Fungal infections in humans have been reported since ancient times by Hippocrates and Galen. The oldest known observations of fungal infections in newborns, infections of the genital tract during pregnancy and relationship between them (vertical transmission) come from the 19th century [1]. Vaginal infection caused by yeast-like fungi of the Candida genus is one of the most common infections occurring in pregnant women [2]. Opportunistic fungal infections in humans are caused by Candida albicans, Candida glabrata, Candida parapsilosis, Candida tropicalis, Candida crusei and Candida lusitaniae [3–5]. In recent years, also congenital infections caused by Candida kefyr were described [6,7]. Although the fetal membranes with placenta protect fetus against infection, both ascending (from the vagina) and hematogenic, fungal infection of the fetus develops in exceptional cases [3,4].

Why saprophytic yeasts [8,9] become disease agents? In the field of general considerations it is worth to refer to the short-term imbalance in the body caused by environmental factor defined by Wołanński as a subpatologic state (close to disease) that may lead to pathological changes and long-term disruption of homeostasis, namely disease [10]. Considering multitude of potential disorders of the organism and biological diversity of microflora, the problem should be considered in a broad range, bearing in mind the relationship between the human body and its ontocenoses and external environment. In order to define a well-known contemporary organic and environmental factors affecting the risk of development of congenital infection due to Candida, a review of the literature on congenital candidiasis with particular emphasis on recent works of original Polish researchers was done.
The composition of the normal flora of women is complex and depends on many organic and environmental factors [11,12]. Ravel et al. [13] demonstrated species diversity of human vaginal microbiota in North American women according to ethnicity and offered an analysis of the relationship between the abundance of species of microorganisms forming ontocenoses based on four hypotheses dynamic equilibrium hypothesis, community space hypothesis, alternative equilibrium states hypothesis and community resilience hypothesis. Many scientific studies were devoted to the reasons why it comes to the development of opportunistic infections of the vagina [14] and congenital candidosis. In 1958 Bret and Coupe described the cause-and-effect relationship of congenital infections and fungal infections of the vagina in the article entitled Vaginitis & neonatal infection; etiology of mycoses in newborn (Vaginites et infection neo-natale: étiologie des mycoses du nouveau-né) [mentioned for 4].

The authors of one of the first works involving microbiological research on congenital candidiasis were Sonnenschein, Clark and Taschdjian. In 1964 in the article Congenital cutaneous candidiasis published in American Journal of Diseases of Children they presented the results of studies on the tolerance of Candida albicans to the pH of the environment. They demonstrated that Candida albicans grows in the amniotic fluid, even when the pH is equal to 10.0 [15]. It is therefore likely that the yeast which overcome the mucosal barrier acid vagina, grow luxuriantly in a slightly alkaline amniotic fluid. Several years earlier, in the 50s, along with the introduction new drugs amphotericin B and nystatin the era of effective treatment of fungal infections began [16]. The review of research on the treatment of vulvovaginitis carried out in this period in the aspect of their relationship with candidiasis of the oral mucosa in newborns was presented by Shrand in the article Thrush in the newborn published in British Medical Journal in 1961 [17] and scientific works of Blaschke-Hellmessen, among others Epidemiological studies of the occurrence of yeasts in children and their mothers (Epidemiologische Untersuchungen zum Vorkommen von Hefepilzen bei Kindern und deren Müttern) published in Mykosen in 1968 [18] laid the groundwork for epidemiological studies on congenital candidiasis.

Nowadays it is known that the risk of Candida infection is increased in women who used oral contraceptives, were subjected to prolonged treatment with antibiotics or steroids or have immune deficiencies [4]. The diagnosis of inflammation of the vagina and vulva is based on symptoms of inflammation in the presence of Candida, with absence of other infectious etiologic agents [19]. Vaginal infection in pregnant women, in most cases respond to treatment without causing further complications. However, ascending intrauterine infection, infection of the amniotic fluid, placenta or umbilical cord can occur. An infection in the fetus and complications, forcing early termination of pregnancy or leading to death of the fetus develops very rarely. Infection of the fetus can occur in the absence of damage of fetal membranes, during premature rupture of membranes or following amniocentesis. Total number of placenta and fetus infections in relation to the number of vaginal infections in pregnant women is small [4]. Not all congenital infections are invasive but newborns are in age group the most vulnerable to invasive candidiasis [20]. A mucus plug, formed from vaginal secretions, plays an important protective role, tightly closing the cervix and fetal membranes with amniotic fluid [4].

