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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Pregnancy is a risk factor for vulvovaginitis. Vulvovaginitis is an infection of the vaginal and vulvar mucosa, most often caused by bacterial vaginosis (BV), vulvovaginal candidiasis (CVV), and trichomoniasis (TR), even in some cases, a mixed infection. CVV is the second most common infection after BV that causes vulvovaginitis. Colonization of Candida sp. in the vagina is at least 20% in non-pregnant women but increases to 30% in pregnant women and increases in the third trimester to 40%, so the increasing gestational age, the higher the risk of CVV. This study aims to determine the relationship between gestational age and the incidence of CVV. This research method is a cross-sectional analytic design, using primary data from anamnesis and vaginal swab examinations on 50 samples of pregnant women at the Jatibening Health Center UPTD, 34 samples (68%) tested positive, and 16 samples (32%) tested negative for vulvovaginitis. CVV was found most often in the third trimester of pregnancy by 50%. The Chi-Square regression test was performed where the p-value = 0.042 (significant). Gestational age affects the incidence of CVV.

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1. INTRODUCTION

In the female external genitalia, normally, there is vaginal fluid or secretions produced from glands in the cervix. This vaginal secretion functions as a moisturizer, cleanser, and defense against various infections in the female genital tract [1]. Normal vaginal discharge, colorless or transparent and odorless. However, an infection in the vagina or vaginitis will be characterized by abnormal vaginal secretions that are colored, smelly, and accompanied by complaints of vaginal itching [2]. Every year nearly 10 million women come to the doctor with gynecological complaints of vaginitis. Thus, vaginitis is often a common gynecological disease [3]. Infectious diseases of the vagina are divided into three types, including Bacterial Vaginosis (BV), Vulvovaginal Candidiasis (CVV), and Trichomoniasis (TR), with prevalence rates of 22-25%, 17-39%, and 4-35% respectively [4]. CVV is the second most common infection after BV that causes vulvovaginitis.

Vulvovaginal candidiasis (CVV) is a fungal infection of the vaginal wall caused by pseudo hyphae and yeast of the genus Candida. It can occur due to the overgrowth of Candida sp., found in the vagina as commensal organisms. Several studies have found Candida sp. in 15-20% of healthy women without symptoms of vulvovaginitis and 29.8% of women with symptoms of vulvovaginitis. At least 70-75% of women have had CVV once in their life, 40-45% have had two or more subsequent episodes, and 5-8% of women also reported having recurrent CVV [5].

Yeast infections are common vaginal infections. Nearly 85-90% of the yeast found in the vagina are strains of Candida albicans and Toluropis glabrata. Most often, CVV cases are caused by C. Albicans around 70-90% and C. glabrata, around 10-20%, but rarely by C. krusei, C. parapsilosis, and C. tropicals, although most of these species are still associated with vaginal infections [3,4]. Candida albicans is one of the normal flora in the vagina; apart from Aerobic Lactobacillus sp., Candida sp. can live as a saprophyte on several organs of the human body (mouth, intestines, lungs, vulva, or vagina) and grows well in acidic conditions (normal vaginal pH <4.5). Normal vaginal pH is maintained by the presence of Lactobacillus sp., namely Basilus doederlein, which prevents the growth of Candida sp. excessively [1]. Candida sp. has opportunistic properties; if the vaginal conditions support it can turn into a pathogenic flora [4].

Many factors can affect the state of the vagina, resulting in the rapid growth of Candida sp., and the prevalence of CVV may increase. Several studies have reported that the most common predisposing factors for the host are uncontrolled diabetes mellitus, immunosuppression, pregnancy, HIV infection, use of oral or hormonal contraceptives, and obesity [3]. The highest prevalence of Candida sp. and symptomatic vaginitis is seen during pregnancy [5]. Colonization of Candida sp. vaginal discharge is at least 20% in non-pregnant women, but this statistic increases to 30% in pregnant women and increases further in the third trimester of pregnancy to 40% [6,7].

Pregnancy is a process that involves many hormonal changes in the body. Begins with nidation of the endometrial lining, the hormones estrogen, and progesterone will continue to increase slowly at the gestational age of 11 weeks to 24 weeks, then decrease and then increase again until the end of pregnancy [8]. This increase in estrogen causes an increase in water content in cervical mucus and glycogen production by vaginal epithelial cells. High glycogen levels in the vagina are a supporting condition for the growth of Candida sp so that it can thrive and multiply into pathogenic flora [9].

The higher the gestational age, the higher the risk of CVV. The relationship between pregnancy and infection with Candida sp. is influenced by hormonal instability and changes in vaginal pH [10]. If there is a severe CVV infection, it can cause complications for the mother and the fetus she is carrying. Complications that can occur are chorioamnionitis, impaired fetal growth, premature rupture of membranes, spontaneous abortion, and congenital Candida infection [2].

