studies.[4-5,15] The previous studies also explained that despite the good predictive values of CA 125 and HE 4, they should not be used independently, but rather in combination with other parameters to diagnose malignant ovarian tumours. This resulted in CA 125 and HE 4 being included as parameters in the ROMA Model. [4-5,15,16]

The pathogenesis and pathophysiology of ovarian tumours are multifactorial, so every diagnostic study did not recommend using a single parameter to be considered a causative factor in the incidence of ovarian tumours. This was the background for formulating various ovarian tumour assessment models, such as the

ROMA and IOTA ADNEX models. [4,5,6-7,11,12,15-20]

In the assessment of ovarian tumours, both the ROMA and IOTA ADNEX models demonstrated better accuracy in predicting cases of malignant tumours rather than benign ones.

The comparative study of both prediction models showed that the IOTA ADNEX criteria had higher sensitivity and specificity than the ROMA Model. (90.0% and 88.2% vs. 65.0% and 64.7%). The AUC of the ROMA model was slightly smaller than the IOTA ADNEX model. (0.734; CI95%=0.572-0.896 vs. 0.979; CI95%=0.944-1.000).

The results of the predictive ability of ROMA in estimating the incidence of malignant tumours in this study differed from those, however, it resembled the results with significantly lower sensitivity and specificity than previous studies.[4,15-17,20,22-24] This could be due to the smaller number of study participants, and the comparative analysis between premenopausal and postmenopausal cases was not done. These findings were in accordance with the study which reported that the ROMA criteria had low sensitivity in premenopausal patients.[16]

The predictive performance of the IOTA ADNEX in this study was in accordance with the studies conducted.[7,21,25] This similar result supported the previous studies that the IOTA ADNEX predictive ability is adequately sensitive in detecting cases of malignant tumours despite the small number of study participants.

Some aspects to be reconsidered in the application of the ADNEX or ROMA Model include the facilities of health services available at the time of diagnosis. The ROMA requires CA-125 and HE-4 levels examination. On the contrary, the ADNEX requires a reliable sonographer and laboratory CA-125 level examination to establish the diagnosis,[11] not to mentioned the good accuracy ADNEX possess without CA-125 levels, but the presence of a clinical sonographer remains essential in diagnosing ovarian cancer malignancies using the ADNEX method.[7]

CONCLUSION

The IOTA ADNEX model had better accuracy than the ROMA model in predicting ovarian epithelial malignancy. The ADNEX model had a higher sensitivity and specificity than the ROMA model.

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ETHICAL CLEARANCE

KOMITE ETIK PENELITIAN KESEHATAN
HEALTH RESEARCH ETHICS COMMITTEE
RSUP PROF. DR. R. D. KANDOU MANADO
RSUP PROF. DR. R. D. KANDOU MANADO HOSPITAL

KETERANGAN LAYAK ETIK
DESCRIPTION OF ETHICAL APPROVAL
"ETHICAL APPROVAL"

No.005/EC/KEPK-KANDOU/I/2022

Protokol penelitian yang diusulkan oleh :
The research protocol proposed by

Peneliti utama : Feibyg Theresia Lumandung
Principal In Investigator

Nama Institusi : RSUP Prof dr. R. D. Kandou Manado
Name of the Institution

Dengan judul:
Title

"PERBANDINGAN AKURASI MODEL RISK OF OVARIAN MALIGNANCY ALGORITHM (ROMA) DENGAN ASSESSMENT OF DIFFERENT NEOPLASIAS IN THE ADNEXA (ADNEX) DALAM MEMPREDIKSI KEGANASAN OVARIUM EPITELIAL"

"COMPARISON OF ACCURACY OF THE RISK OF OVARIAN MALIGNANCY ALGORITHM (ROMA) MODEL WITH ASSESSMENT OF DIFFERENT NEOPLASIAS IN THE ADNEXA (ADNEX) IN PREDICTING OVARIAL EPITELIAL MALIGNANCY"

Dinyatakan layak etik sesuai 7 (tujuh) Standar WHO 2011, yaitu 1) Nilai Sosial, 2) Nilai Ilmiah, 3) Pemerataan Beban dan Manfaat, 4) Risiko, 5) Bujukan/Eksploitasi, 6) Kerahasiaan dan Privacy, dan 7) Persetujuan Setelah Penjelasan, yang merujuk pada Pedoman CIOMS 2016. Hal ini seperti yang ditunjukkan oleh terpenuhinya indikator setiap standar.

Declared to be ethically appropriate in accordance to 7 (seven) WHO 2011 Standards, 1) Social Values, 2) Scientific Values, 3) Equitable Assessment and Benefits, 4) Risks, 5) Persuasion/Exploitation, 6) Confidentiality and Privacy, and 7) Informed Concent, referring to the 2016 CIOMS Guidelines. This is as indicated by the fulfillment of the indicators of each standard.

Pernyataan Laik Etik ini berlaku selama kurun waktu tanggal 14 Januari 2022 sampai dengan tanggal 14 Januari 2023.

This declaration of ethics applies during the period January 14, 2022 until January 14, 2023.

Prof. Dr. dr. Max F. J. Mantik, Sp.A(K)

Research Article

Diagnostic Performance of Urine-based HPV-DNA Test (CerviScan, Bio Farma) as Cervical Cancer Screening Tool in Adult Women

Performa Tes Diagnostik DNA-HPV berbasis Urine (CerviScan, Bio Farma) sebagai Alat Skrining Kanker Serviks pada Perempuan Dewasa

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Abstract

Objective: Detection of high-risk human papillomavirus (hr-HPV) in urine specimens has been introduced recently and a new local PCR kit has been developed in Indonesia (CerviScan, Bio Farma). The objective of this study was to obtain the accuracy of hr-HPV DNA testing using the new kit (CerviScan, Bio Farma) on urine specimens against the gold standard on cervical swabs.

Method: Adult women (aged 20–50 years) underwent routine general check-up or Pap test were enrolled between July and September 2022. Pairs of urine and cervical swab specimens were obtained from all subjects. HPV-DNA tests were performed using the new local PCR kit (CerviScan, Bio Farma) and the standard procedure (COBAS® 6800 HPV, Roche Molecular System). Direct sequencing was done whenever there were dispute results between the two methods. Agreement between both methods was tested using Kappa statistics. Diagnostic performance test was done on CerviScan.

Results: A total of 876 women completed the examination. Agreement between CerviScan and COBAS® 6800 was substantial (κ=0.662; p<0.001) and was almost perfect against COBAS® 6800 plus sequencing (κ=0.828; p<0.001). The accuracy of CerviScan on urine samples was 95.8% against COBAS® 6800 and increased to 97.8% after additional sequencing. The sensitivity and specificity of CerviScan on urine samples compared to cervical swabs are 73.1% and 97.3%, respectively.

Conclusion: Urine-based HPV-DNA testing with CerviScan is a reliable tool to detect high-risk HPV subtypes. It could become an alternative method for HPV-DNA testing to improve the coverage of cervical cancer screening program.

Key words: cervical cancer, HPV-DNA test, HPV molecular test screening, human papilloma virus, urine test.

Abstrak

Tujuan: *Deteksi high-risk human papillomavirus (hr-HPV) pada spesimen urin telah diperkenalkan baru-baru ini dan kit PCR lokal baru telah dikembangkan di Indonesia (CervisScan, Bio Farma). Tujuan dari penelitian ini adalah untuk mengetahui keakuratan pengujian DNA hr-HPV menggunakan kit baru (ServiScan, Bio Farma) pada spesimen urin terhadap baku emas pada apusan serviks.*

Metode: *Perempuan dewasa (usia 20-50 tahun) direkrut untuk menjalani pemeriksaan umum rutin atau Pap tes antara Juli dan September 2022. Spesimen urin dan apusan serviks diperoleh dari seluruh subjek. Tes HPV-DNA dilakukan menggunakan kit PCR lokal baru (CerviScan, Bio Farma) dan baku emas (COBAS® 6800 HPV, Roche Molecular System). Sequencing langsung ditambahkan setiap kali terdapat perbedaan hasil antara kedua metode. Kesepakatan (agreement) antara kedua metode diuji menggunakan statistik Kappa. Uji perfoma diagnostik CerviScan dilakukan terhadap COBAS® 6800 HPV.*

Hasil: *Sebanyak 876 perempuan dewasa mengikuti pemeriksaan. Ditemukan kesepakatan substansial antara CerviScan dan COBAS® 6800 (κ=0.662; p<0.001) dan hampir sempurna terhadap COBAS® 6800 ditambah sequencing (κ=0.828; p<0.001). Keakuratan CerviScan pada sampel urin adalah 95,8% terhadap COBAS® 6800 dan meningkat menjadi 97,8% setelah ditambah sequencing. Sensitivitas dan spesifisitas CerviScan pada sampel urin dibandingkan dengan apusan serviks masing-masing adalah 73,1% dan 97,3%.*

Kesimpulan: *Pengujian HPV-DNA berbasis urin dengan CerviScan memiliki keandalan untuk mendeteksi subtipe HPV risiko tinggi. Pemeriksaan ini dapat menjadi metode alternatif untuk pengujian DNA-HPV dalam memperluas program skrining kanker serviks.*

Kata kunci: *human papilloma virus, kanker serviks, skrining, tes urin, uji HPV-DNA, uji molekuler HPV.*

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INTRODUCTION

Cervical cancer is the second most common female cancer found in Indonesia. In 2020, the Global Burden of Cancer Study (GLOBOCAN) estimated a total of 36,633 cervical cancer cases or 9.2% of all cancers.[1] The incidence rate of cervical cancer in Indonesia was 27 cases per 100,000 women with mortality rate at 3.95 per 100,000 women at all ages.[2]

Almost all cervical cancer cases are caused by persistent infection with high-risk human papillomavirus (hr-HPV) through the action of its oncoproteins.[3] Screening for hr-HPV is now the gold standard to prevent cervical cancer and other HPV-related diseases.[4] In high-resource countries, screening strategies currently used cytological evaluation (Pap smear), nucleic acid HPV-testing or both. Visual inspection with acetic acid (VIA) is another method commonly done in developing countries that aims to detect pre-cancer and early cancer lesions in apparently normal and asymptomatic women.[5] Previous randomized controlled trials found that hr-HPV screening is more sensitive in detecting precancerous lesions than the cytological screening methods.[6]

Although screening is beneficial in cervical cancer prevention, Pap smear is considered physically uncomfortable for women.[7] Two most common barriers to get cervical screening were pain or discomfort (67.2%) and embarrassment (57.9%).[8] Therefore to encourage screening, other strategy should be thought to increase women willingness to attend screening.

Self-collected urine sampling has been introduced for more than a decade to increase screening uptake rates.[9,10] Meta-analyses showed that urinary HPV test had a pooled sensitivity of 77% and specificity of 88% compared with clinician-collected cervical HPV test (cervical HPV test).[11] In Indonesia, a new PCR-based diagnostic kit (CerviScan) has been developed recently to detect 14 high-risk HPV subtypes based on qualitative polymerase-chain reaction (PCR) assay. The kit is developed by Bio Farma in collaboration with Nusantics, a biotechnology company in Indonesia. Bio Farma is a state-owned pharmaceutical company, while Nusantics is a private company focusing on genetic research. However, before providing it for wide clinical application, a proper diagnostic study should be performed. Therefore, the objective of this study was to obtain the accuracy of hr-HPV DNA testing using the new kit (CerviScan, Bio Farma) against the standard PCR-based HPV-DNA testing and to test diagnostic performance of CerviScan on urine specimens against standard PCR-based HPV-DNA testing on cervical swabs.

METHODS

The study design was a diagnostic study comparing the new HPV-DNA diagnostic kit (CerviScan, Bio Farma) with the standard diagnostic kit (COBAS® 6800 HPV, Roche Molecular system). The study was held between July and September 2022. Sample processing and PCR were done in the laboratory of Clinical Pathology Department, Cipto Mangunkusumo National Central General Hospital, Jakarta. DNA sequencing was done to confirm different results in a private laboratory (Nusantics), Jakarta. Ethics approval was granted from the Health Research Ethic Committee of the Faculty of Medicine Universitas Indonesia Dr. Cipto Mangunkusumo Hospital (No. KET- 674 / UN2.F1/XTIK/PPM.00.0212022).

Study subjects were sexually active women aged 20–50 years who came for routine general check-up or cervical cancer screening using PAP test or IVA. Written consent was obtained from all participants. Subjects were recruited from several clinics of pharmaceutical holding companies where specimens were taken. All subjects provided self-collected urine sample with a minimum volume of 30 mL in a sterile container, and cervical swabs were taken by trained health workers using a cytobrush and promptly preserved in liquid transport medium (ThinPrep PreservCyt Solution® - Hologic, Inc. Malborough, MA, USA). The number of subjects required for this study was estimated using the sample size calculation for sensitivity and specificity,[12,13] the normal distribution value (Z) was set to 1.96 at 95% confidence interval and the maximum acceptable width of the 95% confidence interval (W) was set to 10%. Based on the prevalence (P) of HPV infection among Indonesian women of 5.2%[14] the minimum sample size obtained was 666 women. Sexually active women aged 20–50 years who visit company clinics for PAP smear or IVA test were enrolled. Subjects were excluded if they were pregnant, HIV-infected, having menstruation, or have received completed doses of HPV vaccination.

Diagnostic Kit

Diagnostic kit prototype (CerviScan) was made by Nusantics, which was designed to simultaneously detect 14 high-risk HPV types. It consisted of three components, i.e. qPCR ReadyMix, Nuclease-Free Water (NFW), and HPV Positive Control. The qPCR ReadyMix combined enzymes, probes, and buffered need for qPCR reaction. Cerviscan is a qPCR-based molecular diagnostic kit to detect 14 high-risk HPV types (hr-HPV) associated with cervical cancer, namely HPV types 16,18, 31, 33, 35, 39, 45,51,52,56, 58,59,66 and 68. Furthermore, the kit can be specifically genotyping the HPV type 16, 18, 52. The kit can be applied to detect HPV-DNA from both urine and cervical swab specimens.

HPV-DNA Testing on Urine Samples

Urine samples were self-collected using a sterile urine container allowing a collection of 30 mL first-void urine. Samples were labeled and transferred to the laboratory. Upon arrival in the laboratory, samples were stored at 4oC and processed within 2 days or at -80o C when further process will be delayed more than 3 days.

Briefly, the urine samples were homogenized, and urine sediment were obtained from the 5 ml samples by centrifugation at 800 rcf for 10 min and then the supernatant was discarded. After resuspension, the DNA was extracted from 200 µl of the sample using a standard method of spinned column. The eluent were ready for PCR.

The PCR was done by mixing 5 uL DNA eluent and 15 uL CerviScanReadyMix. Amplification on BioRad CFX-96 thermocycler for 45 cycles. Signal of HPV 16 (HEX), HPV18 (Texas Red), HPV52 (Cy5), Other HR type (FAM), and internal control were considered as detected when Ct value ≤ 40 The result were considered invalid when internal control not detected

HPV-DNA Testing on Cervical Swabs

Each cervical swab specimen was divided into two samples for HPV-DNA testing using CerviScan and COBAS® 6800 system. For CerviScan the sample processing procedure followed the same procedure as the urine sample, and for the COBAS® 6800 system followed the procedure from the manufacturer.

Direct Sequencing

Direct sequencing was performed whenever there was a discrepancy of test results between CerviScan and COBAS® 6800 system using next generation sequencing (NGS) technique.

