

Influenza in pregnant women

Violeta Melinte^{1,2}, George Gherlan^{1,2}, Ana Maria Veja², Emanoil Ceausu^{1,2}

¹"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

²"Dr. Victor Babes" Infectious Diseases Hospital, Bucharest, Romania

ABSTRACT

Pregnant and recently postpartum women with influenza are more likely to develop severe illness and die than the general population, based on data from seasonal influenza and from the influenza pandemics of 1918 to 1919, 1957 to 1958, and 2009 to 2010. The increased severity of influenza in pregnant and recently postpartum women is thought to be related to normal physiologic changes that occur during pregnancy. For example, heart rate and oxygen consumption increase and lung capacity decreases. Because of the increased severity of influenza in pregnancy and the postpartum period, inactivated influenza vaccine is recommended for these women, regardless of trimester of pregnancy. In addition, pregnant and postpartum women with suspected or confirmed influenza should receive prompt empiric treatment with an appropriate antiviral medication.

Keywords: pregnancy, influenza, vaccination, antiviral medication

ETIOLOGY

The common cold virus or influenza virus is part of the Orthomyxoviridae family. It is an enveloped virus, with a variable form but most frequently spherical or filamentous, with a diameter of approximately 50-150nm, with a linear RNA nucleus with negative polarity. A distinct feature are the proteic membrane spikes represented by haemagglutinin (HA) and neuraminidase (NA) found in a 5:1 ratio (1). There are 18 distinct subtypes of HA and 11 subtypes of NA, used to annually characterize the viral strain types and subtypes involved in seasonal pathologies (eg.: H1N1, H3N2, etc.). The viral strains known to be pathogenic to humans are Influenza A and B - responsible for endemic and pandemic outbreaks - and Influenza C which determines mild respiratory symptoms (2).

EPIDEMIOLOGY

Influenza virus infections have a seasonal characteristic. In temperate climates, influenza is re-

ported between the months of October until April in the northern hemisphere and between May to September in the southern hemisphere (3). In tropical areas, there are registered cases all through the year, but usually in one or two epidemic episodes per year (4). The seasonal characteristic of influenza is multifactorial, including temperature conditions and humidity in which the virus can develop and multiply, as well as shifts in temperature (cold/hot, outside/inside) during the cold seasons (5).

Isolated cases as well as well as care facility associated outbreaks are recorded all year round, including during summer months. Epidemic outbreaks usually have a duration of 6 to 8 weeks.

In the USA, during the 2015-2016 season there have been 310.000 cases of hospitalized influenza related respiratory illnesses. In Europe during the same season, there have been 8.500 cases in 8 countries, 70% of which were determined by Influenza A virus (6).

The influenza viruses can be transmitted to human from birds or pigs, through direct contact with

the sick animals or through contact with objects or water contaminated with animal excrements. Adequate thermic preparation is mandatory to diminish the risk of infection during avian influenza epidemics (7).

Influenza viruses are transmittable from human to human, through aerosols produced through coughing or sneezing by the infected person. Furthermore, the virus can be transmitted through direct contact with the infected person, or through contact with contaminated surfaces or objects. The virus can spread quickly, is extremely contagious, and the incubation period is short. An infected person is contagious a day before and 5 to 10 days after the beginning of symptoms. Children can be contagious an even longer period, exposing people around them to the infection, especially in close communities. Immunodeficient persons can be contagious for weeks, even months (8). An epidemic will affect between 30% and 60% of the non immunized population.

PHYSIOPATHOLOGY

The flu represent the clinical manifestation of the influenza virus, in susceptible persons, who have inhaled contaminated aerosols. The absence of neutralizing antibodies allows for the multiplication of the virus at the cellular levels of the respiratory mucosa, which alters its function, and leads to cell lysis and the release of new virions. The clinical manifestations are the expression of the release of systemic inflammation mediators.

Incubation varies between 1 and 4 days, and the contagiousness is present a day before the clinical manifestation of symptoms, which makes the transmission of the virus possible from asymptomatic or paucisymptomatic people (9).

Virulence factors are represented by the surface proteins – haemagglutinin (HA) and neuraminidase (NA). These proteins subsequently become the target for specific antibodies. Haemagglutinin adheres to the surface of the epithelium allowing for cellular infection. neuraminidase has the role of cleaving the link between newly formed virions and the cellular surface, which favors the dissemination of infection (10).

