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Research Article

Application of the Doppler Ultrasound in Detecting Foetal Anaemia caused by Anti-Kell Maternal Alloimmunisation: Systematic Review and Meta-Analysis

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ABSTRACT

Background: Past studies have examined the Doppler ultrasounds ability to detect foetal anemia however few focus on Anti-Kell, rather centring on maternal alloimmunisation as a whole. Anti-Kell has proven to be clinically significant in Haemolytic Disease of the Foetus and Newborn (HDFN) due to the suppression of erythroid progenitor cells and the absence of typical signs of anemia. For these reasons, regular procedures to detect foetal anemia are unreliable with Anti-Kell. Therefore, a systematic review and meta-analysis was performed to investigate the reliability of the Doppler ultrasound in Kell-sensitised pregnancies.

Methods: PubMed, SCOPUS, Google Scholar and ProQuest were searched from January 2012 to August 2022 for eligible Doppler ultrasound studies with Anti-Kell specific data. A manual search was performed using relevant references.

Results: Five studies were included in the meta-analysis for two-arm proportion. The Doppler ultrasound correctly identified foetal anemia in 87.4% of Kell cases (Arcsine Risk Difference [ARD], 0.874; 95% Confidence Interval [CI], 0.667-1.080; I2=0%; p-value=<0.001). Four studies were included in the meta-analysis for sensitivity and specificity. The Doppler ultrasound detecting Kell-specific foetal anemia had a sensitivity of 83% (CI, 62.9%-93.4%; I2=0%; p-value=0.003) and a specificity of 82% (CI, 52.7%-94. 9%; I2=0%; p-value=0.035).

Conclusion: In regards to foetal anemia with Anti-Kell the Doppler ultrasound correctly detected 87.4% of cases with a sensitivity of 83% and specificity of 82%.

Keywords: Doppler ultrasound; Foetal anemia; Alloimmunisation; Blood group

INTRODUCTION

Maternal alloimmunisation and foetal anemia

There are a range of causes for foetal anemia such as inherited disorders, pathological conditions, and infections, however this systematic review focuses on maternal alloimmunisation; specifically Anti-Kell. Maternal alloimmunisation occurs when the mothers immune system is exposed to a foreign surface antigen expressed on Red Blood Cells (RBCs) stimulating the production of Immunoglobulin G (IgG) antibodies [1]. This exposure can occur *via* an incompatible blood transfusion, organ transplantation or Fetomaternal Haemorrhage (FMH) during a previous or current pregnancy [2,3]. The IgG antibodies produced, unlike other antibody classes, are capable of crossing the placenta and attaching to the foetuses RBCs if they express the specific red cell surface antigen. The foetus is capable of expressing the antigen the mother lacks if they inherit the allele from the father. This antibody attachment causes the foetuses RBCs to breakdown, a process known as haemolysis. This disease is known as Haemolytic Disease of the Foetus and Newborn (HDFN). While HDFN was most commonly associated with RhD alloimmunisation, this has been significantly reduced since the introduction of anti-D prophylaxis in 1968 administered to RhD-negative women when pregnant [3]. While RhD is still of concern, other blood group systems of significance include other Rh antigens (C, c, E, e), Kell, Duffy and Kidd [1].

HDFN can have many complications depending on the severity of the disease, hence the need for early detection and thorough monitoring. When haemolysis occurs within the foetus the body will attempt to compensate by increasing erythropoiesis (production of RBCs). This

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causes an increase in circulatory volume (hyperdynamic circulation) which can cause oedema in serous cavities and foetal skin known as hydrops fetalis; potentially leading to foetal death due to heart failure. Both anemia and hydrops can present with reduced foetal movement and may be detected by an increase in blood flow rate with a doppler ultrasound. This emphasises the importance of monitoring a foetus with reduced movement and having procedures capable of accurately detecting foetal anemia. Another concern with HDFN is hyperbilirubinaemia due to higher levels of bilirubin being released through haemolysis. While this is less of a concern for a foetus as the bilirubin is cleared *via* the mothers circulation, a newborns immature liver struggles to conjugate the bilirubin which can cause Kernicterus if left untreated; causing permanent damage to the central nervous system [3].

