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A Review: Risk Factors for Developing Vulvovaginal Candidiasis among Pregnant Women

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ABSTRACT

Vulvovaginal candidiasis (VVC) is an opportunistic infection and thus the second most common vaginal infection affecting women. It affects over 75% of women a minimum of once in their lifetime, with approximately 50% of them also suffering a recurrence. The clinical symptoms of VVC include cottage cheese-like vaginal discharge, swelling, pruritis, pain, irritation, burning sensation, dyspareunia, and dysuria. Vulvovaginal candidiasis (VVC) is an infection caused by Candida species, mainly Candida albicans. The development of VVC is usually attributed to the disturbance of the balance between Candida vaginal colonization and the host environment by physiological or non-physiological changes. Several host-related and behavioral risk factors have been proposed as predisposing factors for VVC. Host-related factors include pregnancy, hormone replacement, uncontrolled diabetes, immunodeficiency, antibiotics, glucocorticoid use, and genetic predispositions. Behavioral risk factors include the use of oral contraceptives, intrauterine device, spermicides, and condoms and some habits of hygiene, clothing, and sexual practices. Pregnancy has been considered a really important risk factor for the development of VVC. Among pregnant women, Vulvovaginal Candidiasis is been because of an imbalance in estrogen level, and alteration in vaginal pH. More amounts of estrogen lead to the production of glycogen which helps organisms like yeast or bacteria to grow faster, and it ends up more at risk of infection. Thus, this review provides information about the risk factors for developing Vulvovaginal Candidiasis among pregnant women, also including an insight to risk factors for developing VVC and their complications.

INTRODUCTION:

Vulvovaginal candidiasis (VVC) is an opportunistic infection and thus the second most common vaginal infection affecting women. It affects over 75% of women a minimum of once in their lifetime, with approximately 50% of them also suffering one recurrence. The clinical symptoms of VVC include cottage cheese-like vaginal discharge, swelling, pruritus, pain, irritation, burning sensation, dyspareunia, and dysuria. Several studies have shown that the prevalence of Candida among pregnant women is on top of that in non-pregnant women, and it tends to the extent of the progression of the pregnancy. Some emerging data have also suggested that VVC during pregnancy is associated with an increased risk of complications like premature rupture of membranes, preterm labor, chorioamnionitis, and congenital cutaneous candidiasis. various factors associated with physiologic changes, like decreased cellular immunity, elevated hormone levels, reduced vaginal pH, and increased vaginal glycogen concentration are associated with the following risk of VVC during pregnancy [1]. Pregnancy, DM, and antibiotic treatment are the foremost common predisposing factors. Vulvovaginal candidiasis has been noted to be more common in pregnancy, and pregnant women have higher rates of recurrent infections. The role of Candida colonization in the occurrence of preterm birth has been shown [2].

Candida can be isolated from the amniotic fluid in women with spontaneous preterm birth. Candida increases metalloproteinase 9 productions by chorioamnionitis membranes. Metalloproteinase 9 can be a connective tissue remodeling protein that has a crucial role in the origin of preterm labor and preterm premature rupture of the membranes. Therefore, the mother's vulvovaginal candidiasis may be a significant risk factor for Candida colonization of the newborn [3].

Additional risk factors are hyperestrogenemia, hormonal imbalance, immune suppression after a disease or psycho-emotional stress, hyperglycemia, antibiotic treatment, vaginal dysbacteriosis, oral contraceptives, IUD, spermicides, condoms, and a few habits of hygiene, clothing, and sexual practices. If the chance for the development of vulvovaginal candidiasis in the healthy population is approximately 20%, it increases by 30% during the third trimester of pregnancy. It is believed that the vertical transmission of yeasts during the act of birth encompasses a major role in the colonization of newborns in the first days of life[4]. Vaginal secretions during pregnancy fall from a pH of greater than 7 (an alkaline pH) to 4 or 5 (an acid pH).

This happens because of the action of Lactobacillus acidophilus, bacteria that grow freely within the increased glycogen environment, and by so doing increase the lactic acid content of secretions. This changing acid content helps to create the vagina resistant to bacterial invasion for the length of the pregnancy. This change in pH also, unfortunately, favors the expansion of Candida albicans. Candida infection occurs more frequently in pregnant women. Higher estrogen levels and higher glycogen content in vaginal secretions during pregnancy increase a woman s risk of developing vulvovaginal candidiasis. In pregnant women; vaginal candidiasis has been associated with emotional stress and suppression of the immune system which maximizes the chance of Candida species overgrowth and becoming pathogenic. Other risk factors are related to the eating habits of pregnant women of sugar-rich containing food [5].