Statistical Analyses

Agreement between the two methods was tested using Kappa statistics; results were defined as poor ($\kappa = 0$), slight ($0.01 < \kappa < 0.20$), fair ($0.21 < \kappa < 0.40$), moderate ($0.41 < \kappa < 0.60$), substantial ($0.61 < \kappa < 0.80$), almost perfect ($0.81 < \kappa < 1$) or perfect ($\kappa = 1$).

Diagnostic performance test result was expressed as sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive and negative likelihood ratios (LRs). Statistical analysis was done using IBP SPSS version 26.

RESULTS

The study population consists of 876 women who completed examination. Invalid results of CerviScan was 3.0% on urine samples and 1.8% on cervical swab samples, whereas COBAS® 6800 system was failed in 23.5% urine specimens and 2.7% on cervical swab samples. The prevalence of HPV infection was 5.9% based on the COBAS® 6800 test on the cervical swab as the gold standard. However, the test kit (CerviScan) on urine samples resulted a prevalence of 6.8%.

Agreement between CerviScan on urine samples and standard test on cervical swab is shown in Table 1a and 1b. Additional seven results were detected during sequencing on urine samples which were initially invalid, hence the total sample is change from 826 (table 1a) to 833 (table 1b).

Table 1a. Agreement between CerviScan (Bio Farma, Indonesia) on Urine Samples and COBAS® 6800 on Cervical Swab on the detection of high-risk Human Papiloma Virus (n= 826).

CerviScan	COBAS® 6800	
	HR-HPV +	HR-HPV-
HR-HPV+	38	21
HR-HPV-	14	753

Kappa statistics = 0.662; $p < 0.001$

Table 1b. Agreement between CerviScan (Bio Farma, Indonesia) on Urine Samples and COBAS® 6800 + Direct Sequencing on Cervical Swab on the detection of high-risk Human Papiloma Virus (n= 833).

CerviScan	COBAS® 6800 + Direct Sequencing	
	HR-HPV +	HR-HPV-
HR-HPV+	50	5
HR-HPV-	13	765

Kappa statistics = 0.828; $p < 0.001$

CerviScan showed >95% accuracy against COBAS® 6800 as the standard method, both on urine and cervical swab specimens as shown in table 2.

Table 2. Diagnostic Performance of CerviScan (Bio Farma, Indonesia) on the Detection of High-risk Human Papiloma Virus Compared to COBAS® 6800.

	Cervical Swab (n=838)		Urine (n=658)	
	%	95% CI	%	95% CI
Sensitivity (%)	87.8	75.2 – 95.4	84.3	71.4 – 93.0
Specificity (%)	98.6	97.5 – 99.3	97.5	96.0 – 98.6
PPV (%)	79.6	66.5 – 89.4	74.1	61.0 – 84.7
NPV (%)	99.2	98.3 – 99.7	98.7	97.4 – 99.4
Accuracy (%)	98.0	96.8 – 98.8	96.5	94.8 – 97.8

PPV: positive predictive value, NPV: negative predictive value

Results of CerviScan on urine samples had 95.8% of accuracy compared to the current gold standard, i.e. COBAS® 6800 on cervical swab specimens (95.8%). The accuracy was even better (97.8%) when additional direct sequencing was performed for dispute results as shown in Table 3.

Table 3. Diagnostic Performance of CerviScan (Bio Farma, Indonesia) on the detection of high-risk Human Papiloma Virus on Urine Compared to COBAS® 6800 on Cervical Swab Specimens.

	COBAS® 6800 (n=826)		COBAS® 6800 plus sequencing (n=833)	
	%	95% CI	%	95% CI
Sensitivity (%)	73.1	58.9 – 84.4	79.4	67.3 – 88.5
Specificity (%)	97.3	95.9 – 98.3	99.3	98.5 – 99.8
PPV (%)	64.4	50.9 – 76.4	90.9	80.0 – 96.9
NPV (%)	98.2	96.9 – 99.0	98.3	97.2 – 99.1
Accuracy (%)	95.8	94.2 – 97.0	97.8	96.6 – 98.7
LR-positive	26.9	17.1 – 42.4	122.2	50.6 – 295.5
LR-negative	0.28	0.2 – 0.4	0.21	0.1 – 0.3

PPV: positive predictive value, NPV: negative predictive value; LR: likelihood ratio

DISCUSSION

We showed that the accuracy of urine-based HPV-DNA testing using CerviScan was very high, above 95%, compared to standard method on cervical swab-based method. Specimens that tested negative on standard method but positive on CerviScan were proved to harbor hr-HPV on amplicon sequencing. This showed that specimens were true positive and that CerviScan was superior to the standard method of HPV DNA testing. The higher failure rate of the COBAS® 6800on urine sample were in concordance with the claim of the manufacturer that the system was not validated for urine samples.

There are not many studies comparing diagnostic performance of urine-based HPV detection with the standard test on cervical swab. Our study showed a substantial agreement between CerviScan and the standard method with Kappa value of 0.662 ($p<0.001$). But the agreement was improved when sequencing was added as comparing method, with Kappa value of 0.828 ($p<0.001$). A study in Thailand showed comparable results with our study, they reported a substantial agreement of hr-HPV detection between urine and cervical samples with $\kappa=0.65$. Diagnostic test results were in 68.6% sensitivity, 93.2% specificity, 80.0% PPV, and 88.2% NPV. The gold standard used in the study was Cobas 4800® system.[15] Another study in southern Mexico on 108 pairs of urine and cervical samples from an indigenous population found 68.3% concordance of HPV positivity and 64.5% concordance for hr-

HPV. The sensitivity to detect hr-HPV was 89.7% but the specificity was only 25.7%. The method of HPV genotyping in this study was INNO-LiPA HPV assay.[16]

In our study, we did not look in to the clinical relevances of the HPV infection with regard to cervical intraepithelial lesion (CIN). As HPV infection usually precedes the cervical lesions and has a very long asymptomatic phase of infection. However, recent meta-analysis reported that urinary HPV test was less sensitive than common cervical HPV tests (including COBAS) even though the difference was not statistically significant to detect CIN 2 or worse.[17]

The results of this study may have direct implication on cervical cancer screening program in Indonesia in parallel with a nationwide vaccination programme. As the performance was comparable with the standard method, and due to its convenience, self-sampled urine specimens would be preferable for most women and therefore may increase the rate of HPV-DNA testing by expanding the scope of screening. Moreover, urine sample collection generally requires less consumables, trained personnel, and special facilities, that may result in more affordable test for public heath settings

CONCLUSIONS

In conclusion, urine-based HPV-DNA testing with CerviScan is a reliable tool to detect high-risk HPV subtypes. It is an alternative choice of method for HPV-DNA testing and cervical cancer screening program.

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Case Series

Neuroendocrine Cervical Carcinoma

Karsinoma Serviks Neuroendokrin

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Abstract

Objective: To present a case series of neuroendocrine cervical carcinoma, a rare malignancy of the cervix characterized by varying stages, treatment approaches, and outcomes. The article provides a comprehensive review of diagnostic strategies, treatment modalities, and prognostic considerations for managing neuroendocrine cervical carcinoma.

Methods: Case report

Cases: Three cases of neuroendocrine cervical carcinoma are reported. The first case involves a 40-year-old woman, para 2, diagnosed with stage IIIB neuroendocrine cervical carcinoma, who opted for palliative care. The second case features a 54-year-old woman, para 5, with stage IIB neuroendocrine cervical carcinoma, treated with radiotherapy and achieving a disease-free period of 4 months. The third case showcases a 36-year-old woman, para 2, diagnosed with stage IB1 neuroendocrine cervical carcinoma. She underwent a radical abdominal hysterectomy with pelvic lymphadenectomy and external pelvic radiotherapy, achieving disease control without recurrence for 15 years.

Conclusion: Distinguishing neuroendocrine cervical carcinoma from other cervical malignancies is crucial, with immunohistochemistry (IHC) offering valuable diagnostic insights. Tailored treatment plans are essential for managing these malignancies, with a preference for multimodality approaches to enhance overall outcomes.

Keywords: cervical carcinoma, multimodality treatment, neuroendocrine cervical carcinoma.

Abstrak

Tujuan: *Melaporkan serangkaian kasus neuroendocrine cervical carcinoma, salah satu jenis keganasan langka pada area serviks dengan stadium, tata laksana, dan hasil yang berbeda. Dalam artikel ini juga terdapat ulasan mengenai prosedur diagnosis, manajemen, dan prognosis dari neuroendocrine cervical carcinoma.*

Metode: *Laporan kasus*

Kasus: *Artikel ini melaporkan tiga kasus. Pertama perempuan 40 tahun riwayat partus dua kali dengan karsinoma serviks neuroendokrin stadium IIIB dan hanya memilih perawatan paliatif. Kasus kedua, perempuan 54 tahun, riwayat partus lima kali dengan karsinoma serviks neuroendokrin stadium IIB. Pada pasien dilakukan terapi radiasi dan didapatkan kondisi bebas penyakit selama 4 bulan. Terakhir, pasien perempuan 36 tahun riwayat partus dua kali dengan karsinoma serviks neuroendokrin stadium 1B1. Dilakukan histerektomi radikal dan limfadenektomi kelenjar limfe pelvis serta terapi radiasi. Kondisi pasien terkontrol dan tidak terdapat kekambuhan setelah 15 tahun.*

Kesimpulan: *Karsinoma serviks dengan jenis neuroendokrin harus dibedakan dengan keganasan lain pada daerah serviks. Uji imunohistokimia dapat digunakan untuk membedakan hal tersebut. Selain itu, penyusunan rencana tatalaksana untuk mengatasi keganasan pada serviks juga harus menjadi perhatian penting bagi klinisi. Direkomendasikan untuk menerapkan tata laksana multimodal untuk mencapai hasil terapi yang optimal.*

Kata kunci: *karsinoma serviks, karsinoma serviks neuroendokrin, tata laksana multimodal.*

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INTRODUCTION

Neuroendocrine neoplasms (NENs) constitute an infrequent and heterogeneous category of cancers that can manifest in various locations throughout the body, originating from diffuse neuroendocrine system cells[1]. While NENs are most frequently encountered in the gastrointestinal system, pancreas, and lungs within humans, they can also manifest in diverse organs, including the female genital tract[2]. Referred to as Neuroendocrine Carcinoma of the Cervix (NECC) or simply NECC, this malignancy constitutes approximately 1% of all cervical cancer diagnoses in the United States. Despite its rarity, NECC presents as an aggressively histologic subtype within an otherwise predominantly benign context[3].The rarity of this cancer type imparts challenges and complexities to NECC management. This is exacerbated by the fact that the majority of research concerning neuroendocrine tumor treatment has been conducted on patients with tumors affecting organs other than the cervix, mainly focusing on the lungs and pancreas.

Diverging from characteristics of squamous cell carcinoma or adenocarcinoma of the cervix, NECC exhibits distinct attributes. Notably, NECC tends to infiltrate the lymph-vascular space and extend to local lymph node basins at the time of diagnosis[4]. Furthermore, NECC displays considerably inferior 5-year overall survival rates approximately 30% contrasted with rates exceeding 65% observed in squamous cell carcinoma and adenocarcinoma of the cervix. The incidence of both local and distant relapses is also notably elevated within NECC cases[3].

Case I

A 40-year-old woman, para 2, was admitted with the chief complaint of abnormal uterine bleeding. The patient had a history of post-menstrual spotting. During the gynecological examination, a mass larger than 4 cm was detected in the cervix, extending to the pelvic sidewalls (classified as Stage IIIB in the FIGO staging system). The Papanicolaou smear revealed a high-grade malignant tumor exhibiting lymphovascular invasion, and it was diagnosed as poorly differentiated squamous cervical cancer, grade 3. A tissue biopsy was performed, and Immunohistochemistry (IHC) testing confirmed the presence of neuroendocrine carcinoma. The patient subsequently received palliative treatment.

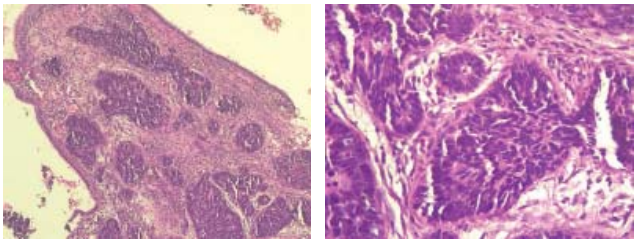

Figure 1. Case I Under microscopy, the neoplasm show a solid structure with round nuclei, forming a rossete like structure and numerous mitoses.

Case II

A 54-year-old woman, para 5, was admitted to the hospital due to abnormal uterine bleeding. A mass larger than 4 cm was identified in the cervix during the gynecological examination. The mass extended to the upper two-thirds of the vagina with parametrial invasion, placing it at Stage IIB according to the FIGO Staging system. Tissue samples were obtained for Papanicolaou smear and Immunohistochemistry (IHC) testing. The Papanicolaou smear revealed the presence of malignant cells, while the results of the Immunohistochemistry (IHC) test indicated neuroendocrine carcinoma. Subsequently, the patient underwent radiotherapy treatment. As of now, the disease is well controlled, and there has been no recurrence within a four-month period.

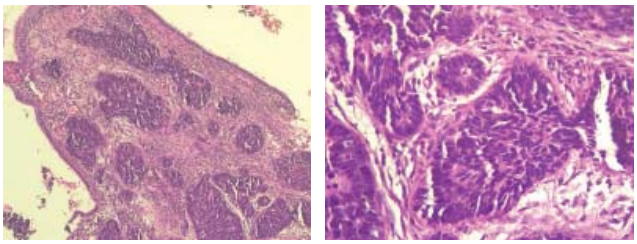

Figure 2. Case II Under microscopy, the neoplasm show a solid structure with evident round or ovoid nuclei, forming a rossete like structure and numerous mitoses.

Case III

A 36-year-old woman, para 2, was admitted to the hospital due to abnormal uterine bleeding. During the gynecological examination, a 4 cm mass was identified in the cervix. The mass was confined to the cervix without extension to the left or right parametrium, classifying it as Stage IB1 in the FIGO Staging system. Tissue samples were obtained for a Papanicolaou smear and Immunohistochemistry (IHC) testing. The

Papanicolaou smear revealed the presence of malignant cells, and the Immunohistochemistry (IHC) test results indicated neuroendocrine carcinoma. Subsequently, the patient underwent a radical abdominal hysterectomy with pelvic lymphadenectomy and received external pelvic radiotherapy. The disease is currently well controlled, and there has been no recurrence over a span of 15 years.

DISCUSSION

Neuroendocrine neoplasms (NENs) represent aggressive malignancies that originate from neuroendocrine cells[5]. These malignancies can manifest in various bodily locations, with common occurrences observed in the gastrointestinal tract, pancreas, and lungs[5]. In rare instances, NENs may also manifest in other organs, including the female genital tract[6]. Neuroendocrine cervical carcinoma (NECC) stands as a rare and aggressive histological variant of cervical cancer, carrying an unfavorable prognosis. These tumors exhibit early lymphatic dissemination and a high incidence of distant recurrence. NECC accounts for approximately 1-1.5% of all cervical cancers[7,8]. The mean overall survival for this form of cervical carcinoma is 40 months, with a 5-year survival rate of 34%[5,9]. Consequently, an assertive therapeutic strategy becomes imperative to achieve effective control over both pelvic and distant disease progression.