Clinical significance of anti-kell related foetal anemia

Kell antigens, unlike other blood group systems, are present on the surface of RBC precursors. Therefore, Kell-positive precursors are destroyed by Anti-Kell at foetal RBC production compared to destroying mature foetal RBCs, like most other blood group systems [4]. In the study conducted by Vaughan et al. it was proven that Anti-Kell antibodies suppress erythropoiesis in progenitor cells shown by the inhibition of growth of Kell-positive progenitor cells in the presence of human monoclonal Anti-Kell antibodies [5]. It is suggested that because progenitor cells do not contain haemoglobin, destruction at this level results in little bilirubin being released, explaining why jaundice is less common in Anti-Kell related foetal anemia [4]. This also makes amniotic fluid bilirubin concentration, detected using bilirubin Delta OD450, unreliable in predicting the severity of the anemia [6-8]. Intensifying the significance of Anti-Kell HDFN is maternal antibody titres not correlating with the severity of anemia therefore; a mild anemia can be seen with a high titre and severe anemia with a low titre [7]. Furthermore, foetuses tend to have a reticulocytosis and reduced erythropoietin level (hypo-regenerative anemia) increasing the severity [6].

Doppler ultrasound

The Doppler ultrasound is useful on the basis that during foetal anaemia the viscosity of blood decreases, therefore the velocity of blood increases due to an increase in cardiac output [1]. Thus, the use of Doppler ultrasonography detects an increase in the Peak Systolic Velocity (PSV) in the Middle Cerebral Artery (MCA). This is performed scanning an axial section of the brain at the MCA measuring the waveform peak.1 An MCA-PSV value of 1.29-1.5 Multiples Of The Median (MoM) is considered mildly anaemic and greater than 1.5 MoM is severely anaemic [1,7].

Current practices for Anti-Kell related pregnancies

Current practice when Anti-Kell is detected in a pregnant woman is to determine the foetuses Kell phenotype by determining the fathers phenotype, or if this is inconclusive, performing foetal KEL genotyping using cell free foetal DNA (Deoxyribonucleic Acid) isolated from the maternal plasma. Due to the risk of miscarriage involved with the invasiveness of amniocentesis or chorionic villus sampling this is less commonly performed to determine the foetuses KEL status and also risks increasing the antibody concentration when piercing the placenta Should the foetus be Kell-positive, regular monitoring must take place in attempt to prevent hydrops. While cordocentesis is the most accurate at detecting foetal haemoglobin, approximately 1% result in foetal loss and therefore is only performed if severe anaemia is highly predicted *via* screening such as the Doppler ultrasound (>1.5 MoM) and Intrauterine Transfusion (IUT) is expected [8]. To reduce the risk involved in birthing a severely anaemic foetus, early delivery may be scheduled and an exchange transfusion may be required to reduce haemolysis by replacing the newborns antigen-positive RBCs with antigen-negative donor cells [9].

LITERATURE REVIEW

Due to the pathophysiology of HDFN associated with Anti-Kell in comparison to other blood group systems, the need for an accurate non-invasive test to screen for foetal anaemia is important. As a result of these differences there are questions regarding the accuracy of the Doppler ultrasound specifically for Anti-Kell alloimmunisation, which this review aims to address. In addition, there are unknowns around the most accurate MCA-PSV value to determine severe anaemia or how accurate the reading is after the foetus has received an IUT [10]. Due to haemoglobin concentration increasing in gestational age, it is suggested the values should be modified based on gestational age. While some data suggests the Doppler ultrasound may not be accurate at detecting mild anaemia, it is suggested this isn't of clinical significance as mild anaemia does not require intervention like severe anaemia at risk of hydrops [11].

