MANAGEMENT IN CONFIDENCE

CLINICAL PRIORITIES ADVISORY GROUP
02/10/19

Agenda Item No	
National Programme	Women & Children
Clinical Reference Group	Neonatal Critical Care
URN	1864

Title
Maternal intravenous immunoglobulin (IVIg) for the prevention of allo- immune fetal and neonatal haemochromatosis.

Actions Requested	1. Support the adoption of the policy proposition
	2. Recommend its approval as an IYSD

Proposition
For routine commissioning. 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. There is no standard treatment at present other than the Urgent Policy Statement (NHS England 170124/P Maternal intravenous immunoglobulin administration for prevention of alloimmune fetal and neonatal haemochromatosis) published in July 2019. 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. The policy will supersede the existing published urgent policy statement. The policy does not propose any change from the published commissioning position.

Clinical Panel recommendation
The Clinical Panel recommended that the policy progress as a routine commissioning policy.

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposal has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.
2.	The Head of Acute Programmes Programme confirms the proposal is supported by an: Impact Assessment; Stakeholder Engagement Report; Consultation Report; Equality Impact and Assessment Report; Clinical Policy Proposition. The relevant National Programme of Care Board has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Clinical Programmes Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Consultation Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality Impact and Assessment Report

a) Maternal intravenous immunoglobulin vs. none to prevent allo-immune neonatal haemochromatosis

No	*Outcome measures*	*Summary from evidence review*
1.	Survival	Not measured
2.	Progression free survival	Not measured
3.	Mobility	Not measured
4.	Self-care	Not measured
5.	Usual activities	Not measured
6.	Pain	Not measured
7.	Anxiety / Depression	Not measured
8.	Replacement of more toxic	Not measured

	treatment	
9.	Dependency on care giver / supporting independence	Not measured
10.	Safety	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 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.
11.	Delivery of intervention	Not measured

IVIg = intravenous immunoglobulin

No	Outcome measure	Summary from evidence review
1.	Affected living offspring	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 fetal 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 large and taken with the reduction in fetal loss also observed, 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 IVIg has a substantial protective effect. Note, however, that the evidence for the reported rates of recurrence of NH in untreated women was not within the scope of this rapid evidence review.
2.	Fetal loss	Fetal 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 fetal 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 fetal losses/number of no fetal 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 fetal loss which was a spontaneous abortion at 15 weeks. For the untreated previous pregnancies in this group (number not reported) 44 resulted in fetal loss (% not reported). Odds ratio was not reported. The results suggest that the proportion of fetal 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 fetal 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 fetal 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 fetal 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 fetal 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 within the scope of this rapid evidence review.

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

b) Maternal intravenous immunoglobulin initiated at 14 weeks Vs. intravenous immunoglobulin initiated at 18 weeks to prevent allo-immune neonatal haemochromatosis

No	*Outcome measures*	*Summary from evidence review*
1.	Survival	Not measured
2.	Progression free survival	Not measured

3.	Mobility	Not measured
4.	Self-care	Not measured
5.	Usual activities	Not measured
6.	Pain	Not measured
7.	Anxiety / Depression	Not measured
8.	Replacement of more toxic treatment	Not measured
9.	Dependency on care giver / supporting independence	Not measured
10.	Safety	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 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.
11.	Delivery of intervention	Not measured

IVIg = intravenous immunoglobulin

No	Outcome measure	Summary from evidence review
1.	Affected living offspring	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 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 fetal loss.
2.	Fetal loss	Fetal 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 fetal loss which was a spontaneous abortion at 15 weeks. For the untreated previous pregnancies in this group (number not reported) 44 resulted in fetal loss (% not reported). For 18 week IVIg initiation, 1 out of 80 treated pregnancies (1%) resulted in fetal loss which was a spontaneous abortion at 21 weeks. For the untreated previous pregnancies in this group (number not reported), 44 resulted in fetal loss (% not reported). No difference was found in the rate of fetal loss between 14 and 18 week IVIg initiation ($p>0.05$).

		The results suggest that there is no difference in the rate of fetal 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 fetal losses from the initiation of treatment (from 14 or 18 weeks). This means it is unable to assess differences in fetal 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 fetal 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 fetal loss due to NH between starting IVIg at 14 weeks or 18 weeks.

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

Considerations from review by Rare Disease Advisory Group
Not applicable.

Pharmaceutical considerations
This policy proposition supports the routine commissioning of intravenous immunoglobulin (IVIg) for the prevention of allo-immune fetal and neonatal haemochromatosis. This is an off-label use of IVIg. IVIg is excluded form tariff.

Considerations from review by National Programme of Care
1) The proposal received the full support of the Women & Children's PoC Board on the 16th September 2019.