The biological characteristics of NECC distinguish it from squamous cell carcinoma or adenocarcinoma of the cervix. NECC exhibits a higher propensity to infiltrate the lymphovascular space and disseminate to nearby regional lymph nodes. This malignancy also demonstrates a heightened frequency of both local and distant relapses, resulting in a notably reduced 5-year survival rate of 34%. In stark contrast, squamous cell carcinoma or adenocarcinoma of the cervix presents a higher 5-year survival rate of 65%[5].

Immunohistochemical (IHC) testing plays a crucial role in confirming the diagnosis of NEEC. Diagnostic indicators for NECC encompass neuroendocrine markers such as synaptophysin (SYN), chromogranin (CHG), CD56 (N-CAM), and neuron-specific enolase (NSE). To establish the diagnosis, a minimum of two positive stainings are requisite[5]. Additionally, assessments for p63 and p40 can aid in distinguishing NECC from squamous cell carcinoma. Positive results for p63 and p40 are specific to squamous cell carcinoma[10].

A well-defined treatment strategy is imperative to effectively manage the disease. Owing to the scarcity of this malignancy, there currently exist no treatment protocols for NECC grounded in prospective clinical trials. Physicians often adopt a multimodal approach, drawing from therapeutic principles applied to cervical cancer at large and insights from neuroendocrine tumor management. The Society of Gynecologic Oncology (SGO) also advocates for this multimodal therapeutic approach, recommending an etoposide/platinum-based chemotherapy regimen for NECC and endorsing radical surgery for early-stage cases, either as a primary intervention or following neoadjuvant chemotherapy. For individuals with advanced-stage disease, the recommendations encompass chemoradiation or systemic chemotherapy, typically involving etoposide and cisplatin. In our case, patients diagnosed with Stage IB1 based on the FIGO staging system underwent radical abdominal hysterectomy accompanied by pelvic lymphadenectomy and external pelvic radiotherapy. Conversely, patients grappling with more advanced stages of the disease were directed towards radiotherapy or exclusively palliative care.

CONCLUSION

Neuroendocrine neoplasms (NENs) constitute a rare and heterogeneous group of cancers. Among these, Neuroendocrine cervical carcinoma (NECC) stands out as a rare and aggressive histological variant of cervical cancer, characterized by an unfavorable prognosis. As a result, the differentiation of neuroendocrine cervical carcinoma from other potential cervix malignancies becomes crucial. Immunohistochemistry (IHC) tests serve as valuable tools for achieving this distinction. Diagnostic indicators such as synaptophysin (SYN), chromogranin (CHG), CD56 (N-CAM), and neuron-specific enolase (NSE) are particularly relevant for confirming NECC. Additionally, assessments for p63 and p40 can be conducted to differentiate NECC from squamous cell carcinoma, where positive p63 and p40 results specifically point to squamous cell carcinoma. The significance of devising a comprehensive treatment plan for managing these malignancies cannot be overstated. Given the rarity and complexity of NECC, a multimodality treatment approach is highly recommended to attain

improved outcomes. It is vital not only to diagnose and differentiate but also to formulate a tailored treatment strategy to effectively address the challenges presented by NECC.

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Case Report

Leiomyoma Ablation with Ultrasonography-Guided Radiofrequency: A Report of Four Cases

Ablasi Mioma denan Radiofrekuensi Terpadu Ultrasonografi: Laporan Empat Kasus

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Abstract:

Objective: This study aims to report the successful application of transvaginal ultrasound-guided radiofrequency ablation (RFA) as a minimally invasive therapy in four women with symptomatic intramural and subserous leiomyomas using a standard protocol.

Methods: A report of four cases.

Case: A case report of four patients was conducted at Soerojo Hospital, Magelang, from September 2021 to January 2022. The first case involved a premenopausal woman experiencing pelvic discomfort. The second case underwent curettage after a diagnosis of a blighted ovum; the third case presented with non-cyclic pain and irregular cycles, while the fourth case had a history of 14-year-old infertility and repeated IVF failures. Three out of the four women with leiomyomas in this report experienced heavy menstrual bleeding. No significant side effects or complications occurred during or after the treatment. Uterine leiomyoma size was monitored for one week and three months, showing an average reduction of 56.9%, indicating a significant decrease in myoma volume. Additionally, the reported symptoms showed improvement.

Conclusion: Transvaginal ultrasound-guided radiofrequency ablation proves to be an effective and minimally invasive therapy with minor side effects, making it a promising primary choice for leiomyoma treatment.

Keywords: leiomyoma, radiofrequency ablation, transvaginal ultrasonography.

Abstrak

Tujuan: *Untuk melaporkan keberhasilan pengaplikasian ablasi radiofrekuensi (ARF) terpandu ultrasonografi transvaginal sebagai terapi minimal invasif pada empat perempuan dengan mioma intramural dan suberosa bergejala dengan menggunakan protokol baku.*

Metode: *Laporan empat kasus.*

Kasus: *Laporan kasus dilakukan di Soerojo Hospital, Magelang dari bulan September 2021 hingga Januari 2022. Kasus pertama adalah seorang perempuan pramenopause dengan keluhan rasa tidak nyaman pada panggul. Pada kasus kedua, pasien menjalani kuretase setelah didiagnosis dengan blighted ovum, kasus ketiga dengan nyeri non-siklus dan siklus haid tidak teratur, dan kasus keempat adalah infertilitas 14 tahun dan kegagalan IVF berulang. Tiga dari empat perempuan pada laporan ini mengalami perdarahan menstruasi yang banyak. Tidak ada efek samping yang berarti atau komplikasi yang terjadi setelah tindakan, dan selama pemantauan. Pemantauan ukuran mioma uteri selama satu minggu dan tiga bulan menunjukkan penurunan rata-rata sebesar 56,9%, menunjukkan penurunan volume mioma yang signifikan. Gejala-gejala yang dilaporkan juga mengalami perbaikan.*

Kesimpulan: *Ablasi radiofrekuensi terpandu ultrasonografi transvaginal merupakan terapi non-invasif yang efektif dengan efek samping minimal, sehingga dapat menjadi pilihan utama untuk terapi mioma uteri.*

Kata kunci: *ablasi radiofrekuensi, mioma, ultrasonografi transvaginal.*

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INTRODUCTION

Leiomyoma, also known as uterine fibroids, is the most common benign solid pelvic tumor in women, affecting 70-80% of them by the age of 50. About one-third of women develop leiomyoma during their lifetimes.[1] Most leiomyomas are asymptomatic.[2] However, 50% of women who have leiomyoma report relevant symptoms that are frequently associated with fibroids, such as abnormal menstrual bleeding, pain, pressure, infertility, and repeated miscarriages.[3]

Currently, there are available management options suitable for leiomyomas, but there are still unmet needs according to patient preferences.[4] Medication is usually used on a short-term basis and is not effective with long-term use.[5] Data shows that most patients avoid suggested procedures such as hysterectomy, myomectomy, and uterine artery embolization.[6] Minimally invasive management of symptomatic leiomyomas is becoming a popular option as an alternative to traditional surgical resection.[7]

Radiofrequency ablation was developed to offer women a new minimally invasive treatment option for leiomyomas that is effective, safe, and suitable for those who want to preserve their uterus.[6] Radiofrequency ablation has also found wide application in treating tumors in various organs such as the adrenal glands, bones, breasts, kidneys, lungs, liver, and prostate.[8] The first use of radiofrequency ablation for fibroids was reported in 2002.[9] The safety and effectiveness of RFA in reducing the volume and symptoms of leiomyomas have been extensively documented. However, transvaginal ultrasound-guided radiofrequency ablation (RFA) in uterine leiomyomas has not been widely reported in Indonesia. As a result, the data presented in this case report are considered preliminary.

CASE 1

A 56-year-old para 2 presented with pelvic discomfort and requested the removal of her intrauterine device (IUD). Despite being in the early stages of menopause, she mentioned experiencing regular periods until last year. During her admission, an ultrasound examination incidentally discovered a subserous leiomyoma, measuring 4.6 cm x 4.3 cm with a volume of 44.6 cm3, located at the posterior corpus of the uterus. After being informed about the radiofrequency ablation (RFA) procedure, the patient agreed to undergo it, hoping for immediate shrinkage of the myoma and relief from pelvic discomfort. The RFA procedure, performed under anesthesia, involved targeting an area of 3 cm x 3.3 cm with RFA needles.

At the one-week follow-up, the patient returned for sonography and found that the volume of the leiomyoma had reduced to 38.7 cm3, resulting in relief from pelvic discomfort.

At the three-month follow-up, the volume of the myoma had decreased by 45% compared to the initial examination. Currently, the patient's menstruation has stopped, and she has no more complaints.

CASE 2

A 41-year-old woman with 4-years of marriage, gravida 1, para 0, abortus 1, presented with heavy menstrual bleeding and a history of bleeding after each sexual intercourse. In her obstetric history, she had experienced a prior anembryonic pregnancy one year ago and had undergone laparoscopic myomectomy and cervical polyp removal in 2019. In September 2021, the patient reported a delayed period. Upon admission, sonography revealed an 11-week empty gestational sac and an intramural leiomyoma measuring 7.3 cm x 6.3 cm with a volume of 164.6 cm3 in the left anterior corpus. The leiomyoma was pushing towards the uterine cavity. After discussing the options, the patient agreed to undergo curettage and radiofrequency ablation (RFA) simultaneously to remove the myoma, with the hope of preserving her uterus for future childbearing. Under anesthesia, a curettage was performed, followed by RFA. The area pierced by the RFA needle measured 2.8 cm x 2.65 cm. After one week of follow-up ultrasonography, the volume of the leiomyoma was found to be 91.9 cm3. At the three-month follow-up, the patient returned for sonography, and it was observed that the leiomyoma size had reduced by 85%. Additionally, the heavy menstrual bleeding was significantly alleviated.

CASE 3

A 31-year-old woman, para 1 abortus 1, reported A 31-year-old woman, presented with complaints of heavy menstrual bleeding, non-cyclic pain, and irregular cycles. The patient had been married for four years, and her child was born three years ago. A sonographic examination

revealed the presence of an intramural leiomyoma in the right fundus, measuring 6.2 cm x 6.2 cm with a volume of 124.7 cm3. The patient was informed about the radiofrequency ablation (RFA) method and agreed to undergo the procedure, hoping for immediate shrinkage of the myoma and relief from her symptoms. The RFA procedure was performed under anesthesia, with the RFA needles piercing an area of 3 cm x 2 cm.

At the one-week follow-up, the volume of the myoma had reduced to 73.6 cm3, resulting in a significant reduction in menstrual complaints. After three months, a sonography examination revealed that the size of the myoma had further decreased to 4.7 cm x 4.3 cm x 4.8 cm, with a volume of 50.9 cm3, representing a 59% reduction. As a result, heavy menstrual bleeding was reduced, and the menstrual cycle became more regular.

CASE 4

A 32-year-old woman, P0A0, has been married for 14 years, complained of heavy and prolonged menstruation. She had a family history of leiomyomas and had undergone laparotomy myomectomy three years ago due to multiple leiomyomas. Despite several attempts at in vitro fertilization (IVF) with no success, she plans to undergo IVF again this year. During ultrasonography, two intramural leiomyomas were detected in the corpus, with dimensions of 5.5 cm x 5.4 cm x 5.3 cm and a volume of 82.4 cm3, and 4.0 cm x 4.0 cm with a volume of 33.5 cm3. The patient was informed about the radiofrequency ablation (RFA) method and agreed to undergo the procedure, hoping for the shrinkage of the leiomyomas and a reduction in symptoms. However, only one myoma was treated, with the RFA needle piercing an area of 3 cm x 3 cm. At the one-week follow-up, the patient returned for a sonographic examination, which showed a reduction in the myoma volume to 65.4 cm3. At the three-month follow-up sonographic examination, the myoma size was found to be reduced by 38% compared to the initial admission. Additionally, heavy menstrual bleeding was also reduced.

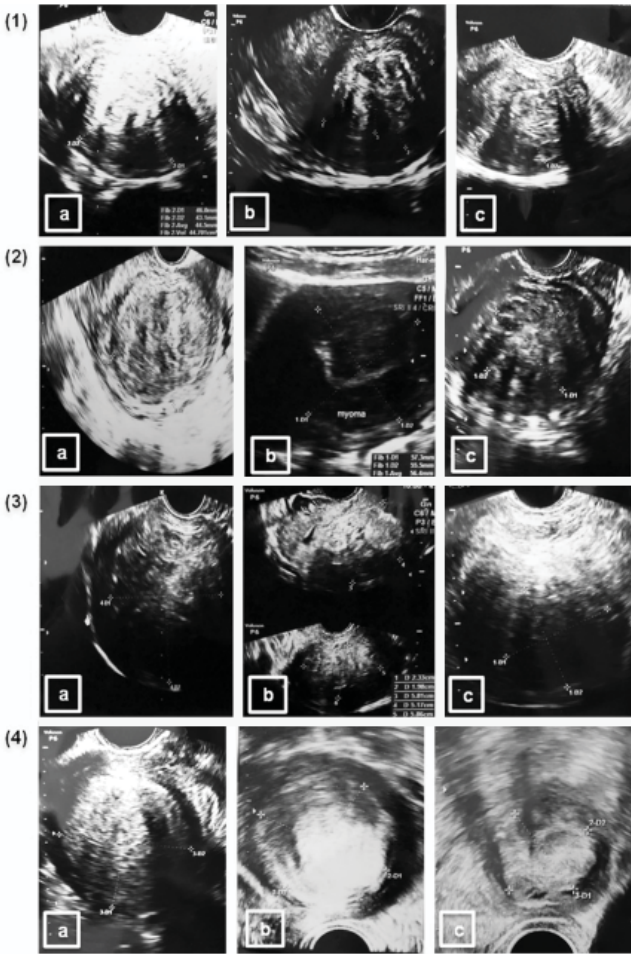

Figure 1. Pelvic ultrasound Case 1 (1), Case 2 (2), Case 3 (3), Case 4 (4) before RFA (a), after 1 week post RFA (b), after 3 months post RFA (c)

There were no adverse events or complications observed in any of the four patients after the procedure and during the observation period. Pelvic examination showed minimal bleeding, with no active bleeding, and the patients reported no complaints of pain. The mean volume reduction at the three-month follow-up was 56.75%.

DISCUSSION

Leiomyomas, the most common neoplasms affecting women, are estimated to be clinically present in 25% of women of reproductive age and are estimated to occur in over 70% of women at the onset of menopause. The increased risk of uterine fibroids in premenopausal women is likely attributed to the influence of female sexual hormones that promote fibroid growth. In our case, three of the women were in the reproductive age, while one woman was in the premenopausal state.

Symptoms caused by leiomyomas vary depending on the number, size, and location

of the tumors. Traditionally, leiomyomas are classified based on their location in the uterus, which includes cervical, submucous, subserous, and intramural leiomyomas. Heavy menstrual bleeding is commonly associated with submucous and intramural leiomyomas, while subserous lesions can lead to pelvic pain. Other symptoms may include non-cyclic pain, painful intercourse, abdominal tightness, or pelvic pressure. In our cases, the myomas were located in the intramural and subserous layers, and the patients presented with symptoms such as profuse menses, pelvic discomfort, pain during intercourse, non-cyclic pain, and irregular cycles.