Female genital organs can be divided into two parts, namely, external genitalia and internal genitalia. Most of these organs are located in the pelvic cavity, which in women is more intended for fulfilling reproductive functions [1]. Regulation of the hormonal system in women through a system called the hypothalamic-pituitary-gonadal (ovarian) axis, as follows: a) Hormones released by the hypothalamus, namely gonadotropin-releasing hormone (GnRH); b) Anterior pituitary sex hormones, namely follicle-stimulating

hormone (FSH) and luteinizing hormone (LH), in response to the release of GnRH; and c) Ovarian hormones, namely estrogen and progesterone, which are secreted by the ovaries in response to the release of the two female sex hormones from the anterior pituitary [1].

These various hormones are not secreted in constant amounts throughout a woman's monthly sexual cycle but are secreted at different rates, as shown in Fig. 1, showing the approximate changes in concentrations of the anterior pituitary and ovarian hormones each month. At each woman's monthly sexual cycle, the reproductive tract is prepared for fertilization (fertilization) and implantation of the ovum released from the ovary at ovulation. So this cycle consists of the ovarian cycle and the uterine cycle. If fertilization does not occur, then the cycle will repeat. However, if fertilization occurs, the cycle stops temporarily to adapt to maintaining and protecting the fertilized product. The ovarian cycle is regulated by a very complex hormonal interaction and is divided into three phases: the follicular, ovulation, and luteal.

During pregnancy, various physiological changes will occur in the mother's body, including hormonal changes. Hormonal changes that occur during pregnancy aim to support the growth and development of the fetus while in the womb [7]. The placenta connects the body of the mother and fetus. The placenta is an organ of exchange between maternal and fetal blood that plays an essential role in maintaining fetal growth. It is because glycogen stores in the endometrium are only sufficient to provide nutrition for the fetus during the first few weeks of pregnancy. The following week the fetus will receive nutrition from the activity of the placenta, which can secrete several steroid and peptide hormones. The hormones consist of a) Human Chorionic Gonadotropin (hCG), Progesterone, and Estrogen.

Vulvovaginitis or vaginitis is an infection that occurs in the vaginal and vulvar mucosa [2]. Vulvovaginitis can occur in women of all ages. It can be caused by: a) fungal infections (called vulvovaginal candidiasis), bacterial infections (called bacterial vaginosis), viral infections, and parasitic infections; b) How to clean the genital organs is wrong; c) Menopause and Pregnancy; and e) Excessive use of female genital cleansing soap and spray.

The most common cause is an infection because the regular vaginal flora changes to pathogenic flora to infect the vagina and vulva. Each infection has characteristic clinical symptoms. Bacterial vaginosis (BV) infection symptoms include vaginal discharge that is thin and watery and smells like rotten fish. Meanwhile, vulvovaginal candidiasis (CVV) infection can cause severe itching in the genital organs, and vaginal secretions appear thick and lumpy. This thesis will discuss CVV in pregnancy, where there will be significant hormonal changes that increase the risk of CVV during pregnancy. In addition to BV and CVV, vulvovaginitis can also be caused by the protozoan Trichomonas vaginalis and trichomoniasis (TR). The symptoms caused by TR are itching and burning in the genitals, and the presence of watery to thick yellowish vaginal secretions, sometimes accompanied by dysuria and urinary incontinence [2].

Diseases caused by Candida can be called Candidiasis (candidiasis) or candidosis (candidosis). Candidiasis comes from Candida with the suffix IASIS for disease in Latin. While candidosis, with the suffix OSIS, comes from Greek because it is a disease caused by fungi (mycosis). Vulvovaginal candidiasis is an infection of the vulva and vaginal walls caused by hyphae and yeasts of Candida species [2].

Candida sp. has been known and studied since the 18th century. Based on the round shape of the cells and white fungal colonies, it was named Oidium Albicans because this fungus forms spores. However, the name Oidium was changed to Monilia because the fungal cells were arranged like a beads string that resembled a necklace. The name Monilia causes confusion because in agriculture, it is known that the Monilia fungus is the cause of plant diseases, and it is very different in morphology and nature. At the end of the Third International Microbiological Congress in New York in 1938, the name Candida was introduced instead of Monilia [11].

Candida is a fungus that belongs to the class of fungi imperfecti. Until now, ± 80 species of Candida have been known. Of those 17 species found in humans, C. Albicans is considered the most pathogenic and disease-causing species, compared to non-C. albicans Candida species such as Candida steltatoidea, Candida tropicalis, Candida pseudotropicalis, Candida crussei, Candida parapsilosis, and Candida guilliermondia [12].

