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Clinical Epidemiological Characterization of Vaginal Infection in Pregnant. "Orlando Matos Mosquera" Polyclinic. 2019 -2021

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Abstract

Introduction: Vaginal infection is a disease with a high incidence in pregnancy. It is associated with maternal-fetal complications, being early diagnosis and fundamental treatment. Objective: To clinically and epidemiologically characterize pregnant women with vaginal infection belonging to the "Orlando Matos Mosquera" Polyclinic in the period 2019-2021. Method: Observational, descriptive and cross-sectional study of pregnant women with vaginal infection. The arithmetic means and standard deviation of the quantitative variables and the absolute frequencies and percentages in qualitative variables whose association was obtained through the Chi-square with 5% significance were obtained. Results: 245 pregnant women were analyzed. The mean age was 25 years. 42.4% were mestizo, 56.4% accompanied or single, 41.2% had an upper secondary level, and 12.7% were housewives. At least 7 out of 10 smoked or had unprotected sex. 80.8% of the examined had vaginal discharge. 75 pregnant women suffered infection by Candida albicans and the average gestational age was 18.58 ± 8.48 weeks of pregnancy, with 37.6% of vaginal infections occurring in the first trimester. 73.0% of the mixed infections had vaginal changes and 66.7% of the infections due to infrequent germs were complicated. 3 out of 10 presented premature rupture of membranes, abortion or preterm delivery. Conclusions: Adolescents and young adults, mestizos, accompanied and with a higher secondary level prevailed. Vaginal discharge as a symptom and Candida albicans infection predominated. There was an association between the variables analyzed and complications.

Keywords: Vaginal infection, pregnancy, primary health care.

Introduction

Reproductive system infections are caused by changes in the vaginal flora, 50% of these infections go unnoticed by women and are only diagnosed during gynecological examination. 1 Pregnancy is an event that is traditionally celebrated around the world. However, for many families, the reproductive process can be grim and dangerous, with

morbidity, sequelae, and ultimately death for the mother, her child, or both. 2, 3 Multiple complications may appear during pregnancy, including vaginal infection, which has a worldwide distribution and constitutes a health problem due to its high incidence and health consequences. 4 These infections have increased in recent years, since they went from having a prevalence of less than 5-10% to 7-20% of cases per year. This type of disease affects women of reproductive age, without discrimination of race, state socioeconomic, educational level or others. Being the lack of knowledge of the subject an influential factor in the increase in the frequency observed.5 The normal discharge from the vagina is white, odorless, and not homogeneous, which is generally found in the entire vaginal fornix, where numerous concomitant microorganisms of the usual flora in that region. However, when the secreted volume increases and is accompanied by irritative symptoms, unpleasant odors and discomfort, a vaginal infection has occurred, which tends to occur with marked frequency in pregnant women. 6-8 Vaginal infection can be present in women of any age, whether or not they are sexually active. Most have had a vaginal infection at least once in their lives.7 Pregnancy is a period in which women are not exempt from suffering from a vaginal infection; Several investigations declare that pregnancy is a factor for the appearance of vaginal infections. Some women live with these and sometimes go unnoticed, but during pregnancy this is a serious problem, since they represent a risk factor for the production of complications such as premature rupture of the membrane (PROM), preterm labor and its consequences, including birth of a low-weight product. 10 The World Health Organization (WHO) estimates that annually 333 million new cases of curable sexually transmitted diseases in people aged 15 to 49, the majority in developing countries, which include member countries of the European community. 11, 12 On the other hand, recent calculations report that each year more than 340 million cases of curable sexually transmitted infections (STIs) occur in the world (they include only fungal and parasitic bacterial infections), which manifest as vaginal discharge syndrome, susceptible to effective treatments and that at least one million infections

