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Use of Varicella Zoster Immunoglobulin (VZIG) in pregnancy during supply shortage: advice to GPs, obstetricians and midwives

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Contents

Executive summary

In response to a significant national shortage of varicella zoster immunoglobulin (VZIG) due to manufacturing issues, from 6th July 2018, VZIG will only be issued to susceptible pregnant women who have had a significant exposure to chickenpox or shingles in the first 20 weeks of pregnancy. As the majority of adults in England are immune to chickenpox, this change is likely to affect a very small proportion of the antenatal population.

This urgent advice has been considered and agreed between Public Health England (PHE) experts and the chair of the Joint Committee on Vaccination and Immunisation[1] (JCVI[1]) varicella subcommittee. This group have also advised that, based on extensive safety evidence, pregnant women who are exposed after 20 weeks, should be offered the oral anti-viral drug, aciclovir (800mg four times a day from day 7 to 14 after exposure).

1.JCVI is an independent expert committee and statutory body that advises UK health departments on immunisation

VZIG and its use

VZIG is a concentrated preparation of antibodies against chickenpox (varicella) derived from healthy non-UK blood donors. It is administered as a single intramuscular injection to exposed individuals at high risk of severe complications who are known to be susceptible to the chickenpox infection. These groups are immunosuppressed individuals, neonates in the first week of life, and pregnant women.

PHE procure and issue VZIG on a named patient basis through over 80 issuing centres across England.

Why VZIG is given to pregnant women

The rationale for the use of VZIG post exposure 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.

In recent years with sufficient VZIG supplies, VZIG has been recommended for VZ antibody negative pregnant contacts exposed to chickenpox at any stage of pregnancy providing it can be given within 10 days of contact with a case. [1]

Efficacy of VZIG in 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 and a further quarter will be infected sub-clinically. Severe maternal varicella may still occur despite VZIG prophylaxis and prompt treatment with aciclovir is indicated in such cases.

Changes to the recommendations for VZIG

There are no changes to the guidance for immunosuppressed patients or neonates. However, 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.

Rationale for the changes for the use of VZIG

Historically, when supplies of VZIG have been limited, its use has been restricted for pregnant women to prioritise those groups likely to have the most severe impact from chickenpox. These are:

- immunosuppressed patients
- neonates
- those in early pregnancy when the developing fetus could be affected.

Chickenpox infection during the first 20 weeks of pregnancy can lead to fetal varicella syndrome, which includes limb hypoplasia, microcephaly, cataracts, growth retardation and skin scarring.
For those exposed from 20 weeks onwards, aciclovir has been shown to be safe and can be given to prevent or attenuate infection.

Recommended action for: pregnant women not eligible for VZIG (20+1 weeks)

Pregnant women in this group who are exposed to chickenpox or shingles should still be assessed for susceptibility as described in the national guidelines. [2]

- If there is a history of chickenpox, the woman can be re-assured.

- If there is no/unknown history of chickenpox, test for the presence of varicella antibodies. For those with levels <100 mIU/ml, oral aciclovir 800mg four times a day from days 7 to 14 after exposure should be considered. The day of exposure is defined as the date of the rash if the index is a household contact and date of first or only contact if the exposure is on multiple or single occasion(s) respectively.

Why aciclovir is being advised

Varicella infection (Chickenpox) can cause severe maternal disease and this risk is greatest in the second or early in the third trimester. Although the majority of pregnant women are likely to be immune, 10% to 20% of susceptible pregnant women who are infected later in pregnancy may develop varicella pneumonia, hepatitis and encephalitis.

Historically, 10 to 14% of varicella cases in pregnancy were reported to have pneumonia based on a small case series [3]; in a more recent study of almost 1000 pregnant patients with chickenpox, the proportion with pneumonia was 2.5% with no maternal deaths, probably reflecting improved medical care and use of aciclovir [4].