Candida sp., morphologically visible on the microscopic and Gram-positive staining, has

several forms of fungal elements, namely yeast cells (blastospores/yeast), hyphae, and intermediate forms/pseudohyphae. As shown in Fig. 2, yeast cells are spherical or oval in shapes ranging from 2 – 5 x 3.– 6 to 2 – 5.5 x 5 – 28. In addition, yeast cells are germinating, called blastospores, as shown in Fig. 3. Candida sp. reproduce through the growth of these shoots, which are increasingly elongated and branched to form pseudomycelium, and finally form pseudohyphae/pseudo hyphae, as shown in Fig. 4. Unlike other Candida species, Candida albicans are dimorphic; in addition to yeast cells and pseudohyphae, Candida albicans can also produce true hyphae, the most pathogenic form [12].

The optimum growth of Candida occurs at a pH between 2.5 – 7.5 and a temperature ranging from 20^0C – 38^0C. Candida is a fungus that grows fast, around 48-72 hours. The ability of Candida to grow at 37^0C is an essential characteristic for identification. Pathogenic species (which attack host cells) will proliferate at a temperature of 25^0C – 37^0C, while species that tend to be saprophytic (which ride on host cells to survive) decrease their growth ability at higher temperatures [13]. Candida can grow at 37^0C under both aerobic and anaerobic conditions. Candida grows well in solid media, but the growth rate is higher in liquid media [14]. On solid medium Saboraud Dextrose Agar (SDA) or glucose-yeast extract-peptone water which is usually used for the isolation of various fungi, all Candida species grow as yeast colonies or yeast-like colonies that cannot be distinguished from each other both microscopically and macroscopically [15]. Generally, the colonies are round in shape with a size of (3.5 – 6) x (6 – 10) m with a slightly convex surface, smooth, slippery, and sometimes slightly folded, especially in older colonies. The colony's size is influenced by the age of the culture/culture. The color of Candida colonies is yellowish-white (soft cream) and has a characteristic odor [13].

Apart from microscopic examination, identification of Candida sp. can also be done macroscopically through chromogenic media (CHROM agar). Candida sp. forms different color colonies in this medium [15]. So that we can distinguish species from Candida just by looking at the color of the colonies formed, among others; C. Albicans formed green colonies, C. tropicals formed light purple colonies with dark purple peaks, C. paraphimosis formed white colonies, C. krusei formed pink to pale white colonies, and C. glabrata formed white colonies with pale pink peaks [15].

The determinants of Candida in infecting the human body include:

a) Species of Candida based on their infecting ability in order from highest to lowest: Candida albicans, Candida stellar idea, Candida tropicalis, Candida parapsilosis, Candida guilliermondii, and Candida krusei;
b) The hyphal form can adhere more strongly than the germ tube, while the germ tube form adheres more strongly than the yeast cell;
c) In Candida sp. The blastospore form is required to initiate or create a tissue lesion. After the lesion is formed, hyphae are formed, which play a role in invading the surrounding tissue; and
d) C. Albicans can produce enzymes that help the invasion of fungi into tissues. These enzymes consist of proteinases and phospholipases. Proteinase enzymes function to hydrolyze peptide bonds and play a direct role in the initial invasion of the stratum corneum, while phospholipase enzymes play a role in the fungal invasion process [16].

Several risk factors can make vaginal conditions an accessible environment for the growth of Candida species or make asymptomatic conditions symptomatic, including endogenous factors (pregnancy, use of oral or hormonal contraceptives, and history of diabetes mellitus) and exogenous factors (trauma or damage to the vaginal mucosa and hygiene of the female genitalia).

In vulvovaginal candidiasis, the typical sign is that the symptoms increase a week before menstruation and decrease slightly at the start because estrogen levels increase in the period before menstruation. It is what causes the production of vaginal secretions to increase in number. Vaginal secretions consist of epithelium and leukocytes. As is well known, leukocytes are essential for killing pathogenic microorganisms, but if the leukocyte content in the secretions increases and the color of the secretions changes, it should be suspected as one of the characteristics of vulvovaginal candidiasis. Normal vaginal discharge usually occurs during the fertile period or after menstruation. The discharge is colorless or transparent, odorless, and does not cause vaginal itching. During

pregnancy, there is an increase in the hormones estrogen and progesterone, and the production of vaginal secretions also increases. These secretions help maintain vaginal moisture and elasticity of the muscles around the vagina to prepare these tissues during parturition (birth) [13].

The typical vaginal environment is described by the dynamic relationship between Lactobacillus dophilus or Doderlein lactobacillus bacteria and other endogenous flora, including estrogen, glycogen, vaginal pH, Candida sp., and other typical flora microorganisms. Lactobacillus species are the most significant members of the rmal flora found in the vagina. Immediately after birth, aerobic lactobacilli (Doderlein lactobacillus) appear in the vagina and persist with Candida as long as the pH remains acidic for several weeks. During childhood, the vaginal pH is neutral, so there is a mixed flora of cocci and bacilli. However, at puberty, Lactobacillus sp. is rediscovered in large numbers; it aims to maintain an acidic vaginal pH by forming lactic acid from carbohydrates, especially glycogen [1].