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occur every day.3 Infections of the vulva and vagina are a frequent reason for consultation in Primary Care, Specialized and Hospital Emergencies, representing 20% of the queries gynecological.13, 14 In the United States it is the most frequent cause of infectious pathologies with an estimated 5 to 7 million cases per year. One in three women in this nation have bacterial vaginosis. While, in Sub-Saharan Africa it registers the highest prevalence, especially in the areas affected by the human immunodeficiency virus (HIV).4 In Cuba, cervicovaginal infections represent 80% of the reasons for gynecological consultations, so these Pathologies constitute a priority health problem.10 The Island is no exception to this situation and reports approximately 831,787 consultations by these entities annually. In Havana, this entity behaves with 227,292 patients assessed by gynecology consultation. According to reports from the National Statistics Office, infections by fungi, protozoa, parasites, and bacteria represent between 40,000 and 50,000 cases annually, with a marked trend toward increase.11 Epidemiological studies conducted in Cuba agree stating that the three most common types of vaginal infections are bacterial vaginosis (40-50%), followed by candidiasis (20-25%), and trichomoniasis (15-20%). Vaginal discharge may also occur if you have an infection of the cervix with gonorrhea or Chlamydia (sexually transmitted diseases). There are also other causes of vaginal infections that are less common.12 The Cuban health program and the development of preventive medicine, with the participation of the family doctor and nurse in gynecologic and obstetric care, together with the substantial technical and organizational changes to improve the quality of care for the mother-child pairing, have made it necessary to seek more dynamic ways that favor the performance of the health team, among which is the early detection of vaginal infections in pregnant women, whose control is decisivo para mejorar la salud reproductiva y de toda la población, lo que constituye uno de los mayores desafíos de la salud pública contemporánea. 13 Teniendo en cuenta lo anterior y la observación del incremento de la incidencia de infección vaginal en las embarazadas del área de salud Párraga y la repercusión que puede tener en el desarrollo del proceso gestacional y su producto, se tardará en realizar esta investigación.

Methods

Between September 2019 and September 2021, an observational, descriptive and cross-sectional study was carried out on 245 pregnant women with positive microbiological studies registered in the obstetric card belonging to the health area of the "Orlando Matos Mosquera" Polyclinic of the Arroyo Naranjo Municipality in Havana, Cuba.

Inclusion criteria:

Pregnant patients with a positive microbiological study registered in the obstetric card belonging to the aforementioned Polyclinic. To agree to participate in the study, an attitude that must be expressed by signing the informed consent, with stable residence in the health area.

Exclusion criteria:

Presenting a mental disability that prevents them from performing adequately in the Obtaining the information.

Theoretical Methods:

Induction-Deduction: Facilitated typifying the processes of reading and interpreting theoretical and empirical data, to arrive, following the logic of scientific thought, to generalizations and conclusions. Historical-Logical: It made it possible to approach the theoretical references of the subject and the analysis of the different criteria consulted by other authors with an approach adjusted to the time and space of its emission and to the corresponding level of scientific-technical development.

Statistical Method:

Calculation of absolute frequencies, percentages, arithmetic mean, standard deviation. Chi Square test of independence with a significance of 5%. Preparation of statistical and contingency tables he study.

Results

Table 1 summarizes the sociodemographic characteristics of the pregnant women studied. Table 1.- Sociodemographic characteristics of pregnant women with vaginal infection. "Orlando Matos Mosquera" Polyclinic, 2019-2021.

Sociodemographic		
Characteristics	N = 245	%
Age (X;SD)	25,01+/-	8,75
Age Group		
Under 15	24	9,8
15 to 24	107	43,7
25 to 34	74	30,2
35 to 44	28	11,4
45 or more	12	4,9
Skin Color		
White	69	28,1
Mixed Race	104	42,4
Black	72	29,5
Civil Status		
Single	76	31,0
Acoompanied	94	38,4
Married	67	27,4
Divorced	8	3,2

Sholarship		
Primary	24	9,8
Secondary		
Pre-University/ Intermedial e	101	41,2
Technician		
University	54	22,0
Occupation		
Student	100	40,8
Female Worker	114	46,5
Housewife	31	12,7

Source: data collection form.

A total of 245 pregnant women with vaginal infection at the defined time and place were analyzed. The average age of the patients was 25.01 ± 8.75 years. The majority age group was 15 to 24 years old with 43.7% of the total (107 pregnant women). The extreme ages (less than 15 years and 45 or more years) represented in each case less than 10%. Most of the patients were mestizo (104 cases; 42.4%). The percentage of whites and blacks was quite similar (28.1% and 29.5% respectively.

