HM Government

National surveillance and safety analysis of COVID-19 vaccination in pregnancy

UK Health Security Agency working with the Medicines & Healthcare products Regulatory Agency

UK Health Security Agency working with the Medicines & Healthcare products Regulatory Agency in partnership with:

Contents

Background 4
COVID-19 pandemic 4
COVID-19 disease in pregnant women 4
COVID-19 vaccination is recommended in pregnant women 5
COVID-19 vaccine safety in pregnant women 5
COVID-19 vaccination in pregnancy 6
Reporting systems for COVID-19 vaccination in pregnancy 7
The Yellow Card scheme 7
Yellow Card vaccine monitor 8
UK surveillance of Vaccination in Pregnancy (VIP) 9
UKTIS and UKOSS surveillance of COVID-19 vaccination in pregnancy 10
Adverse outcomes of pregnancy (methods as in Wider Impacts of COVID-19 on Health (WICH) monitoring tool) 10
National Congenital Anomaly and Rare Disease Registration Service 11
Interpretation and analysis 12
Timing of baby development and how this can help our understanding 12
Interpretation of pharmacovigilance data 13
Descriptive analysis of pregnancy outcomes 13
Data linkage studies to investigate safety of COVID-19 vaccine in pregnant women 14
UK-wide review of key issues 14
Planned analyses in England using linked data 15
References 16
Appendix 18
COVID-19 vaccination background 18
About the UK Health Security Agency 20

Background

COVID-19 pandemic

Coronavirus (COVID-19) disease caused by SARS-CoV-2 virus, a novel coronavirus, first emerged in Wuhan, China in late 2019. There was rapid global spread of the virus with the World Health Organization (WHO) declaring the COVID-19 outbreak a pandemic on 11 March 2020. The first cases of COVID-19 arose in the UK in late January 2020. As of 8 November 2021 there have been 249.7 million confirmed cases worldwide with 5.0 million deaths (1) and 9.3 million cases confirmed in the UK (2) with 141,862 deaths arising within 28 days of a positive test result.

COVID-19 disease in pregnant women

The overall risk from COVID-19 disease in pregnant women and their new babies is low. However, pregnant women with COVID-19 disease, particularly those infected in their late second or third trimester, have been found to be at increased risk of severe outcomes requiring hospitalisation and intensive care unit (ICU) admission compared to non-pregnant women or pregnant women without COVID-19 disease (3 to 6) together with increased risk of adverse outcomes in their neonates (6). A prospective UK population-based cohort study of hospitalised babies aged less than 28 days with confirmed SARS-CoV-2 infection over a 2 month period found severe disease in 42% of 66 cases with just over a third requiring intensive care admission and a third requiring respiratory support, possibly related to other conditions (7). Of pregnant women with COVID-19 disease admitted to UK hospitals, 10% require critical care, and 20% have a pre-term birth. Women with certain underlying medical conditions or with other risk factors are at increased risk of hospital admission with COVID-19 during pregnancy, compared to similar women who are not pregnant (3,4). Increased severity of COVID-19 disease in pregnant and recently pregnant women has been reported after the first SARS-CoV-2 wave in England (8,9) and in Scotland (10). Of 1,714 pregnant women admitted to UK hospitals between February and September 2021 with COVID-19 disease only 1.5% and 0.4% had received 1 and 2 doses of COVID-19 vaccine respectively whilst none of 235 pregnant women admitted to intensive care were fully vaccinated (11) and complications linked with COVID-19 disease in pregnancy (critical care admission and perinatal deaths) in Scotland were far more common in unvaccinated than in vaccinated pregnant women (10,12).

One review and combined analysis of reasonably high-quality studies with appropriate comparison groups found an increased risk of preeclampsia, pre-term birth, and stillbirth among pregnant women with SARS-CoV-2 infection compared with those without SARS-

CoV-2 infection (13). Pregnant women who develop severe disease have increased rates of admission to ICU, need for invasive ventilation and pre-term delivery. Data from the US Centers for Disease Control and Prevention (CDC) found that pregnant women are around 3 times more likely to be admitted to ICU and nearly 3 times more likely to require invasive ventilation compared to non-pregnant women with COVID-19 disease and 25% more likely to die (14).

