Clinical Commissioning Policy: Maternal intravenous immunoglobulin (IVIg) for the prevention of allo-immune fetal and neonatal haemochromatosis

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Contents

Policy Statement

NHS England will commission maternal intravenous immunoglobulin (IVIg) for the prevention of allo-immune fetal and neonatal haemochromatosis in accordance with the criteria outlined in this document.

In creating this policy NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

This policy document outlines the arrangements for funding of this treatment for the population in England.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to review policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and

- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities

Plain Language Summary

About allo-immune neonatal and fetal haemochromatosis

Allo-immune neonatal haemochromatosis (NH) is a rare condition, which can have fatal consequences during pregnancy or the neonatal period, resulting in acute liver failure, stillbirth and death of the newborn baby (Whitington, 2008). The number of pregnancies and babies affected by the condition is relatively unknown and it is likely to be under recognised.

NH is a form of liver disease associated with the build-up of excess iron in the liver (Feldman et al, 2013). This is most commonly caused by gestational allo-immune liver disease (GALD); a form of profound liver failure in the newborn. GALD is caused by the mother's reaction to fetal liver cells (antigens), when the mother does not recognise these as her own. This results in the production of blood proteins (antibodies) by the mother that cross the placenta to the fetus and attack the fetal liver cells, leading to severe liver damage due to liver cell (hepatocyte) injury and intrauterine death.

There is no genetic or hereditary component. A mother can have an affected baby even if she has previously had unaffected pregnancies. However, if a previous baby has been affected, the risk of it occurring again in subsequent pregnancies is approximately 90%. This most commonly results in rapid onset liver (hepatic) failure within hours of birth, the need for plasma (exchange) transfusion, life sustaining intensive care treatment, neonatal liver transplant and often neonatal death. GALD can present any time from 18 weeks gestation to 3 months post-delivery. There is a spectrum of disease severity, ranging from acute liver failure, to 'affected' babies with no clinical disease (Whitington, 2008).

About current treatments

There is no standard treatment at present. In milder cases, where the baby is born alive, supportive treatment for liver failure followed by donor liver transplant is possible; however, overall survival for infants receiving a liver transplant for this indication is approximately 35%. It is unclear why some babies develop this sudden onset (hyperacute) liver failure and why others present with liver failure from birth (congenital cirrhosis); thus, GALD is often underdiagnosed (Feldman, 2013).

About the new treatment

The only preventative management currently available is maternal immunoglobulin (IVIg) treatment.

Immunoglobulin is extracted from donor blood and is a mixture of blood proteins (antibodies) that are made by the immune system. Antibodies are usually formed when the immune system comes into contact with foreign substances such as viruses, bacteria or toxins. These antibodies are normally protective. Immunoglobulin is usually given to patients as an intravenous or subcutaneous infusion, called intravenous immunoglobulin (IVIg) or subcutaneous immunoglobulin (SCIg) (NHS England, 2013).

IVIg has been shown to successfully reduce the risk of liver damage/failure, the need for intensive care support in hospital, donor liver transplant and intrauterine death during pregnancy or neonatal death after birth. A woman who has had a previous baby affected by NH should receive treatment during any subsequent pregnancy to prevent recurrence of neonatal haemochromatosis.

What we have decided

NHS England has carefully reviewed the evidence to prevent allo-immune fetal and neonatal haemochromatosis with maternal intravenous immunoglobulin. We have concluded that there is enough evidence to make the treatment available.

1 Introduction

Clinical Indication

Allo-immune neonatal haemochromatosis (NH) is a rare condition, yet one of the most common causes of liver failure in the neonatal period (Feldman et al, 2013). Based on US data, the incidence is estimated to be 15 per million live births. It is important to note that neonatal haemochromatosis is an underdiagnosed condition, as not all mothers who lose a baby will obtain the diagnosis which is made by post-mortem examination of the baby.

Gestational allo-immune liver disease (GALD) has been established as the cause of fetal liver injury leading to NH in almost all cases (Feldman, 2013). There is no hereditary or genetic component (Feldman, 2013). GALD is caused by a maternal allo-immune reaction from exposure to fetal hepatocyte antigens when the mother does not recognise the fetal antigen as “self”. This exposure results in maternal sensitisation and production of IgG antibodies by the mother that are directed against fetal hepatocytes. Once the mother is sensitised, continued exposure to the fetal antigens leads to persistent overproduction of antibodies by the mother, which cross the placenta to the fetus leading to severe liver damage due to hepatocyte injury and intrauterine death, with fatal consequences either during pregnancy resulting in miscarriage or stillbirth, or in the neonatal period leading to acute liver failure and neonatal death (Whitington, 2008).