The sugar increase ever more the threat of yeast infections powered by these sugary environments [6]. Pregnancy is a physiological state, which produces several normal and expected changes altogether in the maternal organ systems. PH of Vaginal secretions during pregnancy falls from a pH of greater than 7 (an alkaline pH) to 4 or 5 (an acid pH). This happens due to the action of Lactobacillus acidophilus, bacteria that grow freely within the increased glycogen environment, and by so doing increase the lactic acid content of secretions. This changing acid content helps to form the vagina resistant to bacterial invasion for the length of the pregnancy. This variation in pH also, unfortunately, favors the expansion of Candida albicans [16].

RISK FACTORS FOR DEVELOPING VVC:

The premenstrual phase or the pregnancy represents a high vulnerability for women when immune defenses are reduced so it is easier to get infected. The causes are a modification of the vaginal ecosystem that leads to reduced lactobacilli and an increase in local glycogen. Moreover, incorrect lifestyles such as a diet with excess carbohydrates and yeasts increase the risk of developing VVC. The use of synthetic linens, panty liners, and tight fit under wears leads to cause yeast infection by damage to vaginal mucosa and alterations in pH [10]. The vaginal flora is extremely dynamic with a local area of the microbial system. There's a balance between Candida vaginal colonization and therefore the host environment that may be disturbed by physiological or non-physiological changes, making the colonization site favorable for the growth of yeasts. Proposed host-related risk factors include pregnancy, hormone replacement, uncontrolled DM, immune suppression, antibiotics, glucocorticoids

use, and genetic predispositions (Sobel, 2007). Behavioral risk factors for VVC include the use of oral contraceptives, IUDs, spermicides, and condoms, and also some sexual, hygienic, and clothing habits (Patel et al., 2004; Sobel, 2007) (Figure 2) [7].