With increasing gestational age, the levels of estrogen and progesterone gradually increase and, of course, can affect the state or environment of the vagina. In this case, estrogen plays a role in determining sugar levels as energy stores, namely in the form of glycogen. Glycogen is a nutrient from Lactobacillus which will be metabolized for its growth. The rest of this metabolism, through an enzyme, in the form of various lower carbohydrate compounds, will be further broken down into acetaldehyde, then pyruvic acid, and finally lactic acid. This lactic acid determines the acidic atmosphere in the vagina with a hydrogen potential (pH) in the range of 3.8 – 4.2. This vaginal acidity prevents the overgrowth of pathogenic bacteria and fungi [14].

Elevated estrogen levels can also cause the vaginal epithelium to thicken and the surface to be coated with glycoproteins. High glycoprotein levels will be a good carbon source for Candida growth so that it can thrive and develop into pathogens.

Vulvovaginitis is in the form of complaints of redness of the vulva and vagina due to irritation and intense itching, sometimes accompanied by the discharge of secretions. Severe complaints can accompany a feeling of heat, pain after micturition, and dyspareunia. Examination results on mild complaints usually appear hyperemia in the labia minus vaginal introitus and vagina, especially the lower 1/3. In addition, there is also a characteristic abnormality, namely yellowish-white spots. In significant complaints, it can be accompanied by edema on the labia minus shallow ulcers on the labia minus and around the vaginal introitus. However, the most prominent complaint is itching of the vulva, followed by vaginal irritation, which is often minimal. Vaginal discharge in patients with candidiasis vulvovaginitis is usually yellowish. A typical sign is accompanied by yellowish-white lumps like milk or cheese (like broken milk). The clot originates from a mass detached from the vulvar or vaginal wall composed of necrotic material, epithelial cells, and fungi [2]. The cervix is usually normal, so the vaginal pH is also standard. Sometimes the cervix outside is covered by a pseudomembrane that is easily removed with a cotton swab, while the vulva and labia are erythematous and edematous.

The clinical picture of CVV is divided into asymptomatic and symptomatic [14]. If asymptomatic, the patient has no complaints, but on examination, colonies of Candida sp. in the vagina, but the colonies are minor and do not invade the vaginal mucosa, so no therapy is needed. The colony can stay in the vagina long without causing any complaints. While symptomatic, there are colonies of Candida sp. in more significant numbers; the organisms appear to develop from spore forms, blastospores, to pseudohyphae that produce proteases, then the fungus can invade the vaginal mucosa easily. So it is an essential treatment to overcome the emergence of complaints such as vaginal and vulva discharge, a lot of vaginal secretions and clots, intense itching, and redness. One study ved that hypersensitivity to Candida antigens plays a role in the occurrence of complaints in patients.

The clinical diagnosis of Vulvovaginal Candidiasis can be established based on anamnesis, clinical examination, laboratory examination in the form of vaginal swabs through microscopic examination, wet preparations or Gram and fungal culture, as well as an examination of the pH of vaginal fluids. Because the specificity (accuracy of the test in identifying negative results) of symptoms and signs of vulvovaginal candidiasis is low, the diagnosis cannot be made based only on history and clinical examination.

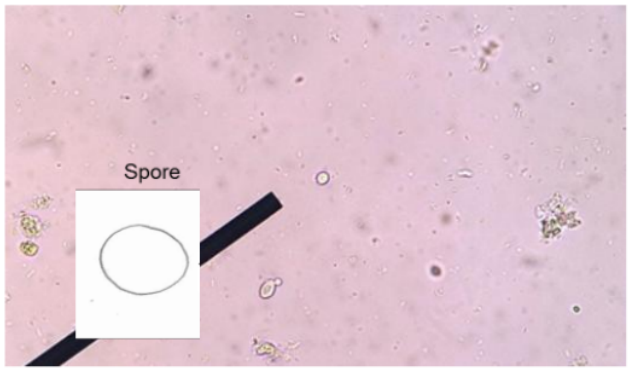

Fig. 1. Spora Candida sp.
(Source: results of microscopic examination of vaginal secretions tube no. 6 with 33 weeks of gestation)

