NHS England

Evidence review: Maternal intravenous immunoglobulin for the prevention of allo-immune neonatal haemochromatosis for women who have had a previous foetus diagnosed with neonatal haemochromatosis

NHS England

Evidence review: Maternal intravenous immunoglobulin for the prevention of allo-immune neonatal haemochromatosis for women who have had a previous foetus diagnosed with neonatal haemochromatosis

First published: April 2019

Updated: Not applicable

Prepared by: Solutions for Public Health (SPH) on behalf of NHS England Specialised Commissioning

Contents

1 Introduction 4

2 Summary of results 5

3 Methodology....7

4 Results....8

5 Discussion....10

6 Conclusion 11

7 Evidence Summary Table 13

8 Grade of Evidence Table....17

9 Literature Search Terms....22

10 Search Strategy 23

11 Evidence Selection....23

12 References....24

1 Introduction

Existing guidance from the National Institute of Health and Care Excellence (NICE)

- There is currently no NICE guidance on maternal intravenous immunoglobulin (IVIg) for allo-immune neonatal haemochromatosis (NH).

The indication and epidemiology

- NH is characterised by severe foetal liver injury which causes disturbed iron homeostasis resulting in iron overload in the liver and tissues surrounding the liver (Lopriore et al 2013).
- Infants are affected in utero leading to a high incidence of foetal loss and acute liver failure in the first weeks of life (Lopriore et al 2013).
- NH should be suspected in infants who manifest liver disease antenatally or immediately after birth, and in cases of unexplained stillbirth, neonatal demise or early infant death. A definitive diagnosis of NH can only be confirmed by the demonstration of severe liver disease along with iron accumulation in extra-hepatic tissues, observed usually by a biopsy of the oral mucosal salivary glands or alternatively by magnetic resonance imaging (Lopriore et al 2013 & Feldman et al 2013).
- The prognosis of NH is poor with approximately 10% survival in those without liver transplantation (Whitington et al 2008). Liver transplantation can be curative, but transplantation is difficult in neonates affected by NH as they are often premature, of low birth weight and can have multiorgan failure. The overall survival in those receiving a liver transplant is approximately 35% (Feldman et al 2013).
- Nearly all cases of NH (over 95%) are now known to be caused by gestational allo-immune liver disease (GALD), not as previously thought by an inherited disturbance of the regulation of iron homeostatsis, and hence NH is often referred to as GALD-NH or allo-immune NH (Lopriore et al 2013).
- GALD is caused by the production of maternal IgG antibodies directed against foetal hepatocyte antigens which cross the placenta and bind to foetal hepatocyte antigens causing hepatocyte injury and death (Whitington et al 2018).
- Once a woman has had a pregnancy affected by NH, the probability that the next pregnancy will be affected by NH is high and is reported to be between 67% and 92% (Whitington et al 2018).
- Allo-immune NH is a rare disorder, yet it is the most common cause of acute liver failure in neonates (Feldman et al 2013).
- The incidence of NH is unknown but is thought to be at least 15 cases per million live births in the United States (Whitington et al 2018). It could be considerably higher as NH is often undiagnosed with not all foetal losses resulting in a post-mortem examination and not all affected offspring presenting with liver failure (Feldman et al 2013).

Standard treatment and pathway of care

- Maternal IVIg is used for the prevention of allo-immune NH in pregnant women with a history of a previous foetus or neonate affected by allo-immune NH in the UK (Whitington et al 2018).
- Treatment for neonates affected with allo-immune NH has evolved since the discovery that it is caused by GALD. Previously a mixture of antioxidants and an iron chelator was used based on the hypothesis that liver injury was secondary to oxidative injury caused by iron overload. Now a combination of double-volume exchange transfusion to remove existing reactive antibody followed immediately by administration of high-dose IVIg is used to block antibody induced complement activation (Feldman et al 2013).

The intervention (and licensed indication)

- Immunoglobulin is a blood product of concentrated antibodies recovered from pooled

human plasma.

- IVIg is currently used for the prevention of allo-immune NH in pregnant women with a history of a previous foetus or neonate affected by allo-immune NH and in the treatment of a neonate affected by NH in the UK (NHS England unpublished communication & Feldman et al 2013).
- A treatment schedule used in the UK for the prevention of allo-immune GALD is to start IVIg at 14 weeks, then fortnightly at 16 and 18 weeks, and then weekly from 18 weeks gestation, until one week prior to delivery at approximately 37 weeks gestation (NHS England unpublished communication).

Rationale for use

- Preventative IVIg treatment is thought to change the natural course of allo-immune NH by reducing the maternal immune response to foetal antigens, flooding the placental IgG transport mechanism with non-reactive antibodies, and/or by non-specific antibody binding that limits the binding of reactive allo-antibodies to target antigens (Tanaka et al 2011).
- The transport of IgG antibodies from the maternal serum to foetus begins from 13 weeks of pregnancy and therefore it is currently thought better to start treatment from 14 weeks. (Tanaka et al 2011).
- The purpose of this review is to assess the evidence for the administration of maternal IVIg, commencing at 14 weeks gestation, in the prevention of allo-immune NH.