This study aims to evaluate whether the non-invasive prenatal Doppler ultrasound is a reliable predictor of foetal anaemia in Kell-immunised patients through a systematic review and meta-analysis using prospective and retrospective studies. The accuracy of the results is determined through cordocentesis if severely anaemic in utero or by measuring the foetuses haemoglobin after birth to determine if they are in fact anaemic and the severity. It is hypothesised that the use of the Doppler ultrasound to measure the systolic velocity in the MCA of foetuses at risk of anaemia in Kell-immunised pregnancies is a reliable predictor of foetal anemia.

MATERIALS AND METHODS

Study design

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was used to conduct this study [12]. The completeness of the included studies were assessed using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist [13].

Search strategy

The electronic databases PubMed, SCOPUS, Google Scholar and ProQuest were systematically searched from January 2012 to August 2022. The search terms used across all databases included "Anti-Kell" OR "Anti-K" and "Doppler ultrasound" OR "MCA-PSV." The search term "Pregna*" was also used for SCOPUS which allows for different variations of the word 'pregnant' to be detected. A manual search was conducted using the references of relevant articles with studies found between January 1995 to December 2018.

Eligibility criteria

Once duplicates were removed the articles were initially screened based on title and abstract. Suitable articles included Anti-Kell sensitised pregnancies, use of the Doppler ultrasound to detect foetal anaemia and articles written in English. The final stages of screening with full-text articles excluded reviews, case reports, clinical opinion articles, studies not providing appropriate data on Kell or the Doppler ultrasound and the full text not being available.

Data extraction

The study design, period and country of each included article along with the total study size, the number of Kell-specific cases, range of gestational age studied, frequency of the Doppler ultrasounds and the type of Doppler machine used was summarised together in Table 1.

Data synthesis and statistical analysis

OpenMeta-Analyst developed by Brown University was used to construct forest plots using the data extracted from the included studies (Table 2) [14]. A two-arm proportion analysis was conducted using a difference in arcsine transformed proportion with the analysis method binary random-effects, and maximum likelihood for the random-effects method. An analysis for the sensitivity and specificity was conducted with OpenMeta-Analyst using the diagnostic random-effects method (DerSimonian-Laird). The software calculated 95% confidence intervals, p-values and heterogeneity, with a p-value <0.05 being considered statistically significant (Figure 1).

RESULTS

Study selection

Through the search strategy mentioned previously using PubMed, SCOPUS, Google Scholar and ProQuest, 1,618 articles were found with an additional 11 articles through manual search and references. A total of 426 duplicates were removed using EndNote (version 20.0.0.16480) with 1,203 remaining for screening. A total of 1,006 articles were excluded based on title, and 168 excluded based on abstract. The remaining 29 articles were assessed using the full-text, with 5 being deemed eligible for the meta-analysis [10,15-18].

Search characteristics

All five eligible studies researched the Doppler ultrasounds ability to predict foetal anaemia in alloimmunised pregnant woman, specifically for Anti-Kell was examined across five countries from 1999-2004 using prospective and retrospective designs (Table 1). Three of the studies focused purely on Anti-Kell cases while two included Anti-Kell specific data as well as other antibody specificities. They all reviewed a similar range of gestational age and three specified the same Acuson Sequoia Doppler was used.

Study quality assessment

The quality of all eligible studies was assessed using the STROBE checklist with the most significant criteria summarised in Table 3. While all articles addressed the objectives, eligibility criteria, study size, outcome data, limitations and interpretation they all failed to specifically state how they had addressed bias. However, they did make a conscious effort to thoroughly address limitations of their studies. It could be said they considered reducing bias by ensuring the same examiners performed the ultrasounds, the same cohort of foetuses were studied when comparing two different management types, patients with incomplete data were excluded and by excluding Kell-negative foetuses whom were not at risk of developing foetal anaemia from alloimmunisation (Figure 2).