The presence of submucosal and/or large intramural myomas has also been linked to adverse pregnancy outcomes, such as increased risk for miscarriage.[13] Eventhough, the evidence related to the effect of uterine fibroids on early miscarriages (which comprises anembryonic pregnancies) is debated, researchers believe that endometrium in areasofanatomicalabnormalitiesmayhaveanaberrantbloodsupplythatisunfavorableforimplantationandcannotsustainthedevelopment of the embryo.[14] In our case, on ultrasound examination of a patient with a blighted ovum 11 weeks pregnant, it was found that the size of the myoma enlarged as the size of the uterus increased during pregnancy. Some previous studies also mentioned that there is an increase in fibroid volume with the largest enlargement occurring in the first trimester and explained human chorionic gonadotropin as an important contributing factor.[15] Then, in the postpartum phase, as the uterus undergoes involution, leiomyomas begin to exhibit vascular degeneration, causing them to diminish due to a lack of nourishment.[16]

In our case, the fourth patient, who had a history of leiomyomas, had been experiencing infertility for 14 years and had undergone repeated in vitro fertilization (IVF) failures. Leiomyomas can be the sole cause of infertility in around 2-3 percent of women. Women with intramural and submucosal leiomyomas that distort the endometrial cavity tend to have lower pregnancy, implantation, and delivery rates in IVF compared to infertile women without leiomyomas. The presence of leiomyomas may influence implantation through various mechanisms, such as increased uterine contractility, dysregulation of cytokines, chronic inflammation, and abnormal vascularization.

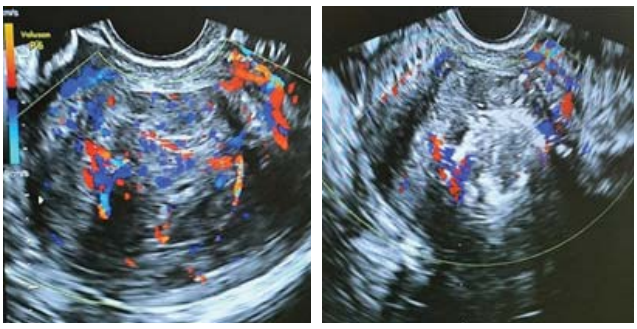

Figure 2. Vascularization before RFA (left), after RFA (right)

Procedure of Radiofrequency ablation

Radiofrequency ablation (RFA) has proven to be an effective and safe alternative treatment for uterine leiomyomas, offering the advantage of being minimally invasive. The procedure can be performed via laparoscopy, transcervical, or transvaginal approach, leading to coagulative necrosis of the leiomyomas and subsequent relief of related symptoms. However, a challenge encountered in these case reports is the higher cost associated with RFA, as it is not currently covered by government insurance.

In this case report, the procedure was carried out under total intravenous anesthesia with the presence of an anesthesiologist. Once the patient was sedated, a transvaginal ultrasound probe with attached needle guidance was inserted. Prior to the ablation procedure, the initial preoperative evaluation was conducted to confirm the number, size, and location of the leiomyomas. The volume of the leiomyomas was calculated using the formula: volume = $4/3\pi r3$, where "r" represents the mean value of the longitudinal, transverse, and anteroposterior radii of the mass.

The device used was an RF generator system type V1000 made in Korea, which consists of an RF generator with an input power frequency of 50/60 Hz and an output radiofrequency of 480000 Hz with a power used of 40-70 atts. The electrode needle was connected to an RF pumping cooling set, which flowed a semi-frozen saline (NaCl) solution, as well as to the RF generator.

The needle electrode was guided under ultrasound to the center of the targeted myoma. The ablation procedure commenced by activating a cooling pump to lower the needle temperature below 15°C. Subsequently, the RF generator was initiated with an automatic protocol, where the power output adjusted automatically based on tissue impedance measurement to maintain stable impedance. Ablation was focused on 60-70% of the entire area of each mass. Three

ablation sessions were performed, each lasting 30 seconds, until the electrode tips in the myoma area turned more hyperechoic on ultrasound images, with the target myolysis temperature set at 60°C. The entire ablation session took approximately 3 minutes to complete. Due to its short procedure time, RFA can be performed within a single day.

CONCLUSION

Transvaginal ultrasound-guided RFA proves to be a viable and effective option for treating leiomyomas, offering a minimally invasive approach with minimal side effects. However, to validate its safety and long-term clinical success, further studies with extended and standardized follow-up periods are essential in patients with leiomyoma.

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Case Report

Management of Spontaneous Cornual Heterotopic Pregnancy in Low-Resources Setting

Tata Laksana Kehamilan Heterotopik Kornual Spontan pada Keadaan Sumber Daya Terbatas

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Abstract

Objective: To report management of spontaneous cornual heterotopic pregnancy in low-resources setting in Ende District, Flores, East Nusa Tenggara.

Methods: Case report.

Case: A 34 year old primigravida with history of 8-9 weeks amenorrhea came to Obstetrics ER with chief complaint of vaginal bleeding and lower abdominal pain. Ultrasound shows intrauterine pregnancy (IUP), an ectopic pregnancy (EP) in right uterine cornu, and free fluid in hepatorenal space, splenorenal space, and pouch of douglas suggesting the occurrence of hemoperitoneum and heterotopic pregnancy. We performed cornual resection by laparotomy and administered progesterone orally before and after the surgery. Successful outcome was achieved.

Discussion: Heterotopic pregnancy (HP) rarely occurs, especially in natural conception. Thus, early diagnosis and treatment of HP are quite a challenge for physicians especially in rural area. Due to the condition of our patient and limited resources, laparotomy was conducted to remove the EP, rather than laparoscopy despite its advantage to lower risk of IUP abortion. Progesterone was then administered orally to prevent threatened abortion of the IUP.

Conclusion: Despite its challenge in diagnosing and treating HP, it is a life-threatening condition that requires accurate and prompt treatment. The treatment goal is to remove the EP and preserve the IUP. Treatment of choice should be decided by takeing the patient's condition and availability of resources into account. Surgical along with administration of progesterone before and after the surgery would likely improve the outcome of the patient and the intrauterine pregnancy.

Keywords: cornual resection, heterotopic pregnancy, laparotomy, low-resources setting, progesterone.

Abstrak

Tujuan: *Untuk membahas tentang penatalaksanaan kehamilan heterotopik kornu spontan di daerah dengan sumber daya rendah khususnya di Kabupaten Ende, Flores, Nusa Tenggara Timur.*

Metode: *Laporan Kasus*

Kasus: *Seorang perempuan primigravida usia 34 tahun dengan riwayat amenore minggu ke-8 dan 9 datang ke IGD Obgyn dengan perdarahan pervaginam dan nyeri perut bagian bawah. Temuan USG menunjukkan kehamilan intrauterin (KIU), kehamilan ektopik (KE) di tanduk rahim kanan, dan cairan bebas di ruang hepato-renal, spleno-renal, dan cavum douglas. Hal ini menunjukkan terjadinya hemoperitoneum dan kehamilan heterotopik. Reseksi kornu dengan laparotomi dilakukan dan pasien diberikan progesteron secara oral sebelum dan setelah operasi. Luaran baik berhasil dicapai.*

Diskusi: *Kehamilan heterotopik jarang terjadi, terutama pada konsepsi alami. Sehingga diagnosis dan tata laksana KH sejak dini menjadi tantangan bagi para dokter, terutama di daerah terpencil Karena kondisi pasien dan sumber daya, laparotomi dilakukan untuk mengangkat KE, daripada laparoskopi meskipun keuntungannya dalam menurunkan risiko keguguran KIU. Progesteron kemudian diberikan secara oral untuk mencegah terjadinya keguguran terancam dari KIU.*

Kesimpulan: *Terlepas dari tantangan untuk diagnosis dan tatalaksananya, KH adalah kondisi yang mengancam jiwa yang membutuhkan penanganan yang akurat dan segera. Tujuan tatalaksananya adalah untuk mengangkat KE dan mempertahankan KIU. Pilihan tata laksana harus diputuskan dengan mempertimbangkan kondisi pasien dan ketersediaan sumber daya. Pendekatan bedah dan obat dengan progesteron yang diberikan sebelum dan sesudah operasi akan meningkatkan kemungkinan luaran pasien dan kehamilan intrauterine yang baik.*

Kata kunci: *kehamilan, heterotopik, laparotomi,progesteron, reseksi kornual, sumber daya rendah.*

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INTRODUCTION

Heterotopic pregnancy (HP) is a rare condition when intrauterine and extrauterine gestations coexist. The incidence of spontaneous heterotopic pregnancy is rare affecting approximately 1 in 30,000 pregnancies. Meanwhile the reported incidence of HP increases from 1:100 to 1:500 with the use of assisted reproductive technology (ART)[1]. The most common ectopic site is the fallopian tube, both in spontaneous and ART heterotopic pregnancies. The second most site is the cornual section. Meanwhile, HP in the cervix, ovary, and abdomen is extremely rare[2]. The diagnosis and management of HP is challenging. Early diagnosis is often complicated due to the co-existence of intrauterine pregnancy (IUP). Delayed diagnosis can result in increased rates of morbidity and mortality both for the mother and IUP. The goal of management of HP is to terminate the ectopic pregnancy (EP) while minimizing the risks towards the IUP[3]. Here we present a rare case of heterotopic pregnancy with threatened abortion of IUP in a natural conception.

CASE

A 34 year-old primigravida with history of 8-9 weeks amenorrhea came to Obstetrics Emergency Room with chief complaint of vaginal bleeding and lower abdominal pain one day before admission. The complaint is associated with nausea and vomit, general weakness, epigastric pain, and bloated stomach. The patient has history of yellow-green vaginal discharge with dyspareunia for the last 3 months.

Further information suggested, pregnancy occurred naturally, no history of both previous pregnancy and an ectopic pregnancy.

On admission, the patient was hemodynamically unstable. Her blood pressure was 80/60 mmHg with heart rate of 115 beats per minute. Other vital signs were within normal limit. The physical examination revealed tenderness on lower-right abdomen. Speculum examination revealed bluish proximal vaginal until the cervix with vaginal discharge came from external orifice of the uterus. Bimanual examination revealed cervical motion tenderness. On ultrasonography examination, an intrauterine pregnancy measuring 8 weeks and 1 day with fetal heart rate of 132 beats per minute and crown rump length of 1.74 cm (Figure 1). A hyperechoic structure with a internal hypoechoic structure was noted in right adnexa, suggesting a gestational sac in right uterine horn (Figure 2). There were free fluid in hepatorenal space, splenorenal space, and pouch of douglas (Figure 3). Laboratory results were notable for positive hCG test, anemia (Hb 10.8 g/dL) , and leukocytosis (13.500/µL).

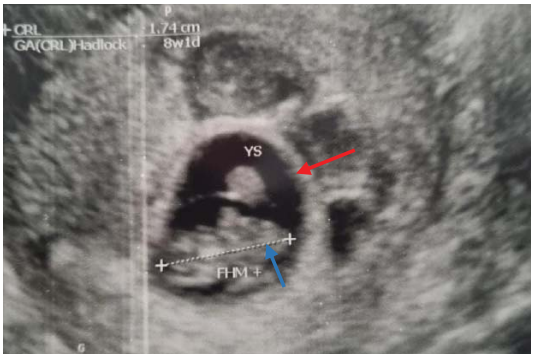

Figure 1. Longitudinal transvaginal ultrasound demonstrates an intrauterine gestational sac (red arrow) with a fetal pole (blue arrow). Crown rump length measures 1.74 cm which correlates to the gestational age of 8 weeks and 1 day. Fetal heart rate was 132 beats per minute.

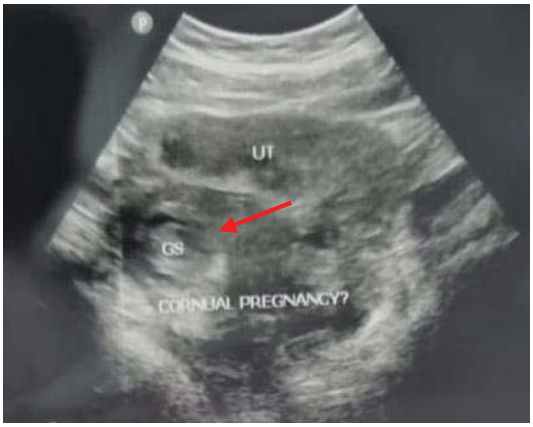

Figure 2. Longitudinal transvaginal ultrasound demonstrates a hyperechoic structure with an internal hypoechoic structure noted in right adnexa (red arrow), suggesting a gestational sac in right uterine horn.

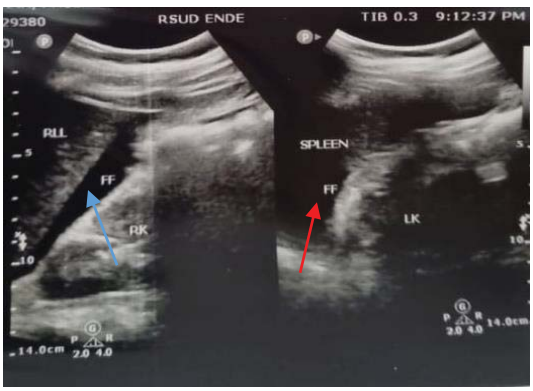

Figure 3. Transabdominal ultrasound demonstrates free fluid in hepatorenal space (blue arrow), splenorenal space (red arrow), and pouch of douglas, suggesting occurence of hemoperitoneum.

The diagnosis of heterotopic pregnancy with ruptured EP was strongly suspected. The patient was managed surgically and medically to remove the EP and preserve the IUP. In order to conserve the threatened IUP, the patient was given one unit of blood transfusion and 200mg micronized progesterone orally 2 times daily before the surgery. Right cornual resection by laparotomy was performed to terminate the EP and the IUP was allowed to continue. The intraoperative findings confirmed ruptured right cornual EP (Figure 4). After the surgery, the progesterone dose was increased to 200 mg 3 times daily. Vaginal swab was conducted to determine the etiology of infection causing vaginal discharge. *Trichomonas vaginalis* was found in the sample. Therefore metronidazole ovula was administered vaginally for 7 days. The patient was scheduled to repeat vaginal swab at 36th week of her pregnancy. The patient then was discharged on postoperative day 5 with IUP viability confirmed. At gestation age of 26 weeks, the patient came for check up and ultrasound monitoring showed normal growth of intrauterine pregnancy.

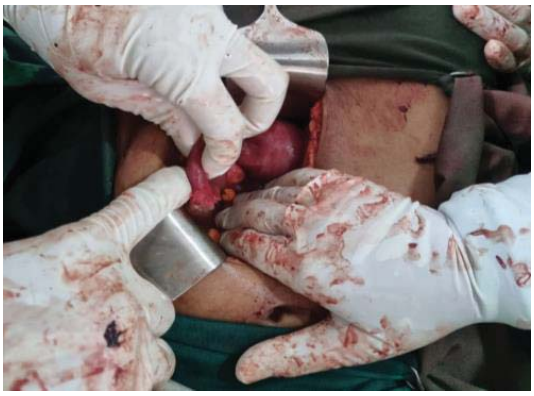

Figure 4. Right cornual section by laparotomy was performed and intraoperative findings confirm ruptured right cornual EP.