2 Summary of results

- 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 ratio[1] 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

[1] OR = number of affected living offspring/number of unaffected living offspring in treated pregnancies divided by the same in untreated pregnancies

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 ratio[2] 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

[2] OR = number of foetal losses/number of no foetal losses in treated pregnancies divided by the same in untreated pregnancies

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.

3 Methodology

- The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Commissioning Products' (2016).
- A description of the relevant Population, Intervention, Comparison and Outcomes (PICO) to be included in this review was prepared by NHS England's Policy Working Group for the topic (see section 9 for PICO).
- The PICO was used to search for relevant publications in EMBASE, MEDLINE and Cochrane (see section 10 for search strategy).
- The search dates for publications were between the 1st of January 2008 and the 31st of January 2019.
- The titles and abstracts of the results from the literature searches were assessed using the criteria from the PICO. Full text versions of papers which appeared potentially useful were obtained and reviewed to determine whether they were appropriate for inclusion. Papers which matched the PICO were selected for inclusion in this review.
- Studies where the majority of women did not start IVIg treatment at 14 weeks were excluded in line with the PICO.
- Evidence from all papers included was extracted and recorded in evidence summary tables, critically appraised and their quality assessed using National Service Framework for Long term Conditions (NSF-LTC) evidence assessment framework (see section 7 below).
- The body of evidence for individual outcomes identified in the papers was graded and

recorded in grade of evidence tables (see section 8 below).

4 Results

This evidence review identified one prospective case series (Whitington et al 2018) of 151 women with a history of affected offspring with allo-immune NH treated with IVIg with initiation either at 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. Full details of the study design and results are summarised in the evidence table in section 7.

Two other small case series were found of eight patients each, but these were excluded as the majority of included women started IVIg treatment at 17 or 18 weeks gestation rather than the 14 week initiation stated in the PICO (Baruteau et al 2014 & Okada et al 2018).

All results below are based on the one included case series (Whitington et al 2018).

1. For the prevention of allo-immune neonatal and foetal haemochromatosis in pregnant mothers with a history of a previous foetus or neonate affected by allo-immune neonatal haemochromatosis (confirmed by a previous adverse pregnancy outcome and clear post-mortem evidence of foetal haemochromatosis or women who have had offspring with neonatal liver failure confirmed to be allo-immune neonatal haemochromatosis) at risk of recurrence:

a) What is the clinical effectiveness of maternal intravenous immunoglobulin (IVIg) starting from 14 weeks compared to no treatment?

Affected living offspring

Whitington et al (2018) found that for women who had IVIg treatment initiated at 14 weeks gestation (n=81), 5 out of 108 (5%) treated pregnancies resulted in an affected living offspring (defined as live-born infants with clinically important liver disease). All five of the affected living offspring had liver failure, two of whom died (one newborn from intracranial complications of liver failure and one at 3 months from respiratory syncytial virus infection) and three survived (one with medical therapy including exchange transfusion and IVIg, one with IVIg and supportive care, and one with liver transplant after no response to medical treatment). 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.

Foetal loss

Whitington et al (2018) found that for women who had IVIg treatment initiated at 14 weeks gestation (n=81), 1 out of 108 (1%) treated pregnancies resulted in foetal loss (defined as spontaneous abortion after initiation of IVIg therapy). This was a spontaneous abortion at 15 weeks. For the untreated previous pregnancies in this group (number not reported) 44 resulted in foetal loss (% not reported).

b) What is the safety for both the mother and the foetus of maternal intravenous immunoglobulin (IVIg) starting from 14 weeks compared to no treatment?

For all 151 women included in the case series (14 & 18 week IVIg initiation), Whitington et al (2018) found that 20 (13%) women experienced minor adverse events occurring during or immediately following the infusion which were headache (n=13), tiredness/malaise (n=4), nausea/vomiting (n=2), hives/itching (n=2) and flu-like syndrome (n=1). Results were not given by treatment initiation week so it is not clear how many of these adverse events are for the 14 week IVIg initiation. One woman (1%) developed a major adverse event (aseptic meningitis) (IVIg initiated at 18 weeks gestation). The infusions were terminated and the pregnancy had a good outcome.

c) What is the cost effectiveness of maternal intravenous immunoglobulin (IVIg) starting from 14 weeks compared to no treatment?

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.

d) From the evidence selected, does the clinical, safety or cost effectiveness of maternal intravenous immunoglobulin (IVIg) vary according to the IVIg treatment schedule used (in terms of eg differences in initiation and/or frequency of administration)?

Whitington et al (2018) treated women with two different treatment schedules depending on when they were recruited into the study. Women recruited after mid-2008 (57%) (108 pregnancies in 81 women) were given IVIg at a dose of 1g/kg body weight with one dose at 14, 16 & 18 weeks, then weekly until one week prior to the end of pregnancy. Women recruited before mid-2008 (43%) (80 pregnancies in 70 women) were given IVIg at a dose of 1g/kg body weight weekly from 18 weeks for 20 doses or until end of pregnancy.

Affected living offspring

No difference was found in the rate of affected living offspring between women who had IVIg treatment initiated at 14 weeks and at 18 weeks gestation ($p>0.05$).