Influenza virus is genetically unstable, having a rate of mutation 300 times higher compared to other microorganisms (11). The viral RNA-polymer-

ase is deficient when it comes to the control mechanisms for transcription errors, which allows for antigenic drift type modifications. These types of mutations appear permanently, and are responsible of the virus' ability to annually avoid specific immune responses secondary to past influenza infections. Drift type antigen differences are reflected in the difference in virulence of strains. Antigenic drift takes place in the same subtype.

Antigenic shift is less frequent in involves the genetic reassortment of two strains, most probable during a coinfection of the same host organism. Antigenic shift takes place in a large susceptible population where more severe forms of illness are possible. The virulence of the strain is augmented and is more often responsible for pandemics.

MATERNAL INFECTION

Risk factors

Influenza infection in pregnant women usually has a more severe evolution. The risk of complications and unfavorable evolution seems to be lower in last trimester pregnancies and in the first four weeks postpartum (12).

Clinical manifestations

Influenza pandemics have allowed for the collection of useful data in regards to the clinical manifestations of influenza infection in pregnant women.

Before the AH1N1 influenza pandemic from 2009, pregnant women were more likely to be hospitalized due to acute respiratory failure more often than non pregnant women (13).

At the same time, during the 2009 pandemic there was a disproportionate number of deaths in pregnant women (5% of the total registered deaths) in the USA (14).

Pregnant women are more at risk of being hospitalized in the ICU compared to the regular population (15). Evolution of the disease is more severe in pregnant women where antiviral therapy was delayed.

The impact of influenza infections of the pregnancy

The effects of the influenza infection on pregnancy have not yet been studied. The transmission

through the placental barrier seems to be rare (16). Even so, influenza infection in pregnancy could affect the fetus even in the absence of transplacental transmission through systemic effects which it triggers. In an observational study from 2013, influenza infections and other viral respiratory infections were associated with a higher risk of congenital malformations such as palatoschisis, hydrocephalus, neuronal development defects, cardiac malformations. Hipertermia and fever represent frequent clinical manifestations which increase the risk for disgravidia or fetus development problems (17). This risk seems to be minimised through the use of antipyretics. Other studies report correlations between influenza infection and miscarriage, premature birth, low birth weight and in utero fetus death (18). The influenza virus during the 2009 pandemic was associated with a high risk of fetal mortality, while immunization during pregnancy reduced the risk of developing the illness (19).

Impactul of pregnancy on the virus

Pregnant women are as likely to develop secondary complications as much as non pregnant women with comorbidities (Table 1) (20). The risk is higher with a higher pregnancy age (21).

TABLE 1. Categories of patients with a higher risk of complications

- Children < 5 years, and especially < 2 years
- Adults > 65 years
- Pregnant women and postpartum women < 2 weeks
- Institutionalized people
- Patients with pathological antecedents:
 - Asthma
 - Neurological disorders
 - Chronic respiratory disorders
 - Cardiac disorders
 - Haematological disorders
 - Endocrinological disorders, includic diabetes mellitus
 - Chronic renal disorders
 - Chronic liver disorders
 - Metabolic disorders
 - Children < 19 years under chronic aspirin treatment
 - Obesity (IMC > 40)

Primary viral pneumonia manifests when the viral infection especially affects the lungs and is usually severe. The persistence or the aggravation of the viral symptomatology, without a decline in symptoms – fever, dispnee, breathing problems and cianosis – are suggestive for this type of complication.

Secondary bacterial pneumonia is evident by the exacerbation of symptoms, after an initial improvement. Fever reappears and expectoration becomes productive. It has been demonstrated that the influenza virus favors the nasal colonization with *S. pneumoniae*, which seems to be the most frequent etiology of secondary influenza infections (22), followed by *S. aureus* (CA-MRSA) (23) and *Haemophilus influenzae* (22).

Myositis and rhabdomyolysis appear more frequently in children (24). Although myalgia is a symptom that defines influenza infections, myositis is less frequently observed. Even if viral load has been emphasised at the muscle cell level, the pathogenesis of myositis is not yet known. Intense muscular pain, especially in the legs, can be observed though laboratory tests through the elevation of creatine phosphokinase associated with myoglobinuria and acute renal failure (25).