Another living systematic review of 192 studies found pregnant and recently pregnant women are more likely to be admitted to ICU or require invasive ventilation than non-pregnant women of similar age (15). Pregnant women with COVID-19 are more likely to deliver pre-term and have an increased risk of maternal death and of being admitted to ICU compared to pregnant women without COVID-19 (15). Their babies are more likely to be admitted to the neonatal unit. Data from the UK Obstetric Surveillance System (UKOSS) clearly shows that increased risk of pre-term birth is due to interventions to deliver early due to maternal COVID-19 reasons, concerns about the health of women with SARS-CoV-2 infection and their babies (4). There may also be lower thresholds for admission to hospital or ICU when pregnant women are ill.

COVID-19 vaccination is recommended in pregnant women

Vaccination of pregnant women alongside their peers has been recommended in the UK and other countries as an important way to protect pregnant women and their unborn children against COVID-19 disease. Vaccination of pregnant women is strongly recommended by the Royal College of Gynaecologists and Obstetricians and the Royal College of Midwives (RCOG).

Pregnant women should be offered the Pfizer-BioNTech or Moderna (mRNA) vaccines where available for their first dose. The second dose is important to achieve high levels of protection. It is advised that everyone, including pregnant women, completes vaccination with the same vaccine as their first dose unless they are contra-indicated. Further information on the vaccines and vaccine policy is detailed in the Appendix.

COVID-19 vaccine safety in pregnant women

COVID-19 vaccines used in the UK programme do not contain live SARS-CoV-2 virus and therefore cannot infect a pregnant woman or her unborn child with the virus. Whilst, as is commonly the case in trials of medicinal products, pregnant women were excluded from the original COVID-19 vaccine trials, there is accumulating experience and evidence of the safe and effective use of mRNA vaccines (such as the Pfizer-BioNTech or Moderna) in pregnant

women. In England more than 80,000 women indicated that they were or could be pregnant at the time they were vaccinated by the end of September 2021 (16), in Scotland more than 14,000 women were vaccinated during pregnancy to the end of August 2021 (17) and in Wales nearly 2000 women were vaccinated by the end of September 2021 (18). In the US more than 175,000 women have indicated they were pregnant at the time they received COVID-19 vaccination (19).

In a US study of over 100,000 pregnancies between 6 and 20 weeks' gestation, there was no increased likelihood of COVID-19 vaccination in the 28 days before miscarriage compared to a similar period in women with ongoing pregnancies (20). A Norwegian case-control study similarly found no increased odds of being vaccinated in 3- or 5-weeks prior to miscarriage in cases or in controls with confirmation of ongoing pregnancy in the first trimester, after adjusting for possible confounders (21). Another US study found no increased risk of self-reported pregnancy loss between 6 to 19 weeks gestation after mRNA vaccination in pregnancy or around conception (22). These study-based data are in line with reporting data in the UK received through the Yellow Card Scheme which do not suggest that there is any risk of miscarriage or stillbirth associated with COVID-19 vaccines. Preliminary analysis of data in the US v-safe pregnancy registry found no safety concerns with no increased risk of stillbirth, death in newborn babies, pre-term birth, babies born small for gestational age or with congenital anomalies in COVID-19 vaccinated women when compared to expected rates (23).

There is evidence of similar high levels of protection against SARS-CoV-2 infection in pregnant, lactating and non-pregnant women after COVID-19 vaccination (24-26) and that vaccination induces higher antibody levels than those after disease (26). The vaccine side-effects appear to be similar in pregnant and non-pregnant populations (23).

COVID-19 vaccination in pregnancy

When women of child-bearing age present for COVID-19 vaccination in England they are asked the question 'are you or could you be pregnant?' and this is recorded on a point of care app. There are 3 point of care (POC) apps in use across England.

The pregnancy flag as defined by the above question has been live on 2 POC apps since 9 January 2021 and the third app since 26 February 2021.

Data on vaccination status are recorded in a central NHS Digital dataset managed by System C called the National Immunisation Management Service (NIMS) and vaccination records are shared with the Immunisation Division of the UK Health Security Agency (UKHSA) (previously Public Health England (PHE)) daily to monitor coverage of the vaccine in eligible populations. The pregnancy flag data also flow into the central NIMS dataset and are then shared with the UKHSA Immunisation Team. This allows ongoing monitoring of

COVID-19 vaccination totals in pregnant women based on this question and early linkage with maternity records in other datasets.