Sensitivity and specificity of the Doppler ultrasound detecting Kell-specific foetal anaemia

A meta-analysis and forest plot was performed on the sensitivity (Figure 2B) and specificity (Figure 2C) of the Doppler ultrasound in accurately predicting foetal anaemia in Kell-sensitised pregnancies. This was determined using the True Positive (TP), True Negative (TN), False Positive (FP) and False Negative (FN) data present within four of the five studies; as the study by Dukler et al. did not provide Kell-specific data for this parameter [10,16-18]. The overall sensitivity was 83% (CI 62.9%-93.4%) which was considered clinically significant with a p-value of 0.003. The overall specificity was 82% (CI: 52.7%-94.9%) with a statistically significant p-value of 0.035. In terms of heterogeneity, an I2 value of 0% was obtained for both indicating all variability is due to sampling error within the studies however the p-value of 0.434 (sensitivity) and 0.819 (specificity) indicates this is of no statistical significance.

Meta-analysis of the Doppler ultrasound correctly and incorrectly detecting Kell-specific foetal anaemia

A meta-analysis and forest plot were conducted on the proportion of the Doppler ultrasound correctly detecting foetal anaemia in Kell-sensitised pregnancies vs. proportion of the Doppler ultrasound incorrectly detecting foetal anaemia in Kell-sensitised pregnancies (Figure 2A). Using a two-arm proportion analysis it was found that the data was highly statistically significant with an Arcsine Risk Difference (ARD) of 0.874; 95% Confidence Interval (CI) of 0.667-1.080; and a p-value of <0.001. This data was calculated by the number of Kell cases correctly identified for the presence or absence of foetal anaemia using the Doppler ultrasound (38 total-25 TP, 11 TN, 2 not specified) over the total number of Kell cases within the study (42 total).10, 15-18 As well as the number of Kell cases with or without foetal anaemia that weren't correctly detected using the Doppler ultrasound (4 total-3 FN, 1 FP) over the total number of Kell-cases within the study (42 cases total).10, 15-18 In terms of heterogeneity, an I2 value of 0% was obtained indicating all variability is due to sampling error within the studies however the p-value of 0.582 indicates this is of no statistical significance.

Table 1: Characteristics of eligible studies investigating the Doppler ultrasound in Kell-sensitised pregnancies.

Study	Study design	Study period	Country	Total study size	Kell positive	Gestational age	Frequency of Doppler scan	Doppler ultrasound used
Van Dongen et al. 2005	Prospective	Jan 2000-Dec 2003	The Netherlands	27 foetuses	pregnancies/foetuses at risk of anemia due to Anti-Kell	21-37 weeks (overall)	Weekly or Bi-weekly	Acuson Sequoia

Rimon et al. 2006	Retrospective and prospective	Total: 1995-2004 (Foetuses specifically monitored by MCA-PSV 2002-2004)	Israel	49 Total: 24 Kell-positive foetuses 25 Kell-negative foetuses	16 Kell-positive foetuses monitored by weekly ultrasounds and titres every 4-6 weeks 8 Kell-positive foetuses monitored using MCA-PSV	20-38 weeks (overall) 20-30 weeks (First FBS)	4-7 days	Acuson Sequoia
Pereira et al. 2003	Retrospective	1999-2002	Philadelphia	28 foetuses	2 Anti-Kell pregnancies	22-34 weeks (overall)	Not Specified	Acuson Sequoia
Santiago et al. 2007	Retrospective	2000-2004	Spain	75 pregnancies	10 Anti-Kell pregnancies (3 with Kell-positive foetuses)	20-37 weeks (overall)	Not Specified	Not Specified
Dukler et al. 2003	Prospective	January-December 2000	Toronto (Canada)	16 foetuses	2 Anti-Kell pregnancies	21-39 weeks (overall)	Weekly or Bi-weekly	ATL 5000 or 3000

Note: Abbreviations: MCA-PSV: Middle Cerebral Artery-Peak Systolic Velocity; FBS: Foetal Blood Sampling.

Table 2: Data of eligible studies included in mMeta-analysis.