Candida albicans development strategy largely depends on its virulence determinants [21,22]: adherence [23], morphogenesis regulation [24,25], enzymatic activity [26–30] and capacity to biofilm formation [31], which are the primary subject of microbiological study and are critical for the course of vaginal candidiasis and congenital candidiasis [32,33]. Diagnostic methods are based on these factors [34–37], which also takes into account the individual characteristics of micro-environments of the body [38–40] and the response of the human immune system to the presence of microorganisms [41].

During vaginal delivery colonization of skin of the newborn by Candida albicans occurs [42,43]. This is rare cause of systemic infection but when the infection is congenital, especially in preterm infants it induces systemic inflammatory response and is associated with a high risk of death. There are congenital mucocutaneous candidiasis and congenital systemic candidiasis [44] (invasive). The diagnosis of congenital candidiasis before birth, based on the examination of amniotic fluid (amniocentesis) is very rare [45]. Several theories about the occupation of the membranes by Candida were formulated, in which fungus are allowed to
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cross that barrier without iatrogenic damage to the membranes. Ito et al. (2013, Japan) are the authors of the article presenting 23-week premature infant born in serious condition with congenital candidiasis (child of asymptomatic mother) and the invasion of the membranes by *Candida albicans* [46]. While Rode et al. (2000, United States of America) [47] described the case of chorioamnionitis, placenta infection and systemic candidiasis in the newborn caused by therapeutic amniocentesis. Watching the placenta and umbilical cord after birth plays an important role in the diagnosis of congenital candidiasis [4,48]. Characteristic fungal infiltrates are macroscopically visible as small and numerous spots of color white and yellow, a diameter of about 0.5−2 mm, occurring on the fetal part of the placenta, and arranged circumferentially around the umbilical cord. They are microabscesses. Inflammation of the umbilical cord may also take the form of outbreaks of acute necrotizing with occurrence of calcification within the umbilical cord. These changes are annular, around the umbilical vessels. It is necessary to biopsy the placenta, both ends of the umbilical cord (placental and fetal) and fetal membranes for histopathological examination [49–51]. The standard hematoxylin/eosin staining can not visualize changes characteristic for mycosis and mycelium. Instead, we can see inflammatory infiltration of the walls of umbilical cord blood vessels, fibrin deposits, numerous leukocytes (PMNL – polymorphonuclear leukocytes), amnion epithelial damage and degeneration of Wharton’s jelly. Carrying out other coloring preparations – silver plating, reveals hyphae of mycelium [4]. Amniotic fluid is muddy [52]. Particularly serious prognosis involves inflammation of the umbilical cord, especially in the group of preterm infants born before 26 weeks of pregnancy [50].

Among the research on congenital candidiasis, clinical observations play an important role. As a result of intrauterine infection occurs an increase of inflammatory parameters in maternal blood (leukocytes, C-reactive protein, procalcitonin), which after birth is also recognized in the child. It is necessary to terminate pregnancy earlier. In newborn maculopapular or erythematous purulent rash occurs. The fungus can attack conjunctiva, mucous membranes, respiratory system and the candidiasis can lead to develop the inflammation of vagina and vulva in a child [45]. In extremely premature infants, skin peel off all over the body [53]. Other symptoms include apnea or respiratory failure, convulsions, hypotension, abdominal distension, reluctance to suck, retention of gastric contents in the stomach, positive control for occult blood in the stool, fluctuations in body temperature, hyperglycemia, moderate hyperbilirubinemia and radiological features of pneumonia [54,55].

A positive blood culture test for *Candida albicans* is some evidence of ongoing infection, but a negative result does not exclude infection. We should carry out a survey of cerebrospinal fluid (positive result indicates the concentration of glucose in the fluid below 30 mg%) and urine (urine culture collected by suprapubic puncture) and ultrasound examination of the brain, kidney and urinary tract. Finding a fluffy white ball in the vitreous body during ophthalmic examination can identify systemic *Candida* infection without positive blood test result [56]. In additional studies, particularly in the field of diagnostic imaging, we should look for possible outbreaks of infection in different locations, including lung, heart (endocarditis), liver (abscess), bones and joints, urinary tract, central nervous system and the eyes [57,58]. Due to the existence of embryonic arteries in the vitreous of the eye to about 30 week of pregnancy, candidemia in preterm infants is associated with the possibility of the development of an abscess of the lens [59]. The differential diagnosis includes listeriosis, a Ritter disease (staphylococcal scalded skin syndrome), impetigo, syphilis, viral infections (especially HSV), congenital ichthyosis and epidermolysis bullosa [60].