Based on the response to the pre-screening question “Are you or could you be pregnant?”, data on the number of women in England who indicated they were or could be pregnant and who went on to be vaccinated were first published on 22 July in the COVID-19 vaccine surveillance report week 29. These data are being published monthly.

COVID-19 vaccination of pregnant women at any point before they give birth is also being determined through linkage of NIMS vaccination records and hospital records for women giving birth (see section on Adverse outcomes of pregnancy (methods as in Wider Impacts of COVID-19 on Health (WICH) monitoring tool). These linked data will show COVID-19 vaccine coverage levels in women who give birth in hospital in England.

Reporting systems for COVID-19 vaccination in pregnancy

There are different ways to monitor women who have been vaccinated during their pregnancy and a combination of these are being used in England. Surveillance can be passive – where it relies on people to report to a system, and this can allow you to follow a woman through her pregnancy, but only a limited proportion of pregnancies may be reported. Active surveillance includes a prompt for information from healthcare professionals or health units, such as maternity units, on a regular basis. Actively requesting this information can lead to more complete reporting. Vaccine safety can also be monitored using electronic health records in different systems that can be linked so that a combined record is generated. This allows one to look at vaccination history together with any medical conditions in the woman that may put her pregnancy at higher risk regardless of vaccination, together with information about the pregnancy and the baby when it is born. The systems being used in England are set out below.

The Yellow Card scheme

The Yellow Card scheme is a passive pharmacovigilance system run by the Medicines and Healthcare products Regulatory Agency (MHRA). It is the standard UK system for collecting and monitoring information on safety concerns such as suspected side-effects or adverse incidents involving medicines and medical devices including those used during pregnancy or while breastfeeding. Reporting is open to healthcare professionals and the public and, as well as accepting reporting through the main Yellow Card channels, a COVID-19 interface focussing on the capture of suspected side-effect reports for COVID-19 products including

vaccines has been introduced. For exposures in pregnancy, suspected side-effects in either the mother or child can be reported. The Yellow Card scheme underpins the MHRA COVID-19 Vaccines Vigilance Strategy, see the report of the Commission on Human Medicines Expert Working Group on COVID-19 vaccine safety surveillance. Weekly summaries of all reports received for COVID-19 vaccines are published on a weekly basis, see the coronavirus weekly summary of Yellow Card reporting. This summary includes evaluation of the Yellow Card data on exposures in pregnancy.

Yellow Card vaccine monitor

MHRA have implemented targeted active monitoring of certain groups of vaccinees, focused particularly on those who may have been excluded or under-represented in clinical trials. Through the NHS England call/recall system, a random selection of vaccinees have been invited to voluntarily register for follow-up via a new platform, called the Yellow Card Vaccine Monitor, which the MHRA developed. This vigilance activity seeks enrolment prior to vaccination (and thereby before any suspected side-effect is experienced) and vaccinees are then contacted at set intervals (for example 7 days, 28 days, 3 to 6 months) to ask whether any adverse reaction occurred. The objective of this is not necessarily to detect very rare risks, as the intention was to recruit the same numbers that are generally included in a clinical trial (several thousand), but to compare the frequency and severity of side-effects to groups that were included in trials to allow further characterisation of the safety profile and to target groups under-represented in clinical trials. Over 30,000 individuals have registered to the platform and these data are helping to support the continuous monitoring of COVID-19 vaccines.

In addition to random invitation, MHRA have collaborated with UKHSA to provide a leaflet to pregnant women who take the vaccine which encourages them to register with the Yellow Card Vaccine Monitor. This activity has contributed to over 2,200 pregnant women registering to 3 November 2021. Pregnant women are asked about their pregnancy, including the trimester they received the vaccine(s) and their estimated due date. Follow up will be sent to each individual 10 weeks after their estimated due date to check on the outcomes of the baby, and the data received to date have supported MHRA communications on the safety of the COVID-19 vaccines in pregnancy.