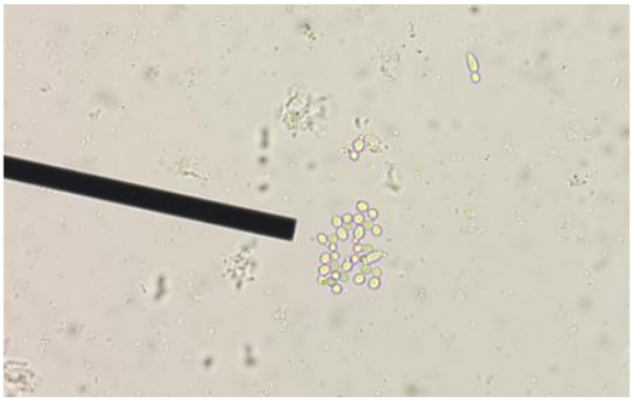

Fig. 2. Blastospora Candida sp.
(Source: results of microscopic examination of vaginal secretions tube no. 5 with a gestational age of 15 weeks)

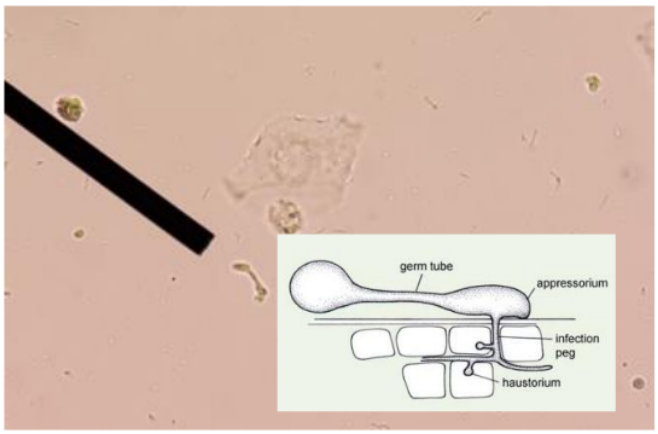

Fig. 3. Germ tube Candida sp.
(Source: results of microscopic examination of vaginal secretions tube no.50 with eight weeks of gestation)

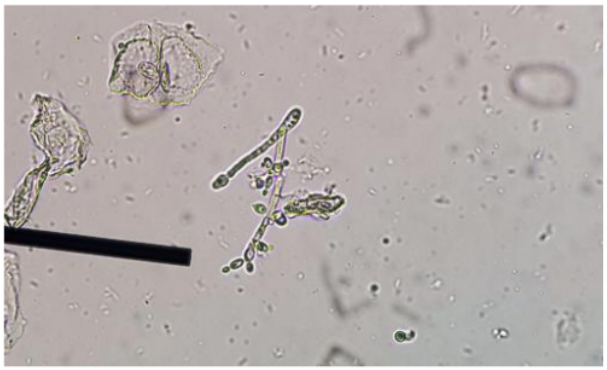

Fig. 4. Hifa semu Candida sp.

(Source: results of microscopic examination of vaginal secretions tube no.29 with a gestational age of 35 weeks)

CVV complications in pregnant women can occur by spreading the infection to the upper part of the reproductive tract (ascending infection) through hematogenous dissemination. Babies born to mothers who suffer from CVV during pregnancy can be infected directly from contamination of amniotic fluid or through the birth canal [17]. The complications that can occur; are prematurity, spontaneous abortion, chorioamnionitis, and congenital Candida infection. Infants with oral thrush who receive breast milk (ASI) can increase the risk of candidiasis on the mother's nipples [18].

Therefore, the authors conducted this study to determine the incidence of vulvovaginal candidiasis in pregnant women at various gestational ages at the Jatibening Health Center UPTD. So through this study, the relationship between gestational age and the incidence of vulvovaginal candidiasis can also be known. The problem of this research is whether gestational age affects the incidence of vulvovaginal candidiasis in pregnant women. This study aimed to determine the effect of gestational age on the incidence of vulvovaginal candidiasis in pregnant women.

2. RESEARCH METHODS

The design used in this study was analytic observation with a cross-sectional approach to find the effect of gestational age on the incidence of vulvovaginal candidiasis in pregnant women. This research was conducted at the Technical Implementation Unit of the Health Service (UPTD) Jatibening Health Center and the Parasitology Laboratory of the Faculty of Medicine, Universitas Kristen Indonesia (FK UKI), from July to August 2015. The sample of the study were the pregnant women who performed ANC at the Jatibening Health Center UPTD from July to August 2015. Anamnesis was carried out at the Jatibening Health Center UPTD, and a vaginal discharge examination was carried out at the Parasitology Laboratory of FKUKI. The research sample was the subject according to the research criteria, and sampling used the total sampling method. This method is often referred to as the saturated sample or census method. The entire population that meets the criteria is used as the research sample. During the research from July to August 2015, 50 samples matched the inclusion and exclusion criteria. In this study, primary data was used, namely data collected during the research. Primary data were obtained based on: a) the results of anamnesis complaints experienced by the patient; and b) the microscopic examination of vaginal discharge samples and examination of the amine test using 10% KOH solution. Univariate or descriptive analysis was carried out to describe the distribution and frequency of the independent and dependent variables studied. Nominal and ordinal data will be expressed in frequency and percent. Hypothesis testing was analyzed by bivariate analysis on categorical-scale data tested using the Chi-square regression test to obtain p-values to look for associations between the independent variable and the dependent variable. All subject data will only be used for research purposes and kept confidential. If the subject asks, research subjects have the right to know the results.