Cardiac complications involve transitory EKG modifications, but also myocardial infarction, myocarditis and pericarditis. The risk of acute ischemic infarction is higher in the first seven days of illness, influenza B virus more frequently associated in this particular pathology than influenza A virus, and three times more frequently than syncytial respiratory virus (26).

Central nervous system complication include encephalopathy, encephalitis, transverse myelitis, aseptic meningitis and Guillain-Barré syndrome.

Toxic shock syndrome has been described in influenza patients – especially influenza B virus infections – who associate *S. aureus* infections (27).

Prenatal diagnosis

Diagnosis of influenza in pregnant women involves the same steps as in the regular population, except the pulmonary X-ray.

Clinical diagnosis during an influenza epidemic is suggested by any respiratory disease with fever, with a probability of 79%, that involves at least two of the four other symptoms: cough, myalgia, odyndophagia and headache (28). Outside season epidemics, influenza A and B viruses account for only 10% of viral respiratory infections etiology, after rhinovirus (52%) and coronavirus (26%), and clinical diagnosis is difficult to establish (29).

Laboratory diagnosis involves the confirmation of the initial clinical supposition through various

TABLE 2. Diagnostic tests for influenza virus

Test	Time until positive result	Biological material	Comments
Conventional RT-PCR and other molecular tests	1-8 hours	Naso-oro-pharyngeal exudate, bronchial lavage, tracheal aspirate;	High sensibility and specificity; recommended; can differentiate between influenza A and B virus as well as subtypes;
Quick molecular tests (detect viral RNA)	<20 min	Nasal exudate, pharyngeal exudate;	High sensibility and specificity; recommended; can differentiate between influenza A and B virus but not subtypes
Immunofluorescence	1-4 hours	Naso-oro-pharyngeal exudate, bronchial lavage, tracheal aspirate;	Moderate sensibility, high specificity; recommended; can differentiate between influenza A and B virus and other viral types;
Quick detection of viral antigen through immunochromatography	10-15 min	Naso-pharyngeal exudate	Moderate sensibility, high specificity; can differentiate between influenza A and B virus as well as subtypes;
Quick tests (detection of viral antigen or neuraminidase)	< 15 min	Naso-pharyngeal exudate	Low sensibility and low/medium specificity; recommended; a negative test does not exclude an infection;
Viral culture		Naso-oro-pharyngeal exudate, bronchial lavage, tracheal aspirate; special transport medium;	Moderate/high sensibility and high specificity; recommended for screening confirmation and in public health management; not useful in clinical management;
Viral envelope culture Isolation from cellular cultures	24-72 hours 3-10 days		
Serological tests		Serum	Available only in specialty laboratories; useful for retrospective diagnosis;

tests, adjusted to the possibilities of the medical center.

Out of the molecular tests, RT-PCR is the most sensitive and specific diagnostic tests, with quick results, which also establishes viral subtype (Table 2).

Quick molecular tests provide fast results, under 20 minutes, in the ER, with a sensibility of 80% for influenza A and 77% for influenza B, compared to classical molecular tests where sensibility varies between 92% and 95% for influenza A and B respectively (30).

Quick antigen tests are based on immunoserological methods of detection of nucleoprotidic viral antigens in biological material taken from the respiratory passage. The tests give results in approximately 15 minutes but with a much lower sensibility compared to RT-PCR or quick molecular tests, of almost 53-54% (30).

Direct or indirect immunofluorescence tests detect the presence of viral antigens, but have a low sensibility and specificity.

Digital immune tests ((Digital immunoassay – DIAs) are quick tests that detect the presence of antigens though immunochromatography. Results are available in 1-15 minutes (31) with a sensibility of approximately 80% (32).

Viral culture is considered a traditional “gold standard” for a certified diagnosis, but takes up to

48-72 hours until positive results. It is not used as a routine diagnosis rests, but as a screening tests and for public health management.

Serological tests are not useful for the diagnosis of an acute infection, because it involves the pre-levation of materials form both the acute phase of illness as well as post infection, which determine the antibody levels in dynamic. It is useful for a retrospective diagnosis in clinical studies.

MANAGEMENT OF INFLUENZA INFECTION DIAGNOSIS DURING PREGNANCY

Treatment should begin promptly, from the very first suggestive symptoms, indiferent of the immunization status, considering vaccination is not 100% efficient (33). Empirical treatment can be initiated in relation to the activity of the virus in the community in that respective moment.