The most frequent marital status was accompanied (94 pregnant women for 38.4%), followed by single women (at

least 3 out of 10 studied). Only 8 pregnant women were divorced (3.2%). 41.2% of those analyzed (101 pregnant women) had a higher average level. Following them in frequency were those with completed secondary school (66 cases; 26.9%). More than 80% of the pregnant women were linked to some activity (studying or working).

Table 2 lists the symptoms reported by pregnant women with vaginal infection at the polyclinic and in the period analyzed.

Table 2. Symptoms reported by pregnant women with vaginal infection. Polyclinic "Orlando Matos Mosquera".

Referred Symptoms	N = 245	%
Vaginal disharge	178	72,6
Fever	29	11,8
Vulvodynia	43	17,6
Urinary symptoms	57	23,2
Vaginal itching	65	26,5
Lower abdominal pain	19	7,8
Stink	60	24,5
Others	21	8,5

Source: Data collectio form. Others: Vesical urgency, hypogastric pain.

El flujo vaginal fue el síntoma más frecuente en 178 pacientes (72,6%), seguido del prurito vaginal y la fetidez (65 casos; 26,5% y 60 casos; 24,5% respectivamente). El dolor abdominal bajo se present en menos del 10% de las

analizadas. El porcentaje individual de los incluidos en Otros no superó el 5%. En la tabla 3 se resumen los resultados microbiológicos y la relación con el gestacional de las embarazadas.

Tabla 3. Resultado microbiológico y trimestre de gestación. Policlínico "Orlando Matos Mosquera", 2019-2021.

Microbiological		Gestation Trimester					P		
Result	Fi	rst	Sec	ond	Th	nird	To	tal	
	Trim	ester	Trim	ester	Trim	iester			
									0,000
	n	%a	n	%a	n	%a	n	%b	0,000
Cándida Albicans	26	34,7	35	46,7	14	18,6	75	30,6	
Trichomonas	16	28,6	10	17,8	30	53,6	56	22,9	
Gardnerella	29	46,8	16	25,8	17	27,4	62	25,3	
Vaginalis									
Mixed	16	43,3	7	18,9	14	37,8	37	15,1	
Others	5	33,3	7	46,7	3	20,2	15	6,1	
Total	92	37,6	75	30,6	78	31,8	245	100	

a.- Calculated from the total number of patients in each row; b.- Calculated from the general total. Trimester of gestation: g (8); x2=29.69. Others: Escherichia coli, Streptococcus Group Bo Streptococcus agalactiae. Source: data collection form.

The average gestational age of the patients studied was 18.58 ± 8.48 weeks of pregnancy, with 37.6% of all vaginal infections occurring in the first trimester of pregnancy (92 of the pregnant women). Candida albicans was the most prevalent etiological agent (75 pregnant women; 30.6%) among all those studied. While 46.7% of pregnant women

with candidiasis were in the second trimester of pregnancy, 53.6% of those infected with Trichomonas were in the third trimester and 46.8% of those infected with Gardnerella vaginalis were found. in the first trimester. Mixed infections predominated in the first trimester (16 pregnant women; 43.23%) and those caused by other germs such as Escherichia coli, Group B Streptococcus or Streptococcus

agalactiae (which were the least frequent in general with only 15 pregnant women and 6 0.1% of the total) prevailed in the second trimester of pregnancy. The association between these variables was notorious with a statistical significance level of 5%. Table 4 relates the microbiological result with the presence of cervical changes in the pregnant women studied.

Tabla 4. Resultado microbiológico y modificaciones cervicales en gestantes con infección vaginal. Policlínico "Orlando Matos Mosquera", 2019-2021.