3. RESULTS

Below are the univariate and bivariate analysis results, which are presented in several tables.

Based on Table 1, it can be seen that the most samples were found in pregnant women aged 20-30 years, as many as 23 people (48%), compared to those aged 31-40 years, as many as 22 people (44%) and over 40 years as many as four people. (8%). From 50 samples, 25 (50%) samples with a gestational were found in pregnant women aged 29-40 weeks, compared to a gestational age of 13-28 weeks in as many as 17 people (34%) and 0-12 weeks as many as eight people (16%). In addition, the number of samples with a history of second and third gravidity was as many as 13 people (26%), while the first history of gravidity was ten people (23%), then the fourth history of gravidity.

There are eight people (16%) and a history of the fifth gravidity, as many as six people (12%). From the anamnesis and direct vaginal swab examination, 34 people (68%) tested positive for vulvovaginitis (VVC, BV, and Mixed Infection), and 16 people (32%) tested negative for vulvovaginitis.

The distribution and frequency of vulvovaginitis can be seen in Table 2; the samples that tested positive for vulvovaginal candidiasis (CVV + mixed infection) were mostly found in the third trimester of pregnancy, namely 11 people (50%), then in the second trimester and first trimester, respectively by 36% and 14%. Furthermore, samples that tested positive for BV (BV + mixed infection) were mostly found in the third trimester of pregnancy, namely 13 people (56%), then samples that tested positive for mixed infections were also mostly found in the third trimester, namely seven people (64 %).

From the history that has been done, it was found that the symptoms in the samples with vulvovaginitis included vaginal discharge, painful or reddish vulva, itching, and smelling bad. It can be seen in Table 3 that from 11 people who had vulvovaginal candidiasis, the dominant symptoms were vaginal discharge and itching in 10 people (91%). In addition, out of 12 people who experienced bacterial vulvovaginitis, the most common symptoms were vaginal discharge and an unpleasant-smelling vulva, respectively, in 12 people (100%) and 10 (83%). While in 11 people who had mixed infections, all experienced vaginal discharge (100%), and other dominant symptoms, such as itching and smelling vulva, were felt in 10 people (91%).

Table 4 shows the results of the Chi-Square regression test. The value used is the Pearson Chi-square value which shows a significance of 0.042 ($p < 0.05$), which means that there is a relationship between gestational age and the incidence of vulvovaginal candidiasis. The following is how many forms of Candida sp. Those found on direct (microscopic) examination of vaginal discharge samples at the Parasitology Laboratory of FK UKI, among others.

Table 1. Characteristics of the research sample

Variable	Category	Total*	(%)
Age of pregnant mother	20 - 30 years	24	(48)
	31 - 40 years	22	(44)
	> 40 years	4	(8)
Gestational Age	0 - 12 weeks	8	(16)
	13 - 28 weeks	17	(34)
	29 - 40 weeks	25	(50)
History of pregnancy- (Gravida)	1	10	(20)
	2	13	(26)
	3	13	(26)
	4	8	(16)
	5	6	(12)
Diagnosis of Vulvovaginitis	CVV	11	(22)
	BV	12	(24)
	Mixed infection **	11	(22)
	Not Infected	16	(32)

** Total sample = 50 orang*

*** Mixed infection (CVV+BV), Vulvovaginal candidiasis (CVV), Bacterial Vaginosis (BV)*

Table 2. Distribution and frequency of vulvovaginitis by gestational Age

Gestational age *	Vulvovaginitis							
	CVV (%)		BV (%)		Mixed infection (%)		Not infected (%)	
1st trimester	2	(18)	2	(17)	1	(9)	3	(19)
2nd trimester	5	(45)	4	(33)	3	(27)	5	(31)
3rd trimester	4	(36)	6	(50)	7	(64)	8	(50)
Total**	11	(100)	12	(100)	11	(100)	16	(100)

** first trimester (0 – 12 weeks) total of 8 people; 2nd the trimester (13 – 28 weeks) total of 17 people; In the third trimester (29 – 40 weeks) total of 25 people*
*** Total sample = 50 people*

Table 3. Symptoms of vulvovaginitis

Symptoms of the vulva and vagina		Vulvovaginitis					
		CVV (%)		BV (%)		Mixed infection (%)	
Vaginal discharge	Positive	10	(91)	12	(100)	11	(100)
	Negative	1	(9)	0	(0)	0	(0)
Pain and redness	Positive	2	(18)	8	(67)	7	(64)
	Negative	9	(82)	4	(33)	4	(36)
Itchy	Positive	10	(91)	6	(50)	10	(91)
	Negative	1	(9)	6	(50)	1	(9)
Smell	Positive	5	(45)	10	(83)	10	(91)
	Negative	6	(55)	2	(17)	1	(9)

