Public Health England

Serial number 2018/032 **Date 06/07/2018**

Event: Guidance on use of Varicella Zoster Immunoglobulin (VZIG) during supply shortage

Notified by	**Immunisation and Countermeasures Division, National Infection Service**
Authorised by	**Mary Ramsay, Vanessa Macgregor**
Contact	Gayatri Amirthalingam, Kevin Brown
PHE NIRP Level	**N/A**
Incident Lead	**N/A**

Background and Interpretation:

Chicken pox (varicella) is a common and generally mild childhood illness. Although the incidence of varicella in the UK is seasonal, classically peaking between March to May, in recent years, seasonality appears less marked.

Infection in neonates, immunosuppressed individuals and pregnant women can result in severe and even life-threatening varicella disease. To prevent severe varicella infection in these at risk individuals, post-exposure prophylaxis with varicella-zoster specific immunoglobulin (VZIG) is recommended according to national guidelines.[1] The rationale for offering prophylaxis to vulnerable close contacts is to attenuate disease and reduce the risk of complications such as pneumonitis, rather than to prevent infection.

Varicella infection in pregnancy can lead to both maternal and fetal complications depending on the timing of infections during pregnancy:

- **Fetal complications**: The highest risk of fetal varicella syndrome (including limb hypoplasia, microcephaly, cataracts, growth retardation and skin scarring) occurs during the first 20 weeks. Incidence of fetal varicella syndrome has been estimated to be less than 1% in the first 12 weeks and approximately 2% between weeks 13-20.[2]
- **Maternal complications**: The greatest risk of maternal complications such as pneumonitis appears to be from 20 weeks onwards.[3]

The rationale for the use of VZIG prophylaxis in pregnant women is twofold: reduction in severity of maternal disease and theoretical reduction in the risk of fetal infection for women contracting varicella in the first 20 weeks of pregnancy. About 50% of susceptible pregnant women given VZIG after a household exposure to chickenpox will develop clinical varicella, although the disease may be attenuated; the clinical attack rates are similar whether VZIG is given within 72 hours or four to ten days after contact.[4,5] A further quarter will be infected sub-clinically.[5] Severe maternal varicella may still occur despite VZIG prophylaxis. Prompt treatment with aciclovir is indicated in such cases.

Although the majority of adults in the UK are likely to be immune, approximately two thirds of all VZIG stock issued are for susceptible women exposed during pregnancy. Current guidance recommends VZIG (4 vials; 1000mg) for VZ antibody-negative pregnant contacts exposed at any stage of pregnancy, providing VZIG can be given within ten days of contact.[1]

VZIG is a scarce blood product that is centrally procured and issued by Public Health England (PHE) and from over 80 issuing centres across England.

Historically when supplies of VZIG have been short, issues of VZIG have been restricted for pregnant women. In response to a current shortage of VZIG, restrictions on issues of VZIG are being implemented with immediate effect. **From 6th July 2018, VZIG will only be issued to VZ antibody negative pregnant contacts exposed in the first 20 weeks of pregnancy i.e. up to and including 20+0 weeks. For women exposed after 20 weeks i.e. from 20+1 weeks to delivery, oral aciclovir at 800mg four times a day from days 7 to 14 after exposure should be considered.**

The efficacy of oral aciclovir as post exposure prophylaxis is largely derived from studies in healthy immunocompetent and immunosuppressed children. The Royal College of Paediatrics and Child Health recommends aciclovir prophylaxis as a suitable alternative to VZIG for immunosuppressed children.[6] In one study of 13 immunocompetent children who had household exposure to varicella and received 10mg/kg four times a day from days 7-14 after an exposure, 12 showed evidence of seroconversion, 10 of whom showed no symptoms and two with mild illness. Only one child developed typical varicella illness.[7]

There is growing evidence supporting the safety of oral aciclovir in pregnancy, especially after 20 weeks gestation, with no increase in the risk of fetal malformations following exposure in pregnancy.[8,9] Of over 1200 pregnancies that received either oral or iv aciclovir across all stages of pregnancy, followed up in 24 countries between 1984-1998, there were no unusual defects or patterns of defects observed.[9] Oral aciclovir is also the recommended treatment for women presenting within 24 hours of a chickenpox rash for women who are 20 weeks gestation or beyond, and may be considered for women in earlier stages of pregnancy.[8]