For women who had a 14 week initiation of IVIg, 5 out of 108 (5%) treated pregnancies resulted in an affected living offspring. All five of the affected living offspring had liver failure, two of whom died. A total of 102 out of 108 (94%) treated pregnancies resulted in an unaffected living offspring (confidence intervals were not reported).

For 18 week IVIg initiation, 4 out of 80 (5%) treated pregnancies resulted in an affected living offspring. Three of the affected living offspring had liver failure, one of whom died (awaiting liver transplant) and two survived (both with medical therapy). 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).

No comparative results were given for previous untreated pregnancies by IVIg initiation week.

Foetal loss

No difference was found in the rate of foetal loss between women who had IVIg initiated at 14 weeks and at 18 weeks gestation ($p>0.05$).

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. 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 (but note that foetal losses before 18 weeks are not included in this group). For the untreated previous pregnancies in this group (number not reported), 44 resulted in foetal loss (% not reported).

Adverse events

Whitington et al (2018) did not provide evidence of a difference in the safety profile of IVIg initiated at 14 weeks vs. 18 weeks gestation. 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. Whitington et al (2018) did not report minor adverse events separately for each treatment regimen.

Cost-effectiveness

No studies were identified that assessed the relative cost-effectiveness of different schedules of maternal IVIg for pregnant women with a history of allo-immune NH.

5 Discussion

The evidence surrounding the clinical effectiveness of maternal IVIg for NH is limited. No randomised controlled trials were found. This is unsurprising, given the rarity of the disease and the ethical implications of denying women a treatment with an apparently dramatic effect. Only one large case series was found that included pregnant women with a history of affected offspring with allo-immune NH (Whitington et al 2018). This prospective study included 151 pregnant women treated from 1997 to 2015 in 19 centres worldwide. IVIg treatment was either initiated at 14 weeks gestation (57%) (108 pregnancies in 81 women recruited post mid-2008) or at 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).

The case series found that the proportion of affected living offspring and foetal loss was lower in the treated pregnancies at 5% and 1%, respectively, compared to the previous untreated pregnancies in the same women at 45% and 25%. No difference was found between the 14 and 18 week initiation regimens (5% risk of affected living offspring and 1% risk of foetal loss for both regimens). 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.

Whilst the study is generally of good quality with a large representative sample, there are issues with the design of the study that affect the comparisons made with untreated previous pregnancies, and the comparisons between 14 and 18 week IVIg initiation.

The first relates to the choice of control group, which consisted of all previous pregnancies in the treated women and therefore inclusion is defined by the outcome of interest (affected living offspring or foetal loss due to NH). In order to be included in the case series, women had to have had at least one affected living offspring or foetal loss due to NH, therefore comparing their subsequent treated pregnancies with previous pregnancies produces a bias in favour of treatment (for example, even if the risk of recurrence in a subsequent pregnancy were zero, such an analysis would infer a protective effect of IVIg). Conversely, it is also inappropriate to include pregnancies *before* a case of NH in the control group, as there is no reason to expect that these would have a similar risk of NH to pregnancies after a case of NH. A more appropriate design would compare outcomes in the treatment group to the risk of recurrence after a case of NH in an untreated group of women, possibly historical controls before IVIg was a treatment option. However, it is generally accepted that the risk of recurrence after the first case of NH is very high,

and is reported to be in the range of 67% to 92% (Whitington et al 2018), (although we have not reviewed the evidence relating to this). For example, in an earlier paper of this case series 19 out of 21 (90%) untreated pregnancies after a case of NH were affected (Whitington et al 2008). This is far higher than the recurrence rate seen in the treated group in Whitington et al (2018) and therefore, despite these quality issues, the study does suggest a substantial protective effect of maternal IVIg treatment in this group.

A further issue relates to the use of different gestational periods in which foetal losses were included between the groups, 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. Of 88 foetal losses in the untreated group, 33 occurred before 18 weeks and 22 at unknown gestational age. This produces a bias in favour of treatment, as it includes foetal losses in the control group that could not have been included in the treatment group. This also creates a problem in comparing 14 and 18 week initiation of IVIg on foetal loss in the 14-18 week time period, as we do not know about all women who might have received IVIg starting at 18 weeks but did not do so because of foetal loss in the four weeks beforehand. In fact, in their discussion the authors mention two women known to have had foetal loss just before 18 week IVIg was scheduled to start (not included in analyses), but state that there could also have been others. Outcomes from 18 weeks onwards should still be comparable between the two treatment groups, and in this period, foetal loss was observed in 0/108 (0%) and 1/80 (1%) of pregnancies with 14 and 18 week IVIg initiation, respectively. However the reason for starting IVIg earlier at 14 weeks is to prevent foetal losses in the 14-18 week period and this study is not able to assess differences during this time period.

Despite these issues, the reductions observed in foetal loss and affected living offspring are so large, and the rate is so much lower than previously reported rates of recurrence in women with a previous pregnancy affected by allo-immune NH (although we did not review the evidence for these reported rates), that it implies a strong treatment effect. However uncertainty remains of the true size of the treatment effect and if any difference exists between 14 and 18 week IVIg initiation.

No evidence was found assessing the cost-effectiveness of maternal IVIg for pregnant women with a history of allo-immune NH.