It is unclear how antigen exposure to the maternal circulation occurs. A mother can have unaffected children prior to having an affected baby. If a previous child is affected, the risk of recurrence in subsequent pregnancies is approximately 90%, resulting most commonly in rapid onset hepatic failure within hours of birth, the need for exchange transfusion, life sustaining intensive care treatment, neonatal liver transplant and often neonatal death. GALD can present any time from 18 weeks gestation to 3 months post-delivery. There is a spectrum of disease severity, ranging from acute liver failure to ‘affected’ babies with no clinical disease (Whitington, 2008).

Current Treatment

There is no current standard treatment. Untreated, the inevitable outcome of these cases is either miscarriage, stillbirth or severe neonatal liver failure, leading to death in infancy unless treated by donor liver transplant. In milder cases where the baby is born alive, supportive treatment by exchange transfusion suffices, but in severe cases often a donor liver transplant is required. However, overall survival for infants receiving a liver transplant for this indication is approximately 35% (Feldman, 2013).

Proposed Treatment

The administration of IVIg, at a dose of 1g/kg (dose capped at 60 grams per week) is first administered to at risk mothers at 14 weeks, then fortnightly (16 and 18 weeks) and then weekly from 18 weeks gestation until delivery between 37 and 38 weeks. IVIg works to prevent fetal haemochromatosis by:
1) blunting maternal immune response to fetal antigens;
2) by flooding the placental IgG transport mechanism with non-specific antibodies;
3) by non-specific antibody binding that limits the binding of reactive allo-antibodies to target antigens.

It has been shown to be effective at stopping or reducing the risk of fetal liver damage, subsequently reducing the need for neonatal intensive care support and liver transplant. In addition, it has been shown to reduce intrauterine death, miscarriage and stillbirth (Whitington, 2018).

There is limited published evidence on the IVIg side effects on the fetus, however studies addressing this have found no evidence of fetal harm (Radder et al, 2004). Because of the pro-thrombotic effects of high-dose IVIg, caution should be exercised in high risk pregnancies (e.g. in mothers with systemic lupus erythematosus or pre-existing maternal autoimmune disorders associated with a higher risk of thrombosis).

2 Definitions

Antibody: (immunoglobulin) Blood proteins produced in the body to neutralise the effect of bacteria, viruses or toxins.

Antigen: A toxin or foreign substance which induces an immune response in the body, especially the production of antibodies.

Allo-immune: An immune response against antigens from members of the same species (in this case, antibodies from the mother mistakenly attacking the fetus).

Fetus: unborn offspring (from 8 weeks until birth).

Gestational allo-immune liver disease (GALD): A form of liver disease that occurs during pregnancy when women become sensitised to their fetus' liver cells. This results in production of 'antibodies' that cross the placenta and attack the fetal liver cells, resulting in liver failure in the baby. Zellweger spectrum disorders – types of peroxisomal disorder.

Immunoglobulin: Blood proteins, made from plasma separated out from donated blood, which are able to fight bacteria and viruses.

Intrauterine: inside the uterus

Neonatal Haemochromatosis (NH): A form of liver disease in the fetus and new born baby associated with the build-up of excess iron in the liver and body. It is most commonly caused by gestational allo-immune liver disease (GALD).

3 Aims and Objectives

This policy considered the clinical circumstances in which NHS England might commission and fund the use of intravenous immunoglobulin in the treatment of allo-immune fetal and neonatal haemochromatosis.

The objectives were to:

- assess the evidence for the clinical effectiveness, safety and cost effectiveness of IVIg given to the mother, to prevent fetal and neonatal haemochromatosis; and
- clarify the commissioning position of NHS England in order to ensure equal access to IVIg treatment for pregnant mothers with a history of a previous fetus or newborn affected by allo-immune neonatal haemochromatosis. Suitable women are identified from a previous adverse pregnancy outcome and clear post-mortem evidence of fetal haemochromatosis or women who have had an offspring with neonatal liver failure confirmed to be due to allo-immune neonatal haemochromatosis.

4 Epidemiology and Needs Assessment

The incidence of GALD and GALD-related NH is unknown, but it is considered to be rare. One estimate from the United States is an incidence rate of 15 per million live births. It is important to note that neonatal haemochromatosis is an underdiagnosed condition, as not all mothers who lose a baby will obtain the diagnosis from a post-mortem examination on the baby (Whitington et al, 2008). A woman could have multiple unaffected infants prior to having an affected infant however, after having an affected infant, there is a 90% chance that each subsequent baby will be affected by neonatal haemochromatosis.