DISCUSSION

Heterotopic pregnancy (HP) occurs when intrauterine and ectopic pregnancies exist at the same time. The reported incidence varies widely from 1 in 100 to 1 in 30,000 pregnancies[1]. Heterotopic pregnancy patients who have a spontaneous conception are rarer than those who underwent assisted reproduction. The estimated incidence of HP in spontaneous pregnancies is 1/7,000 to 1/30,000[3]. An intrauterine pregnancy is detected during ultrasonography examination, and an extrauterine pregnancy may be overlooked, causing delay to HP diagnosis[1]. The notable risk factors for the occurrence of a heterotopic pregnancy include family history, a history of extrauterine pregnancy, previous surgery (including salpingectomy, salpingostomy, or reconstructive tubal surgery), endometriosis, tubal disease, history of pelvic inflammation, high hormone levels, embryo transfer technique[4,5]. Our patient conceived naturally and had one of the risk factors which is history of pelvic inflammation caused by *trichomoniasis*. Tubal pregnancy is the most common location, while interstitial, cornual, and cervical ectopic pregnancies were less frequent[5]. Our case was located on cornual part, which makes our case less common.

The most common symptoms of HP are abdominal pain, vaginal bleeding, adnexal mass, peritoneal irritation and uterine enlargement[6]. Late detection may evolve towards hemoperitoneum following rupture of the EP, and cause hypovolemic shock to the mother[7]. Our case presents with similar signs and symptoms which are lower abdominal pain and vaginal bleeding. The patient was also suspected of rupture of EP because of the unstable hemodynamic and severe abdominal pain.

The first-line adjunct examination is abdominal and transvaginal ultrasound to confirm the diagnosis of both pregnancies. It could also help to evaluate viability of the intrauterine pregnancy and the site of the ectopic pregnancy[7]. In our case, both intrauterine and ectopic pregnancies were visible by ultrasound.

The goal of management of HP is to terminate the ectopic pregnancy while minimizing the risks to IUP. In addition to that, it aims to preserve the patient's fertility and avoid recurrence7. Treatment approach for HP should be executed surgically and medically as early as possible. Treatment depends on the patient's condition, the size and site of an EP, previous pregnancies, the viability of intrauterine and extrauterine gestation, and the expertise of the physicians[8]. For patients with unstable hemodynamics or with any signs indicating the rupture of extrauterine pregnancy, emergency surgery is strongly indicated. The benefit of surgical treatment is the ability to completely eliminate the EP, though there might be a higher risk of abortion of the IUP. In their study found that the total abortion rate was 26.56% in all HP patients and the abortion rate in surgery management group was 25.93%[9]. The surgery can be conducted with laparoscopy or laparotomy. Laparoscopy has the advantage of avoiding the risk of uterine manipulation,

compared to laparotomy, which can increase the risk of spontaneous abortion. However, laparotomy is indicated in cases of hemodynamic instability or large hemoperitoneum[7].

In our case, we combined surgical treatment to remove the EP and medical supplementation to preserve the IUP. Cornual resection by laparotomy method was chosen as the surgical option rather than laparoscopy, considering the hemodynamic instability condition of our patient and the unavailability of laparoscopic resources in our hospital that is located in rural area. The surgery was successful with normal growth of IU embryo. About 60–70% of HP cases result in live childbirth with outcomes similar to that of singleton pregnancies[8]. In order to help preserving the viability of the IUP and decrease the risk of its spontaneous abortion, we administered postsurgical progesterone supplementation to the patient.

Progesterone is often termed as "pregnancy hormone", as it functions to prepare endometrium for the implantation as well as gestational sac maintenance in the uterus throughout early pregnancy[10]. It was found that for women who have both bleeding in the first trimester and a history of previous miscarriage, progesterone can have benefit in reducing the risk of miscarrying a fetus[8]. There were some possible mechanisms behind antiabortive effects of progesterone in early pregnancy. It was reported that progesterone functions as an immunomodulator that shifts the maternal cytokine balance from a Th1 or pro-inflammatory bias towards a Th2 or anti-inflammatory bias[11,12]. Thus, in our case it was hoped the administration of progesterone supplementation will reduce inflammation caused by surgical wound and prevent threatened abortion of the IUP (Figure 5). Similar case as ours prescribed vaginal progesterone postsurgical for luteal phase support[8]. They reported good outcome of the IUP. However, we chose to administer progesterone orally as it was found that oral management was demonstrated to be more effective and have a lower risk of miscarriage compared with vaginal administration[10,11].

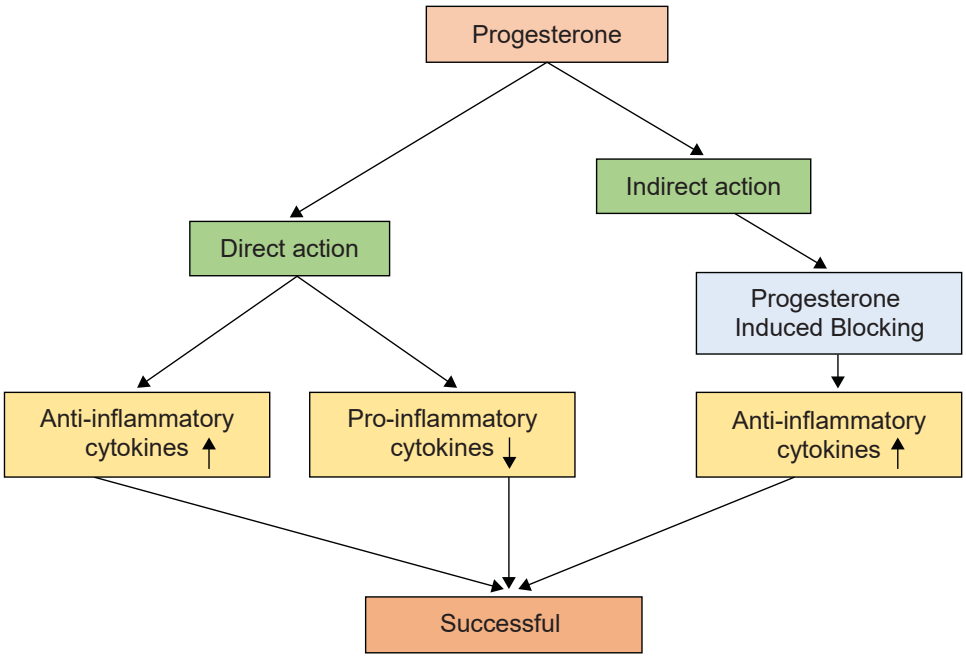

Figure 5. Possible mechanisms of progesterone in reducing inflammation and preventing abortion[12]

CONCLUSIONS

Heterotopic pregnancy is a rare condition. Despite a rather challenging condition, early diagnosis and prompt treatment are required to improve outcome both for the patient and the pregnancy. The treatment approach should be considered based on the patient's condition and availability of resources. Surgical approach and medical approach with progesterone given before and after the surgery would likely improve the outcome of the patient and the intrauterine pregnancy.

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Systematic Review

The Effect of Water Intake during Pregnancy on Birth Weight

Pengaruh Asupan Air selama Kehamilan pada Berat Lahir Bayi

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Abstract

Objective: This systematic review aimed to investigate the effect of water intake during pregnancy on infant birth weight.

Methods: A comprehensive search was conducted using the keywords "water intake," "dehydration," "pregnancy," "outcome," "hydration," "birth weight," and "birth outcome" in databases such as "SCOPUS," "EBSCO," "PUBMED," "COCHRANE," and through "Google Search." MeSH headings "pregnancy" and "hydration" were used for the search. Inclusion criteria encompassed pregnant women without pathological disorders, birth weight as a studied outcome, prospective cohorts, clinical trial study designs, and English-language papers. Out of the 254 articles retrieved, six met the specified requirements and were included in this review.

Results: The findings from the six studies consistently demonstrated a positive correlation between higher water intake, improved hydration, and increased birth weight. All studies measured water consumption or hydration status between 8-37 weeks of gestation. Regardless of the duration of the studies, underhydration or low water intake was consistently associated with lower birth weight.

Conclusion: This review highlights that increasing water intake among pregnant women positively affects infant birth weight. Adequate water intake during pregnancy is recommended to be in the range of 2180 – 3000 mL daily, considering hydration status and the stage of pregnancy.

Keywords: birth weight, hydration, pregnancy, water intake.

Abstrak

Tujuan: *Untuk mengungkap pengaruh asupan air selama kehamilan terhadap berat lahir bayi.*

Metode: *Menggunakan kata kunci "water intake," "dehydration," "pregnancy," "outcome," "hydration," "birth weight," dan "birth outcome,", artikel dicari. Data diambil dari database "SCOPUS," "EBSCO," "PUBMED," "COCHRANE," dan "Google Search". Kami menggunakan MeSH headings kehamilan dan hidrasi untuk istilah pencarian. Kriteria inklusi adalah perempuan hamil tanpa kelainan patologis, berat badan lahir adalah salah satu luaran penelitian, desain studi berupa kohort prospektif dan uji klinis, serta artikel dalam bahasa Inggris. Dari 254 artikel yang diperoleh, enam artikel memenuhi persyaratan dan digunakan untuk review ini.*

Hasil: *Dari keenam penelitian menunjukkan bahwa semakin tinggi asupan air, semakin baik hidrasi atau asupan air meningkatkan berat bayi lahir. Semua penelitian mengukur konsumsi air atau status hidrasi antara 8-37 minggu. Studi-studi ini secara konsisten memberikan bukti bahwa asupan air yang rendah atau kondisi kekurangan cairan dikaitkan dengan berat badan lahir rendah, terlepas dari durasi studi.*

Kesimpulan: *Kajian ini menunjukkan bahwa peningkatan asupan air ibu hamil berpengaruh positif terhadap berat lahir bayi. Asupan air yang cukup pada ibu hamil adalah 2180 – 3000 mL setiap hari bergantung pada status hidrasi dan usia kehamilan.*

Kata kunci: *asupan air, berat lahir, hidrasi, kehamilan.*

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INTRODUCTION

Water is an essential nutrient crucial for maintaining proper metabolic function, hydration, and overall health, especially for the fluid balancing system.[1] Intrauterine growth and development represent the most vulnerable phases of the human life cycle, with profound implications on later life resulting from developmental abnormalities during this period. Fetal brain development throughout pregnancy heavily relies on maternal nutrition and behavior, and the mother's physiological and metabolic adaptations during pregnancy can significantly impact fetal development.[2,3] During pregnancy, plasma volume gradually rises, with most of the 50% gain occurring around the 34-week mark of gestation, which is proportional to birth weight. However, as plasma volume increases more rapidly than red blood cell (RBC) mass,[4] hemoglobin concentration, hematocrit, and RBC count decrease. Maintaining a proper balance of amniotic fluid throughout pregnancy is vital for fetal health, and a lack of amniotic fluid, known as oligohydramnios, can lead to various negative effects during pregnancy.[5] A previous systematic review determined the recommended daily water intake increase for pregnant women with oligohydramnios to enhance the amniotic fluid index (AFI).[6] During the first trimester, amniotic fluid primarily consists of water and electrolytes, with negligible protein content. The flow and volume of amniotic fluid in the second and third trimesters are influenced by hydrostatic and osmotic pressure.[7] Full-term newborn infants contain approximately 70-80% of their body weight as water. The body's increased demand for water during pregnancy is due to factors such as the rise in blood volume, amniotic fluid production, and fetal circulation, and this demand can be influenced by maternal activity, ambient temperature, and environmental factors.[8] The American Institute of Medicine recommends a fluid consumption of 2.7 liters per day for pregnant women, while the Ministry of Health and the Indonesian Association of Obstetrics and Gynecology (POGI) suggest a range of 2450 - 2650 mL or approximately 8-10 glasses per day for pregnant women.[9]

Several studies have addressed the impact of water intake on birth outcomes, with a focus on how contaminants affect the results. High tap water consumption (>35 glasses per week) has not been significantly associated with small gestational age (SGA) or preterm delivery (PTD) in Aggazzotti's studies (ORs = 1.0 and 1.1, respectively).[10] In contrast, increased bottled water consumption has been linked to a lower incidence of spontaneous abortion and heart abnormalities.[11] However, drinking more water has been associated with a higher risk of PTD and low birth weight.[12] Low birth weight (LBW) is defined by the Indonesian Pediatric Society as a weight at birth of less than 2500 grams.[13]

Despite the importance of pregnancy-related hydration studies, there is still a lack of research in this area. A systematic review of the literature on the role of water intake on birth outcomes, particularly infant birth weight, has not been conducted yet. Considering that low birth weight can have both short-term and irreversible long-term effects, this systematic literature review was compiled to determine the role of water intake during pregnancy on infant birth weight and prevent the incidence of low birth weight infants from the beginning of pregnancy.

METHODS

The following conceptual framework and hypotheses serve as the foundation for this review: Does drinking water during pregnancy affect the infant's weight at birth? (Figure 1). This review process, which included studies using numerical data, was a systematic quantitative review. Prior to inclusion and analysis, studies were evaluated for quality. Quality appraisal was conducted using CASP (Critical Appraisal Skills Programme) Checklist for appropriate study design reported. The checklist included questions on research questions, methods, and analysis techniques used to assess the validity of results.

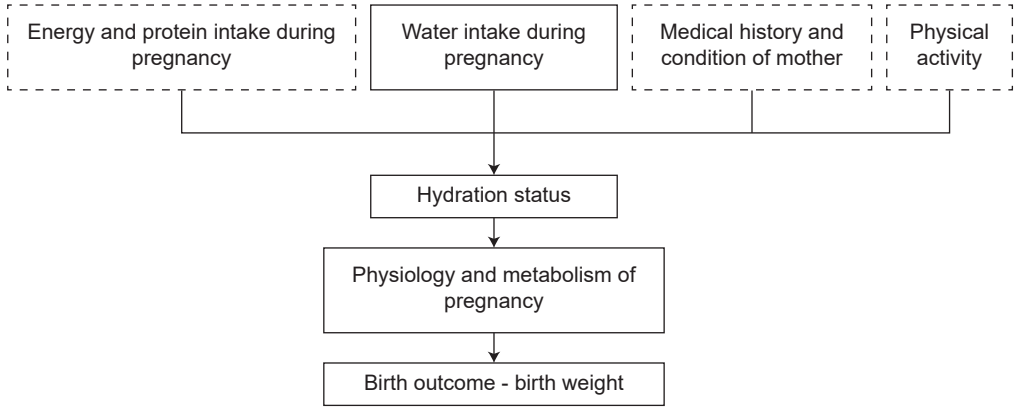

Figure 1. Conceptual Framework

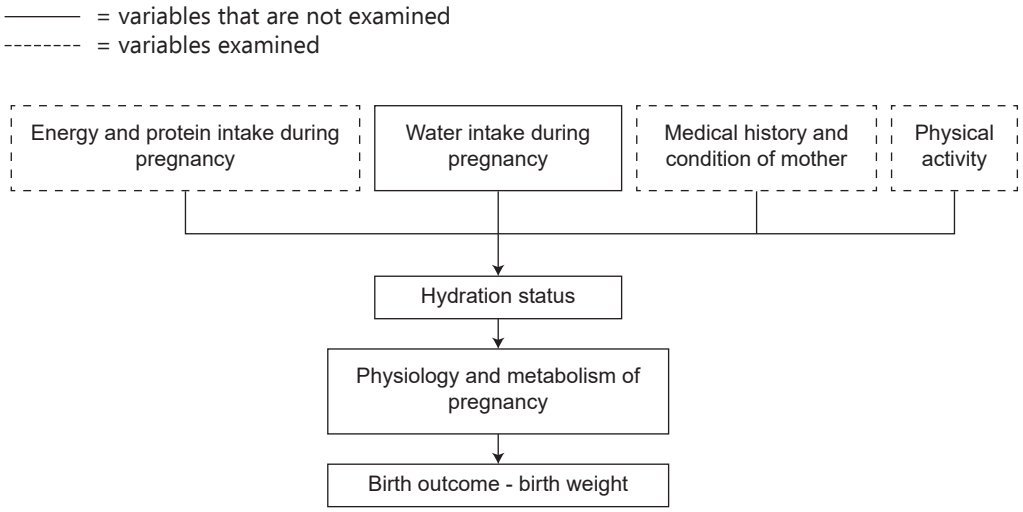

Figure 2. PRISMA Flow Diagram

Design, location, and time

This systematic review followed PRISMA principles. The study's steps included eligibility requirements, information sources, study selection, method of data collection, and data item selection, which are the first five factors (Figure 2).[14] The information was primarily sourced from secondary sources, mainly findings from other study projects. The authors ensured that the predetermined inclusion criteria were met by the data sources. The initial inclusion criteria (IC1) consisted of studies that were original, peer-reviewed, and published in English during the previous 15 years (2007-2022). The second step of inclusion criteria (IC2) involved pregnant women without any comorbidities, and the studies were either clinical trials or prospective cohorts.