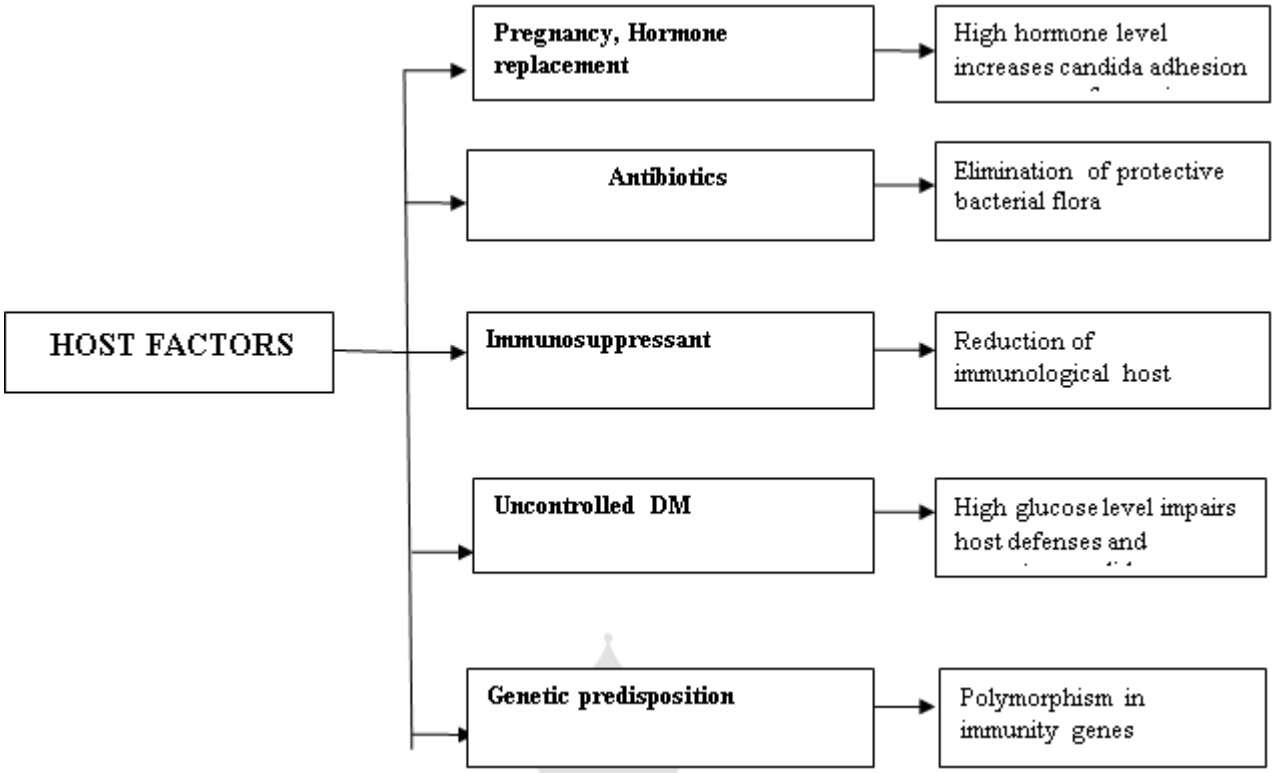

Figure 1: Host-related risk factors for VVC and respective effects

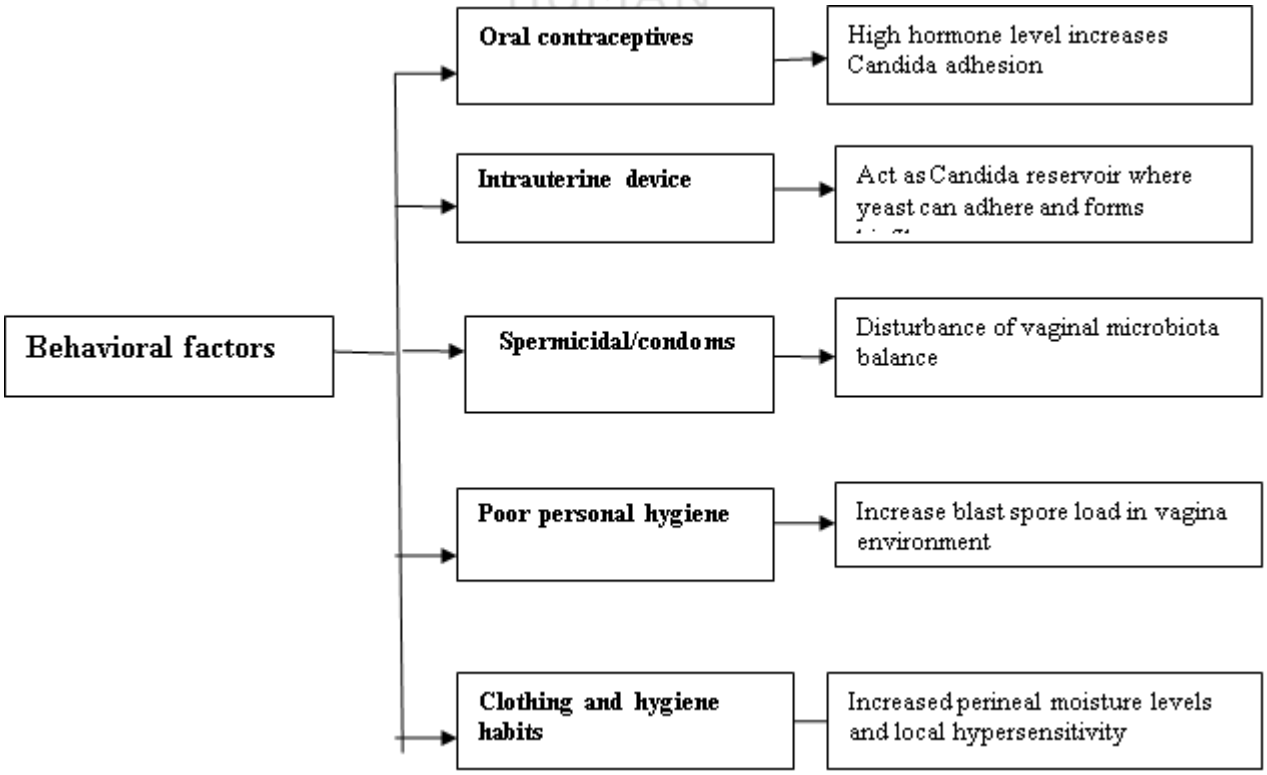

Figure 2: Behavioral-related risk factors for VVC and respective effects

RISK FACTORS OF VVC DURING PREGNANCY:

Pregnancy is found to be a risk factor because of the oversensitivity of the vagina during that period, facilitating infections to occur more frequently. The pregnancy leads to the occurrence of VVC [15]. The expression of symptomatic VVC and pregnancy is mainly dependent on some demographical, clinical, and behavioral factors [16]. Some host-related factors like genetic predisposition, uncontrolled DM, behavioral factors (e.g., antibiotic use, contraceptive use, etc), and physical conditions with higher reproductive hormone levels during pregnancy have also been described to be related to VVC [18]. Among pregnant women vulvovaginal candidiasis is been because of an imbalance in estrogen level, alteration in vaginal pH more amount of estrogen leads to the production of glycogen which helps the organism like yeast or bacteria to grow faster, and it ends up in more at risk of infection.

