



Management of chickenpox in pregnant women: an Italian perspective

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Abstract

Chickenpox is a highly contagious disease caused by primary infection of varicella zoster virus (VZV). The disease is spread worldwide and is usually benign but, in some groups of population like pregnant women, can have a severe outcome. Due to a not optimal vaccination coverage, a relatively high number of childbearing-aged women in a European country such as Italy tested seronegative for VZV and so are currently at risk of acquiring chickenpox during pregnancy, especially if they live in contact with children for family or work reasons. Only few data are available about the risk of infection in this setting: the incidence of chickenpox may range from 1.5 to 4.6 cases/1000 childbearing females and from 1.21 to 6 cases/10,000 pregnant women, respectively. This review is aimed to focus on the epidemiology and the clinical management of exposure to chickenpox during pregnancy. Particular emphasis is given to the accurate screening of childbearing women at the time of the first gynecological approach — the females who tested susceptible to infection can be counseled about the risks and instructed on procedure should contact occur — and to the early prophylaxis of the at-risk exposure. Lastly, the achievement of adequate vaccination coverage of the Italian population remains a cornerstone in the prevention of chickenpox in pregnancy.

Keywords Chickenpox · Pregnancy · Prophylaxis · Management · Vaccine

Introduction

Chickenpox (or varicella) is a highly contagious infective disease caused by varicella zoster virus (VZV), characterized by a vesicular exanthema and fever [1]. The virus is spread worldwide and is commonly transmitted from person to person by direct contact, e.g., with skin rash or by inhalation of aerosolized droplets from respiratory tract secretions of patients with chickenpox [2]. Rarely, the infection is spread by the inhalation of aerosolized droplets from vesicular fluid of skin lesions of patients with chickenpox or disseminated herpes zoster (HZ) [2]. After primary infection, VZV remains latent in the sensory nerve ganglia and can reactivate later in life, causing HZ [2].

In Italy, in the past, the primary infection occurred in childhood and consequently nearly more than 95% of adults were naturally immunized; today, due to the poor adherence to the

infant vaccination program in the last years, the primary infection may take place in mid-adulthood and can be burdened by serious complications and by a fatal outcome, especially if contracted during pregnancy [3].

This review, from an Italian perspective, is aimed to (i) investigate the risk of primary infection by VZV in pregnancy, (ii) identify the pregnant women who may acquire VZV infection, and (iii) manage the exposure to VZV.

What is the risk of VZV primary infection in Italian pregnant woman?

The risk of VZV primary infection in pregnant woman is closely linked both to the prevalence of seronegative adult subjects in the population and to the spread of virus circulation in childhood.

It is well known that epidemiology of chickenpox shows differences between the high-income and low-income areas of the world. In high-income countries, before the implementation of infant vaccination program, the infection by VZV was usually acquired during childhood and so the seroprevalence of protective antibodies (namely anti-VZV class IgG) was very high in adulthood, exceeding 95%. Differently, in low-

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income countries, the infection still today is more often acquired in the adult age and most childbearing women are at risk of acquiring infection also during pregnancy [4, 5].

The last data indicated that in the European Union (EU) about 5.5 million (95% confidence interval 4.7–6.4) of chickenpox cases is annually reported; the incidence is slightly higher in the western European countries (300 to 1291 cases per 100,000 persons) compared to that in southern European nations (164 to 1240 cases per 100,000 persons) [3]. Most European cases of chickenpox (about 3 million, 95% confidence interval 2.7–3.3) occurred in children aged less than 5 years [3].

In the period 2001–2010, in Italy, the mean annual incidence of chickenpox had been 150.7 cases per 100,000 population, and most of these cases occurred in childhood (incidence of 948.6 cases per 100,000); in 2010, the annual incidence declined to lower value (102.6 per 100,000 population) [6]. These data indicate a reduced circulation of the virus compared with the previous years, but this phenomenon can assume a different value when associated to not-optimal vaccination coverage of the population; in this case, the two conditions, namely persistent virus spread and not sufficient immunization coverage, might lead to an increased “pool” of adult people susceptible to primary infection in Italy.