Study Selection

The studies selection process consisted of the following four steps. Data were found using the search terms "water intake," "dehydration," "pregnancy," "outcome," "hydration," "birth weight," and "birth outcome" in the databases "SCOPUS," "EBSCO," "PUBMED," "COCHRANE," and "Google Search." Based on the eligibility criteria, the titles, abstracts, and keywords of the found papers were investigated and chosen (Phase 1).

Based on the eligibility requirements, the remaining papers were either fully or partially read to determine whether or not they should be reviewed. Starting with Phase 2, the reference lists of the papers were investigated to find related studies.

The authors carried out these steps collaboratively in an iterative assessment procedure. Any disagreements were discussed among the authors until a consensus was established. This review's summary table was compiled manually using information collected from the studies included in the review. A data extraction form was used, including fields for the journal, year, study setting, participants, study methods, study outcome, and conclusion.Each writer surveyed what they considered the most relevant existing literature, and both the entire text and the retrieved data were reviewed during the evaluation process. Any disagreements between the authors were resolved through conversation. Out of the 254 articles resulting from the search, six articles met the inclusion criteria (Table 1).

Table 1. Search Strategies

Databases	Search strategies	Found	Used
SCOPUS	*"hydration pregnancy" [MeSH Terms] OR ("pregnant"[All Fields] AND "birth outcome" [All Fields]) OR " birth weight" [all fields]*	55	1
EBSCO	*"hydration pregnancy" [MeSH Terms] OR ("pregnant"[All Fields] AND "birth outcome" [All Fields]) OR " birth weight" [all fields]*	8	0
PUBMED	*"hydration pregnancy" [MeSH Terms] OR ("pregnant"[All Fields] AND "birth outcome" [All Fields]) OR " birth weight" [all fields]*	98	2
COCHRANE	*"hydration pregnancy" [MeSH Terms] OR ("pregnant"[All Fields] AND "birth outcome" [All Fields]) OR " birth weight" [all fields]*	10	0
Google search	*Hydration pregnancy and birth weight, hydration pregnancy and birth length, hydration pregnancy and birth outcome, water intake in pregnancy*	83	3

RESULTS

Six papers were accepted for the journal analysis because they met the prerequisites. Each of these six studies is briefly discussed in Table 2, highlighting their respective strengths, weaknesses, methodology, sample size, interventions, and outcomes. The main focus of these studies was to explore the relationship between maternal hydration and delivery outcomes. Notably, all six studies found a positive association between better hydration or increased water intake and higher birth weight. The assessment of water consumption or hydration status in these studies was conducted between 8-37 weeks of pregnancy. Three studies determined hydration status using urine biomarkers, while five studies collected data on water consumption. Importantly, all subjects in these studies had no pathological conditions.The consistent evidence provided by these studies indicates that low water intake or underhydration during pregnancy is associated with lower birth weight, irrespective of the duration of the studies. Based on the results of this review, it is clinically recommended to pay attention to the adequacy of water intake for every pregnant woman, as it significantly affects birth weight. However, further research is still required to explore the optimal amount of water intake, the timing, and the duration of adequate water intake during pregnancy. Additionally, it is advisable to regularly check the hydration status of pregnant women during antenatal care to ensure proper maternal and fetal health.

Table 2. Descriptive analysis of trials included in the systematic review

Authors and year	Study Setting	Method	Results	Conclusion
Wright et al., 2010[15]	A prospective cohort studies including 2766 expectant women was carried out between December 2000 and May 2004 at three study locations in the US. Pregnant (within 12 weeks of gestation) or intending to become pregnant is acceptable inclusion criteria. Women at least 18 years old intended to give birth in the studies area and did not get any reproductive treatments during the pregnancy.	Prior to 16 weeks of pregnancy, (baseline interview) and between 20 and 24 weeks of pregnancy (interview period), telephone interviews were used to gather information on exposures (including water intake) and potential confounding factors (follow-up interview). Comparing water intake ≤ 5 1 ounces/day (≤1508 mL) over >51 ounces/day	The adjusted mean birth weight was 27 (95% [CI]: -34, 87] grams higher for the top three total water consumption quartiles (> 51-78], > 78-114], and > 114 ounces/day) compared to the lowest quartile (51 ounces/day). Bottled water, cold tap water, and overall tap water consumption all had similar adjusted birth weight values. Both preterm delivery and SGA, which increased total and tap water intake, did not show an exposure-response gradient. Nonetheless, all three higher quartiles of SGA had adjusted relative risks that were less than 1.00. (range: 0.6-0.90).	After adjusting for confounders, these findings imply that increasing water intake may be linked to higher mean birth weight.
Akter et al. 2012	Sixty-four pregnant women between the ages of 32 and 35 weeks gestation participated in a randomized controlled trial to ascertain the impact of maternal oral water intake on the oligohydramnios amniotic fluid index (AFI) 5.	The studies participants were all females and were randomly split into two groups. Group A (the intervention group) women were instructed to drink two liters of water within two hours and then two more liters daily for seven days. Women in Group B (the control group) were allowed to consume water frequently. AFI was evaluated in both groups after oral hydration treatment for two hours, twenty-four hours, and seven days.	Grup A (intervention) = Normal 71%, Sectio 29%, LBW 12.5% Grup B (control) = Normal 21.8%, Sectio 78.2%, LBW 81.25% The foetal outcome was healthy in 87.1% vs. 59.4% of the intervention and control groups, asphyxiated in 12.9% vs. 50%, and perinatal death was 3.22 vs. 21.8%. 6.3% of the infants in the control group were stillborn.	Maternal oral hydration therapy considerably improves the fetal prognosis, lowers the rate of cesarean sections, and raises the AFI.
Ernawati et al. 2017	A prospective cohort studies at the Jagir Health Center in Surabaya included 34 healthy newborns and healthy pregnant women in the third trimester, aged 20 to 35. Pregnant women between the ages of 20 and 35, singleton pregnancies, the third trimester (28 to 42 weeks gestation), anamnesis-declared good health, physical examination, normal third-trimester ultrasound, BMI (18.5 to 29.9 kg/m2), at least one year of residence in Surabaya, at least a high school diploma, and a willingness to participate in the study were the inclusion criteria for this study.	A seven-day fluid intake log was put into place.	Fluid consumption positively correlated with birth weight in pregnant women throughout the third trimester (r: 0.469 p: 0.005). In Surabaya's Jagir Health Center, the frequency of LBW is 14.7%. The average amount of water consumed was 746.12±401.29 mL. Minimum 302 mL, maximum 2276 mL.	There was a positive correlation between fluid intake and birth weight.
Mulyani et al., 2018	From December 2016 to January 2018, 66 pregnant women aged 18 to 35 who were in their second trimester (more than 12 weeks along) were enrolled in a prospective cohort study. Participants were drawn from seven health centers (Puskesmas) in Kebon Jeruk, West Jakarta. The following requirements must be met in order to be included in the study. received antenatal treatment at the study site's health center; were in the second trimester (>12–24 weeks); were in good health (no secondary infections), No prior cesarean section experience and history of never giving birth to a child under 48 cm tall and with low birth weight. 150 to 165 cm tall; BMI of 18.5-25.0 intend to give birth at the medical facility	Blood and urine samples were taken six times: three times at 32–34 weeks and three times at 35–37 weeks. The hydration status was evaluated between 32 and 37 weeks. The newborn's birth weight and length (parturition stage) were measured at the time of delivery. The degree of hydration was evaluated using five biomarkers: urine color, urine osmolality, urine specific gravity, serum osmolality, and serum sodium. Based on the earlier biomarkers, subjects were split into dehydrated (DG) and normal (NG); 51.5% were in the DG and 48.5% were in the NG, respectively.	Water intake levels in DG were 72.53±14.41% lower than in NG (118.68±14.37%). The reported difference in child birth weight, length, chest circumference, and head circumference were 491.84 g, 0.98 cm, 0.98 cm, and 1.11 cm, respectively, with infants from the NG having greater measures than infants from the DG. When controlling for water intake, the DG infant birth weight and length (2,798.5397.85 g; 47.320.32 cm) were lower than the NG (3,371.77102.60 g; 49.090.33 cm). The acknowledged difference between the two groups in infant birth weight and length was 596.1 g and 1.8 cm, respectively.	The influence of pregnant women's hydration state on birth weight was studied after correcting for possible confounders. Pregnant women should keep track of their weight and have a basic checkup to determine their hydration condition (urine color) and prenatal care. Pregnant women should carefully manage their nutritional and water consumption to get at least 3.0 L of water daily.
Mulyani et al. 2021	Thirty-eight pregnant women in their second trimester who participated in a prospective cohort study were investigated. Doing a pregnancy examination at the study location is a requirement for inclusion. second and third trimesters; . according to the medical report, in good health (no secondary infection); was never underweight at birth or short (less than 48 cm); aged 18 to 35 years; being between 150 and 165 cm tall; body mass index (BMI) of 18.5-25.0; planned to deliver at the study site; never had a cesarean delivery.	Direct measurements and interviews were used to collect the data used to characterize the subjects. During the third and fourth trimesters of pregnancy (weeks 32–34 and 35–37), the mother's hydration status was evaluated by collecting urine and blood samples. Food recollection was used to gauge food intake, whereas anthropometric measurements were taken 30 minutes after birth to gauge birth weight and length.	In all, 52.6% of pregnant individuals developed dehydration. There are disparities between dehydrated and normal mothers' water consumption. The neonates of the two groups of pregnant mothers had different body weights, lengths, head circumferences, and chest circumferences.	Birth weight, length, and head and chest circumference varied by 500.6 g, 0.4 cm, 0.8 cm, and 1.4 cm between the two groups, respectively, suggesting a positive relationship between hydration status and pregnancy outcome.
Rosinger et al. (2021).	A randomized control trial study design among 27 overweight/obese pregnant women. Inclusion criteria; aged 18 to 40; pregnancy BMI of 25 to 45 kg/m2; singleton pregnancy with a gestational age of 8 to 12 weeks. The physician's approval for participation Multiple pregnancies, diabetes at screening, and other factors are excluded. Severe allergies or dietary restrictions, BMI outside the overweight/obese range; Restrictions on exercising during pregnancy	Fourteen women got standard treatment; 13 also received weekly counseling on diet, physical activity, water intake (64 oz = 1894.4 mL), and health-promoting activities. Using nocturnal urine osmolality (Uosm), hydration status was assessed weekly in pregnant women between the ages of 8 and 36 weeks; underhydration was categorized (Uosm500 mOsm/kg). The birth weight, length z scores, and percentiles were standardized for gestational age and sex. Both mixed-effect and linear regression tests were run.	Exploratory studies reveal that underhydration was related to birth weight, but not length, in different ways in the second and third trimesters. A lower birth weight z score (B= 0.32 z score, SE=0.13; p=0.024) and percentile (9.3%, SE=3.3; p=0.012) were substantially correlated with each ten percentage point increase in the proportion of time a woman was dehydrated throughout the second trimester. In contrast, the birth weight percentile was positively correlated with each ten percentage point rise in third trimester dehydration (B = 7.45%, SE = 3.3, p = 0.038). The percentile or z-score of birth length did not correlate with the percentage of dehydration.	Preliminary evidence from this study suggests that a higher percentage of time spent being dehydrated during the second trimester of pregnancy may be associated with lower birth weight. Pregnant women should drink 300 ml more water each day. The fetal body needs 500 mOsm/kg Uosm for optimal development.

In this review, two studies utilized an RCT study design. The first study compared a standard care group with a daily water intake group of pregnant women (64 oz = 1844 ml). The intervention group also received education on nutrition and physical activity. This study revealed that the longer the duration of underhydration, the lower the birth weight of infants.[16]

The second RCT study instructed individuals in their third trimester of pregnancy to drink 2 liters of water within 2 hours and an additional 2 liters per day for seven days. The intervention group had a higher rate of normal vaginal deliveries (71.0%) compared to the control group

(21.8%). Conversely, the intervention group had a lower rate of cesarean deliveries compared to the control group (29.0% vs. 78.2%). Additionally, the percentage of low birth weight infants was significantly lower in the intervention group (12.5%) compared to the control group (81.25%).[17]

The design of a prospective cohort study was utilized in the other four studies. One of these studies used a bivariate approach for analysis, while the other three employed multivariate analysis. All four studies examined different aspects of nutrient intake and its relationship to pregnancy outcomes, as outlined in Table 2. Overall, this review demonstrates that there are significant variations in pregnancy outcomes as determined by anthropometric assessment, particularly birth weight. The studies show that infant birth weight and length are negatively impacted when hypohydration is present ($p<0.05$).[18] Another study found a positive correlation between hydration status and pregnancy outcome based on the difference in birth weight between the two groups, with a weight difference at birth of 500.6 g. [19] Based on the findings from this review and the Indonesian Society of Obstetrics and Gynecology, it is recommended that pregnant women should routinely monitor their health, including body weight, and assess their hydration status. Adequate water intake for pregnant women is suggested to be in the range of 2180 – 3000 mL daily, depending on hydration status and the stage of pregnancy. [20]

DISCUSSION

Water intake is derived from both solid food (around twenty percent) and fluids, including drinking water (about eighty percent). [21] Maintaining proper hydration is essential, and urine osmolality serves as an indicator of hydration status. [22, 23] To reduce the risk of complications during pregnancy, maintaining a healthy level of nutrient consumption, especially water, is crucial throughout the entire pregnancy.

Around 32 weeks of pregnancy, fetal weight gain accelerates, peaking at 34 weeks. Fetal development slows at weeks 34-36 due to limited uterine space. However, additional uterine development occurs dramatically within the first six months following birth, especially in the first eight weeks. [24] During late pregnancy, mothers may feel full and have a reduced appetite for eating and drinking due to increased fetal growth. Nevertheless, adequate nutrients and water are required for fetal development.

Hydration is essential for maintaining appropriate body temperature and blood pressure, as well as for the digestion, absorption, and transportation of essential nutrients into cells. Hydration signals cells to create energy, allowing the body to carry out its functions, and helps eliminate waste products of metabolism and chemical processes in the cells. [25, 26] The quantity and quality of nutrients consumed play a role in the occurrence of low birth weight. [12] An efficient hydration system helps cells absorb the highest possible quality and quantity of nutrients.