During pregnancy, both progesterone and estrogen hormones are elevated. Progesterone has suppressive effects on the anti-Candida activity of neutrophils, while estrogen is found to reduce the capacity of vaginal epithelial cells to inhibit the growth of Candida albicans and also decreases immunoglobins in vaginal secretions leading to increased vulnerability of pregnant women to vaginal Candidiasis [17]. Vulvovaginal candidiasis is the most common in the second and third trimester of pregnancy and hence it is very essential to cure this infection as soon as possible to avoidance of spreading it to the baby at the time of vaginal delivery. The factors which contract during pregnancy are hormonal changes in pregnancy, hormone medications, taking antibiotics and steroids, high levels of blood sugar, and impaired immune system [10].

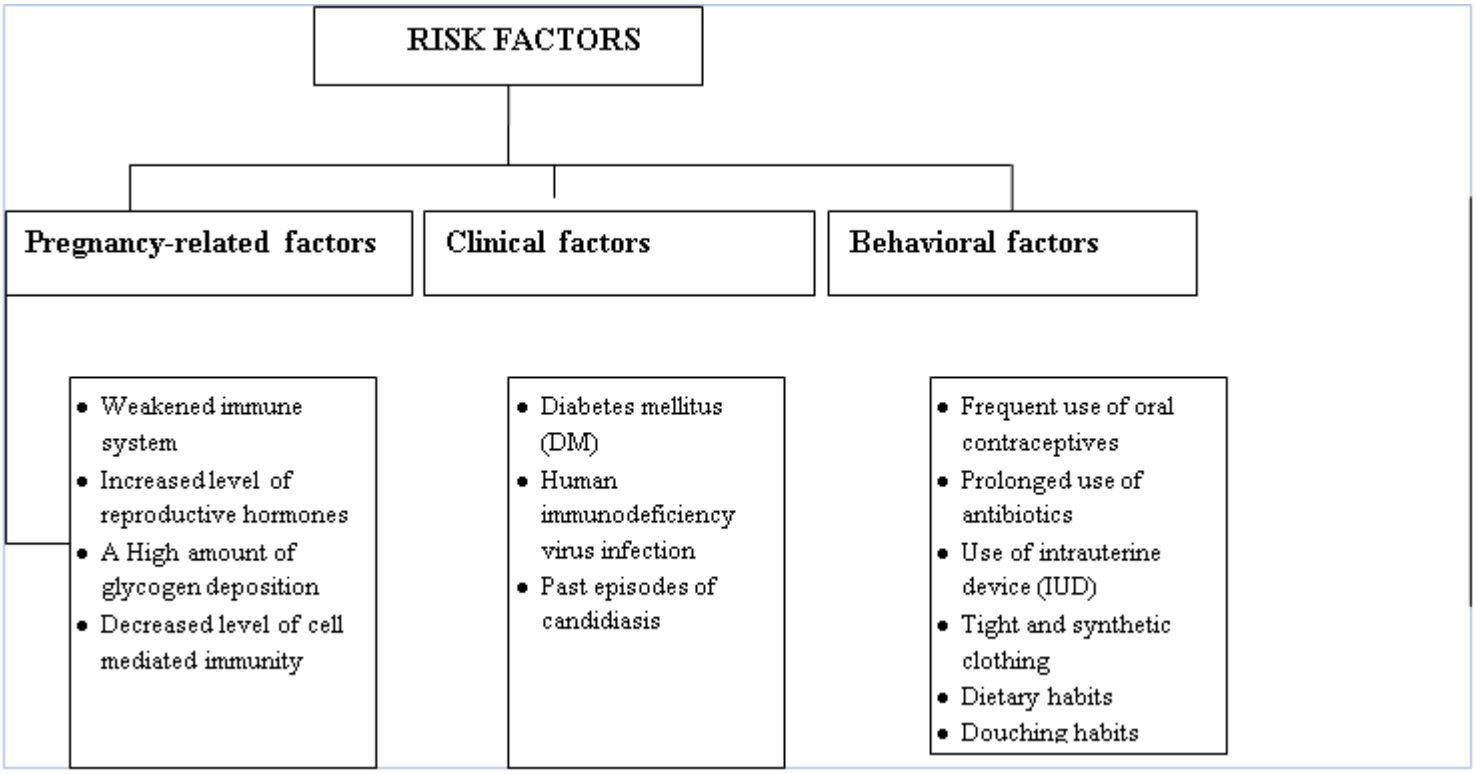

Figure 3: Compilation of different factors associated with VVC during pregnancy

PREGNANCY-RELATED FACTORS:

During pregnancy, several physiologic changes and the related factors which includes the weakened immune system, more level of reproductive hormones, glycogen deposition in the body, low vaginal pH, and reduced cell-mediated immunity are addressed in literature as risk factors for VVC [10].

1. Weakened Immune System: The impaired immune system makes pregnant women more prone to infections. Excess stress is described as a possible reason for this VVC [19]. Emotional stress increases as a woman are expecting a child, which ends with the suppression of the immune system. The weakened immune system ultimately steps up the overgrowth fungus Candida spp. and becomes pathogenic [19].

2. Increased Level of Reproductive Hormones: During pregnancy, hormone levels fluctuate more drastically than at the normal time in pregnancy, there is an elevated secretion of sex hormones, both progesterone and estrogen and it leads to the formation of infection. A higher level of progesterone allows the Candida yeast to hold within the vagina and it results from the alteration within the vaginal epithelium. And progesterone has inhibitory effects on the anti-candida activity of neutrophils. The healthy balance of microorganisms in the vagina

can get upset by the increased estrogen level, which will enhance the possibility of causing vaginal candidiasis elevated levels of estrogen hormone which facilitate the attachment of yeast to mucosal epithelial cells of the vagina [4]. Along with that, it stimulates growth, multiplication, hyphal formation, and enzyme elaboration for secreted aspartyl proteinase and phospholipases which increase colonization [8]. A higher level of estrogen reduces the immunoglobulins in vaginal secretions and reduces the epithelial cells' ability to suppress the growth of fungus, Candida albicans resulting in the increased vulnerability to vaginitis during pregnancy.