In Mexico, Torres-Alvarez et al. [61] described uncomplicated congenital candidiasis of the skin in newborn born in 37 week of gestation, treated with topical nystatin. Mother had no symptoms of genital tract infection in the perinatal period but candidiasis in a child can be associated with a history of the mother urinary tract infection diagnosed and treated successfully nitrofurantoin in the last month of pregnancy [61]. Nitrofurantoin was also used in pregnant mothers of other infants with congenital candidiasis [46,48].

In Japan, Iwatani et al. [62] described an effective treatment for premature infant with congenital skin candidiasis born in 25 week of pregnancy (infection of non-invasive, without candidemia). Examples of characteristics of complications in congenital candidiasis are cases examined by Tinsa et al. [63], Skoczylas et al. [52]...
component of the immune system increase the risk of infection in neonatal period (severe combined immunodeficiency) and in the later stages of human life (e.g., DiGeorge syndrome and autoimmune polyglandular syndrome type I) [68–71]. In an aspect of antifungal immunity among signs of immaturity of preterm infants the relationship shown by Gloning should be mention that neutrophil adhesion capacity depends on birth age [72].

Difficulties in the treatment of congenital candidiasis and vaginal candidiasis justify the interest of clinicians in progress of antifungal therapy. An expression of interest was the review article by Dalhoff and Hartwell published in Danish periodical *Ugeskrift for læger* in March 2000 [73], several months after the publication of articles summarizing the clinical trials conducted by Czeizel team on data from The Hungarian Case-Control Surveillance of Congenital Abnormalities from the years 1980–1992. The results of these studies showed a reduction in the incidence of preterm births as a result of topical treatment with clotrimazole and lack of teratogenic effects of this drug [74,75]. Also in 1999 in Denmark it was demonstrated that fluconazole administered to women in a single oral dose before conception or during pregnancy does not increase the risk of birth defects in fetuses [76]. It was postulated that a reduction in the number of preterm births as a result of antifungal therapy is the effect of genital organs infections treatment of pregnant women, the category of disorders known as risk factors for preterm delivery [74]. A supposed causality between vulvovaginitis and preterm delivery was studied and discussed in medical literature by many researchers with different opinions [77–79].

Studies on the oral treatment of vaginal candidiasis are important for the prevention of congenital candidiasis, which illustrates an example of a premature birth due to congenital candidiasis, which has developed despite the topical treatment of vaginal candidiasis with clotrimazole, presented by Skoczylas et al. [52].

The therapeutic success described by Huttova et al. [80] shows the efficiency of fluconazole in the treatment of neonatal infection with involvement of the central nervous system. Good treatment results prompted clinicians to conduct further research, including the risk of late complications of congenital fungal infections [81] and invasive candidiasis [82].
The second turn etiological agent of vulvovaginal candidiasis beside Candida albicans is Candida glabrata, which not all strains are sensitive to fluconazole (like Candida crusei) [83]. This fact requires the selection of antymicotic drug for the newborn after the results of microbiological tests.

Knowledge of the presence of infection with a rare etiology (including non-albicans Candida species) in premature infants, neonates and in the other groups (such as babies long-term treated with antibiotics), making doctors ready to incorporate them in their future professional practice. Such rare infection with Candida kefyr was described by Weichert et al. [6] in full term infant with anal atresia, renal agenesis, vesicoureteral reflux and rectovesical fistula, treated from urosepsy caused by Enterococcus faecalis with cefotaxime, cefepime, piperacillin, imipenem, gentamicin and vancomycin. After confirmation of the fungal etiology they used liposomal amphotericin B and then the fluconazole after antibiogram.