** Number of Vulvovaginal Candidiasis = 11 people*
*** Number of Vulvovaginal Bacterial = 12 people*
**** Number of mixed infections = 11 people*

Table 4. The Effect of gestational age on the incidence of vulvovaginal candidiasis

Chi-Square Tests			
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	8.202[a]	2	.042
Likelihood Ratio	6.203	2	.006
Linear-by-Linear Association	8.040	1	.002
N of Valid Cases	50		

a. Two cells (33,3%) have an expected count of less than 5. The minimum expected count is 3,52.
b. Only for 2x2 table

4. DISCUSSION

To monitor pregnant women's and fetuses' health, the World Health Organization (WHO) recommends that pregnant women routinely perform ANC during pregnancy. ANC is carried out in 4 visits divided into each gestational age, namely, one visit in the first trimester, one in the second trimester, and two in the third trimester. In this regard, 50 pregnant women doing ANC at the Jatibening Health Center UPTD were involved as samples in this study. After examining vaginal discharge samples, it can be seen in Table 1 that as many as 16 people (32%) tested negative for vulvovaginitis and 34 people (68%) tested positive for vulvovaginitis, including 11 people (32.5%) suffering from CVV, 12 people (35%)) had BV, and 11 people (32.5%) had mixed infection (BV + CVV). The results of this study are following the study by Lamichhane et al. (2014) on pregnant women at the Paropakar Maternity and Women's Hospital Nepal, of 92 people who tested positive for vulvovaginitis, of which 36 people (39%) positive for BV, 28 people (30%) positive for CVV, 27 people (30%) positive for BV+CVV, and one person (1%) positive for BV+CVV+Trichomoniasis [19]. During pregnancy, significant hormonal changes affect the condition of the vagina and vulva, showing a high sensitivity to infection.

The characteristics of the sample of this study can be seen in Table 4. The most samples were pregnant women aged 20 - 30 years, as many as 24 people (48%). These results are consistent with the research that found most of the samples

were aged 21-30 years (82%). It is related to ovarian hormone activity, which peaks in women aged 20-30. Increased ovarian hormones (especially estrogen and progesterone) can maintain vaginal acid pH, increase the ability of Candida sp. with vaginal epithelial cells, and increase cervical gland secretion resulting in abnormal vaginal discharge [20]. Besides, vaginal discharge is also more common in younger pregnant women because it is thought to be related to the lack of experience regarding personal hygiene during pregnancy.

Based on gestational age, most samples were in the third trimester of pregnancy (29-40 weeks), with as many as 25 people (50%). The results follow the research of Onuorah et al. (2015) on 30 samples of pregnant women in Nigerian Awka Hospital, showing that the distribution of the sample was mostly in the third trimester of 19 people (63.3%), then in the second trimester of 8 people (26.7%).) and the first as many as three people (10.0%) [21]. From a total sample of 50 samples, 3 (26%) samples have a history of second and third gravidity. The results of this study following the research of Eza et al. (2012) at the Obstetrics and Gynecology Polyclinic of Arifin Achmad Hospital Pekanbaru; of the 41 samples, most had a history of gravidity 2 - 3, which was 52.9% and gravidity 1 was 35.3%, the rest gravidity 4 - 5 that is equal to 11.8% [21].

The distribution and frequency of vulvovaginitis based on gestational age can be seen in Table 2. In this study, vulvovaginal candidiasis (CVV + mixed infection) was most common in samples with the third-trimester gestational age of as many as 11 people (50%). Lamichhane et al. (2014) also presented a graph of the distribution of vulvovaginal candidiasis in pregnant women at the Paropakar Maternity and Women's Hospital Nepal, most of which occurred in the third trimester of pregnancy [19]. However, this result is not following the research conducted by Kanagal et al. (2014) in the Department of Obstetrics and Gynecology at the Mangalore Tertiary Hospital in India. From 118 samples, there were 50 people (42.37%) who tested positive for vulvovaginal candidiasis with the distribution based on gestational age, namely 27 people (54%) in the second trimester, 15 (30%) in the third trimester, and 8 (16%) in the first trimester [22]. The literature explains that during pregnancy, there is an increase in the hormones estrogen and progesterone starting at 11-24 weeks of gestation, then decreases slightly and then increases again and reaches a peak at the end of pregnancy [7]. The increase in hormones will further disrupt the defense mechanism against Candida sp. in the vagina because progesterone suppresses the anti-candida activity of neutrophils [22]. In contrast, estrogen can reduce the ability of vaginal epithelial cells to inhibit the abnormal growth of Candia sp. and decrease immunoglobulin levels in vaginal secretions, thereby increasing the susceptibility of pregnant women to vaginitis [21].