UK surveillance of Vaccination in Pregnancy (VIP)

The UKHSA Immunisation Division has responsibility for surveillance of women inadvertently vaccinated with specific vaccines in pregnancy (VIP). This surveillance is undertaken in collaboration with the MHRA, the UK Teratology Information Service (UKTIS) and with Public Health Scotland, Public Health Wales and Public Health Agency in Northern Ireland. VIP surveillance was established in 1981 specifically for the rubella vaccine, originally under the auspices of the National Congenital Rubella Surveillance Programme. It was set up to address concerns of a theoretical risk from vaccinating pregnant women with live rubella-containing vaccine virus because of the known risk of congenital rubella syndrome after rubella infection in early pregnancy. The surveillance now covers MMR (measles, mumps, rubella) vaccine which has superceded the rubella vaccine. Similar surveillance for chickenpox vaccine, and more recently shingles vaccine, was later established to address concerns of a theoretical risk from these live virus vaccines because of the known risk of congenital varicella following a wild infection. Available data consistently show the safety of these vaccines when given inadvertently in pregnancy.

With the early advice that pregnant women should not be vaccinated due to lack of safety data, VIP surveillance was initially extended to cover inadvertent COVID-19 vaccine receipt in pregnancy and, when advice was updated in late December 2020, it was further expanded to cover any vaccine exposure in pregnancy. As the Joint Committee on Vaccination and Immunisation (JCVI) recommended more groups of women who were pregnant to be offered COVID-19 vaccination alongside comparable risk or age groups, VIP surveillance was focussed on inadvertent vaccinations as such exposures would not be readily captured in electronic records. Once the data flows were established, VIP surveillance was closed to reports of COVID-19 vaccination in pregnancy by choice administered from 15 March 2021. VIP surveillance continues to capture COVID-19 vaccinations administered before women are aware that they are pregnant when the vaccine is given from the first day of their last menstrual period to any time in pregnancy.

The COVID-19 chapter 14a in the Immunisation Handbook (‘the Green Book’) states that cases of inadvertent exposure should be reported to the UK VIP surveillance when this occurs and most VIP pregnancies are reported around the time of exposure. Anyone can report to VIP using the VIP notification form but follow up is routinely through General Practice unless there is a specific request to follow up with an alternate health professional. At 14 weeks’ gestation, a VIP1 surveillance form is sent to the General Practice that the pregnant woman is registered with to request additional medical and obstetric history. The pregnancy is subsequently followed up at 10 weeks post estimated date of delivery and when the baby reaches their first birthday.

UKTIS and UKOSS surveillance of COVID-19 vaccination in pregnancy

Following the JCVI announcement on the 30 December 2020 that pregnant women could be vaccinated, an interim system to collect data on women vaccinated at any stage in pregnancy was set up until dataflows were established. Maternity units were asked to report cases of pregnant women who had been vaccinated via the UK Obstetric Surveillance System (UKOSS). UKOSS is an established national research platform which conducts active negative surveillance of severe pregnancy complications from nominated reporting clinicians based at each of the 194 consultant-led hospital maternity units in the UK. Units are requested to report cases to UKOSS each month and it was a simple process (after rapid ethical approval was granted) to ask maternity units to report women who had received COVID-19 vaccination. UKTIS have a national remit for pharmacovigilance in pregnancy and have the necessary approvals and systems to collect confidential patient information via Confidentiality Advisory Group (CAG) section 251.

UKOSS first informed their reporting clinicians of this study on 1 March 2021 and sent reminder emails to request exposure notifications for any COVID-19 vaccine given up to 31 March 2021. When notified of a vaccination exposure, UKOSS generated an electronic data collection form requesting additional details. All notification forms were sent to the UKTIS and processed in a national teratogen surveillance system for follow-up of maternal and pregnancy outcome. The second route into the monitoring system involved direct self-reporting by vaccinated women to UKTIS via telephone or email. Reports of COVID-19 vaccination in pregnancy have been received by UKTIS since January 2021. UKTIS self-reporters were asked the same baseline details as collected via the UKOSS data collection form.

Adverse outcomes of pregnancy (methods as in Wider Impacts of COVID-19 on Health (WICH) monitoring tool)

Identifiable hospital episode statistics (HES) data will be linked to the COVID-19 vaccination data for the purposes of routinely monitoring the impact of COVID-19 vaccine safety during pregnancy in England. Women giving birth identified from HES will be linked to the NIMS to establish vaccine exposure before giving birth.

This linkage will be used to generate updates on specified pregnancy outcomes already presented in the Wider Impacts of COVID-19 on Health (WICH) monitoring tool ‘pregnancy

and birth' grouping Wider Impacts of COVID-19. This will look at the current pregnancy outcome indicators (deliveries with low birthweight, deliveries with very low birthweight, premature deliveries and stillbirths) in COVID-19 vaccinated and unvaccinated women. Other outcome indicators will also be considered.