Microbiological	Cervical	Modification	ons				P
Result	Yes	No	Yes	No	Total	Total	
	n	%a	n	%a	n	%b	
Candida Albicans	12	16,0	63	84,0	75	30,6	0,000
Trichomonas	26	46,4	30	53,6	56	22.9	
Gardenerella	29	62,9	23	37,1	62	25,3	
Varginalis							
Mixed	27	73,0	10	27,0	37	15,1	
Others	9	60,0	6	40,0	15	6,1	
Total	113	46,1	132	53,9	245	100	

a.- Calculated from the total number of patients in each row; b.- Calculated from the general total. Modifications cervicals: g (4); x2=46.31. Others: Escherichia coli, Streptococcus Group Bo Streptococcus agalactiae. Source: data collection form A total of 113 pregnant women (46.1%) presented cervical modifications. 73.0% of pregnant women with Mixed infections had cervical modifications. Also 62.9% of those infected by Gardnerella vaginalis and 6 out of 10 with Escherichia coli, Group B Streptococcus or Streptococcus agalactiae. There was an association between these

Table 5. Complications in pregnant women with vaginal infection. Polyclinic "Orlando Matos Mosquera ".2019-2021.

Complications	n= 104	%
Premature rupture of membranes	35	33,7
Abortion / preterm delibery	32	30,8
Puerperal infection	13	12,5
Underweigh /CIUR	18	17,3
Neonatal infection	6	5,7

CIUR: Restricted intrautrrine grouth. Seurce: data collection form.

Discussion

The development of a community medicine that focuses its axis on prevention and timely diagnosis characterizes primary health care today. Likewise, the care of the pregnant woman and the product of conception are fundamental pillars in the programs of the Ministry of Public Health of Cuba. Since the introduction of the Maternal and Child Care Program (PAMI), the monitoring of this population group has benefited in various ways. The recognition of the same, as a vulnerable group and susceptible to preventable diseases, led to the standardization of strategies in the care of pregnant women that involve not only a multidisciplinary team of health professionals, but also social actors from governments at all levels. Infectious diseases are becoming more frequent in the general population, displacing chronic

variables at the statistical analysis with a high level of significance.

The complications of pregnant women with vaginal infection were summarized in Table 5. It can be seen that of the 104 pregnant women with complications, the 33.7% presented PROM, this being the most frequent, followed by abortion or preterm delivery (32 pregnant women; 30.8%) and low weight or CIUR (18 cases; 17.3%).

non-communicable diseases as the fundamental cause of morbidity and mortality and often with an unfavorable impact on those who are affected. Pregnancy is a situation that modifies the physiology of different organs and systems. The appearance of concomitant diseases or the presence of these prior to pregnancy makes it necessary to know these modifications and their influence on the disease, as well as the repercussion of the disease and of the diagnostic and therapeutic means in the pregnant woman and the fetus. In the course of a normal pregnancy, vulvovaginal infections are among the most common, often because their existence was ignored until the moment when the changes typical of pregnancy favor the course, sometimes florid, symptomatic and unfavorable. of this type of illness.14. The sociodemographic characterization regarding the age of the patients analyzed showed, in the current study, an average of 25.01 ± 8.75 years, prevailing patients between 15 and 24 years (43.7%). Vidal Borras and Ugarte Rodríguez 15 found that the age group that predominated in their study was that of 25 to 29 years, with 22.6% of their studied. While, Mendoza A, Sánchez J 16 and Montes E and 17 others showed a mean age of 23 and 24 years respectively and a predominance of adolescents. Results that correspond to that of the current series. Several studies have shown that younger women have a greater tendency to have pathological vaginal discharge during pregnancy. Furthermore, adolescence is considered the most difficult stage of life where drastic changes occur in the sexual sphere and their inexperience makes them more prone to infections of this type.18, 19 The data correspond to those published