In this study, the incidence of bacterial vaginosis was mostly found in the third trimester of pregnancy, namely 13 people (56%). As the time of delivery approaches, vaginal and pelvic examinations are carried out in preparation for labor, and the increased emotional stress of pregnant women is a predisposing factor for bacterial vaginosis [21]. This result is not following the study of Lamichhane et al. (2014), which presented a graph of the distribution of the incidence of vulvovaginal bacteria in pregnant women at the Paropakar Maternity and Women's Hospital Nepal, most of which occurred in the second trimester of pregnancy [21]. There is a discrepancy in this study's results with previous studies due to differences in the sample number used. In addition, there is also a time difference between the collection and examination of vaginal secretions in this study.

Symptoms that arise due to vulvovaginitis can be seen in Table 3, that all samples suffering from vulvovaginitis experienced vaginal discharge (100%). The dominant symptom of 11 positive people suffering from vulvovaginal candidiasis was vaginal itching, which occurred in 10 people (91%). These results followed research by Maleeha et al. (2008) at the Department of Obstetrics and Gynecology at Lahore Hospital Pakistan from 50 samples of pregnant women. All of them experienced vaginal discharge (100%), then vaginal itching in 44 people (82%), a burning sensation in 28 people (56%), and dyspareunia and pain when urinating in 8 people (16%) and six people (12%). It is related to the vaginal hormonal environment of pregnant women and several other factors that increase the colonization of Candida sp. and trigger a hypersensitivity reaction to Candida antigens [23].

The dominant symptom in 12 positive people suffering from bacterial vaginosis was foul-smelling discharge, occurring in 10 people (83%). These results follow the research of Katarina (2011) at the Swedish Department of Clinical and Experimental Health, stating that the

signs and symptoms that often occur in BV sufferers are vaginal discharge that smells like rotten fish and an itchy vulva. According to the literature, the bacteria that cause bacterial vaginosis, Gardnerella vaginalis, can release the same amine compounds as those produced by decomposing fish [24].

In this study, bivariate analysis of the Chi-Square Test was also carried out to find the relationship between the dependent and independent variables. Table 4 shows the results of the significance of the Chi-Square regression test, with a p-value of 0.042 ($p < 0.05$), which means that there is a relationship between gestational age and the incidence of vulvovaginal candidiasis. This study's results do not follow the research by Kanagal et al. (2014) at the Department of Obstetrics and Gynecology at the Mangalore Tertiary Hospital in India, which statistically stated that the distribution of the incidence of vulvovaginal candidiasis based on gestational age was not significant. It can be seen from the results of his research, namely from 118 samples there were 50 people (42.37%) who tested positive for vulvovaginal candidiasis with the distribution based on gestational age, namely 27 people (54%) in the second trimester, 15 people (30%) in the third trimester, and eight people (16%) in the first trimester [22]. According to the literature, during pregnancy, there are very significant hormonal changes that can increase high glycoprotein levels in vaginal epithelial cells so that they will become a good carbon source for the growth and development of Candida sp. become pathogenic [23]. As gestational age increases, the risk of CVV increases due to high estrogen levels, progesterone, and glycoproteins in vaginal epithelial cells. However, it should be noted that the growth and development of Candida sp. are also supported by other risk factors, one of which is the cleanliness of the genital organs. The condition of the genital organs of pregnant women that are too humid and do not get enough air can be a favorable environment for the growth and development of Candida sp. [2]. There is a discrepancy in this study's results with previous studies due to differences in the sample number used, thus affecting the significance of the data obtained.

5. CONCLUSION

Based on the results of the study, it can be concluded that: a) Gestational age affects the incidence of vulvovaginal candidiasis in pregnant women; b) There was a significant relationship ($p = 0.042$) between gestational age and the incidence of vulvovaginal candidiasis, the increasing gestational age, the higher the frequency of CVV incidence; c) The incidence of vulvovaginal candidiasis (CVV+mixed infection) was mostly found in the third trimester of pregnancy as many as 11 people (50%), then in the second trimester as many as eight people (36%) and in the first trimester as many as three people (14%). Thus, pregnant women are encouraged to create healthy and clean behavior of the genital organs by installing pictures, stickers, or posters of the health and hygiene of the genital organs in the puskesmas environment, especially the obstetrics and gynecology poly. In addition, comprehensive services for pregnant women are provided, starting from promotive, preventive, and curative measures against CVV. In addition, pregnant women are expected to always maintain the health and hygiene of the genital organs and not take it lightly if there is vaginal discharge that begins to change color or smell and cause itching and burning in the vagina and vulva, and immediately get the condition checked.

CONSENT

As per international standard or university standard, patient(s) written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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