Pregnant or postpartum women under 2 weeks, who have symptoms suggestive of the flu, require prompt empirical treatment with antiviral medication. The initiation of treatment as quick as possible, in the first days of symptoms, is associated with less severe forms of illness and a lower mortality index. Other studies confirm the benefit of treatment initiated after 2 days of illness. The risk of antiviral medications is considered low com-

pared to the benefits, especially in pregnant women with severe forms of illness (34).

If the partner is diagnosed with influenza during pregnancy, there are no side effects associated to the fetus as well as in the development of assisted reproduction procedures.

Currently there is a new antiviral agent - Baloxavir marboxil – that is FDA approved starting with october 2018 after phase III studies, from which pregnant women have been excluded. Until more data is made possible and the safety of the drug is proven, oseltamivir remains the choice of first line antiviral therapy.

Antivirals

Neuraminidase inhibitors currently in use are: oseltamivir – oral administration, zanamivir - inhalation administration and peramivir – intravenous administration. Oseltamivir, although class C, is the preferred treatment, assuming the low prevalence of viral resistance. Doses are the same as in the general population: Oseltamivir 75 mg every 12 hours for 5 days; Zanamivir 10 mg 2 inhalations per day, 5 days; Peramivir 600 mg iv in 15-30 minutes as a single dose (35). Treatment can be prolonged in more severe forms of illness, over 5 days, some clinicians recommending a double dose (Oseltamivir 150 mg/zi) although there is no clinical proof of a higher benefit with a higher dose (36).

The intravenous form of viral medication has been approved by the FDA in 2014 for Peramivir, and currently there is work on an intravenous formulation of Zanamivir. Data to prove the efficiency of iv medication are lacking currently, but oseltamivir administered in severe forms via nasogastric tube seems to be absorbed in a sufficient concentration for favorable results.

Antipyretics

Acetaminofen (paracetamolul) is the preferred treatment of fever, considering the fact that hyperthermia in the first trimester of pregnancy is associated with neural tube defects or other congenital malformations. Furthermore, the presence of fever during labor is a risk factor for neonatal convulsions, encephalopathy, paralysis, or death (37). Other antipyretics (aspirin, ibuprofen) were associated with diverse adverse effects in the newborn,

which is a reason why they're not advised in pregnancy.

Antibiotics

Antibiotic treatment is only indicated in special cases of overlaid bacterial infection of the superior respiratory tract (sinusitis, otitis) and inferior respiratory tract (pneumonia). Treatment is similar with that in the general population, but taking into account the teratogenic potential of certain antibiotics which should be avoided in pregnant women (Table 3).

TABLE 3. Antibiotics not indicated in pregnancy

- Tetracyclines
- Tigeciclina
- Clarithromycin
- Erythromycin
- Fluoroquinolones
- Cloranfenicol
- Aminoglycosides

Pregnant women that develop secondary pneumonia are predisposed for an earlier birth (38), and are at a higher risk for pulmonary edema. It is then of utmost importance that bacterial pneumonia as a complication of influenza infection should be treated promptly. Pregnant women are predisposed to developing pneumonia because of physiological changes that take place during pregnancy: the ascension of the diaphragm up to 4cm, the decline residual capacity, the rise in oxygen consumption and water and salt retention at the pulmonary level. The treatment of pneumonia in pregnant women is summarized in Table 4.

Community acquired pneumonia in its less severe form should be treated with associated amoxicillin-clavulanate and azithromycin. Hospitalized patients should receive an association of beta lactamines (ceftriaxone, cefotaxime, ampicillin-sulbactam) and azithromycin, and severe forms require vancomycin as an anti-staphylococcal and anti-pneumococcal agent.

Breastfeeding is not contraindicated. The virus is not transmittable through breastfeeding. During the respiratory phase, the mother will transmit maternal antibodies to the newborn, offering immunization, if she isn't hospitalized. In cases requiring hospitalization and the separation of mother and newborn, the mother should be encouraged to

maintain lactation. Oseltamivir is transmitted through breast milk at a very low dose and does not affect the newborn (39), which is why breastfeeding is encouraged in new mothers with influenza even if they are under antiviral treatment.