by López Torres L. and another 20 21in the Peruvian Journal of Medicine Experimental and Public Health where an analysis of the association of several risk factors in vaginal infections was carried out in 20 cities of the Latin American country. One of the results was that single women suffer 1.23 times more vaginal infections than married women. Although it was not a significant factor (lower limit of the confidence interval less than 1), the result was relevant. In the same way, and with statistical impact, the age of the pregnant woman turned out, since when it comes to single adolescents the risk multiplied considerably. There are several factors that predispose to the acquisition of vaginal infections and the more is known about the host factors that condition the appearance of these infections and the more attention is paid to them, the frequency and complications will tend to decrease. There are risk factors that trigger or precipitate the appearance of changes in the normal vaginal flora of pregnant women, and others considered individual factors -personal hygiene and obstetric history- and social factors -sexual conduct-.22 Castillo Pacheco MC. indicates that 86.30% of women who reported systematic condom use did not present vaginal infection, this can be explained by the protective effect Condoms are contraceptives that reduce the risk of STIs and prevent unwanted pregnancy. Also, Navarro García YE and 23 others explain that currently it is related to PROM (the most frequent complication in this series) with multiple causes, but mainly vaginal and cervical sepsis is the most relevant factor 24.25. Vaginal infection is currently maintained as an obstetric problem that makes pregnancy difficult and sometimes produces fatal outcomes. Among the limitations of the study, it is worth mentioning the biases inherent in its methodological design. of condoms on various Sexually Transmitted Infections (STIs) such as vaginal infections. Above all, when compared with research that, even addressing the same subject, focuses on designs that are generally quite heterogeneous 26. However, this work provides local institutions with a characterization of pregnant women with vaginal infections, which allows longterm identification of term strengths and weaknesses in relation to its diagnosis and management, in addition to facilitating the generation of strategies aimed at improving maternal and fetal health care, based on the results of new studies.

Conclusions

Adolescent and young adult patients predominated. Vaginal discharge and stench appeared as the predominant clinical symptoms and findings among those studied. Candida albicans was the most frequent etiological agent, as well as early infections. The minority presented cervical modifications and complications and these were mainly associated with mixed infections or by infrequent germs such as Escherichia coli, Group B Streptococcus or Streptococcus agalactiae. There was a statistically significant relationship between the microbiological results and the trimester of pregnancy, cervical changes and complication.

Conflicts of Interest: There are no conflicts of Interest.

Reference

- Lugo González Ana María, Arteaga Bolaño María de los Ángeles, Bécker Montesino Miriela, CarreiroIhovany, Martínez Mederos Idolidia, Quintana García Teresa. Estrategia de atención al síndrome de vaginal en gestantes. Sancti Spíritus. GacMédEspirit[Internet]. 2014 Ago [citado 2020 Feb 26 41-54.Disponible 16(2): en:http://scielo.sld.cu/scielo.php?script=sci_arttext&pid= S1608-89212014000200006&Ing=es
- da Fonseca TM, Cesar JA, Mendoza-Sassi RA, Schmidt EB. Pathological Vaginal Discharge among Pregnant Women: Pattern of Occurrence and Association in a Population-Based Survey. ObstetGynecolInt. 2013; 20(3):416-90.
- 3. Chacón O'Farrill D, Cortes Alfaro D. Intervención educativa del síndrome de flujo vaginal en gestantes. RevCubanaObstGinecol 2017; 43(3): 1-13.
- 4. Abdelaziz ZA, Ibrahim ME, Bilal NE, Hamid ME. Vaginal infections among pregnant women at Omdurman Maternity Hospital in Khartoum, Sudan. J InfectDevCtries. 2014; 8(4): 490-7.
- Álvarez Rodríguez JM, Méndez Hernández A, García Verdecia O, Rodríguez Fernández I, Ramos Mustelier F. Epidemiología de la infección vaginal en gestantes diabéticas. Medisan 2014; 18(1): 84-89.
- RigolSantiesteban O. Afecciones de vulva y vagina. Infecciones de transmisión sexual. En: Obstetricia y Ginecología. 3ra ed. Tomo I. La Habana: Editorial Ciencias Médicas; 2014. P.123-43
- Álvarez Sintes R. Temas de Medicina General Integral.
 3ra ed. Volumen 2. LaHabana: Editorial Ciencias Médicas; 2014.
- Jawetz E, Melnick JL, AdelbergEdwart A. Manual de Microbiología Médica. La Habana: Pueblo y Educación; 1985.
- Gálvez Henry F, Rodríguez Sánchez B, Lugones Botell M. Características epidemiológicas del embarazo en la adolescencia. RevCubanaObstGinecol 2017; 43(3):15-27.
- 10. Álvarez Mesa MI, Domínguez Gómez J. Factores relacionados con el contagio de las infecciones de transmisión sexual en la adolescencia. Revista Habanera de Ciencias Médicas 2014;13(2): 270-83.
- 11. Alonso Uría MR, Rodríguez Alonso B, Yanes Morales CD, Castillo Isaac E.Caracterización del neonato bajo peso hijo de madre adolescente. RevCubanaObstGinecol 2018; 44(1): 1-10.
- 12. Pérez Pupo AJ, Pla Acebedo ME. Caracterización de embarazadas con productos de bajo peso al nacer del Policlínico Aquiles Espinosa Salgado. Revista Electrónica Dr. Zoilo E. Marinello Vidaurreta [Internet] 2014 [citado 2021 May 05]39(11)Disponible en:http://revzoilomarinello.sld.cu/index.php/zmv/article/ view/1377
- 13. Sociedad Española de Ginecología y Obstetricia. Diagnóstico y tratamiento de las infecciones vulvovaginales. ProgObstetGinecol. 2016; 59:350-362.
- 14. Cannoni G., Bórquez S. Vulvovaginitis e Infecciones de Transmisión Sexual en la Adolescencia.Rev. Med. Clin. Condes. 2016; 22(1) 49 57.