Neonatal haemochromatosis can present at any time from 18 weeks gestation until 3 months post-delivery. Most infants present with liver failure within hours of birth, but there is a spectrum of disease severity ranging from acute liver failure to ‘affected babies’ with no clinical disease.

If untreated, there is an extremely high incidence of fetal death and miscarriage (approximately 31%) and of those live born infants, approximately 89% die or require liver transplant.

5 Evidence Base

NHS England has concluded that there is sufficient evidence to support a policy for the routine commissioning of this treatment for the indication.

This review is based on one large prospective case series (Whitington et al 2018) of 151 women with a previous pregnancy affected with allo-immune NH. Women were treated with IVIg initiated at either 14 weeks gestation (57%) (108 pregnancies in 81 women recruited post mid-2008) or 18 weeks gestation (43%) (80 pregnancies in 70 women recruited up to mid-2008). Results were compared with historical self-controls (untreated previous pregnancies in the same women). Women were recruited from 1997 to 2015 from 19 countries including the UK.

Clinical effectiveness

Affected living offspring:

- For all 151 women included in the case series, 9 out of 188 (5%) treated pregnancies (14 & 18 week IVIg initiation) resulted in an affected living offspring and 177 (94%) resulted in an unaffected living offspring, compared with 157 (45%) affected and 105 (30%) unaffected living offspring in all 350 previous untreated pregnancies in the same women (confidence intervals were not reported). This resulted in an odds ratio1 of 0.034 (95% CI 0.017 to 0.069, $p<0.0001$) in favour of maternal IVIg treatment.

- For women who had a 14 week initiation of IVIg, 5 out of 108 (5%) treated pregnancies resulted in an affected living offspring (confidence intervals were not reported). All five of the affected living offspring had liver failure, two of whom died (one newborn and one at three months) and three survived. A total of 102 out of 108 (94%) treated pregnancies resulted in an unaffected living offspring (confidence intervals were not reported). No comparative results were given for previous untreated pregnancies in the 14 week initiation group alone.

- For 18 week IVIg initiation, 4 out of 80 (5%) treated pregnancies resulted in an affected living offspring (confidence intervals were not reported). Three of the affected living offspring had liver failure, one of whom died and two survived. One

affected offspring died immediately after premature delivery at 22 weeks. A total of 75 out of 80 (94%) treated pregnancies resulted in an unaffected living offspring (confidence intervals were not reported). Again, no comparative results were given for previous untreated pregnancies in this group alone.

- No difference was found in the rate of affected living offspring between 14 and 18 week IVIg initiation ($p>0.05$).

Foetal loss:

- For all 151 women included in the case series, 2 out of 188 (1%) treated pregnancies (14 & 18 week IVIg initiation) resulted in foetal loss, compared with 88 out of 350 (25%) previous untreated pregnancies in the same women (confidence intervals were not reported). This resulted in an odds ratio2 of 0.032 (95% CI 0.008 to 0.132, $p<0.0001$) in favour of maternal IVIg treatment.

- For women who had a 14 week initiation of IVIg, 1 out of 108 (1%) treated pregnancies resulted in foetal loss which was a spontaneous abortion at 15 weeks (confidence intervals were not reported). For the untreated previous pregnancies in this group (number not reported), 44 resulted in foetal loss (% not reported).
- For 18 week IVIg initiation, 1 out of 80 (1%) treated pregnancies resulted in foetal loss which was a spontaneous abortion at 21 weeks (confidence intervals were not reported). For the untreated previous pregnancies in this group (number not reported), 44 resulted in foetal loss (% not reported).

No difference was found in the rate of foetal loss between 14 and 18 week IVIg initiation ($p>0.05$).

Safety

- The short-term safety profile for maternal IVIg appears to be good. One woman with an 18 week IVIg initiation developed a major adverse event (aseptic meningitis). The infusions were terminated and the pregnancy had a good outcome. No major adverse events were reported for the 14 week initiation.

Twenty women (13%) reported minor adverse events. These were not reported separately by 14 and 18 week IVIg initiation regimen.

Cost-effectiveness

- No studies assessing the cost-effectiveness of maternal IVIg starting at 14 weeks gestation for pregnant women with a history of allo-immune NH were identified.