Occasional cases of fetal damage have been reported following maternal varicella between 20 and 28 weeks' gestation but the risk is substantially lower than in the first

20 weeks of pregnancy when typical fetal varicella syndrome occurs. Newborn babies whose mothers develop a chickenpox rash from 5 days before to 2 days after delivery are at risk of severe neonatal varicella, and around 30% of these infant cases die.

Safety and efficacy of aciclovir in pregnancy

The efficacy of oral aciclovir as post exposure prophylaxis has been demonstrated in healthy immunocompetent and immunosuppressed children. In a study of 13 immunocompetent children who were household contacts and treated 7-14 days after exposure, only one developed typical varicella illness. Two children developed a mild illness and the remaining ten seroconverted without any symptoms. The recommended dose in pregnant women (800mg 4 times a day) is in line with the Royal College of Paediatrics and Child Health recommendations for prophylaxis in immunocompromised children[8].
Oral aciclovir is not licensed in pregnancy but there is extensive evidence for safety of use in pregnancy, including from two large registries of infants whose mothers were exposed to aciclovir in pregnancy.[5] Aciclovir is recommended for treatment of infection in pregnant women who are more than 20 weeks pregnant.[6] From follow up across 24 countries of over 1200 pregnancies between 1984 -1999 that received either oral or IV aciclovir across all stages of pregnancy, no unusual defects or patterns of defects were observed.[7]

Off label use of aciclovir

As oral aciclovir is not licensed for use in pregnancy, its use for women exposed after 20 weeks would be ‘off label’. Clinicians are able to prescribe medicines outside the terms of the licence when it is in the best interest of the patient on the basis of available evidence. This evidence has been considered and agreed with PHE experts and the chair of the JCVI varicella subcommittee.

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 of 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.

Contraindications and precautions to aciclovir

The dose may need to be adjusted in women with renal impairment. See the British National Formulary (BNF) for more information and seek expert advice.

Potential side effects of aciclovir

The most commonly reported side effects from aciclovir can include dizziness, headache, nausea, vomiting, diarrhoea, abdominal pain, skin rashes, photosensitivity, pruritus, urticaria and fatigue. Further information about side effects is available in the BNF.

Pregnant woman who are also immunosuppressed

If a pregnant woman is also immunosuppressed, VZIG would still be recommended due to their immunosuppression according to the national guidelines[2]

Subsequent exposure to chickenpox or shingles during the same pregnancy

Women who have a second exposure during pregnancy, should be risk assessed following national guidelines[2]. Given the rates of seroconversion with both VZIG and aciclovir, women who have a second exposure after 20 weeks should have a repeat VZV antibody test prior to considering a course of aciclovir.

Pregnant women presenting with chickenpox

If, despite having taken prophylactic aciclovir, a pregnant woman presents with a chickenpox rash, they should be changed onto a therapeutic dose of aciclovir of 800mg five times a day for seven days, starting from the day of onset of the rash. If severe chickenpox develops, the woman should be hospitalised and given IV aciclovir.

Refer to the Viral Rash in Pregnancy[4] guidance for further details.

Duration of restrictions

PHE is keeping the situation under constant review. This guidance will remain in place until further notice.

References

1. Chapter 34. Varicella. Immunisation against Infectious Diseases. Available at https://www.gov.uk/government/publications/varicella-the-green-book-chapter-34
2. 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
3. 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
4. Health Protection Agency. Guidance on viral rash in pregnancy. Colindale: Health

Protection Agency, 2011.
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/322688/Viral_rash_in_pregnancy_guidance.pdf

5. Stone KM1, Reiff-Eldridge R, White AD, Cordero JF, Brown Z, Alexander ER, Andrews EB. Pregnancy outcomes following systemic prenatal acyclovir exposure: Conclusions from the international acyclovir pregnancy registry, 1984-1999
Birth Defects Res A Clin Mol Teratol. 2004 Apr;70(4):201-7.
6. 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
7. http://www.medicinesinpregnancy.org/bumps/monographs/USE-OF-ACICLOVIR-IN-PREGNANCY/
8. 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