This work will be undertaken as part of the UKHSA Immunisation Division COVID-19 response to monitor the COVID-19 vaccination programme under Section 60 of the Health and Social Care Act to process confidential patient information for the purposes of monitoring the efficacy and safety of the vaccination programme. The WICH monitoring tool allows a relatively quick and ongoing surveillance of pregnancy outcomes using hospital data to produce rapid analyses, with methods as similar to the established official statistics (ONS) for these pregnancy outcomes as possible. The work will be undertaken alongside additional surveillance and record-linkage methods used to monitor vaccine safety in pregnancy.

National Congenital Anomaly and Rare Disease Registration Service

The National Disease Registration Service (NDRS) has expanded congenital anomaly and rare disease registration to cover the whole population of England, to meet national requirements for high quality public health disease surveillance identified by the Chief Medical Officer. The National Congenital Anomaly and Rare Disease Registration Service (NCARDRS), part of NDRS, records those people with congenital abnormalities and rare diseases across England. Congenital anomalies are defined as being present at delivery, originating before birth, and include structural, chromosomal and genetic anomalies. On 1 October 2021, responsibility for the NDRS transferred from Public Health England (PHE) to NHS Digital.

Women identified as having been vaccinated during pregnancy through the NIMS pregnancy flag and after 2-way validation with maternity outcomes in the HES dataset will be linked with babies registered in NCARDRS. This will allow additional analysis of COVID-19 vaccine exposure in pregnancy with a review of individual reports of congenital anomaly. This will be a retrospective analysis due to inherent delays in a complete and comprehensive NCARDRS registration and follow up.

Interpretation and analysis

Timing of baby development and how this can help our understanding

Fetal development occurs in a stepwise manner and external exposures (such as to certain viruses and chemicals) can disrupt different features of a baby's development depending on the timing of the exposure. Such agents that can cross the placenta and cause damage to the fetus are known as teratogens.

The first 2 weeks after conception involve the early period of cell division and implantation into the womb. Exposure to teratogens at this time may be subject to the 'all or nothing' rule — whereby the result will be either death of the embryo if damage is too great, or if not, cells at this stage are able to develop into any specialised cells which means that damaged cells can be sacrificed without any notable adverse effect. However, whether the all or nothing rule applies to all teratogenic exposures is unclear since the hypothesis was based on studies of radiation. A risk of damage from other very early exposures cannot be ruled out.

From around 2 weeks after conception, the central nervous system is developing, followed by heart, upper limbs, lower limbs, ears, eyes, teeth, palate, and external genitalia. Development is largely complete by 9 weeks after conception (11 weeks of pregnancy). Exceptions include the nervous system, teeth and external genitalia which continue to develop into the neonatal period. A teratogenic exposure at 5 weeks post conception could affect the development of the heart and eyes, whereas a teratogenic exposure at 7 weeks could cause a cleft palate. Teratogenic exposures at any stage of pregnancy could affect the central nervous system albeit with different effects. It is unlikely that all developing tissues, organs, and structures are vulnerable to the effects of teratogenic exposure. For harm to occur, the exposure has to coincide with a developmental process that is sensitive to the effects of the teratogen. This is why exposure after 9 weeks (11 weeks of pregnancy) generally has less or little impact, except for exposures that affect the nervous system, skeletal system and genitalia.

The background rate for congenital anomalies in the UK is around 2 to 3%. Consideration of timing of exposure is critical when assessing whether any exposure, including vaccination, may have contributed to a congenital defect. Exposure needs to occur at the time of structural development in utero for any causative association to be inferred.

Interpretation of pharmacovigilance data

Yellow card reporting does not necessarily implicate vaccination as the cause of the reported adverse event. Rather, the system is designed to raise potential issues that could be associated and trigger further assessment. Furthermore, for exposures in pregnancy, a high level of under-reporting is possible although this is likely to be less of an issue for events occurring soon after vaccination. However, disproportionality analyses can be and are applied to look for potential safety signals. The detailed narratives provided with individual cases are highly valuable in considering potential causality on a more individual case basis. Active surveillance data from the Yellow Card Vaccine Monitor, where patients are recruited before or close to the point of vaccination, is more robust for identifying and quantifying possible risks. Reports of adverse events received through both methods are assessed by the MHRA on a continuous ongoing basis.