First, differently from most EU countries where the implementation of national vaccination policies had led to a three-fold or more reduction of chickenpox incidence in the last years, although VZV vaccine has been universally recommended for pediatric vaccination, in Italy only eight regions (which represent nearly 40% of the Italian population) included varicella in their immunization programs with different schedules in children up to 2017; for this reason, the national level vaccine coverage has been always very far from optimal coverage suggested by WHO, reaching about 30.7% in 2015 [7] and 46.06% in 2017 [8]. It is noteworthy that a suboptimal coverage (< 80%) of children could lead to an increasing number of cases in adults [9].

Second, also the prevalence of seronegative adult subjects in the Italian population is quite different from that in the other European countries. Several serological studies across the EU/European Economic Area (EEA) showed that most individuals (> 95%) had acquired antibodies to VZV before the class age 15–19 years, although the seroprevalence rates had been found to be slightly lower among young adults living in southern and eastern European countries with respect to northern and western European ones [9] and geometric mean concentrations for VZV antibodies had been found lower in women aged 20 years with respect to men [10]. In Italy, several local epidemiological studies have reported reduced seroprevalence rates of VZV IgG antibodies in the adult Italian population with respect to that in the EU population.

A study carried out in 2008 on serum samples collected from all 20 Italian regions has found a global prevalence of

IgG VZV of 70%; among women of childbearing age (15–40 years), the prevalence ranged from 85.4 to 91% [11].

A similar study carried out in 2013–2014 has found a global prevalence of IgG antibodies to VZV below 82% [12]; comparing the data by age group, the seroprevalence of IgG antibodies to VZV in the class aged 15–40 years was similar (89–93%) to that in a previous study [11, 12]. Although the seroprevalence has been found higher in some age groups living in North and Central Italy with respect to those living in Southern Italy, the only variable associated with the prevalence by multivariate analysis was age group [11].

Lastly, a study carried out in 2011–2012 has found that 93% of blood donors from Apulia (a region in South Italy) presented anti-VZV IgG [13].

Although these data indicated that at least 7–15% of adult Italian people is seronegative to VZV antibodies, the problem remains to understand how many childbearing and pregnant women are susceptible to VZV infection.

Specifically in the setting of pregnant women, five studies focused on VZV IgG seroprevalence reported a quite higher rates of seronegativity both in Spain (12%) and in Italy (10.6%) with respect to the overall rate (less than 5%) reported in other EU countries [14–18].

Lastly, a study carried out in 2007 had found a total seroprevalence of IgG anti-VZV antibodies among childbearing-aged women living in Central Italy of 80.9% (74.6–87.6), with lower seroprevalence in the youngest women [19]; and a cohort study on childbearing women carried out in 2001 has showed in southern Italy comparable results with a seroprevalence of 89.4% (81.6–97.8) [18].

All these data confirm that a not negligible number of Italian childbearing and pregnant women are seronegative to VZV IgG; although a real estimate of their number is quite difficult, according to recent data [20] referring to 2017, 10,469,419 women of childbearing age (between 15 and 44 years old) were living in Italy; assuming a seroprevalence of 90% for anti-VZV IgG seropositivity, there were approximately 100,000 women who are seronegative for VZV IgG. However, this number might be underestimated since the migratory flows bring to Italy most childbearing women seronegative for VZV IgG who come from low-income Countries.

The risk of acquiring chickenpox in at-risk pregnant women is not easy to quantify. In the absence of Italian data, only data by three studies from Western countries (two from UK and one from US) can be extrapolated.