Conclusions

- The evidence regarding the clinical effectiveness of maternal IVIg initiated at 14 weeks gestation for women with a previous pregnancy affected by allo-immune NH is limited to one large, international, prospective case series which suggests that IVIg is a safe and effective intervention for preventing the recurrence of allo-immune NH. No difference was found between starting IVIg at 14 or 18 weeks. The safety profile of maternal IVIg was found to be good, in the short term at least, with one major adverse event and relatively few minor adverse events reported.The case series is generally of good quality and gives reliable data on outcomes in treated women. However the use of historical self-controls provides an inappropriate untreated comparator as inclusion depended on having had the outcome of interest which means it is not possible to accurately quantify the effect of IVIg. Furthermore, different gestational periods in which foetal losses were included between the groups were used, as foetal losses in the treatment group were only counted after initiation of IVIg, but the untreated group includes losses at less than 18 weeks. This is likely to have exaggerated the perceived effects of IVIg. However, despite these issues, the reduction in NH observed in the treated women is so large, and the rate is so much lower than previously reported rates of recurrence in untreated women with a previous pregnancy affected by allo-immune NH (although we did not review the evidence for these reported rates), that it does imply a substantial protective effect.

- Starting IVIg at 14 or 18 weeks led to similar outcomes after 18 weeks gestation, but the series was unable to assess differences in foetal loss in the 14-18 week period, as these data were not available for women starting treatment at 18 weeks.

No studies were found assessing the cost-effectiveness of maternal IVIg starting at 14 weeks gestation for pregnant women with a history of allo-immune NH.

6 Criteria for Commissioning

Eligibility Criteria

Pregnant mothers with a previous adverse pregnancy outcome and clear post-mortem evidence of fetal haemochromatosis or women who have had an offspring with neonatal liver failure confirmed to be due to allo-immune neonatal haemochromatosis.

Treatment Regime

Immunoglobulin is administered by intravenous infusion at a dose of 1g/kg (dose capped at 60g per week) to at risk mothers at 14 weeks, 16 weeks and then weekly from 18 weeks gestation until delivery between 37 and 38 weeks.
The weight used to calculate the dose will be the mother's weight at booking. The decision to treat with intravenous immunoglobulin must be made by:

- Consultant obstetrician with input from a liver unit specialist, subject to prior approval by a Sub regional Immunoglobulin Assessment panel (SRIAP) (the responsibility for clinical supervision remains with the lead obstetrician)
- It must be prescribed by the Consultant Obstetrician.
- The infusion will be given as a day case procedure, in an appropriate local setting, determined by local policy with access to safe monitoring.
- The product with the lowest acquisition cost (unless clinically inappropriate) should be used.

Stopping / Pausing Criteria

- A decision to stop will be made by the Consultant Obstetrician
- Ideally, where possible all decisions will be discussed with the wider MDT

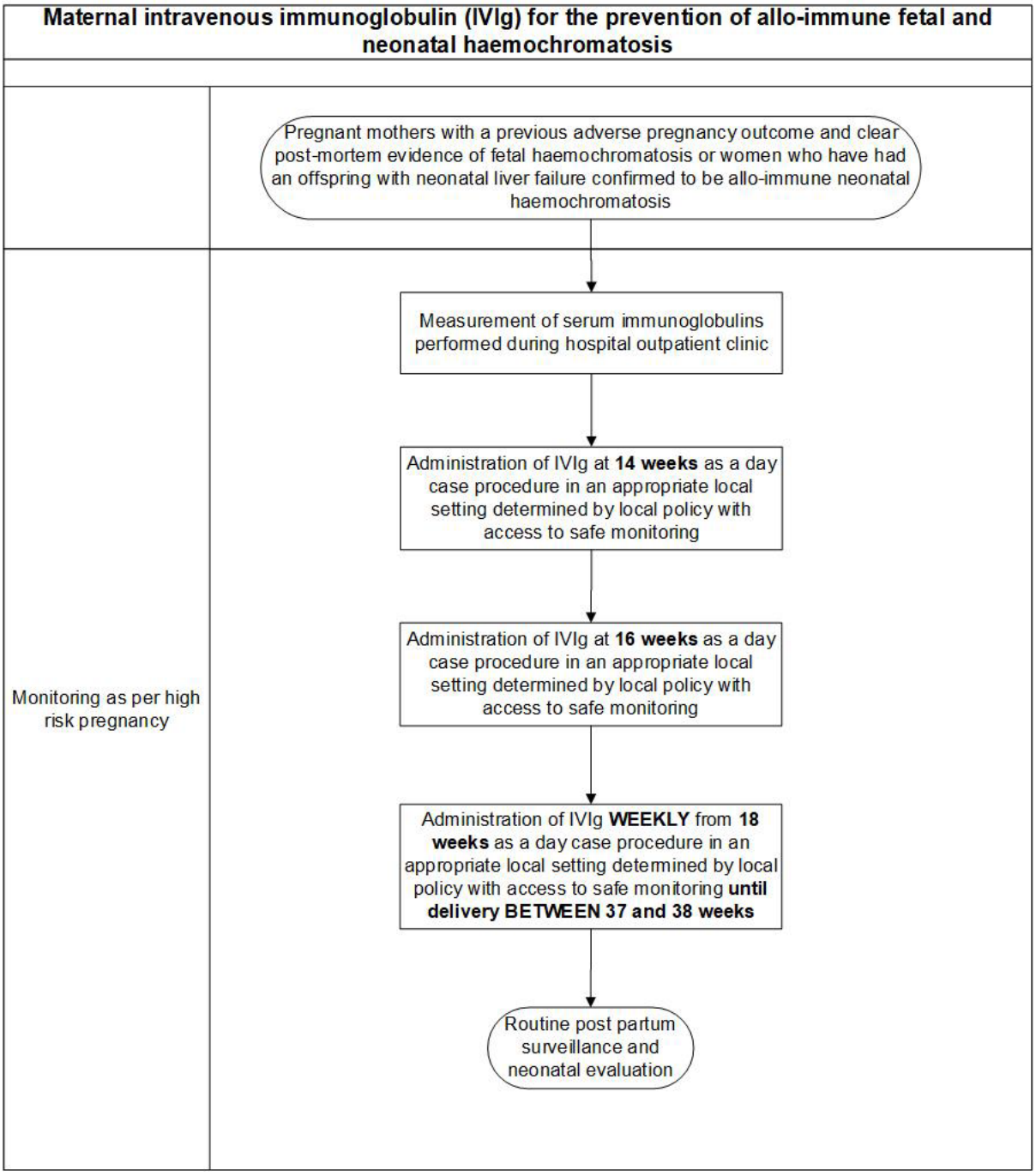
Absolute stopping criteria include:

- Lethal congenital abnormality
- Intrauterine death/ non- viable pregnancy
- Premature delivery
- Anaphylaxis
- Aseptic meningitis
- Patient choice

All other adverse events will require an obstetric review:

- Acute renal failure
- Haemolytic anaemia
- Intolerable side effects
- Hypersensitivity
- Development of any medical complications such as thrombosis or hypertension.

7 Patient Pathway



8 Governance Arrangements

Any provider organisation treating patients with this intervention will be required to assure itself that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements will be through the regional SRIAP and NHS England may ask for assurance of this process.

Governance will be managed by the current IVIg NHS England guidance:

England.nhs.uk. (2018). Updated Commissioning Guidance for the use of therapeutic immunoglobulin (Ig) in immunology, haematology, neurology and infectious diseases in England January 2019. [online] Available at: http://igd.mdsas.com/wp-content/uploads/Ig-PWG-Guidance-for-the-use-of-Ig-V1.3-12022019. [Accessed 26 Apr. 2019].

9 Mechanism for Funding

Reimbursement for the use of IVIg for mothers at risk of alloimmune fetal and neonatal haemochromatosis meeting the criteria within this policy will be managed, through local contract agreements and terms, by the local NHS England Specialised Commissioning Teams. It is expected that new funding will be required to commission IVIg for the prevention of alloimmune neonatal and fetal haemochromatosis. Funding will be reliant on the registering of the patient and recording of doses provided on the National Immunoglobulin database.

10 Audit Requirements

All women receiving IVIg will be registered through the National MDSAS Immunoglobulin database and the following outcomes monitored using this register:

- Fetal loss (including gestation)
- Gestation at delivery
- Neonatal outcomes
- Adverse events

11 Documents which have informed this Policy

England.nhs.uk. (2013). *Clinical Commissioning National Intravenous Immunoglobulin (IVIG) Guidelines*. [online] Available at: https://www.england.nhs.uk/wp-content/uploads/2013/04/b09-ps-a.pdf [Accessed 25 Apr. 2019].

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12 Date of Review

This document will be reviewed when information is received which indicates that the policy requires revision.

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Whitington, P. Kelly, S. (2008). Outcome of Pregnancies at Risk for Neonatal Haemochromatosis Is Improved by Treatment With High Dose Intravenous Immunoglobulin. PEDIATRICS, 121 (6), pp. 1615-1621

Whitington, P., Kelly, S., Taylor, S., Nóbrega, S., Schreiber, R., Sokal, E., Hibbard, J. (2018). Antenatal Treatment with Intravenous Immunoglobulin to Prevent Gestational Alloimmune Liver Disease: Comparative Effectiveness of 14-Week versus 18-Week Initiation. Fetal Diagnosis and Therapy, 43(3), pp.218-225

END