Review of research on the role of metallic chemical elements in yeast biology with implications for the mechanisms of action of antymicotic drugs developed Krajewska-Kulak and Niczyporuk [84]. Among the numerous works on the sensitivity of fungi to antifungal agents in vitro and in vivo, there are the work of Polish researchers like Macura et al. [85] and Sulik-Tyszka et al. [86,87]. The results of studies of Krajewska-Kulak et al. [88] suggest no effect of cyclosporine A on the susceptibility of Candida albicans to amphotericin B, nystatin, pimaricin, clotrimazole, miconazole, ketoconazole, tioconazole, fluconazole and econazole. Strains isolated from vaginal ontocenoses of women suffering from chronic, recurrent candidiasis, refractory to treatment with multiple antymicotic drugs were tested. While, Phillips et al. [89] examined the effects of stress and amphotericin B for apoptosis of Candida albicans.

Despite the progress of molecular studies still a serious problem is the resistance of fungi to antymycotics, including multidrug resistance [90]. One of the most important developments in medicine in the field of resistance is resistance for effective and well tolerated fluconazole: efflux-pumps system [91]. Difficulties in the treatment of recurrent vaginal and vulvar candidiasis result from not only fungal resistance to drugs. The colonization of sexual partner skin is important [92]. In Poland, the mycological examination of sexual partners led, among others, Bukowska et al. [93] and Kwaśniewska et al. [94]. Kwaśniewska et al. [95–98] studied multifocal infections too. The search for the source of infection, especially during pregnancy, should take into account the carriage of Candida on the skin of the male genitalia and medical history in the direction of balanitis [99–101] and prostatitis [92]. Results of studies on the epidemiology of balanitis pay attention to the two independent risk factors for this infection – age over 40 years, and diabetes [102]. Although not all studies conducted so far have shown a connection of vaginal candidiasis with potentially predisposing comorbidities, extended diagnostics should include physical examination focused on risk factors for fungal infections of various locations (including the oral cavity and respiratory tract), for example: cancer, cervical epithelial dysplasia, diabetes, immunosuppression, HIV infection and a history of antibiotic therapy [37,99,103–111]. According to the study of Maleszka et al. [112] the coexistence of nail body candidiasis and mixed nail infections caused by dermatophytes and Candida fungi is important for the success of treatment of candidiasis of the genitourinary system. The above examples suggest the consideration of hygiene in the treatment of candidal vulvovaginitis and – what follows from this – also in the prevention of congenital candidiasis.

The risk of transmission to the baby after birth depends on, among others, of the sanitary condition of obstetric-neonatal ward, the hygiene practices of medical staff and parents in the hospital and at home [113–117]. In terms of the impact of the environment on the human body important observations on disease processes occurring in the mother-fetal unit and their relationship with maternal diet have made Pineda et al. [7] in United States. They described candidemia (Candida kefyr) in one of the two twins with dichorionic and diamniotic pregnancy completed by caesarean section at 29 weeks due to sepsis caused by Candida kefyr, whose mother was consuming large amounts of dairy products, including at least 2 servings of yogurt, cheese and milk a day. This case is probably a rare example of hematogenous inherent candidiasis with microscopically confirmed inflammation of the membranes and decidua in the absence of genital tract infection. Before the embryo transfer (IVF) culture test results from the cervix were negative. This example suggests to avoid or minimize the consumption of unpasteurized milk in pregnancy.

Treatment of relapsing forms of recurrent
candidal vulvovaginitis and congenital candidiasis is one of the most difficult challenges of modern medical mycology [118–120]. Guidelines and thematic publications on the treatment of vulvovaginitis, congenital candidiosis and related conditions are developed by national scientific societies, for instance Danish Dermatological Society [99], British Society for Sexual Health and HIV [121], German Dermatological Society [122], German Society for Gynecology and Obstetrics [122,123], German-Speaking Mycological Society [122], Polish Gynecological Society [124,125] and Polish Neonatal Society [126–128].

Physician knowledge of the activity of microorganisms of Candida genus in a specific compartments of the microenvironment of human organism and in the course of defined disorders of homeostasis [39,40,129] makes it easier to predict the course of the disease and allows the development of procedures that can be extremely helpful in an individualized diagnostic and therapeutic process. Therefore, for solving clinical problems conditioned by disorders of vaginal ontogenesis findings of the microflora of the mouth [103,105,130], intestine [8] and genitalia are important [92,100]. Also relationships between genotype and immune status of the organism and the composition of the microflora have a great value [68,131]. Analysis of co-occurrence of different types of features and probability of developing a certain type of diseases connected with them is possible only after determining their characteristics. It should be noted that this is a step towards adapting the idea of personalized medicine into everyday medical practice.

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