6 Conclusion

The evidence regarding the clinical effectiveness of maternal IVIg commencing at 14 weeks gestation for pregnant women with a previous pregnancy affected by allo-immune NH is limited to one large international case series which suggests that IVIg starting at 14 weeks 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. In light of this, 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 included losses

at less than 18 weeks. However, despite these issues, the reduction in rate of NH observed in the treated pregnant women is so large, and the rate is so much lower than previously reported rates of recurrence in untreated pregnant women with a previous affected pregnancy affected by allo-immune NH, that it does imply that IVIg has a substantial protective effect. Note, however, that the evidence for the reported recurrence rates of NH in untreated women was not reviewed and is based only on rates found coincidentally in the course of carrying out this rapid evidence review, and hence may not be accurate.

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.

7 Evidence Summary Table

For abbreviations see list after each table

Use of maternal intravenous immunoglobulin Vs. none to prevent allo-immune neonatal haemochromatosis									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Whitington et al 2018	P1-Prospective case series with historical self-controls (all untreated previous pregnancies in the same women) International multicentre study of 19 countries including the UK (8% of patients) Recruitment 1997 to 2015	n=188 treated pregnancies in 151 women Women with a history of affected offspring with neonatal haemochromatosis (NH) due to gestational allo-immune liver disease (GALD) confirmed either clinically by severe liver disease with demonstration of siderosis of extrahepatic tissues or by postmortem examination Baseline characteristi	Intravenous immunoglobulin (IVIg) 1g/kg body weight with 1 dose either at: 14, 16 & 18 weeks, then weekly until 1 week prior to the end of pregnancy for 108 pregnancies in 81 women after mid-2008 (57%) or weekly from 18 weeks for 20 doses or until end of pregnancy for 80 pregnancies in 70 women before mid-2008 (43%) Historical self-controls: n=364 (previous untreated	Primary Clinical effectiveness	Affected living offspring (live born infants with clinically important liver disease defined as having an international normalised ratio of greater than 2) (proportion of pregnancies)	F/up period not reported All women (n=151): Treated pregnancies 9/188 (5%) affected, 177/188 (94%) unaffected. Untreated pregnancies 157/350 (45%) affected, 105/350 (30%) unaffected. No CIs reported Treated vs. untreated OR[3] = 0.034 (95% CI 0.017 to 0.069, p<0.0001) Women with IVIg initiated at 14 weeks (n=81): Treated pregnancies 5/108 (5%) affected, 102/108 (94%) unaffected. No comparisons made with previous untreated pregnancies in this group No CIs reported Outcome of affected living offspring 5 (100%) had liver failure, 2 of whom died (one newborn from intracranial complications of liver failure and one at 3 months from respiratory syncytial virus infection) and 3 survived (one with medical therapy including exchange transfusion and IVIg, one with IVIg and	7	Direct	This international case series is generally of good quality and is less likely to be subjected to selection bias inherent in case series due to its large sample size and prospective design. The main issue with the study is the use of all previous untreated pregnancies of the women included in the series as historical controls. It is inappropriate to use a control group in which the inclusion is defined by the outcome of interest (affected living offspring or foetal loss due to NH) as this will bias the results in favour of the treated group. It is also inappropriate to include pregnancies *before* a case of NH in the control group, as there is no reason to expect that these would have a similar risk of NH to pregnancies after a case of NH. A more appropriate design would be to compare results of the treatment group to the risk of recurrence after the index case in an untreated group of unrelated historical cases before IVIg was a treatment option. The risk of recurrence after the first case is reported in the literature to be in the range of 67% to 92% (Whitington et al 2018). Another issue with the study is that it includes foetal losses of less than 18 weeks in the untreated group, but in the treatment group losses were restricted to after initiation of treatment (14 or 18 weeks). Of the 88 foetal losses in the untreated group, 33 occurred at a gestational age of <18 weeks and 22 at unrecorded gestation. This biases the results in favour of the treated group. This also presents a problem for comparing 14 to 18 week initiation regimens as the 14 week group has a longer time

[3] OR = number of affected living offspring/number of unaffected living offspring in treated pregnancies divided by the same in untreated pregnancies

Use of maternal intravenous immunoglobulin Vs. none to prevent allo-immune neonatal haemochromatosis									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		cs not reported	pregnancies in the same 151 women included in case series)			supportive care, and one with liver transplant after no response to medical treatment). Women with 18 week initiation (n=70): Treated pregnancies 4/80 (5%) affected, 75/80 (94%) unaffected. No comparisons made with previous untreated pregnancies in this group No CIs reported Outcome of affected living offspring 3 (4%) had liver failure, 1 of whom died (awaiting liver transplant) and 2 survived (both with medical therapy). 14 weeks vs. 18 weeks: No difference in rate of affected living offspring (p>0.05)			period to accrue foetal losses, biasing the results in favour of the 18 week group. Furthermore, we do not know about all women who might have received IVIg starting at 18 weeks but did not do so because of foetal loss in the 4 weeks beforehand. Some women were recruited over 20 years ago, but this is unlikely to affect the applicability of results as preventative IVIg treatment, other than initiation week, was not reported to have changed significantly in this time. However, despite these issues, the reduction in NH observed in the treated women is so large and considerably lower than previously reported rates of recurrence in untreated women with a previous affected pregnancy (although we did not review the evidence for those reported rates), that it does imply that IVIg has a substantial protective effect.
				Primary Clinical effectiveness	Foetal loss (Spontaneous abortion after initiation of therapy in treated pregnancies. Definition is unclear for untreated pregnancies)	All women (n=151): Treated pregnancies 2/188 (1%), Untreated pregnancies 88/350 (25%) No CIs reported Treated vs. untreated OR[4] = 0.032 (95% CI 0.008 to 0.132, p<0.0001) Women with 14 week initiation (n=81) Treated pregnancies 1/108 (1%) which was a spontaneous			