As oral aciclovir is not licensed for in pregnancy, prescribing for pregnant women would constitute 'off-label' use. Clinicians are able to prescribe medicines outside the terms of the licence (i.e. 'off-label') when this is in the best interest of the patient on the basis of available evidence. Further advice on off-label prescribing is on the MHRA website

https://www.gov.uk/drug-safety-update/off-label-or-unlicensed-use-of-medicines-prescribers-responsibilities#prescribing-in-a-patients-best-interests

When current practice supports the use a medicine outside the terms of its licence, the MHRA advise that it may not be necessary to draw attention to this when seeking consent from patients. However, it is good practice to give as much information as patients or carers require or which they may see as relevant. An FAQ for prescribing clinicians with information that is suitable for pregnant women will be available on the PHE website. https://www.gov.uk/government/collections/chickenpox-public-health-management-and-guidance

Recommendations for VZIG for immunosuppressed contacts and neonates remain unchanged and risk assessment should proceed according to national guidelines.[1]

Implications and Recommendations for PHE Centres

Health Protection Teams (HPTs) are often undertaking risk assessment for VZIG and are asked to note the current restrictions for VZIG in pregnancy.

Health Protection Teams should facilitate the cascade of this briefing note to their local maternity units and General Practitioners through local systems, to ensure they are aware of the latest advice.

Implications and Recommendations for PHE sites and services

The Specialist microbiology network often support the risk assessment and laboratory investigation of high risk contacts exposed to varicella and are asked to note the current restrictions on VZIG supplies and indications for its use in pregnancy.

Lead Public Health microbiologists are requested to forward this briefing note to their local NHS Laboratories / microbiologists who may be involved in urgent requests for VZ IgG testing and the risk assessment for high risk contacts exposed to varicella.

Implications and recommendations for local authorities

N/A

References/ Sources of information

1. PHE Guidance for issuing varicella zoster immunoglobulin. August 2017. Available at https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/638221/VZIG_Gudiance_Version_7_August_2017__.pdf
2. Enders G, Miller E, Cradock-Watson JE et al. (1994) The consequences of chickenpox and herpes zoster in pregnancy; a prospective study of 1739 cases. Lancet 343: 1548–51.
3. Chapter 34. Varicella. Immunisation against Infectious Diseases. Available at https://www.gov.uk/government/publications/varicella-the-green-book-chapter-34
4. Enders G and Miller E (2000) Varicella and herpes zoster in pregnancy and the newborn. In: Arvin AM and Gershon AA (eds) Varicella-zoster virus. Cambridge: Cambridge University Press.
5. Miller E, Marshall R and Vurdien JE (1993) Epidemiology, outcome and control of varicella-zoster infection. Rev Med Microbiol 4: 222–30.
6. Immunisation of the Immunocompromised Child. Best Practice Statement. Royal College of Paediatrics and Child Health. February 2002. Available at http://rcpch.adlibhosting.com/files/Immunisation%20of%20the%20Immunocompromised%20Child%C2%A02002-02.pdf
7. Kumagai T1, Kamada M, Igarashi C, Yuri K, Furukawa H, Chiba S, Kojima H, Saito A, Okui T, Yano S. Varicella-zoster virus-specific cellular immunity in subjects given acyclovir after household chickenpox exposure. J Infect Dis. 1999 Sep;180(3):834-7.
8. Royal College of Obstetricians and Gynaecologists. Chickenpox in Pregnancy. Green Top Guidelines No. 13. January 2015. Available at https://www.rcog.org.uk/globalassets/documents/guidelines/gtg13.pdf
9. Stone KM1, Reiff-Eldridge R, White AD, Cordero JF, Brown Z, Alexander ER, Andrews EB. Birth Defects Res A Clin Mol Teratol. 2004 Apr;70(4):201-7. Pregnancy outcomes following systemic prenatal acyclovir exposure: Conclusions from the international acyclovir pregnancy registry, 1984-1999.