



MEASLES INFECTION IN PREGNANCY – PREVENTION, COMPLICATIONS AND POST-EXPOSURE PROPHYLAXIS

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RUNNING TITLE	Measles in Pregnancy
KEYWORDS	measles; measles virus; pregnancy
WORD COUNT	1752
CONFLICT OF INTERESTS	no conflicts of interest

ABSTRACT

Measles is a viral infection which is nowadays neither gone nor forgotten. It is transmitted by respiratory route after direct contact with airborne spread or infectious droplets and is one of the most contagious infectious diseases. Before live attenuated vaccine development, which is nowadays the best prevention, measles had its great influence on human morbidity and mortality, especially among children. Nevertheless, due to insufficient vaccine coverage, resurgence of measles has been reported in recent years. Pregnant women are a population at greater risk of severe clinical course of the disease and its complications. Observational studies indicate that measles infection in pregnancy increases the risk of adverse pregnancy outcomes, including both maternal and perinatal complications. A higher incidence of fever and pneumonia occur in pregnant women as well as spontaneous abortion, prematurity, NICU admissions and prolonged NICU hospitalizations. Unvaccinated individuals exposed to measles along with those with unknown vaccination status should be offered immune globulin as a post-exposure prophylaxis. If patient develops clinical features of measles despite immunoprophylaxis, careful observation and symptomatic treatment should be introduced as prevention of severe complications.

BACKGROUND

Measles is a highly transmissible, contagious disease which is caused by measles virus from *Paramyxoviridae* family [1]. As a result of effective vaccine development and its widespread use since 1974, when World Health Organization launched Expanded Program on Immunization, number of measles cases dropped greatly in comparison to pre-vaccine era [2]. It is estimated that only during the period 2000-2015 measles incidence decreased by 75% and its annual mortality dropped by 79% worldwide [3]. Nevertheless, in the late 1990s concerns about reported correlation between Measles-Mumps-Rubella vaccine and the risk of autism were raised. Even though the Global Advisory Committee on Vaccine Safety (GACVS) claimed that there is no evidence for this association and recommended that there should be no change in MMR vaccination practices [2]. We can observe that fear of vaccines has grown in many societies. Vaccine hesitancy, together with many other factors, caused that measles has re-emerged recently. 2017 Measles and Rubella Surveillance Report of the European Centre of Disease Prevention and Control showed that in 2017 twenty-eight EU/EAA countries reported 14600 measles cases which is more than triple of the number of cases in both 2015 and 2016 [4, 5]. Most of the measles cases concerned unvaccinated individuals and one of the greatest proportion of those as well as proportion of patients with unknown vaccination status occurred in population aged 25-29 [4]. Since this group includes women in reproductive age we should further examine the topic of measles in pregnancy and its maternal and foetal complications.

MEASLES CHARACTERISTICS

The disease is highly infectious - with exposure, 75% to 90% of susceptible contacts become infected [7]. The incubation period lasts between 10 to 14 days, although it varies from person to person, with the longest reported period of incubation of 23 days [7, 8]. The infectious period coincides with the onset of rash and is associated with peak levels of viremia and most intense respiratory symptoms, which conduce transmission [8]. The prodromal symptoms may include fever, myalgia, malaise, and a headache. They are followed by photophobia and conjunctivitis. Koplik's spots (small white papules) appear lateral to the molar teeth, on the buccal mucosa [7]. Since they are pathognomonic to the disease, the spots provide an opportunity to diagnose the illness 1-2 days before the rash onset [8]. Rash appears typically 2-7 days following the prodromal symptoms. It initially presents on head or neck as a blotchy erythema, and later on spreads to the trunk and the extremities taking the maculopapular appearance [7]. It tends to disappear after 5 days. Other symptoms, including high fever and cough can last several days longer. Lymphadenopathy accompanies the fever and can linger for several weeks [7]. People with an uncomplicated measles usually recover within 7 days [8]. Complications of measles can include diarrhoea and a concomitant dehydration, laryngitis, bronchiolitis, pneumonia, and

otitis media due to secondary bacterial infections [8]. Rare complications include hepatitis, atypical measles, and acute encephalitis [7]. The complications are most common in infants, immunodeficient (e.g. HIV-infected) or malnourished (especially with low vitamin A levels) individuals and pregnant women [8].