The first study was carried out in the Northern England between 1997 and 2002 in an area with a population of 513,000 people. Among 30,595 pregnancies, 19 cases of chickenpox were diagnosed, with an incidence of 6 cases for 10,000 pregnancies. Three out of 19 patients developed the most dangerous complication of chickenpox such as pneumonia [21]. The second study, carried out in Scotland from 1981 to 1998, reported an overall incidence of chickenpox in

pregnant women of 0.38 per 1000 live births [22]. The last study was performed in a large cohort of pregnant women (7.7 million) from the United States (US) and reported an incidence of 1.21 cases/10,000 pregnancy admissions. In this cohort, incidence of chickenpox pneumonia was 2.5 and 0.3% of patients experienced ARDS requiring ventilation but with no maternal deaths [23]. Based on these literature data, the incidence of acquiring chickenpox during pregnancy may range from 1.21 to 6 per 10,000 pregnancies.

Other literature data had reported values of annual incidence of chickenpox ranging from 1.5 to 4.6 cases/1000 referred to childbearing women [24].

No additional data are available from other high-income countries.

What clinical impact may chickenpox have on maternal health and delivery?

The primary infection acquired during the pregnancy may have an impact both on the maternal morbidity and mortality, and also on delivery outcome [25]. Usually, the clinical evolution of chickenpox is characterized by a benign outcome and about 2 to 6% of cases estimated in EU may develop serious complications, including secondary bacterial infections, pneumonia, aseptic meningitis or encephalitis, cerebral ataxia, and hemorrhagic complications; every year, from 18,000 to 23,500 European patients with chickenpox require hospitalization [3]. The risk of complications such as pneumonia seems to be increased in pregnant women compared with that of non-gravid subjects, reaching rates of about 10–20% of cases of chickenpox [26, 27]. Some risk factors have been related to the risk for maternal VZV-related pneumonia: (i) primary infection acquired during the third trimester of pregnancy, (ii) active smoking, and (iii) skin eruption above 100 lesions [28].

Clinically, the onset of the pneumonia is sneaky; the patient develops a non-productive cough 2 to 5 days after the exanthema that can rapidly progress to respiratory failure requiring intensive care [29]. Pregnant women with respiratory symptoms or VZV pneumonia should be quickly hospitalized for monitoring and starting antiviral therapy; up to 40% of women may need mechanical ventilation [30]. In severe cases, namely those who require mechanical ventilation, the mortality rate in the pre-antiviral era was 20–45% while currently estimated to be lowered up to 3–14% [31, 32]. In addition, a pregnancy loss is possible, especially due to maternal sepsis or hypoxia [33].

Another important issue related to maternal chickenpox is represented by the outcome on delivery and offspring. The literature data seem to indicate an increased rate of spontaneous preterm birth in pregnant women with chickenpox (14.3%) when compared with gravid individuals without VZV infection (5.6%, $p = 0.05$) [34]. Also, the risk of vertical

transmission to the fetus/newborn during the intrauterine stage (congenital infection), during labor (perinatal infection), or after birth (postnatal infection) has been reported [35]. The rate of vertical transmission is about 25% before 20 week gestation [36]. The offspring infection can result in fetal death, abortion, premature birth, intrauterine growth retardation, and different defects, already evident at birth or, more frequently, occurring as sequelae [34, 37, 38]. The incidence of congenital infection is overall 0.91%, with rates ranging from 0.55 during the first trimester to 1.4 during the second one, and during the third trimester is virtually absent [39, 40].

How to manage the infection in pregnant women? From the diagnosis to the early treatment

Diagnosis The diagnosis of chickenpox is mainly clinical. A biological confirmation, by the analysis of the skin vesicle's samples, would be the gold standard but is not routinely performed in pregnant women; in this case, the detection of viral DNA by PCR is today the reference technique for virologic diagnosis. Indeed, the detection of virus antigens by immunofluorescence is not sensitive and the viral culture, although more sensitive than immunofluorescence, is longer and laborious [40].

In most cases, the serology may be partially useful for diagnosis. The anti-VZV antibody class IgM usually appears 2 to 3 days after the onset of the exanthema and persists thereafter for several months after the primary infection and reappears in case of reactivation; therefore, their presence may be useless outside the initial phase of the disease. Anti-VZV antibody class IgG becomes positive 10 or more days after the exposure; therefore, a serological positive in this window period (namely before 10 days) translates into a prior contact and immunity to the virus, while a serological positive after the 10th day from the contact may reveal a recent immunological response, i.e., an early chickenpox [41]. In Table 1, the interpretation of serological test for VZV is reported.