3. High Amount of Glycogen Deposition: Both progesterone and estrogen contribute to the elevation of vaginal tissue glycogen content. This high level of glycogen deposition provides an adequate source of carbon, thus favoring the growth and germination of Candida spp. on the wall of the vagina. Hence, it may be responsible for the increased susceptibility of pregnant women to VVC by giving a favorable room for Candida enhancement [33].

4. Decreased Level of pH: Typically, the vaginal pH is maintained at 4.0-4.5, and this level of acidic environment prevents the establishment of many vaginal pathogens. Vaginal microorganisms alter the acidity of the vagina which reduces its pH to 5.0-6.5; this may thereby enhance the establishment of pathogenic organisms like Candida. Increased level of progesterone during pregnancy has been shown to decrease the vaginal pH, thus favoring an acceptable environment for Candida yeast overgrowth.

5. Decreased Cell-Mediated Immunity: The immunologic changes during pregnancy have a role in the alteration of severity and susceptibility to infections during that period. The immune system and reproductive hormones have a complex and important interplay between them. Cell-mediated immunity during pregnancy causes altered responses to infections [51]. Estrogen-enriched condition within the last trimester of pregnancy results in the suppression of cell-mediated immunity. Progesterone causes a change in the balance between Th1 and Th2 responses and it suppresses the maternal immune response. As gestation advances, estradiol levels can increase as much as 500-fold in the maternal serum level and high estradiol concentrations are involved in the augmentation of humoral immunity As well as CD4+ type 2 helper T –cells (Th2) responses. Cytokine level increases during pregnancy and it will stimulate phagocyte cell recruitment or activity. A current approach suggested a change from Th1 to Th2 immunity in the pregnancy period. Th2 cells reduce cell-mediated immunity by inducing B lymphocytes, and then increase antibody production, and

suppressing the cytotoxic T lymphocyte response [20]. Existing evidence claims that featuring factors of innate immunity (phagocytic activity, levels of α-defensin, monocytes, neutrophils, and dendritic cell numbers) are increased with the progression of pregnancy, mainly in the second and third trimesters. In contrast, CD3+ T lymphocytes (both CD4+ and CD8+) count decreased in blood. [22].