Citation: Rizo MEP, Puentes AA, Puentes RA, Tejeda MM, Rodríguez PRL (2023) Clinical Epidemiological Characterization of Vaginal Infection in Pregnant. "Orlando Matos Mosquera" Polyclinic. 2019 -2021. Anna Clin Rev Cas Rep -103.

- 15. Vidal Borras E, Ugarte Rodríguez CJ. Síndrome de flujo vaginal. Rev. Cubana Obstet. Ginecol. [revista en internet]. 2010 [citado 2022 Abr 11]; 36(4): 594-602. Disponible en: http://scielo.sld.cu/pdf/gin/v36n4/gin13410.pdf
- 16. Mendoza A, Sánchez J. Frecuencia de vaginosis producida por Gardnerella vaginalis y su asociación con otros patógenos causantes de infección vaginal en la mujer. GinecolObstretMex 2016; 69(7):272-6.
- 17. Montes E, Payan M, Pérez M, Loyola M. Comportamiento clínico epidemiológico de la infección vaginal en gestantes de dos consultorios. AMC2015; 9(3):1-9.
- 18. Larsson PG, Fåhraeus L, Carlsson B, Jakobsson T, Forsum U. Predisposing factors for bacterial vaginosis, treatment efficacy and pregnancy outcome among term deliveries; results from a preterm delivery study. BMC Womens Health 2017; 7:20
- 19. Ibrahim SM, Bukar M, Mohammed Y, Audu BM, Ibrahim HM. Prevalence of vaginal candidiasis among pregnant

- women with abnormal vaginal discharge in Maiduguri. Niger J Med 2013; 22(2):138-42.
- 20. LópezTorres L, Chiappe M, Cárcamo C, Garnett G, Holmes K, García P.
- 21. Prevalencia de vaginosis bacteriana y factores asociados en ciudades del Perú. Revista Peruana De Medicina Experimental Y Salud Pública. 2018;33(3): 1-7.
- 22. Pradenas AM. Infecciones cérvico-vaginales y embarazo. Rev Med Clin Condes [Internet]. 2014 [citado 2022May03]; 25(6):925-35. Disponible en: http://www.clc.cl/Dev_CLC/media/Imagenes/PDF%20revi sta%20m%C3%A9di ca/2014/6%20Nov/12-pradenas.pdf
- 23. Felipe González N, et al. Factores de riesgo asociados a infección vaginal en mujeres embarazadas. Multimed 2019; 23(3): 430-446.
- 24. Navarro García YE, Cobas-Planchez L, Mezquia-de-Pedro N, Goodridge- Salomón M. Gestantes con infección vaginal pertenecientes a un área de

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