TABLE 4. Algorithm for treatment of pneumonia in pregnant women

1. Direction for pulmonary X-Ray is the same in pregnant women as in non-pregnant women;
2. O₂ administration for maintaining a peripheral saturation of >95% or pO₂ >70 mmHg. Careful and constant monitoring is advised;
3. Monitoring of acid-base balance (ABB), especially in case of suspected of CO₂ retention (a pCO₂ in pregnancy is normally 25-33 mmHg; any pCO₂ of 35 mmHg represents a retention of CO₂ and suggests respiratory failure);
4. Fever is treated with acetaminophen;
5. Monitoring in an obstetric-gynecological service;
6. Close monitoring of hidroelectrolitic balance, because patients are at risk of developing pulmonary edema;
7. Blood cultures and sputum collection for bacteriological examination;
8. Out of the indicated antibiotics, tetracyclines, fluoroquinolones and clarithromycin.
 - For primary community-associated pneumonia, mild forms, beta lactam therapy (ceftriaxone, cefotaxime, ampicillin- sulbactam) associated with azithromycin.
 - Patients allergic to cephalosporins can be treated with clindamycin associated with aztreonam;.
 - Severe forms recommend the association of vancomycin with azithromycin and aztreonam;
9. If deemed necessary, serological testing for *Mycoplasma* sp, *Chlamydia* and *Legionella* sp urinary antigen and pneumococcus.
10. Anticipate the possibility and indication for orotracheal intubation and make sure the necessary equipment is on hand
11. Correctly position the patient so to avoid the obstruction of venous circulation by the pregnancy (left lateral decubitus).
12. Bronchoscopy if this test is able to offer important information in regards to patient management;
13. For patient who are immobilized, deep vein thrombosis prophylaxis is recommended.

PROPHYLAXY

Vaccination

Starting with 2014, the CDC recommended immunization of all pregnant women with inactivated virus vaccine, regardless of trimester (40). Currently there are two types of vaccines available commercially: tetravalent (2 strains influenza A and 2 strains influenza B) and trivalent (2 strains influenza A and 1 strain influenza B), either preferred in pregnancy in absence of comparative data. A recombinant vaccine without egg protein is available for people with egg allergies, including pregnant women (41).

Although immunization recommendations are unanimously accepted, the rate of immunization in pregnant women remains low, only 36% in november 2017 in the USA (42). The rate of immunisation increases if personal practitioners recommend and administer the vaccine themselves.

Immunization is not 100% efficient, but reduces the risk of developing the acute illness. Pregnant women develop passive immunity in equal measure compared with regular population (43), although there are certain differences in the immune response in pregnancy (44). Some studies have demonstrated that immunization through vaccination has been associated with a reduced risk of pregnancy stopping in evolution, but has no effect on miscarriage (45).

Immunization protects the mother, but also the newborn for the first months after birth (46). Immunization involves the development of anti-influenza IgG antibodies, which traverse the placenta (47), protecting the newborn after birth, as well IgA antibodies which the mother transfers to the child through breastfeeding (48). Because of this, immunization of pregnant women becomes an important instrument in the prophylaxis of influenza infections in newborns, considering they are exposed to a higher risk of contracting the virus and developing more severe forms of disease and they are not eligible for direct immunization through vaccination until 6 months because of a insufficient and inefficient immune response (49). In a study in Bangladesh, the vaccination of pregnant women in the last trimester of pregnancy led to a 63% decrease in the risk of newborns developing the disease in the first 6 months of life (50).

Even though in the general population, but especially in pregnant populations there are certain worries in regards to the adverse effects of vaccination, numerous studies have proved that the change of these side effects is low. Even though vaccination is associated with a low risk of Guillain-Barré syndrome, the risk/benefit balance is in favour of influenza immunization (51). One single study seems to support the evidence of a possible correlation between miscarriage and vaccination with the product containing the strain H1N1pdm09, administered in the period of 2010-2011 and 2011-2012, but this data needs confirmation through further studies (52).

ALGORITHM FOR MANAGEMENT OF INFECTION

Unvaccinated pregnant women are exposed to a higher risk (Fig. 1) of developing severe secondary

complications associated with influenza virus infection which might need admission in the ICU.