[4] OR = number of foetal losses/number of no foetal losses in treated pregnancies divided by the same in untreated pregnancies

Use of maternal intravenous immunoglobulin Vs. none to prevent allo-immune neonatal haemochromatosis									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						abortion at 15 weeks (foetal losses before 14 weeks not included in this group) Untreated pregnancies 44 (includes foetal losses at <14 weeks; % or number of previous pregnancies in this group not reported) No CIs reported Women with 18 week initiation (n=70): Treated pregnancies 1/80 (1%) which was a spontaneous abortion at 21 weeks (foetal losses before 18 weeks not included in this group), Untreated pregnancies 44 (includes foetal losses at <18 weeks; % or number of previous pregnancies in this group not reported) No CIs reported 14 weeks vs. 18 weeks: No difference in rate of foetal loss (p-value not reported)			
				Secondary Safety	Adverse events (AEs)	F/up period not reported Major AEs: 1 woman (1%) developed aseptic meningitis after 3 infusions starting at 18 weeks. The infusions were terminated and the pregnancy had a good outcome. Minor AEs: 20 women (13%) experienced minor adverse events occurring during or immediately following the infusion which			

Use of maternal intravenous immunoglobulin Vs. none to prevent allo-immune neonatal haemochromatosis									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						were: Headache (n=13) Tiredness/malaise (n=4) Nausea/vomiting (n=2) Hives/itching (n=2) Flu-like syndrome (n=1) Results not given by treatment initiation week.			

AE = Adverse event; GALD = gestational allo-immune liver disease; NH = neonatal haemochromatosis; IVIg = intravenous immunoglobulin; OR = odds ratio; CI = confidence interval

8 Grade of Evidence Table

For abbreviations see list after each table

a) **Use of maternal intravenous immunoglobulin initiated at 14 weeks Vs. none to prevent allo-immune neonatal haemochromatosis**					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Affected living offspring	Whitington et al 2018	7	Direct	B	Affected living offspring is defined by Whitington et al (2018) as live-born infants with clinically important liver disease defined as having an international normalised ratio (laboratory measure of how long it takes blood to form a clot) of greater than 2. Whitington et al (2018) found that for all 151 women included in the case series, 9 out of 188 (5%) treated pregnancies (including where IVIg treatment was initiated at 14 weeks (57% of pregnancies) and at 18 weeks gestation (43% of pregnancies)) resulted in an affected living offspring and 177 (94%) resulted in an unaffected living offspring. This compared with 157 out of 350 (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 ratio (number of affected living offspring/number of unaffected living offspring in treated pregnancies divided by the same in untreated pregnancies) of 0.034 (95% CI 0.017 to 0.069, p<0.0001) in favour of treatment. For only those women who had a 14 week initiation of IVIg, 5 out of 108 treated pregnancies (5%) resulted in an affected living offspring. All five of the affected living offspring had liver failure, two of whom died (one newborn from intracranial complications of liver failure and one at three months from respiratory syncytial virus infection) and three survived (one with medical therapy including exchange transfusion and IVIg, one with IVIg and supportive care, and one with liver transplant after no response to medical treatment). A total of 102 out of 108 (94%) treated pregnancies resulted in an unaffected living offspring (confidence intervals were not reported). No results were given for previous untreated pregnancies in this group (14 week IVIg initiation) alone. The results suggest that the proportion of affected living offspring is considerably lower in the treated pregnancies (initiated at 14 & 18 weeks) compared to the previous untreated pregnancies in the same women. This treatment effect was also observed for the 14 week initiation group, but no comparison was made with untreated pregnancies in this group. This is clearly a clinically important result as liver disease due to NH has a poor prognosis with liver failure requiring transplant and high neonatal death rates. This international case series is generally of good quality and is less likely to be subjected to selection bias inherent in case series due to its large sample size and prospective design. However there is an issue with use of all previous untreated pregnancies of the women included in the series as historical controls. It is inappropriate to use a control group in which the inclusion is defined by the outcome of interest (affected living offspring or foetal loss due to NH) as this will bias the results in favour of the treated group. It is also inappropriate to include pregnancies *before* a case of NH in the control group, as there is no reason to expect that these would have a similar risk of NH to pregnancies after a case of NH. Despite these issues, the reduction in the rate of affected living offspring observed in the treated women is so much lower than previously reported rates of NH recurrence in untreated women with a previous affected pregnancy (67% to 92%, Whitington et al 2018), that it does imply that