Descriptive analysis of pregnancy outcomes

Passive reports of vaccine exposures reported to VIP and UKTIS are likely to comprise relatively small numbers of pregnancies. These are being actively followed up using comparable surveillance forms at similar time points in each pregnancy. The UKTIS/UKOSS study is an active surveillance system employing comparable data collection forms and follow up of each reported pregnancy at similar time points to VIP.

Reports to both systems will be de-duplicated and reviewed. If the overall features of reported pregnancies appear similar with no indication of bias in any individual system (for example, towards the reporting of adverse outcomes or in the timing of reporting with respect to exposure) then the information collected will be combined before being reviewed and pregnancy outcomes compared to background population rates. An early descriptive review of reported exposures to identify any signals of adverse events will then be followed up through other analyses.

With data collection ongoing as pregnancies complete, it is anticipated that pregnancy outcome data from UK VIP, UKOSS and UKTIS will be available by December 2021 to enable a combined analysis.

Data linkage studies to investigate safety of COVID-19 vaccine in pregnant women

UK-wide review of key issues

Representatives from each of the 4 UK nations have agreed to develop a consistent approach to COVID-19 vaccine safety studies in pregnant women. The intention is to align methodologies as far as possible across all 4 nations using 3 main approaches:

- observed versus expected events in similar pregnant populations (background rates)
- matched cohort analysis based on vaccinated pregnant women matched with contemporaneous unvaccinated pregnant women
- matched cohort analysis based on vaccinated pregnant women matched with historical unvaccinated pregnant women (would need to pre-date COVID-19 or take SARS-CoV-2 infection into account)

Each country may use one or more approach with different available datasets but using agreed outcomes where possible. Linked data from across primary and secondary care will be required to fully identify vaccinations, confounders, pregnancies, events, and outcomes. Maternal, pregnancy and neonatal outcomes of interest have been developed by the COVID-19 in Pregnancy in Scotland (COPS) group building on their protocol for the study of COVID-19 infection in pregnancy (27). In a similar way, certain factors have been identified that might influence pregnancy outcome in an adverse way, such as smoking, pre-existing medical conditions or maternal age, and are considered potential confounders (covariates).

It is likely that these outcomes of interest, covariates and vaccination details will be available in different datasets that will need to be linked in order to undertake an analysis. Analyses will be adjusted for potential confounders where available including trimester/gestational age when vaccinated (first dose in pregnancy). There are established limitations to conducting studies on the safety of medicines and vaccines in pregnancy using electronic healthcare record databases, particularly challenges in identifying pregnancy dates and child outcomes. All results will need to be carefully interpreted considering the deployment patterns of the vaccines. Protocols detailing the different data sources to be used and the analysis to be undertaken will be published once these are finalised (see The COVID-19 in Pregnancy in Scotland (COPS) study for details.

Planned analyses in England using linked data

Within England, a collaborative study will be led by the National Institute for Health Research (NIHR) Health Protection Research Unit in Vaccines and Immunisation (a partnership between London School of Hygiene and Tropical Medicine (LSHTM) and UKHSA), working with MHRA and UKTIS with input from RCOG.

The epidemiological analyses using linked data will focus on women vaccinated routinely as part of age-based risk groups from April 2021. Pregnancies will be identified retrospectively using records of completed pregnancies in primary and secondary care, and so these analyses will be undertaken in 2022 to allow completion of pregnancies, occurrence and recording of events, and data linkage. So that results can be available as quickly as possible for pregnant women and policy makers, interim analysis will focus first on second and third trimester vaccinations among women vaccinated soon after April 2021. Analysis later in 2022 will include a fuller picture of first trimester vaccination and women in younger age groups. The epidemiological studies using linked data are planned to complement the more rapid analysis possible using the other data sources above. The study methods and findings will be published in peer-reviewed publications on completion.

References

1 World Health Organization COVID-19 dashboard.

2 GOV.UK COVID-19 in the UK dashboard.

3 Knight M and others. Saving Lives, Improving Mothers' Care Rapid Report: Learning from SARS-CoV-2-related and associated maternal deaths in the UK March – May 2020 Mothers and babies: reducing the risk though audits and confidential enquries across the UK (MBRRACE-UK); 2020

4 Vousden N and others. The incidence, characteristics and outcomes of pregnant women hospitalized with symptomatic and asymptomatic SARS-CoV-2 infection in the UK from March to September 2020: A national cohort study using the UK Obstetric Surveillance System (UKOSS). Plos One. 2021;volume 16 issue 5.