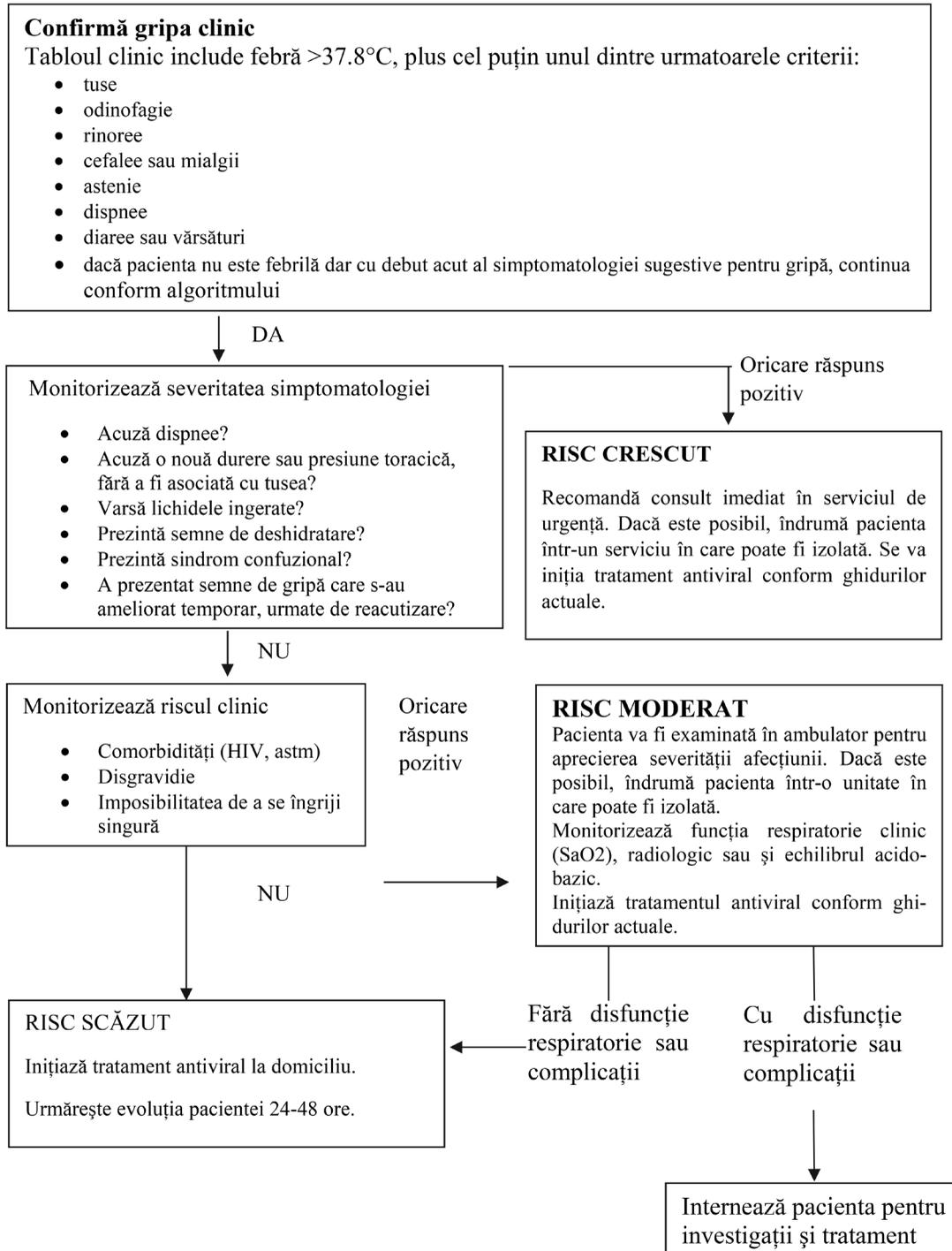


FIGURE 1. Algorithm for the management of influenza infection in pregnancy

POSOLOGY OF RECOMMENDED TREATMENT

Antiviral agent	Dose
Oseltamivir	
Treatment for influenza A and B	75 mg every 12 hours po, 5 days
Prophylaxis for influenza A and B	75 mg po once a day, 10 days
Zanamivir	
Treatment for influenza A and B	10 mg (2 inhalations) every 12 hours po, 5 days
Prophylaxis for influenza A and B	10 mg (2 inhalations) daily, 10 days
Peramivir	
Treatment for influenza A and B	600 mg i.v. single dose

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