a) Use of maternal intravenous immunoglobulin initiated at 14 weeks Vs. none to prevent allo-immune neonatal haemochromatosis					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					IVIg has a substantial protective effect. Note, however, that the evidence for the reported rates of recurrence of NH in untreated women was not reviewed and is based only on rates found coincidentally in the course of carrying out this rapid evidence review.
Foetal loss	Whitington et al 2018	7	Direct	B	Foetal loss is defined by Whitington et al (2018) as a spontaneous abortion after initiation of IVIg therapy. Whitington et al (2018) found that for all 151 women included in the case series, 2 out of 188 (1%) treated pregnancies (including where IVIg treatment was initiated at 14 weeks (57% of pregnancies) and at 18 weeks gestation (43% of pregnancies)) resulted in foetal loss. This compared with 88 out of 350 (25%) previous untreated pregnancies in the same women (confidence intervals were not reported). This resulted in an odds ratio (number of foetal losses/number of no foetal losses in treated pregnancies divided by the same in untreated pregnancies) of 0.032 (95% CI 0.008 to 0.132, p<0.0001) in favour of treatment. For only those women who had a 14 week initiation of IVIg, 1 out of 108 treated pregnancies (1%) resulted in foetal loss which was a spontaneous abortion at 15 weeks. For the untreated previous pregnancies in this group (number not reported) 44 resulted in foetal loss (% not reported). Odds ratio was not reported. The results suggest that the proportion of foetal loss is considerably lower in the treated pregnancies (initiated at 14 & 18 weeks) compared to the previous untreated pregnancies in the same women. This treatment effect was also observed for the 14 week initiation group, but no comparison was made with untreated pregnancies in this group. This size of result is clearly clinically important. This international case series is generally of good quality and is less likely to be subjected to selection bias inherent in case series due to its large sample size and prospective design. However there is an issue with use of all previous untreated pregnancies of the women included in the series as historical controls. It is inappropriate to use a control group in which the inclusion is defined by the outcome of interest (affected living offspring or foetal loss due to NH) as this will bias the results in favour of the treated group. It is also inappropriate to include pregnancies *before* a case of NH in the control group, as there is no reason to expect that these would have a similar risk of NH to pregnancies after a case of NH. Another issue with the study is that it includes foetal losses of less than 18 weeks in the untreated group, but in the treatment group losses were restricted to after initiation of treatment (14 or 18 weeks). Of the 88 foetal losses in the untreated group, 33 occurred at a gestational age of <18 weeks and 22 at unrecorded gestation ages. This biases the results in favour of the treated group. Despite these issues, the reduction in the rate of foetal loss observed in the treated women is so large, and taken with the reduction in affected living offspring also observed, is so much lower than previously reported rates of recurrence in untreated women with a previous affected pregnancy, that it does imply that IVIg has a substantial protective effect. Note, however, that the evidence for the reported rates of recurrence of NH in untreated women was not reviewed and is based only on rates found coincidentally in the course of carrying out this rapid evidence review.
Adverse events	Whitington et al 2018	7	Direct	B	Adverse events are important because if serious and/or common they may outweigh the benefits associated with maternal IVIg. Adverse events were recorded in the study if a

a) **Use of maternal intravenous immunoglobulin initiated at 14 weeks Vs. none to prevent allo-immune neonatal haemochromatosis**					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					physician or woman (or her family) requested advice as to how to manage a complaint or symptom thought to be related to the treatment. For all 151 women included in the case series reported by Whitington et al (2018) (including where IVIg treatment was initiated at 14 weeks (57% of pregnancies) and at 18 weeks gestation (43% of pregnancies)), 20 women (13%) experienced minor adverse events occurring during or immediately following the infusion which were headache (n=13), tiredness/malaise (n=4), nausea/vomiting (n=2), hives/itching (n=2) and flu-like syndrome (n=1). One woman (1%) developed a major adverse event which was aseptic meningitis after 3 infusions starting at 18 weeks. The infusions were terminated and the pregnancy had a good outcome. Results for minor adverse events were not provided by treatment initiation week. The safety profile of maternal IVIg (initiated at 14 & 18 weeks) appears to be good with relatively few minor adverse events and one major event reported in 151 women. This international case series is generally of good quality and is less likely to be subjected to selection bias inherent in case series due to its large sample size and prospective design. Adverse events were not reported for the historical controls so it is not known if the adverse advents observed in the treatment group are related to IVIg. The follow-up period for adverse events is not reported, and these data may not include any long-term safety effects of IVIg.

NH = neonatal haemochromatosis; IVIg = intravenous immunoglobulin; CI = confidence interval

b) **Use of maternal intravenous immunoglobulin initiated at 14 weeks Vs. intravenous immunoglobulin initiated at 18 weeks to prevent allo-immune neonatal haemochromatosis**					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Affected living offspring	Whitington et al 2018	7	Direct	B	Affected living offspring is defined by Whitington et al (2018) as live-born infants with clinically important liver disease defined as having an international normalised ratio (laboratory measure of how long it takes blood to form a clot) of greater than 2. For women who had a 14 week initiation of IVIg, 5 out of 108 treated pregnancies (5%) resulted in an affected living offspring. All five of the affected living offspring had liver failure, two of whom died (one newborn from intracranial complications of liver failure and one at three months from respiratory syncytial virus infection) and three survived (one with medical therapy including exchange transfusion and IVIg, one with IVIg and supportive care, and one with liver transplant after no response to medical treatment). A total of 102 out of 108 (94%) treated pregnancies resulted in an unaffected living offspring (confidence intervals were not reported). No results were given for previous untreated pregnancies in this group alone. For 18 week IVIg initiation, 4 out of 80 treated pregnancies (5%) resulted in an affected living offspring. Three of the affected living offspring had liver failure, one of whom died (awaiting liver transplant) and two survived (both with medical therapy). One