5 Overtoom EM and others. SARS-CoV-2 infection in pregnancy during the first wave of COVID-19 in the Netherlands: a prospective nationwide population-based cohort study (NethOSS). BJOG: An International Journal of Obstetrics and Gynaecology. 2021.

6 Badr DA and others. Severe Acute Respiratory Syndrome Coronavirus 2 and pregnancy outcomes according to gestational age at time of infection. Emerging Infectious Diseases, 2021, volume 27 issue 10, pages 2535-43.

7 Gale C and others. Characteristics and outcomes of neonatal SARS-CoV-2 infection in the UK: a prospective national cohort study using active surveillance. The Lancet Child and Adolescent Health. 2021, volume 5 issue 2, pages113-121.

8 Kadiwar S and others. Were pregnant women more affected by COVID-19 in the second wave of the pandemic?. The Lancet, 2021, volume 397 issue 10284, pages 1539-40.

9 Vousden N and others. Impact of SARS-CoV-2 variant on the severity of maternal infection and perinatal outcomes: Data from the UK Obstetric Surveillance System national cohort. medRxiv, 2021.

10 Public Health Scotland, Scottish Intensive Care Society Audit Group report on COVID-19, 23 September 2021

11 Mothers and babies: reducing the risk though audits and confidential enquries across the UK (MBRRACE-UK), Key information infographic February 2021 to September 2021.

12 Stock S and others. COVID-19 vaccination rates and SARS-CoV-2 infection in pregnant women in Scotland. Research Square, 2021

13 Wei SQ and others. The impact of COVID-19 on pregnancy outcomes: a systematic review and meta-analysis. Canadian Medical Association Journal, 2021, volume 193 issue 16, pages 540-E8.

14 Zambrano LD and others. Update: characteristics of symptomatic women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status - United States, January 22-October 3, Morbidity and Mortality Weekly Report, 2020, volume 69 issue 44, pages 1641-7.

15 Allotey J and others. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. BMJ, 2020, 370:m3320.

16 UKHSA, COVID-19 vaccine weekly surveillance report week 42, 21 October 2021.

17 University of Edinburgh, Outputs and information for the public.

18 Public Health Wales, Wales COVID-19 vaccination enhanced surveillance, Equality Report 9, 28 October 2021.

19 Centers for Disease Control and Prevention, Vaccine Pregnancy Registry.

20 Kharbanda EO and others. Spontaneous abortion following COVID-19 vaccination during pregnancy. Journal of the American Medical Association, 2021, volume 326, issue 16, pages 1629-1631.

21 Magnus MC and others. COVID-19 vaccination during pregnancy and first-trimester miscarriage. New England Journal of Medicine. 2021.

22 Zauche LH and others. Receipt of mRNA COVID-19 vaccines and risk of spontaneous abortion. New England Journal of Medicine, 2021 volume 385, issue 16, pages 1533-5.

23 Shimabukuro TT and others. Preliminary findings of mRNA COVID-19 vaccine safety in pregnant persons. New England Journal of Medicine, 2021, volume 384, issue 24, pages 2273-82.

24 Goldshtein I and others. Association between BNT162b2 vaccination and incidence of SARS-CoV-2 infection inpregnant women. Journal of the American Medical Association, 2021, volume 326 issue 8, pages 728-35.

25 Dagan N and others. Effectiveness of the BNT162b2 mRNA COVID-19 vaccine in pregnancy. Nature Medicine. 2021, volume 27, issue 10, pages 1693-5.

26 Gray KJ and others. Coronavirus disease 2019 vaccine response in pregnant and lactating women: a cohort study. American Journal of Obstetrics and Gynecology. 2021, volume 225, issue 3: pages 303 e1- e17.

27 Stock SJ and others. COVID-19 in Pregnancy in Scotland (COPS): protocol for an observational study using linked Scottish national data. BMJ Open, 2020, volume 10, issue 11, e042813.