MEASLES PREVENTION

The most effective way of preventing measles infection is vaccination in a two-dose series, usually as a component of the trivalent MMR vaccine [7]. The vaccination contains live attenuated viruses and is administered subcutaneously in a dose of 0,5ml [10]. Routinely in developed countries it is administered in two doses at 12-15 months and 4-6 years, which often mandatory, although different countries have their own strategies [7, 10]. Vaccine can be also administered in case of measles outbreak, provided it is given within 72 hours after exposure in order to either prevent or modify the disease course. The second dose may be given earlier than at the age of 4 years old, as long as there has been a 4-week interval.

Most infants are born with an immunity to measles due to maternal antibodies transferred during pregnancy. The antibodies decay over the first year of life, hence the suggested age for the first dose of the vaccine [11]. The quantity of antibody transferred and therefore the duration of protection is determined by several maternal and infant factors. Vaccinated mothers have lower antibody titers than those who were previously infected with measles, and therefore transfer fewer antibodies to their infant. Since humoral immunity in vaccinated individuals can wane over time, especially in settings where measles does not circulate and there is no immunity boosting, in vaccinated mothers maternal age is strictly correlated to the number of transferred antibodies. Gestational age is another factor directly correlating with the number of antibodies transferred through placenta [11].

Women planning pregnancy should be recommended the use of contraception for 3 months after immunization, although so far there have been no cases of congenital measles infection secondary to the measles vaccination reported. Even though most pregnant women had been previously vaccinated, some of them might be seronegative [7].

INFECTION IN PREGNANCY

An immunosuppressive state developed during pregnancy makes it possible for foetal allograft to grow but it can also be responsible for a stormy course and high incidence of complications of infections during this time [12]. Since it is a highly infectious disease, measles had a major contribution to childhood mortality and morbidity in the past and therefore infection in young adults, including pregnant women, was uncommon. Since vaccine coverage increased worldwide, occurrence of measles includes more often young women in their reproductive age [13]. A literature review from 1993 compared data concerning complications of measles in pregnancy, encompassing 200 cases.

Obtained findings are summarized in Table 1 [14, 15, 16, 17, 18, 19].

This review showed a deleterious effect of measles on both maternal morbidity and foetal outcome [14, 15, 16, 17, 18, 19]. Maternal complications such as fever and pneumonia occurred, ranging from 32.5% to 80.0% and from 7.5% to 30.8%, respectively. There were no fatal cases in 4 out of 6 studies researched, however there was high mortality rate in study conducted in Eastern Sudan in 2011-2012, reaching 18.0% [14, 15, 16, 17, 18, 19]. The causes of those 11 maternal deaths were intracranial haemorrhage (9.1%), encephalitis (9.1%) and pneumonia (81.8%) [15]. Adverse pregnancy outcomes included increased risk of spontaneous abortion, prematurity, more neonatal admissions and prolonged stay in Neonatal Intensive Care Unit (NICU) [14, 15, 16, 17, 18, 19]. According to data presented in the study conducted in Saudi Arabia prematurity rate was 25.0% in the measles group in comparison to 6.7% in the group of normal pregnancy, which was statistically significant ($P=0.003$). Neonatal admissions reached 17.5% in neonates from measles affected pregnancies as compared to 1.7% in neonates from pregnancies without measles and NICU duration of hospitalization lasted 7 ± 1.4 and 2 ± 0.3 days, respectively. Both complications were statistically significant [18]. Other studies showed similar, unfavourable outcomes [14, 15, 16, 17, 18, 19]. Interesting results were reported in the study performed in Japan, where three out of four measles cases diagnosed before 24 weeks of gestation ended with stillbirth or spontaneous abortion, whereas all pregnancies with infections diagnosed after 25 weeks of gestation resulted in live-term delivery [17]. Drawing conclusions from this literature review including 6 research studies from different parts of the world, since pregnancies complicated by measles run tempestuous courses, all the cases of suspected measles in pregnancy should be promptly diagnosed and carefully monitored because of increased risk of pre-term labour and spontaneous abortion [14, 15, 16, 17, 18, 19].

PLACENTAL INFECTION

Since higher incidence of spontaneous abortion, stillbirths and pre-term deliveries was reported in reviewed cases, placenta infection should be further examined. Oyhama et al. described a case of monozygotic, monochronic, diamniotic twin pregnancy complicated by measles infection. One of the twins survived without any evidence of measles and the other one was stillborn. The placenta was examined, and fibrin deposition was revealed in 70% of stillbirth's placenta surface, X-cell proliferation, ghost-like villi as well as some trophoblastic cells turned out to be positive for measles virus antigen. The placenta of the other twin was only mildly affected by fibrin and only few syncytiotrophoblasts were MV antigen positive. No evidence of infection was present in any of stillbirth's organ and surviving twin did not develop any clinical feature of measles infection, which may suggest protective role of trophoblast, giving enough time for maternal antibodies to be transferred to both twins and therefore defend transplacental infection [20].