6. Gestation Period: Several studies have linked the trimester of pregnancy with the vulnerability of pregnant women to VVC. The vulnerability of pregnant mothers to infection increases with the progression of pregnancy, hence the very best prevalence within the trimester [21]. Consistent with Nelson et al. [31], an increased estrogen level and corticoids within the 3rd-trimester decrease the vaginal defense mechanism against such opportunistic fungus. Together with that, the repetitive vaginal and pelvic examination, and reduction in hygiene statuses like failure to clean undies and pelvic areas thanks to fatigue or the stomach size of the pregnant mothers could encourage vaginal infection and predispose them to greater chances of VVC within the last trimester of pregnancy.

CLINICAL FACTORS:

Diabetes mellitus, HIV infection, and previous encounters with candidiasis are discussed in several studies as potential factors contributing to vaginal colonization during pregnancy [23].

1. Diabetes Mellitus: Uncontrolled DM acts as a main predisposing factor to VVC. Patients with clinical diabetes have an increased risk of Candida infections of the skin and vagina. In diabetes, glucose concentrations get increased within the vaginal secretions which stimulate adherence of Candida to epithelial cells and promotes its development and effective expression of virulence factors. The potential of eliminating pathogens by neutrophils and also phagocytosis is restricted by hyperglycemia conditions. Additionally, hyperglycemia can stimulate protein production in Candida spp., which facilitates yeast adherence and also destroys phagocytosis by the host. Hence, pregnant women with diabetes could also be more vulnerable to VVC because it enhances the expansion of yeasts [23].

2. HIV Infection: Immunocompromised women are generally at higher risk of developing fungal infections. It's been shown in studies conducted earlier that increased vaginal colonization with fungi has been caused by a loss of immune-protective mechanisms. In immunosuppressed patients, vaginal candidiasis will be correlated well with reduced cell-

mediated immunity, Predisposing host factors, like HIV infection and other immunosuppressive diseases, play the leading role in the development of VVC. Moreover, proteinase activity acts as a key role in the pathogenesis of VVC, which gets increased in HIV-positive women, hence making them vulnerable to VVC.

3. Past Episodes of Candidiasis: Patients with a previous history of candidiasis are considered at a greater risk of developing VVC during pregnancy by some authors. It would flow from the hormonal milieu and suppressed system which contributes to the increased susceptibility.

BEHAVIORAL FACTORS:

Several behavioral characteristics of pregnant women might affect the speed of candida colonization during pregnancy. Behavioral factors like the use of antibiotics, oral contraceptives, intrauterine devices; tight clothing; douching habits and poor personal hygiene, and poor dietary habits are assessed as risk factors.

1. **Frequent Use of Oral Contraceptives**: Pregnant women who are using contraception are considered to be at an increased risk of developing vulvovaginal candidiasis. Oral contraceptives cause many changes within the vaginal environment which may be related to the decreased ability to resist Candida infection. Usage of high-dose contraceptive pills (75-150 μg of mestranol) has been observed to affect glucose resistance over a little period which can, in turn, promote Candida adhesion or virulence by affecting the carbohydrate source within the vaginal epithelial cells the carbohydrate source. Additionally, oral contraceptives are found to be related to immunological changes, including the elevation of antibodies in cervical mucus and therefore the sera [24], and doubtless the Great Depression of T-lymphocyte proliferation. Furthermore, most oral contraceptives are found to contain estrogen and progesterone, which creates "estrogen dominance" by disrupting the hormonal balance that ends up enhancing Candida's growth of VVC during pregnancy in several studies.

2. **Prolonged Use of Antibiotics**: An expanded chance of developing symptomatic VVC in pregnant women following a course of oral antibiotics has been depicted. Continuous misuse of medication results in resistance to drugs, particularly towards the common antifungal agents utilized for the treatment of vaginal candidiasis [29]. Broad-spectrum antibiotic usage (e.g., tetracycline, ampicillin, and cephalosporin) results in eliminating Lactobacillus spp.

present within the normal defensive bacterial flora of the vagina, which prevents germination of Candida by providing a colonization resistance mechanism [43]. Moreover, antibiotics may play a significant role in the overgrowth and increased virulence of the Candida spp. by reducing the prevalence of other competitive bacterial organisms to Candida for the substrate.