Pregnant women need hydration for various reasons, including maintaining amniotic fluid balance, which is crucial for fetal health. Oligohydramnios, or amniotic fluid shortage, can have several effects on the pregnancy's prognosis. This condition affects around 3-5% of subsequent pregnancies and can be caused by factors such as membrane rupture, placental insufficiency, congenital defects, and other medical conditions. [5, 27, 28] Previous studies have demonstrated that inadequate water intake can affect amniotic fluid index (AFI), and sufficient water intake may increase AFI. [29]

A higher proportion of dehydrated urine samples was associated with a lower birth weight when tested in the second trimester.16 The findings from this study are significant because of the increased demand for water during pregnancy and the widespread failure of pregnant women in many parts of the world to consume enough amounts of water.[9,30,31] Although water consumption appears to be highest in the second trimester and lowest in the third[6,7], When morning sickness and nausea begin to fade in the second trimester, it removes one potential barrier to exercise. Suppose that women exercise regularly throughout the second trimester. In such a situation, the person might produce more water than usual, which could increase the danger of dehydration if it is not properly supplied by fluid consumption.

The transport of fluid from the amniotic fluid to the circulation of the fetus through the mechanism of hydrostatic and osmotic pressure is a vital part of the circulatory system and the management of amniotic fluid volume in the second and third trimesters of pregnancy. Because fluid consumption encourages fetal circulation, the production of amniotic fluid, and blood volume, will increase during pregnancy. The fluid demand is influenced by numerous variables, including

maternal activity, the surrounding environment, and where people live.[8] In previous studies, the average fluid consumption of pregnant women in their third trimester was 746.12 mL, far below the recommended amount.[32] According to the studies, the association between fluid consumption and birth weight was statistically significant ($p<0.005$). The overall change in fetal water and protein levels became proportional to the birth weight. The average birth weight is believed to contain 2400 g of water and 400 g of protein. Throughout pregnancy, the quantity of water often falls, reversing the rise in protein, fat, and minerals. It is vital to pay more attention to pregnant women's nutrients and water consumption to support fetal growth and development. Water is essential for sustaining the body's metabolic activity and contributes to cell-volume homeostasis. Variations in cell volume significantly affect the regulation of nutritional intake and metabolic waste, as well as cell metabolism and gene expression.[33–35]

The weaknesses of this review are the limited numbers of studies, small sample size, various methods in water intake data collection, and various length of intervention. Regardless the weaknesses, there is also strengths of the study such as the study design are RCT and cohort, standardized LBW measurements, and based on recent publications.

Low birth weight is common worldwide with the prevalence of 15-20% of 20 million births yearly.[36] LBW is a condition that needs attention because it can cause short-term and long-term effects, such as infant mortality, stunted growth, cognitive impairment, and abortion.[13] In children aged 0 to 60 months, being LBW is estimated to increase the incidence of stunting up to 3.64 times more frequently than not being LBW (OR = 3.64; 95% CI = 2.70), according to primary studies carried out in Ethiopia, Brazil, and Indonesia.[37] However, this disorder may have long-term consequences like an increased risk of diabetes and cardiovascular disease.[36] The many short-term and long-term effects of LBW indicate the need for prevention since pregnancy, one of which is regulating pregnant women's fluid intake.[38] Meanwhile, this study results showed that increasing in water intake on pregnant women improve the infant birth weight. These implies that the important health authority in each country to promotes adequate water intake for pregnant women.

CONCLUSIONS

In conclusion, this review has demonstrated a significant association between specific measures of water intake and the risk of adverse pregnancy outcomes, particularly birth weight. The optimal range of water intake associated with increased birth weight was found to be between 2180 - 3000 mL. The review has also established a positive correlation between fluid intake and birth weight. Thus, pregnant mothers should not only focus on nutrient intake and weight gain but also pay attention to their fluid intake to support their health and promote fetal growth. For future research, it is recommended to conduct longitudinal studies with larger sample sizes and consider additional factors like energy intake and other potential risk factors in the analysis. Replicating the findings on the relationships between hydration status and birth outcomes is crucial as it may have important implications for maternal hydration status in the long term. By gathering more comprehensive data and considering a broader range of factors, we can gain deeper insights into the impact of hydration on pregnancy outcomes, ultimately contributing to better maternal and fetal health.

DISCLOSURES

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Conflict of interest

There is no conflict of interest in this present study.

Author contribution

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

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Systematic Review

The Role of Probiotics in Urinary Tract Infections in Women

Peran Probiotik dalam Infeksi Saluran Kemih pada Perempuan

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Abstract

Objective: To review the role of probiotics in urinary tract infections in women

Methods: Systematic review was conducted by searching five databases with several keywords, namely "urinary tract infection", "cystitis", "women" and "probiotics". Articles that have gone through peer review are included in the study if they meet the inclusion and exclusion criteria. Reporting follows the PRISMA rules.

Results: The women included in this study varied from early adulthood to postmenopausal, most of whom were sexually active, used birth control methods, and had recurrent urinary tract infections. The results showed that the use of probiotics in varied outcomes, either positive or not showed significant results. This is also due to the differences in the outcomes studied and the additional materials used. This also contributed to the emergence of adverse effects.

Conclusion: The use of probiotics in the treatment of cystitis and urinary tract infections has hope, although not all studies show significant results. The side effects found are still tolerable although they need to be considered.

Keywords: cystitis, probiotic, urinary tract infection, women.

Abstrak

Tujuan: *Meninjau peran probiotik dalam infeksi saluran kemih pada perempuan.*

Metode: *Tinjauan sistematis dilakukan dengan mencari lima database dengan beberapa kata kunci, yaitu "infeksi saluran kemih", "sistitis", "perempuan" dan "probiotik". Artikel yang telah melalui peer review diikutsertakan dalam penelitian jika memenuhi kriteria inklusi dan eksklusi. Pelaporan mengikuti aturan PRISMA.*

Hasil: *Perempuan yang diikutsertakan dalam penelitian ini bervariasi mulai dari dewasa awal hingga pascamenopause, sebagian besar aktif secara seksual, menggunakan metode kontrasepsi, dan mengalami infeksi saluran kemih berulang. Hasil penelitian menunjukkan bahwa penggunaan probiotik pada infeksi saluran kemih menunjukkan hasil yang positif maupun tidak menunjukkan hasil yang signifikan. Hal ini juga disebabkan perbedaan outcome dan bahan tambahan yang digunakan. Penggunaan bahan juga berkontribusi pada munculnya efek samping.*

Kesimpulan: *Penggunaan probiotik dalam pengobatan sistitis dan infeksi saluran kemih memiliki harapan, walaupun tidak semua penelitian menunjukkan hasil yang signifikan. Efek samping yang ditemukan masih dapat ditoleransi meskipun perlu diperhatikan.*

Kata kunci: *infeksi saluran kemih, perempuan, probiotik, sistitis.*

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INTRODUCTION

One of the diseases that disproportionately affects women with a high risk of recurrence is Urinary Tract Infection (UTI). This disease can result in an economic burden due to the need for repeated health services[1]. Untreated urinary tract infections can lead to adverse conditions such as kidney stones, diabetes, complications from urethral catheterization, incontinence, and chronic diarrhea. The morbidity caused by UTIs is enormous, even though the chance of death is low[2] Moreover, compared to men, women have a 30 times higher chance of being affected [3]. Causes of UTI include clinical bacterial infections which account for as many as 50-60% every woman will have a chance of experiencing a UTI in her lifetime[4].

This occurrence is due to anatomical differences between women and men, as well as hormonal and behavioral effects[5]. UTI is a common infection that affects 150 million people per year. A study found an increase in UTI-related medical consultations among women over 18 years of age in France[6].

There are many types of causes for urinary tract infections. Pathogenic bacteria such as Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Enterococcus faecalis, and Staphylococcus saprophyticus are the main contributors[1]. UTIs do not occur in just one part but can involve various organs around the urinary tract[3.] One example is the case of cystitis, a specific inflammatory condition of the bladder[7]. Cystitis is characterized by the presence of bacteriuria. These bacteria cause complaints of dysuria, frequency, or urinary urgency in the absence of pyelonephritis criteria[8]. Properly treating UTIs can make the disease easy to manage and prevent further episodes[9].

Antibiotic exposure needs to be reduced due to the risk of recurrence. While initial treatment is antimicrobial therapy, using different prophylactic regimens and alternative strategies to reduce antibiotic exposure is suggested [10]. Complicated cystitis is associated with the virulence of infection or the potential for failure of antibiotic therapy [7]. Doctors face challenges in diagnosing and managing upper and lower UTIs due to the large number of cases, the risk of recurrence, and inappropriate treatment. Inaccurate history and diagnosis procedures can lead to antibiotic resistance[11].

Probiotics are live microorganisms that can provide health benefits when used in sufficient quantities[12]. Previous studies have shown that using probiotics is beneficial in boosting the immune system, preventing intestinal diseases, aiding lactose digestion, and balancing gut microbial levels. Apart from their role in digestion, probiotics contain anti-hypercholesterolemic agents and antihypertensive properties. They also help reduce postmenopausal disorders and diarrhea [13]. Although the use of probiotics has shown efficacy in various conditions, the optimal dose, frequency, and duration still need to be studied. Probiotics modulate various physiological functions in the body[14]. This study aims to review the role of probiotics in urinary tract infections in women.

METHODS

This systematic study examines the role of probiotics in urinary tract infections, including cystitis, in women. The Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines were followed as a reference. Data was collected between July and August 2022. A search for English-language articles was conducted across five databases: Google Scholar, ScienceDirect, PubMed, ProQuest, and Scopus. The keywords used for the search included "urinary tract infection," "probiotics," "cystitis," and "women."

Table 1. PICO framework

Criteria	Criteria
P (Population)	Women complain urinary tract infection or cystitis
I (Intervention)	Administration of probiotic
C (Comparison)	Provision of placebo or none
O (outcome)	Reduction of complaints and other indicators related to the healing of urinary tract infections and cystitis

This study applies both inclusion and exclusion criteria. The research included in the study comprises observational and experimental studies written in English, discussing the role of probiotics in UTIs. The focus is on research published within the last twelve years, spanning from 2000 to 2022. Case reports, animal studies, letters to the editor, study reviews, preprints, and abstracts without full-text content were excluded from the review.

For title and/or abstract screening, the authors employed standard Microsoft Excel forms. The data collected were consolidated into a single folder, and subsequent assessment was

conducted. Each author individually analyzed all manuscripts, and the results were then compared. In cases of disagreement, a third external collaborator was consulted to reach a consensus. The authors conducted a risk-of-bias assessment using critical appraisal tools.

This process involved checking titles and/or abstracts independently using standard Microsoft Excel forms. When necessary, a third party was engaged to facilitate consensus when no agreement was reached. The risk-of-bias assessment utilized critical appraisal tools, specifically the Mixed Methods Appraisal Tool (MMAT) version 2018. The MMAT was employed for evaluating the quality of qualitative, quantitative, and mixed methods studies[15].The results of the critical appraisal are presented in table 2.

The authors extracted relevant results, organized, and analyzed them to identify sub-themes and overarching themes. Table 3 presents the characteristics of the research, including author, year, country, research type, disease type, sample size, probiotic type, administration method, results, side effects, and findings/statistics. The impact of administering probiotics is evident through reductions in UTI symptoms and related indicators.

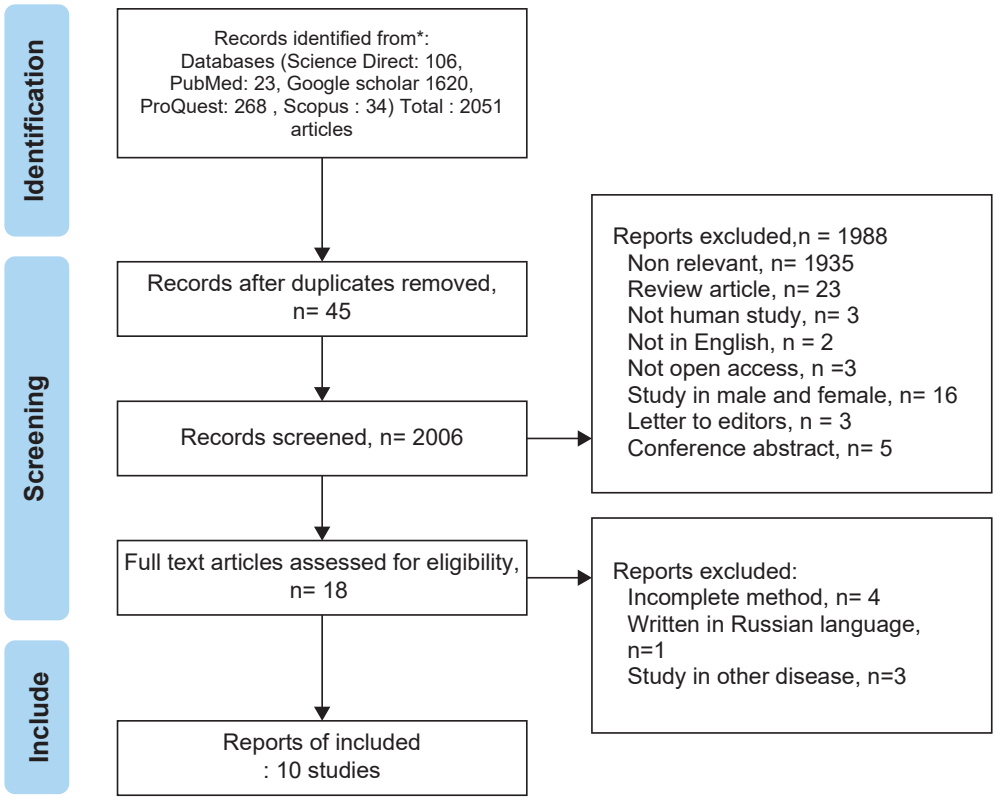

Figure 1. Prisma Flow Chart

RESULTS

The database search using keywords yielded a total of 2051 articles. Out of this initial pool, 1988 articles were screened and subsequently excluded as they did not meet the inclusion and exclusion criteria. A total of 18 full-text articles were evaluated for eligibility, and among them, 10 articles were included in the qualitative analysis. The article search process is illustrated in the PRISMA flowchart, as shown in Figure 1. The quality assessment results of the studies indicate that all articles fell within the moderate to good category. The detailed results of this assessment are presented in Table 1.