Fibrin deposits covering at least 25% of placenta might be responsible for intrauterine death as in case of one of described twins [21].

POST-EXPOSURE PROPHYLAXIS

Pregnant women who have developed measles symptoms or those who could have a direct contact with an infected individual and cannot recall if they had been vaccinated are advised to visit their obstetrician or GP at their earliest convenience [9]. They are also advised to avoid antenatal clinics or other pregnant women until the clinical assessment, to avoid exposing others to a potential infection.

The clinical diagnosis of measles is based on the presence of a maculopapular rash occurring 1 to 2 days after a pathognomonic exanthematous rash (Koplik's spots), photophobia, and upper respiratory symptoms. Recent measles infection can also be confirmed or excluded by testing for measles-specific antibodies in serum sample collected after four days but within one month from the rash onset [6]. A serum sample should be collected for laboratory testing for measles-specific IgM and IgG at first presentation. Antibodies levels correlate with timing of vaccination or exposure to the disease, as presented in Table 2 [22]. In addition, a diagnosis can also be confirmed by isolating the virus or using RT-PCR from throat swabs [23].

Seronegative women who are susceptible to the disease should be treated with an intravenous or intramuscular immunoglobulin (respectively IVIG or IMIG) up to 6 days after exposure [7, 24]. Suggested dose is 0.25 ml/kg i.m., up to a maximum dose of 15 ml. If a patient develops the disease despite the immunoprophylaxis, she should be observed and treated symptomatically, since there is no causal treatment [25]. Croup can be treated with cough suppressants. Fever, especially high, requires use of antipyretics. Measles pneumonia may require antibiotics if caused by superimposed bacteria. Even if there are no life-threatening symptoms, pregnant patients should be closely monitored for the duration of the acute measles [24, 25].

Patient should be informed that the risk of injury to her foetus is less than 3%. Method considered most valuable for evaluating the foetus for prenatal infection is an ultrasound examination. Infant whose mother developed the infection 7 to 10 days before delivery should be administered intramuscular immunoglobulin in a dose of 0.25 ml/kg to reduce the risk of infection transmission during the delivery. These neonates should also receive the attenuated measles vaccine when they reach 15 months [25].

CITE THIS AS

MEDtube Science Jun, 2019, Vol. VII (2), 46 – 50

ABBREVIATIONS

EU/EAA – the European Union and European Economic Area

GACVS – Global Advisory Committee on Vaccine Safety

GP – general physician

MMR – measles-mumps-rubella
NICU – Neonatal Intensive Care Unit

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TAB. 1. COMPARISON OF COMPLICATIONS IN MEASLES AFFECTED PREGNANCIES [14,15,16,17,18,19].

Study Characteristics		Study results					
		[14]	[15]	[16]	[17]	[18]	[19]
Study Period		2014-2015	January 1, 2011-December 31, 2012	January 1-December 2011	Late 2000-early 2001	January 1-December 31, 1993	January 1, 1988-December 31, 1991
Country		Kazakhstan	Sudan	France	Japan	Saudi Arabia	USA
Number of cases		20	61	13	8	40	58
Maternal Complications	Fever	80.0%	-	61.5%	50.0%	32.5%	60.3%
	Pneumonia	7.5%	-	30.8%	25.0%	10.0%	25.9%
	Elevated liver enzymes	-	-	33.3%*	-	65.0%	0%
	Maternal death	0.0%	18.0%	0.0%	0.0%	0.0%	3.4%
Foetal outcome	Abortion	8.3%	11.3%	0.0%	25.0%	15.0%	1.7%
	Prematurity	25.0%**	7.5%	7.7%	12.5%	25.0%	3.5%
	Intra-uterine foetal death	-	5.7%	0.0%	12.5%	5.0%	1.7%

TAB. 2. RESULTS OF MEASLES SPECIFICS ANTIBODIES AND THEIR MEANING [22].

IgG Index Value (IV)	Results	IgM Arbitrary Units (AU)	Results
<0.89	Negative - no infection or past vaccination	<0.89	Negative - no infection or past vaccination
0.9-1.09	Equivocal - Repeat testing in 2 weeks	0.9-1.10	Equivocal - Repeat testing in 2 weeks
≥1.10	Positive - current or past exposure to or immunization to rubeola - immunity if no symptoms are present	≥1.11	Positive - current or recent infection or immunization



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