3. **Tight and artificial Clothing:** In literature, the kinds of undergarments and clothing that sometimes women wear are proposed as a risk factor for vulvovaginal candidiasis. Increased temperature, moisture, or direct irritation of the vaginal area is considered the possible mechanisms associated with this. Wearing tight clothes and artificial underwear appears to extend the local acidity by nourishing friction and maceration [32].

4. **Dietary Habits**: The role of dietary habits in VVC has been suggested as a risk factor due to the altered virulence of Candida in response to the heightened availability of sugar substrates. Patients with VVC were more likely to excrete sugars like sucrose, arabinose, and ribose. The associated dietary patterns with these sugars were an elevated intake of milk, yogurt, farm cheese, and artificial sweeteners. Reductions in both the speed of VVC and also the presence of sugars in urine were reported by less dairy ingestion. There is a strong relationship between the diet with the prevalence of VVC during pregnancy are scarce. Maximum studies couldn't prove the role of excess or deficient diet within the etiology of sporadic or recurrent vulvovaginal candidiasis [31].

5. **Stress**: The validity of the hypothesis considers stress because the root explanation for candida vulvovaginitis has been confirmed in many cases. The explanation is often explained by the difference between the strain of a woman's surroundings and her ability to deal with them which causes the stressors to occur. Women who have their psychological and physical capacities pushed to the utmost or perhaps exceeded are subjected to those stressors. The patient's system gets physiologically attenuated as a bearing of the stressors[32].

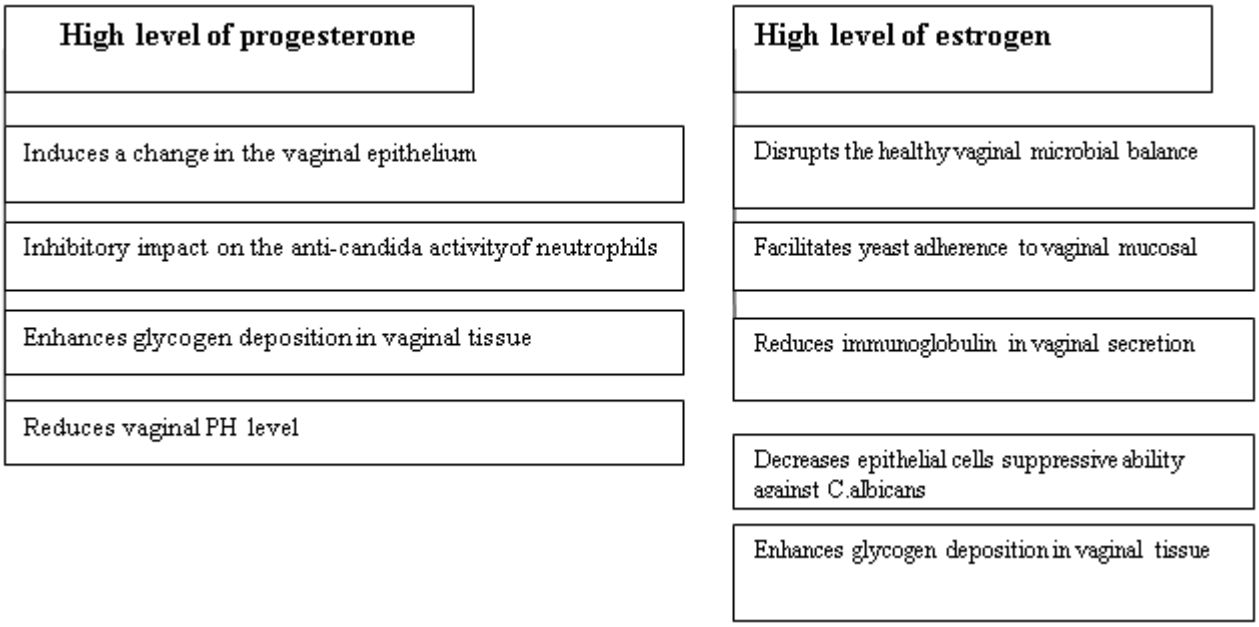

Figure: 4: Summary of the consequence of the elevated level of progesterone and estrogen during pregnancy

VVC IN PREGNANCY

Vaginal candidiasis causes discomfort to pregnant women by producing thick, whitish creamy, or yellowish discharge. This infection may cause a threat to the well-being of the baby. VVC could be common in pregnancy the prevalence of genital candidiasis infection among women presented in the antenatal clinic was 38 %. Immune down-regulation of physiology lower genital tract occur in late pregnancy, higher amount of circulating estrogen and progestin and corticosteroids level ends up in reduced vaginal defense and it results in to enhance the adherence of candida to the vagina mucosa Which then causes persistent infection. there is some evidence that candida vaginitis related to adverse pregnancy outcomes patients with positive candida culture has significantly lower mean birth weight and mean fertilization age at delivery compared to candida negative women[35]. Other researchers reported that colonization wasn't related to preterm delivery. VVC is more common in the second trimester.