A positive IgM ELISA result, although suggestive of a primary infection, does not exclude reinfection or reactivation of latent VZV. Careful clinical evaluation may be needed to determine if a rash is varicella or herpes zoster. Nevertheless, IgM testing is readily available and a positive result from a

Table 1 Interpretation of serological antibodies to VZV and immune status to chickenpox

	Class IgM	Class IgG
Susceptibility	–	–
Infection	+	–
Infection	+	+ *
Immunity	–	+

*After the 10th day from contact

person with a generalized rash is usually interpreted as laboratory confirmation of varicella. A single positive IgG ELISA result cannot be used to confirm a varicella case [42].

IgG avidity has been used in research settings to determine if a person who is IgG positive for VZV was infected with the virus in the past or more recently. The test however is not available commercially and is not used routinely in clinical practice [42].

Treatment Once the infection is diagnosed, starting very soon the therapy is crucial. Today, the antiviral therapy alone or in combination with hyperimmune globulins against VZV (VZIG) has been recommended in the management of VZV infection during pregnancy [43, 44].

The available drugs include acyclovir, valacyclovir, and famciclovir. Acyclovir is a synthetic nucleoside analogue of guanine which is highly specific for cells infected by VZV or herpes simplex virus [45]. When phosphorylated by viral thymidine kinase in the VZV-infected cells, the drug inhibits viral DNA polymerase and stops the viral replication. Since the oral formulation has low bioavailability, acyclovir must be given in frequent doses per os to achieve therapeutic levels; the optimal dosage is 800 mg five times daily per os for 7 days [35]. Further bioavailability data suggest that the pregnancy-related physiological changes do not alter the maternal pharmacokinetics compared with the non-pregnant women [46, 47].

Valacyclovir and famciclovir are pro-drugs of acyclovir and penciclovir, respectively. These pro-drugs have a longer half-life and better oral absorption and bioavailability; this entails less frequency of administration and so an improved patient's compliance. All pregnant women should receive valacyclovir 1 g three times daily for 7 days or famciclovir 500 mg three times daily [35].

Compared with placebo, antiviral therapy reduces the duration of fever and symptoms of chickenpox in immunocompetent adults, if started within 24 h of rash development [48]. If given within 24 h and up to 72 h of the development of rash, acyclovir is effective in reducing the maternal mortality and morbidity associated with VZV infection [49], particularly if used intravenously (i.v.) [50–52]. In the case of VZV pneumonia, the optimal dosage is usually 10–15 mg/kg of body weight i.v. every 8 h for 5–10 days [50–52].

Acyclovir may inhibit viral replication during maternal viremia and potentially might inhibit transplacental transmission of VZV. Animal studies have shown that this drug readily crosses the placenta [46]. Although acyclovir crosses the placenta and can be found in the umbilical cord blood and other fetal tissues, actually there is no evidence of benefit on preventing congenital varicella syndrome [37].

No teratogenicity has been found when administered to animal models throughout the period of major organogenesis [53]. From 1984 to 1999, a pregnancy registry established by

the manufacturer and the Centers for Disease Control and Prevention (CDC) collected data for 749 pregnancies (756 outcomes) and found the rate of birth defects for women exposed to systemic drug during the first trimester of pregnancy approximated that of the general population. Acyclovir is classified as pregnancy category B [54] by US Food and Drug Administration according to the standard classification [55].

A larger study carried out in Denmark analyzed a total of 5739 women treated with acyclovir, valacyclovir, and famciclovir in a period ranging from 4 weeks before conception to the delivery time. In this cohort, no significant association between birth defects or miscarriage and antiviral treatments has been detected [53]. Furthermore, registries of neonates exposed to acyclovir in utero have found no significant risk of teratogenesis from the use of the drug in pregnancy [55]; nevertheless, theoretical risks exist in case of administration in the first trimester, warranting the contraindication of the drug up until 20 weeks of gestation [55].