b) **Use of maternal intravenous immunoglobulin initiated at 14 weeks Vs. intravenous immunoglobulin initiated at 18 weeks to prevent allo-immune neonatal haemochromatosis**					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					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 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). The results suggest that there is no difference in the rate of living offspring affected with NH in pregnant women starting IVIg at 14 weeks gestation compared to 18 weeks gestation. This international case series is generally of good quality and is less likely to be subjected to selection bias inherent in case series due to its large sample size and prospective design. However, the effect on the rate of living offspring with NH should be interpreted in conjunction with the effect that 14 week versus 18 week initiation of IVIg might have on the rate of foetal loss.
Foetal loss	Whitington et al 2018	7	Direct	B	Foetal loss is defined by Whitington et al (2018) as a spontaneous abortion after initiation of IVIg therapy. For women who had a 14 week initiation of IVIg, 1 out of 108 treated pregnancies (1%) resulted in foetal loss which was a spontaneous abortion at 15 weeks. 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 treated pregnancies (1%) resulted in foetal loss which was a spontaneous abortion at 21 weeks. 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). The results suggest that there is no difference in the rate of foetal loss due to NH in pregnant women starting IVIg at 14 weeks gestation compared to 18 weeks gestation. This international case series is generally of good quality and is less likely to be subjected to selection bias inherent in case series due to its large sample size and prospective design. However a major problem with the study is that it only recorded foetal losses from the initiation of treatment (from 14 or 18 weeks). This means it is unable to assess differences in foetal loss in the 14 to 18 week period, as these data were not available for women starting treatment at 18 weeks. This also results in the 14 week initiation group having more time to accrue foetal losses than the 18 week group, biasing the results in favour of the 18 week group. For these reasons it is not possible to determine whether there is a difference in the rate of foetal loss due to NH between starting IVIg at 14 weeks or 18 weeks.
Adverse events	Whitington et al 2018	7	Direct	B	Adverse events are important because if serious and/or common they may outweigh the benefits associated with maternal IVIg. Adverse events were recorded in the study if a physician or woman (or her family) requested advice as to how to manage a complaint or symptom thought to be related to the treatment. For all 151 women included in the case series reported by Whitington et al (2018) (including where IVIg treatment was initiated at 14 weeks (57% of pregnancies) and at 18

b) **Use of maternal intravenous immunoglobulin initiated at 14 weeks Vs. intravenous immunoglobulin initiated at 18 weeks to prevent allo-immune neonatal haemochromatosis**					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					weeks gestation 43%)), 20 women (13%) experienced minor adverse events occurring during or immediately following the infusion which were headache (n=13), tiredness/malaise (n=4), nausea/vomiting (n=2), hives/itching (n=2) and flu-like syndrome (n=1). One woman (1%) developed a major adverse event which was aseptic meningitis after 3 infusions starting at 18 weeks. The infusions were terminated and the pregnancy had a good outcome. Results for minor adverse events were not provided by treatment initiation week. It is not possible, from the results of this study, to determine whether there is a difference in the safety profile of IVIg starting at 14 weeks gestation compared to 18 weeks gestation. This international case series is generally of good quality and is less likely to be subjected to selection bias inherent in case series due to its large sample size and prospective design. Adverse events were not reported for the historical controls so it is not known if the adverse advents observed in the treatment group are related to IVIg. The follow-up period for adverse events is not reported, and these data may not include any long-term safety effects of IVIg.

NH = neonatal haemochromatosis; IVIg = intravenous immunoglobulin; CI = confidence interval

9 Literature Search Terms

PICO Table *Indicate all terms used in the search*	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	Pregnant mothers with a history of a previous foetus or neonate affected by allo- immune neonatal haemochromatosis, in who there is a clear risk of recurrence (Confirmed by a previous adverse pregnancy outcome and clear post-mortem evidence of foetal haemochromatosis or women who have had offspring with neonatal liver failure confirmed to be allo-immune neonatal haemochromatosis).
I – Intervention Which intervention, treatment or approach should be used?	Maternal intravenous immunoglobulin (IVIg) (1g/kg up to 60g) starting from 14 weeks [then at 16 weeks, and then weekly from 18 weeks until delivery at approx. 37 weeks gestation]
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	• No treatment • Maternal intravenous immunoglobulin (IVIg) (alternative treatment schedule including initiation and/or frequency of administration)
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.	*Critical to decision-making:* Live births Intra-uterine death Still birth Neonatal death/ Infant death Number of survivors developing liver failure Number of survivors requiring liver transplant Number of survivors requiring tertiary supportive treatment Toxicity/ adverse events *Important to decision-making:* Cost effectiveness Quality of life for mother and child Time to discharge from hospital

Assumptions / limits applied to search

Inclusion
Study Design: Systematic Review, Meta-analysis, randomised controlled trials, cohort studies, case series (if no better data is available)
Search limits: 2008- to search date
Language limits: Studies published in English

Exclusion
Study Design: Case reports
Publication type: conference abstracts, narrative reviews, commentaries, letters and editorials

10 Search Strategy

We searched Medline, Embase and Cochrane Library limiting the search to papers published in England from the 1st of January 2008 to the 31st of January 2019. We excluded conference abstracts, commentaries, letters, editorials and case reports.