Table 2. Quality Assessment using MMAT

Study design and studies	Assessment criteria					Total Score
Quantitative non randomized	Are the participants representative of the target population?	Are measurements appropriate regarding both the outcome and intervention (or exposure)?	Are there complete outcome data?	Are the confounders accounted for in the design and analysis?	During the study period, is the intervention administered (or exposure occurred) as intended?	
Pugliese et al, 2020, Italy [16]	Y	Y	Y	Y	N	4
Uehara et al, 2006, Japan [17]	Y	Y	Y	Y/N	N	3.5
Montorsi et al, 2016, Italy [18]	Y	Y	Y	N	Y	4
Randomized controlled trials	Is randomization appropriately performed?	Are the groups comparable at baseline?	Are there complete outcome data?	Are outcome assessors blinded to the intervention provided?	Did the participants adhere to the assigned intervention?	
Koradia et al, 2019, India [19]	Y	Y	Y	Y	N	4
Czaja et al, 2007, USA [20]	Y	Y	Y	Y	N	4
Birte J. Wolf et al, 2019, USA [21]	Y	Y	Y	N	Y	4
Stapleton et al, 2011, USA [22]	Y	Y	Y	Y	N	4
Sadahira et al, 2021, Japan [23]	Y	Y	Y	Y/N	N	3.5
Kontiokari et al, 2001, Finland [24]	Y	Y	Y	Y	N	4
Beerepoot et al, 2012, Denmark [25]	Y	Y	Y	N	Y	4

A total of 2 articles discussed the role of probiotics in cystitis, while 8 articles discussed the role of probiotics in urinary tract infections. This study encompassed women of various ages. In the case of cystitis, two studies utilized samples with different average ages, namely 38 ± 11.2 years and 68.3 years. The study also included postmenopausal women, those with controlled diabetes mellitus, and those with cystocele. Among the studies focusing on urinary tract infections, there was considerable age variation and a wide age range. The average age was 21 years in some groups, with research also involving students in their 20s. Another study had a sample mean age ranging from 29.1 to 35 years. Some studies concentrated on postmenopausal women over 60 years old, while others included samples spanning ages 21 to 80 years. Most respondents were sexually active, with varying patterns of birth control usage, including some samples with less than 10% usage and others where the majority used birth control. Recurrent UTIs were common among the respondents.

The research results indicate diverse types. outcomes, and methodologies. Table 2 illustrates the journal characteristic. Researchers scrutinized the findings of each study to discern common themes. Conclusions were drawn regarding the potential and positive impact of probiotics.

However, the results do not consistently indicate a significant role of probiotics, as their usage often involves combination with other ingredients. Positive improvements were observed in the prevention and treatment of recurrent urinary tract infections, such as reduced recurrence rates, extended intervals between recurrent UTIs, shorter active UTI durations, fewer subjects requiring antibiotics, and decreased antibiotic treatment durations. In cystitis cases, there were decreases in average ACSS scores and average cystic episode numbers. Yet, some studies demonstrated no significant difference in cumulative recurrence rates between the experimental and placebo groups. Similar mean U/L ratios were observed between placebo and probiotic groups. No discernible difference in microbiota diversity between the groups was found. There were also reported declines in

average quality of life scores.

Table 2 displays a comparison of study results, revealing disparities in terms of probiotic types (including various strains of Lactobacillus), additional therapies (such as cranberry, vitamins), and treatment dosages that varied. Lactobacillus, particularly Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus rhamnosus, Lactobacillus reuteri, and Lactobacillus crispatus Lactin, emerged as the most commonly used probiotics. Probiotics were combined with other ingredients like cranberry extract, vitamin A, D-mannose (2 g), prebiotics (fructo-oligosaccharide 1g), pomegranate extract, cranberry-lingonberry, vitamin C, and proanthocyanidins. The dosage and probiotic microbe count varied, as did the administration regimen, ranging from once to three times daily for up to a year. Moreover, administration methods spanned from oral intake to suppositories. The outcomes examined were diverse, encompassing the absence of UTIs, U/L ratio of daily voided urine, quality of life (QoL), Acute Cystitis Symptom Score (ACSS), changes in urine bacteria and vaginal microbiome, and development of antibiotic resistance. Outcome assessment involved self-reported symptoms, physical examination findings, and laboratory studies.

While most studies did not report side effects, further investigation is necessary to determine if these side effects stem from probiotics alone or from additional ingredients used. Side effects that were reported include vaginal discharge or itching, mild abdominal discomfort, mild asymptomatic inflammation of the lower urinary tract, diarrhea, or allergic reaction.

Table 3. Research characteristics

Authors, year, country	Study type	Type of disease	Number of samples	Probiotics type	Administration procedure	Outcome	Adverse effect	Finding/ statictical test results
Koradia et al, 2019, India [19]	Randomized double-blind, placebo-controlled, parallel group	Recurrent uncomplicated urinary tract infections	44 experiment / 45 placebo	BKPro-Cyan is a capsule formulation containing: cranberry extract (Vaccinium macrocarpon); probiotics (Lactobacillus acidophilus PXN 35, Lactobacillus plantarum PXN 47); and vitamin A (retinyl acetate; 160 µg/capsule). Each capsule contains a minimum of 18mg cranberry PACs and >500 million live probiotic microorganisms (>5 x 108 CFU/capsule).	Twice-daily for 26 weeks	Absence of UTI, UTI symptoms (dysuria, urinary frequency, urgency, suprapubic pain, hematuria)	Not found in articles	Lower number recurrent UTIs, Improvements multiple secondary endpoints, longer time to first UTI, shorter duration of active UTI, Fewer subjects requiring antibiotics and shorter median duration of antibiotic treatment
Birte J. Wolf et al, 2019, USA[21]	Double-blinded randomized controlled trial	Urinary tract infection	4 experiment / 3 placebo	Lacctobacillus rhamnosus GR-1 and Lactobacillus reuteri RC-14 at sum of 10^9 viable organisms	Orally twice daily	U/L ratio of daily voided urine	No	No diference mean U/L ratio. No changes in terms of microbiota diversity
Pugliese et al, 2020, Italy[16]	Uncontrolled experimental pilot study	Acute cystitis	Thirty-three patients	A dose of a new combination of agents, (Prolactis IVU©, Omega Pharma, Cantù, Italy). Prolactis IVU contains D-mannose 2 g, Prebiotics (fructo-oligosaccharide 1g), pomegranate extract 250 mg (with 70% titration of ellagic acid 175 mg) and Probiotics (Lactobacillus plantarum Lp115 ≥ 2 billion colony-forming unit).	Twice daily for 5 days and then once a day for 10 days.	Changes in patients' symptoms, the therapeutic effects and changes in quality of life (QoL), the Acute Cystitis Symptom Score (ACSS) at the first visit (T0), 15 (T1) and 30 (T2) days later.	No	No symptoms or the majority of symptoms went. The mean score reported at all the ACSS sub-scales significantly decreased Typical symptoms decreased; Differential symptoms decreased QoL mean score also decrease
Sadahira et al, 2021, Japan[23]	Single-arm, open-label, phase II clinical trial,	Recurrent cystitis	21 patients	Vaginal suppositories containing the GAI 98322 strain of Lactobacillus crispatus	1 year either every 2 days or three times per week	The primary end-point was the response rate, as assessed by the number of episodes of recurrent cystitis during the year of administration. The secondary end-points were the response rate, as assessed by episodes of recurrent cystitis during the 1 year after completion of the administration period; the total number of episodes of recurrent cystitis before, during and after administration; adverse events; and changes in urine bacteria and	No	An effective response (86%) during administration. The suppressive effects continued up to 1 year after the last suppository was administered. There was a significant reduction in the mean number of episodes of cystitis, both during and after administration of Lactobacillus vaginal suppositories

						the vaginal microbiome		
Stapleton et al, 2011, USA [22]	Randomized, Placebo-Controlled Phase 2 Trial	Recurrent Urinary Tract Infection	One hundred young women	Lactin-V or placebo	Daily for 5 days, then once weekly for 10 weeks	Urine samples for culture and vaginal swabs for real-time quantitative 16S ribosomal RNA gene polymerase chain reaction for L. crispatus	Adverse effects were reported by 56% of participants who received Lactin-V and by 50% of participants who received placebo; the most common adverse effects included vaginal discharge or itching or moderate abdominal discomfort	Recurrent UTI occurred in a small proportion of respondents.High-level vaginal colonization with L. crispatus was associated with a significant reduction in recurrent UTI only for Lactin-V.
Czaja et al, 2007, USA[20]	Phase I Trial	Recurrent Urinary Tract Infection	30 women	L. crispatus CTV-05 or placebo vaginal suppositories	Daily for five days	The primary outcome of safety as assessed through self-reported symptoms, physical exam findings, and laboratory studies. Secondary outcomes included shifts in	Mild to moderate side effects related to suppository use occur but do not affect compliance. L. crispatus CTV-05 may cause mild asymptomatic inflammation of the lower urinary tract. Mild to moderate vaginal discharge	L. crispatus CTV-05 is well tolerated when given as a vaginal suppository to healthy women with a history of recurrent UTI

Authors, year, country	Study type	Type of disease	Number of samples	Probiotics type	Administration procedure	Outcome	Adverse effect	Finding/ statictical test results
Koradia et al, 2019, India [19]	Randomized double-blind, placebo-controlled, parallel group	Recurrent uncomplicated urinary tract infections	44 experiment / 45 placebo	BKPro-Cyan is a capsule formulation containing: cranberry extract (Vaccinium macrocarpon); probiotics (Lactobacillus acidophilus PXN 35, Lactobacillus plantarum PXN 47); and vitamin A (retinyl acetate; 160 µg/capsule). Each capsule contains a minimum of 18mg cranberry PACs and >500 million live probiotic microorganisms (>5 x 108 CFU/capsule).	Twice-daily for 26 weeks	Absence of UTI, UTI symptoms (dysuria, urinary frequency, urgency, suprapubic pain, hematuria)	Not found in articles	Lower number recurrent UTIs, Improvements multiple secondary endpoints, longer time to first UTI, shorter duration of active UTI, Fewer subjects requiring antibiotics and shorter median duration of antibiotic treatment
Birte J. Wolf et al, 2019, USA[21]	Double-blinded randomized controlled trial	Urinary tract infection	4 experiment / 3 placebo	Lacctobacillus rhamnosus GR-1 and Lactobacillus reuteri RC-14 at sum of 10^9 viable organisms	Orally twice daily	U/L ratio of daily voided urine	No	No diference mean U/L ratio. No changes in terms of microbiota diversity
Pugliese et al, 2020, Italy[16]	Uncontrolled experimental pilot study	Acute cystitis	Thirty-three patients	A dose of a new combination of agents, (Prolactis IVU©, Omega Pharma, Cantù, Italy). Prolactis IVU contains D-mannose 2 g, Prebiotics (fructo-oligosaccharide 1g), pomegranate extract 250 mg (with 70% titration of ellagic acid 175 mg) and Probiotics (Lactobacillus plantarum Lp115 ≥ 2 billion colony-forming unit).	Twice daily for 5 days and then once a day for 10 days.	Changes in patients' symptoms, the therapeutic effects and changes in quality of life (QoL), the Acute Cystitis Symptom Score (ACSS) at the first visit (T0), 15 (T1) and 30 (T2) days later.	No	No symptoms or the majority of symptoms went. The mean score reported at all the ACSS sub-scales significantly decreased Typical symptoms decreased; Differential symptoms decreased QoL mean score also decrease
Sadahira et al, 2021, Japan[23]	Single-arm, open-label, phase II clinical trial,	Recurrent cystitis	21 patients	Vaginal suppositories containing the GAI 98322 strain of Lactobacillus crispatus	1 year either every 2 days or three times per week	The primary end-point was the response rate, as assessed by the number of episodes of recurrent cystitis during the year of administration. The secondary end-points were the response rate, as assessed by episodes of recurrent cystitis during the 1 year after completion of the administration period; the total number of episodes of recurrent cystitis before, during and after administration; adverse events; and changes in urine bacteria and the vaginal microbiome	No	An effective response (86%) during administration. The suppressive effects continued up to 1 year after the last suppository was administered. There was a significant reduction in the mean number of episodes of cystitis, both during and after administration of Lactobacillus vaginal suppositories
Stapleton et al, 2011, USA [22]	Randomized, Placebo-Controlled Phase 2 Trial	Recurrent Urinary Tract Infection	One hundred young women	Lactin-V or placebo	Daily for 5 days, then once weekly for 10 weeks	Urine samples for culture and vaginal swabs for real-time quantitative 16S ribosomal RNA gene polymerase chain reaction for L. crispatus	Adverse effects were reported by 56% of participants who received Lactin-V and by 50% of participants who received placebo; the most common adverse	Recurrent UTI occurred in a small proportion of respondents.High-level vaginal colonization with L. crispatus was associated with a significant reduction in recurrent UTI only for Lactin-V.

DISCUSSION

The study outcomes revealed varying results of using probiotics for urinary tract infections, with both positive outcomes and results that didn't show significant effects. Another study evaluated probiotic efficacy in preventing UTIs among premenopausal women. Systematic studies and meta-analyses demonstrated significant benefits in reducing recurrent UTIs compared to placebo in this group. However, more conclusive data are necessary to determine the effect of probiotics in strengthening the urogenital microbial barrier against pathogenic bacteria and protecting against UTI recurrence[26]. Other studies also yielded varying conclusions from the use of different probiotics. While two studies suggested that probiotics can reduce the risk of recurrent UTIs, others presented inconclusive results[27]. Results from another meta-analysis examining probiotics' impact on UTI incidence in children indicated that probiotic therapy had no significant beneficial effect on incidence or recurrence. Subgroup analysis indicated a reduction in UTI incidence when probiotics were used in combination with antibiotics[28].

The diverse results obtained stem from variations in usage methods and additional materials. This discrepancy also contributes to the appearance of side effects resulting from each ingredient. Other substances like cranberry extract, vitamin A, D-mannose, prebiotics (fructo-oligosaccharide 1g), pomegranate extract, cranberry-lingonberry, vitamin C, and proanthocyanidins can complicate decision-making regarding the overall role of probiotics in managing cystitis and urinary tract infections. For instance, cranberry extract, used prophylactically in UTIs among young and middle-aged women, demonstrated effectiveness in some studies, including findings by the Cochrane Collaboration[29]. Another meta-analysis corroborated these findings, asserting that cranberry supplementation significantly reduced UTI risk in susceptible populations [30]. Certain vitamins, such as vitamin C, have also been linked to UTI management. Vitamin C is considered safe for post-kidney disease UTI treatment[31] However, conflicting studies suggest that ascorbic acid (vitamin C) might not be recommended for UTI prevention [25]Other vitamins, like vitamin A, are also under discussion. Vitamin A supplementation appears effective for treating UTIs and reducing kidney injury and scarring following acute pyelonephritis in girls with initial acute pyelonephritis [32].

The results found indicated that Lactobacillus was the most widely used probiotic. In healthy premenopausal women, the female urogenital flora is predominantly dominated by Lactobacillus. This bacterial strain may offer protection against UTIs [33]. Lactobacillus is the preferred probiotic agent for preventing and treating urogynecological infections due to properties such as hydrogen peroxide production and biosurfactant generation[34].

The characteristics of the respondents in this study varied. UTI incidence spans from early adulthood to postmenopause. Most respondents were sexually active, and family planning practices varied, including both samples with less than 10% usage and those with the majority using family planning methods. Recurrent UTIs were common. Established risk factors for uncomplicated recurrent UTIs encompass frequent intercourse, vulvovaginal atrophy, changes in local bacterial flora, history of UTIs during premenopause or childhood, family history, and nonsecretory blood type. Complicated urinary tract infections manifest in patients with other medical conditions like diabetes, old age, pregnancy, or immunocompromised status[2].

This study is advantageous for exploring the potential and limitations of using probiotics in managing urinary tract infections, both in general and specifically in cystitis cases. However, various limitations, including variations in dosage, probiotic microbe count, and additional ingredient use, emphasize the need for further research focusing exclusively on probiotic utilization. Such research could enhance knowledge progression, as decades of study have yet to pinpoint an accurate dosage for optimal outcomes.

CONCLUSION

The utilization of probiotics for treating cystitis and urinary tract infections holds promise, even though not all studies yield significant results. The identified side effects, while generally tolerable, warrant consideration.

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