Though there is a potential for complications of in utero exposure, small studies of valacyclovir use in late pregnancy have found no clinical or laboratory evidence of toxicity in infants followed up to 1 or 6 months of age [45].

As abovementioned, the antiviral therapy may be given alone or associated with VZIG at the dosage of 125 UI/10 kg body weight (see “Prevention”).

Prevention Last, but not least, prevention is an issue of VZV infection in pregnant women. Since primary infection is a major threat if acquired during pregnancy, the main objective for the clinicians must be to identify all pregnant women who are susceptible to the virus and offer an adequate prophylaxis. From this point of view, the gold standard should be to identify the women who do not have protective antibodies (VZV IgG seronegative) by routinely performing serological tests for women already in childbearing age, before conception. Unfortunately, in the clinical practice, many women perform this test only in the first trimester of pregnancy [25, 56].

The susceptible pregnant women who have a significant VZV exposure should be offered VZIG in order to prevent or attenuate maternal disease. The first problem is the definition itself of “significant VZV exposure” that can vary according to the different guidelines, but it relies on (I) the proximity and duration of contact with the infected source, and (II) the potential contact of infected droplets and vesicular fluid with the conjunctivae and nasopharyngeal mucous membranes of the susceptible subjects. A history of chickenpox actually negates the need for performing the serological testing or offering a passive prophylaxis with VZIG, as well as the available previous test positive for anti-VZV IgG. Without a history of chickenpox or previous testing, the serology should be checked if the time permits, otherwise also if in doubt the passive prophylaxis with VZIG should be given [56, 57].

Since the rationale of prophylaxis is to modify the maternal disease and to prevent the maternal morbidity, VZIG should be given to susceptible women within 72 h of exposure to the virus although it can be given up to 96 h. Beyond 96 h, VZIG has not been evaluated, nevertheless some authors recommend VZIG for up to 10 days after exposure, likely due to the availability of more concentrated immunoglobulin formation in some countries. VZIG is ineffective and should not be given once clinical illness has developed [58].

The optimal dose of VZIG is unclear and differs worldwide; for example in the US and Italy, VZIG is recommended at a dosage of 125 U/10 kg to a maximum of 625 U (equivalent to a weight of 50 kg) [49]; alternatively, 1 mg/kg body weight can be administered i.v. [59]. Whether 625 U is sufficient for women weighing > 50 kg is not clear [60]. Intravenous administration appears to demonstrate benefit over intramuscular one achieving optimal serum levels more quickly [61]. The duration of action of VZIG is unknown but is likely to be at least one half-life of the IgG (3 weeks). Accordingly, subsequent VZV exposure within 3 weeks after a dose of VZIG may require additional doses [49].

In Fig. 1, a practice algorithm for the management of VZV exposure and infection in pregnant women is reported. Lastly, the active prophylaxis with VZV vaccine, that has been shown to be effective in preventing infection following exposure and is most effective when given within 3 days of exposure, cannot be offered to a pregnant woman because the VZV vaccine is a live attenuated vaccine [49, 62]. The live attenuated vaccine against chickenpox is contraindicated for pregnant women and childbearing women should avoid pregnancy for at least 1 month after vaccination [49].

What to do if a patient has been inadvertently vaccinated during the first weeks of gestation? There are no guidelines; the data collected on 860 pregnant women who had inadvertently received VZV vaccine within 3 months before gestation or during the first weeks showed no cases of congenital chickenpox syndrome or birth defects [63].

For this reason, it is important to implement the vaccine coverage not only in infants but also in childbearing woman who have not been vaccinated yet; the optimal strategy should be to offer vaccine 1 to 3 months before pregnancy though no birth defects related to inadvertent vaccine exposure have been reported [35, 64]. Ideally, every woman of childbearing age should be offered screening at the time of the first gynecological visit in case of no or unknown history of VZV exposure and not only after at-risk exposure.