Search date: 31 January 2019
Medline search:

# ▲	Searches
1	Hemochromatosis/
2	h?emochromatosis.ti,ab.
3	Liver Diseases/
4	1 or 2 or 3
5	Prenatal Care/
6	Pregnancy/
7	Fetus/
8	Infant, Newborn/
9	Maternal Health/ or Maternal Health Services/ or MOTHERS/
10	(gestational or maternal or prenatal or pre-natal or antenatal or ante-natal or fetal or foetal or fetus or foetus or neonat* or newborn*).ti.
11	5 or 6 or 7 or 8 or 9 or 10
12	4 and 11
13	((gestational or maternal or mother? or pregnan* or prenatal or pre-natal or antenatal or ante-natal or fetal or foetal or fetus or foetus or neonat* or newborn*) adj5 (h?emochromatosis or liver disease)).ti,ab.
14	gald.ti,ab.
15	12 or 13 or 14
16	exp Immunoglobulins/
17	exp Administration, Intravenous/
18	16 and 17
19	(((intravenous or inject* or infus*) adj5 (immunoglobulin* or immuno-globulin* or ig)) or ivig).ti,ab.
20	18 or 19
21	15 and 20
22	((gestational or maternal or prenatal or pre-natal or antenatal or ante-natal or fetal or foetal or fetus or foetus or neonat* or newborn*) adj5 (immunoglobulin* or immuno-globulin* or ig or ivig)).ti,ab.
23	4 and 22
24	21 or 23

11 Evidence Selection

- Total number of publications reviewed: 8
- Total number of publications considered potentially relevant: 6
- Total number of publications selected for inclusion in this briefing: 1

References from the PWG supplied in the PPP	Paper selection decision and rationale if excluded
1 Whitington, P., & Kelly, S. (2008). Outcome of Pregnancies at Risk for Neonatal Hemochromatosis Is Improved by Treatment With High-Dose Intravenous Immunoglobulin. PEDIATRICS, 121(6), pp. 1615-1621	Excluded: Patients in this paper are included in a more recent larger case series (Whitington et al 2018) which was included in this review.
2 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	Included
3 Tanaka, H., Haba, R., Itoh, S., Sakamoto, H., & Hata, T. (2011). Prenatal high-dose immunoglobulin treatment for neonatal hemochromatosis: A case report and review of the literature. Journal of Obstetrics and Gynaecology Research, 37 (12), pp.1891-1894	Excluded: This is a case report and general review of the literature (not a systematic review). The PICO states that case reports are excluded.

12 References

Baruteau J. Heissat S. Broue P. Collardeau-Frachon S. Bouvier R. Fabre M. Debiec H. Ronco P. Uzan M. Narcy P. Cordier M. Lachaux A. Lamireau T. Elleau C. Filet J.P. Mitanchez D. Dupuy M. Salaun J.F. Odent S. Davison J. Debray D. Guigonis V. 2014. Transient neonatal liver disease after maternal antenatal intravenous Ig infusions in gestational alloimmune liver disease associated with neonatal haemochromatosis. Journal of Pediatric *Gastroenterology & Nutrition*, 59(5): 629-35.

Feldman A.G. Whitington P.F. 2013. Neonatal Hemochromatosis. *Journal of Clinical and Experimental Hepatology*, 3: 313–320.

Lopriore E. Mearin M.L. Oepkes D. Devlieger R. Whitington P.F. 2013. Neonatal hemochromatosis: management, outcome, and prevention. *Prenatal Diagnosis*, 33: 1221–1225.

Okada N. Sasaki A. Saito J. Mitani Y. Yachie A. Takahashi H. Matsubar S. Tenkumo C. Tanaka H. Hata T. Motomura K. Nagasawa J. Wada Y. Sako M. Yamaguchi K. Matsumoto K. Nakamura H. Sago H. Mizuta K. 2018. The Japanese experience and pharmacokinetics of antenatal maternal high-dose immunoglobulin treatment as a prophylaxis for neonatal hemochromatosis in siblings. *Journal of Maternal-Fetal & Neonatal Medicine*, 1-7.

Tanaka H. Haba R. Itoh S. Sakamoto H. Hata T. 2011. Prenatal high-dose immunoglobulin treatment for neonatal hemochromatosis: A case report and review of the literature. *Journal of Obstetrics and Gynaecology Research*, 37(12): 1891-1894.

Whitington P. Kelly S. 2008. Outcome of Pregnancies at Risk for Neonatal Hemochromatosis Is Improved by Treatment With High-Dose Intravenous Immunoglobulin. *Pediatrics,* 121(6): 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): 218-225.