ANEMIA IS A RISK FACTOR TO DEVELOP VVC DURING PREGNANCY

The WHO (WHO 1972) defines anemia – regardless of its cause – as the presence of a Hb level of less than 11.0 g/dl during pregnancy and less than 10.0 g/dl during the postpartum period. Iron deficiency is the most common deficiency in women of childbearing age

throughout the world, and is even more common in pregnancy, as might be expected from the increasing iron requirement during that period [29]. So, ID can cause lower immunity to infection because of impaired cellular immunity, the deficient bactericidal activity of polymorphonuclear leukocytes, inadequate antibody response, and epithelial abnormality. Iron deficiency anemia (IDA) is one of all the causes of dysfunction of CMI and humoral immunity, which in turn predispose the host to certain clinical infections. Cytokines are important mediators of cellular immune activity and their micro-environmental profile determines the balance between, and the intensity of, Th1 and Th2 kinds of response. IDA, resulting in various levels of reduction within the performance and activation of immune cells, induces significant a predominant Response that ends up in resistance and therefore the onset of protective immunity through IL-2, IFN-production, and macrophage activation, whereas a Th2 response (IL-4, IL-10, and TGF β) exacerbates the disease through the inactivation of fungicidal effectors cells changes within the cytokines production [17].

COMPLICATIONS OF VVC IN PREGNANCY

The main symptoms of VVC include itching, burning, redness, swelling, and discharge. Treatment of pregnant women is indicated to relieve the symptoms. Particularly, recurrent vulvovaginal candidiasis adds considerably to the discomfort of pregnancy. candidiasis during pregnancy could also be related to an increased risk of pregnancy complications, like premature rupture of membranes and poor pregnancy outcome. Vaginal Candida infections causing chorioamnionitis are rare. There are however several case reports of the intraamniotic infection caused by C. Albicans and C. glabrata resulting in preterm rupture of membranes or preterm labor, and progression that might prove fatal to the fetus. Chorioamnionitis has also been related to maternal vaginal candidal colonization, but almost only within the presence of foreign bodies like IUD or cerclage, and prolonged rupture of membranes. C. Albicans requires a hyphal formation to locally invade and cross intact fetal membranes [11]. Access to the cavum is often achieved hematogenous from the intervillous space or through an ascending route. Intraamniotic Candida infection might also cause systemic congenital infection, cerebral candidiasis, or fetal demise. The danger of ascending infection is increased by ruptured membranes, the presence of a uterine or cervical foreign body, and a history of vaginal candidiasis. The foremost common presentation may be a cutaneous generalized eruption of erythematous macules, papules, and/or pustules, with a benign outcome. Oral thrush is also present at birth, and yellow-white papules could also be observed on the duct.

Occasionally, term babies with congenital candidiasis have systemic manifestations, like pneumonia or clinical evidence of sepsis [22].

CONCLUSION

Changes in the vaginal environment are generally required for the alteration of the opportunistic Candida organisms from commensal to pathogenic. The rate of Candida colonization was found to increase during pregnancy, particularly in the 3rd trimester, has become a matter of concern due to the emerging evidence on the association of VVC with increased risk of pregnancy-related complications, for example, premature delivery and low birth weight.

Risk factors of VVC during pregnancy have been summarized in the review article. And also Reviewed pieces of literature have assessed multiple pregnancy-related, clinical, and behavioral factors as risk factors for developing VVC during pregnancy, but not all have been found associated significantly with increased risk of VVC. Increased level of reproductive hormones, especially estrogen and progesterone, has been found to significantly influence several physiological and immunological changes in pregnant women, which further favors Candida colonization in the vagina. Thus, this review provides information about the risk factors for developing Vulvovaginal Candidiasis among pregnant women, also including an insight to risk factors for developing VVC and their complications. Proper treatment and care should provide in pregnancy time in order to avoid risks of VVC. Therefore, studies on the prevalence rate and risk factors of vulvovaginal candidiasis during pregnancy should be carried out more across the world.

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