Although virus excretion in breast milk is unknown (but post VZV vaccination breast milk samples have failed to detect any VZV DNA), the vaccination is not contraindicated in lactating women [65, 66]. Lastly, household contacts of pregnant woman can be vaccinated, although one case of development of chickenpox in a VZV-susceptible pregnant woman, following vaccination of her 1-year-old child, has been

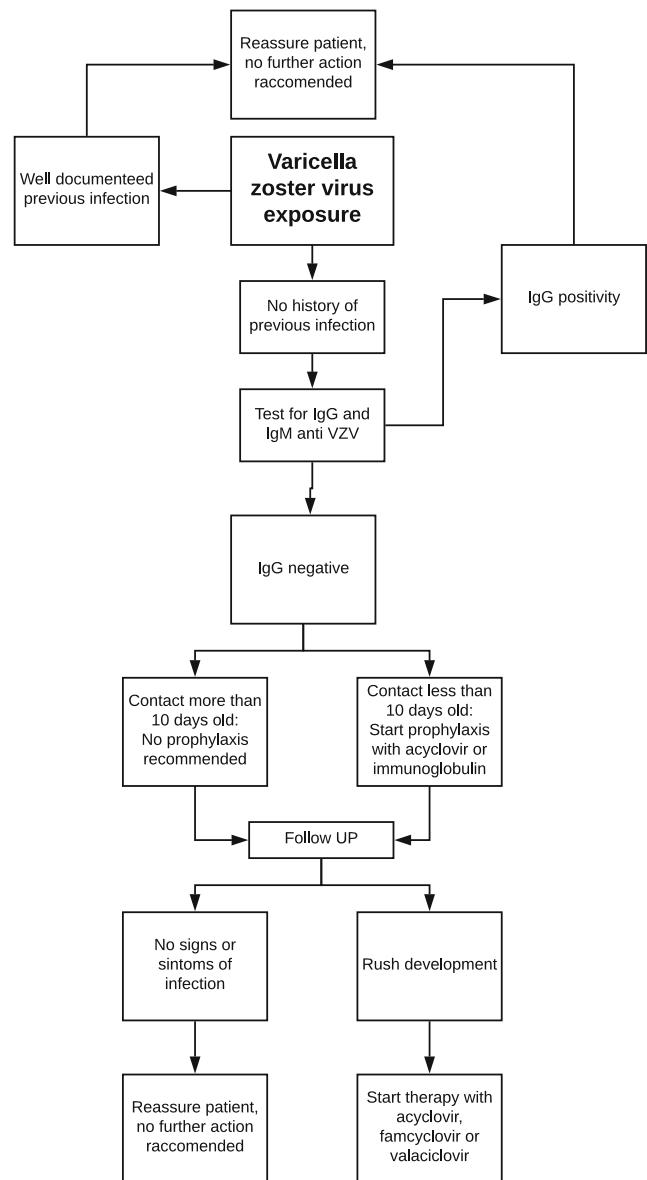


Fig. 1 The practice algorithm for the management of VZV exposure and infection in pregnant women

reported. In this case, the transmission was confirmed using polymerase chain reaction; after therapeutic termination of pregnancy, no virus was isolated from fetal tissue [67].

All vaccine recipients who develop chickenpox < 42 days after vaccination are likely to represent wild virus infection [68], but in them, the disease is mild, the infectivity is low, and there is little or no risk of complications [69].

In conclusion, an essential part of the prevention strategy is to avoid or reduce the incidence of chickenpox in pregnancy and the cost of managing the cases requires an organized approach to management of exposure incidents and treatment of primary infection, as well as an accurate screening. This should be carried out before pregnancy at the time of the first gynecological approach. Screening should also be carried out

in early pregnancy so that those who are uncertain can be tested, and those who are susceptible can be counseled about the risks, instructed on procedure should contact occur, and co-opted into a protocol for management of exposure incidents.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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