Appendix

COVID-19 vaccination background

The pandemic generated interest in the development and testing of many candidate vaccines using different technologies such as nucleic acid vaccines, inactivated and attenuated live virus vaccines, subunit vaccines and viral vector vaccines. The first candidate vaccine licensed for use in the UK by the Medicines and Healthcare products Regulatory Agency (MHRA) was the Pfizer BioNTech COVID-19 mRNA vaccine (approved on 2 December 2020), followed by the AstraZeneca COVID-19 vaccine which uses an adenovirus vector (approved on 30 December 2020) and most recently the Moderna mRNA vaccine (approved in January 2021). These vaccines were all shown to be highly effective and to have no safety concerns during clinical trials involving tens of thousands of volunteers. None of the COVID-19 vaccines that are used in the UK contain live coronavirus and cannot infect a pregnant woman or her unborn child.

Based on the absence of available safety data when vaccine policy was first discussed, the Joint Committee on Vaccination and Immunisation (JCVI) which advises UK health departments on immunisation, first recommended (meeting 2 of Tuesday 1 December) that pregnant and breast-feeding women should not be vaccinated and women should avoid pregnancy for 3 months after vaccination. As further data from animal reproductive toxicology studies for the Pfizer-BioNTech vaccine became available and the AstraZeneca COVID-19 vaccine was licensed, the JCVI recommendation was updated. Updated JCVI advice was that COVID-19 vaccination, in women who were pregnant and were offered vaccine under the JCVI priority risk group categories 1, 2, 4 or 6 (Priority groups for coronavirus (COVID-19) vaccination: advice from the JCVI, 30 December 2020), should be considered if risk of exposure was high and could not be avoided (meeting of 22 December 2020), or where the woman had underlying conditions that put her at very high risk of serious complications of COVID-19. In these circumstances, clinicians should discuss the benefits and risks of vaccination with the woman, who should be told about the absence of safety data for the vaccine in pregnant women at that time.

The Committee agreed that routine pregnancy testing before receipt of a COVID-19 vaccine would not be required, there was no need to avoid pregnancy after vaccination and that breastfeeding women could be offered vaccination.

With the rollout of the COVID-19 vaccine to increasingly younger people within the population and data emerging about the increased risks of COVID-19 in later pregnancy, the JCVI updated its advice in April 2021 to recommend that pregnant women should be offered the COVID-19 vaccine at the same time as the rest of the population, based on their age and clinical risk group. Real-world data were available from the US showing that at that point around 120,000 pregnant women had been vaccinated (Vaccine Pregnancy Registry, CDC),

mainly with mRNA vaccines including Pfizer-BioNTech and Moderna, without any safety concerns being raised. Based on these data, the JCVI advised that pregnant women in the UK should be offered the Pfizer-BioNTech or Moderna vaccines where available for their first dose. It is advised that everyone, including pregnant women, completes vaccination with the same vaccine type unless they are contra-indicated. It is known that the second dose is important to achieve high levels of protection. There is no evidence to suggest that other vaccines are unsafe for pregnant women, but it was considered that more research was needed. There are no safety signals of concern following a second dose of the AstraZeneca vaccine and the second dose is reported to be less reactogenic.

A very rare association between the first dose of AstraZeneca COVID-19 vaccine and cerebral venous sinus thrombosis (CVST) occurring together with low levels of platelets (thrombocytopenia) has been identified. These, together with similar conditions (thromboembolic events alongside low platelet levels) are being reviewed and monitored by the MHRA, UK and other national and international licensing agencies and health bodies. Available data suggest that there is a trend for increasing risk of this condition following vaccination with decreasing age; this contrasts with the risk of severe disease which increases with increasing age. No specific risk factors, including pregnancy, have been identified for this very rare vaccine-associated event. The JCVI currently advises that it is preferable for adults aged under 40 years without underlying health conditions that put them at higher risk of severe COVID-19 disease, to be offered an alternative COVID-19 vaccine, if available.

There is no suggestion that these conditions are associated with pregnancy. The advice is that women who have received a first dose of AstraZneca vaccine can safely go on to receive their second dose. Women can be reassured that a safety signal for this condition has not been linked to a second dose.

To see current recommendations for COVID-19 vaccination of pregnant women please see JCVI minutes, publications and statements.

About the UK Health Security Agency

The UK Health Security Agency is an executive agency, sponsored by the Department of Health and Social Care.

Version 1

Prepared by: Immunisation and Vaccine-Preventable Diseases Division

For queries relating to this document, please contact: immunisation@phe.gov.uk

Published: November 2021
Publishing reference: GOV-10517