

Review articles

Congenital candidiasis as a subject of research in medicine and human ecology

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ABSTRACT. Congenital candidiasis is a severe complication of candidal vulvovaginitis. It occurs in two forms, congenital mucocutaneous candidiasis and congenital systemic candidiasis. Also newborns are in age group the most vulnerable to invasive candidiasis. Congenital candidiasis should be considered as an interdisciplinary problem including maternal and fetal condition (including antibiotic therapy during pregnancy), birth age and rare genetic predispositions as severe combined immunodeficiency or neutrophil-specific granule deficiency. Environmental factors are no less important to investigate in diagnosing, treatment and prevention. External factors (e.g., food) and microenvironment of human organism (microflora of the mouth, intestine and genitalia) are important for solving clinical problems connected to congenital candidiasis. Physician knowledge about microorganisms in a specific compartments of the microenvironment of human organism and in the course of defined disorders of homeostasis makes it easier to predict the course of the disease and allows the development of procedures that can be extremely helpful in individualized diagnostic and therapeutic process.

Key words: invasive candidiasis, candidemia, *Candida*, pregnant woman, newborn, host-parasite interactions

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 lusitanae* [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 Wolański 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 candidiasis. 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 overcomes the mucosal barrier of the vagina, grows luxuriantly in a slightly alkaline amniotic fluid. Several years earlier, in the 50s, along with the introduction of 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

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 pustular 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]

and Basu et al. [64].

In Tunisia, Tinsa et al. [63] observed the occurrence of respiratory distress syndrome without candidemia or occupance of central nervous system in full-term infant with congenital candidiasis of the skin in 50 hours after birth, despite the topical treatment of econazole. After empiric antibiotic therapy using ampicillin, cefotaxime, and amikacin, they effectively changed treatment to intravenously administered fluconazole.

Topically treated chronic vaginal candidiasis in pregnancy woman and course of treatment of congenital invasive candidiasis in the neonate born at 25 weeks gestation in a serious condition was described in Poland by Skoczylas et al. [52]. After a short stay in the hospital district pregnant woman was admitted to the clinic where caesarean section was performed. Amniotic fluid was gray and dense. Newborn and fetal membranes, placenta and umbilical cord were covered with a thick layer of gray matter. After cleaning, the baby's skin was bleeding, which was caused by a large, invasive infection of all skin with *Candida albicans*. Mechanical ventilation (SIMV) and empirical antibiotic therapy including fluconazole were conducted. Initially, the infant responded to the treatment, but superinfection with strain of hospital *Klebsiella pneumoniae* resulted in deterioration of the state and death due to extreme immaturity, congenital defects and massive sepsis.

Endophthalmitis, cornea perforation and phthisis bulbi despite the treatment with amphotericin B are the complications of congenital candidiasis in the neonate described by Basu et al. [64] in India.

Symptomatology of congenital candidiasis is varied. The case of the onset of symptoms of respiratory failure and increased levels of liver enzymes in the blood in the course of extensive congenital cutaneous candidiasis is known [65] and another case with congenital infection of *Candida* in the form of septic shock without skin lesions, radiological features inflammation of the lungs or the typical macroscopic changes in the placenta was described [66].

Invasive fungal infection is particularly important for premature babies and newborns with congenital heart disease [52,67]. Among rare organic causes of weakened immunity against *Candida albicans* there is neutrophil-specific granule deficiency (neutrophil lactoferrin deficiency) [22]. Immunodeficiency and disease processes associated with autoantibodies against

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 true 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 antimycotic 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 urosepsis 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 antimycotic drugs developed Krajewska-Kułak and Niczypruk [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-Kułak et al. [88] suggest no effect of cyclosporine A on the susceptibility of *Candida albicans* to amphotericin B, nystatin, pimarin, clotrimazole, miconazole, ketoconazole, tioconazole, fluconazole and econazole. Strains isolated from vaginal ontocenoses of women suffering from chronic, recurrent candidiasis, refractory to treatment with multiple antimycotic 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 antimycotics, 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 Kwaśniew-

ska 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 candidosis 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 ontocenosis 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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