Study	Total Kell-positive fotueses	Anaemic Kell-positive foetuses	Doppler results compared with	MCA-PSV cut off	Hb concentration cut off	Median GA at first FBS	Mean Hb conc.at first FBS	Kell-specific TP,FP,TN,FN
Van Dongen et al. 2005	27 foetuses Kell-positive	17 severe anaemia requiring IUT (FBS performed) 1 moderate anaemia (FBS performed) 9 No IUT needed(1 foetus severly anaemic at birth)	Foetal Hb conc. E11values at fist FBS and delivery	>1.5MoM	5 SD or more below the mean for GA	24 weeks (21-30 weeks)	4.0g d/L (1.6-8.9 g d/L)	TP=16 FP=1 TN=8 FN=2
Rimon et al. 2006	24 Total (165 Kell-positive foetuses monitored by weekly ultrasounds and titres every 4-6 weeks 8 Kell-positive foetuses monitored using MCA-PSV)	7 anaemic foetuses specifically monitored using MCA-PSV	Hct at first FBS HCT at birth hb conc. (MoM)	>1.5 MoM	Mild: 0.84 to 0.66 MoM Moderate: <0.65 to 0.55 MoM	25 weeks (20-30 weeks)	Not Specified	TP=7 FP=0 TN=1 FN=0
Pereira et al. 2003	2 Kell-positive foetuses	2 mild foetal anaemia cases	Footal Hb	>1.5 MoM	Mild:<0.84 MoM Moderate: <0.65 MoM OR below 90 g/L Severe: <0.55 MoM OR below 90 g/L	Not Specified	Not Specified	TP=0 FP=0 TN=2 FN=0
Santioago et al. 2007	3 Kell-positive fortuses	3 severe foetal anaemia cases	Hb conc. (pre and post IUT)	Not Specified	Mild: 0.65-0.85 MoM Moderate: 0.55-0.64 MoM Severe: <0.55 MoM	21 weeks (21-30 weeks)	9.7 g/dL	TP=2 Fp=0 TN=0 FN=1
Dukler et al. 2003	2 Kell-positive foetuses	Not specified (6 anaemic foetuses total requiring IUT)	Hb conc. (pre and post IUT)	1.5 MoM	Hb deficit of 5SD or greator	Not pecified	402 g/dL	

Note: Abbrivations: SD: Standard Deviation; Hb Conc.: Heamoglobin Concentration; FBS: Foetal Blood Sampling; GA: Gestational Age; TP: True Positive; FP: False Positive; TN: True Negative; FN: False Negative; MCA-PSV: Middle Cerebral Aretery Peak Systolic Velocity; IUT: Intrauterine Transfusion; MoM: Multiple of the Median; Hb: Heamoglobin; Hct: Haematocrit.

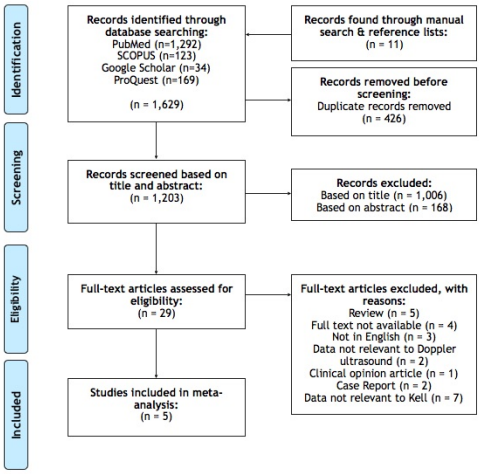

Figure 1: PRISMA flow chart demonstrating the process of identification, screening, eligibility and included studies for the meta-analysis arriving at a total of five eligible studies.

Table 3: Quality assessment of studies included in meta-analysis using Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist.

	Van Dongen, 2005	Rimon, 2006	Pereira, 2003	Santiago, 2007	Dukler, 2003
Title and abstract	Y	Y	Y	Y	Y
Objectives	Y	Y	Y	Y	Y
Eligibility criteria	Y	Y	Ya	Y	Y
Addresses bias	N	N	N	N	N
Study Size	Y	Y	Y	Y	Y
Outcome data	Y	Y	Y	Y	Yb
Limitations	Y	Y	Y	Y	Y
Interpretation	Y	Y	Y	Y	Y

Note: Y=Yes (Criteria fulfilled); N=No (Criteria not fulfilled).

[a]States no cases in the study period were excluded.

[b]Total results stated and graphed (not antibody specific).

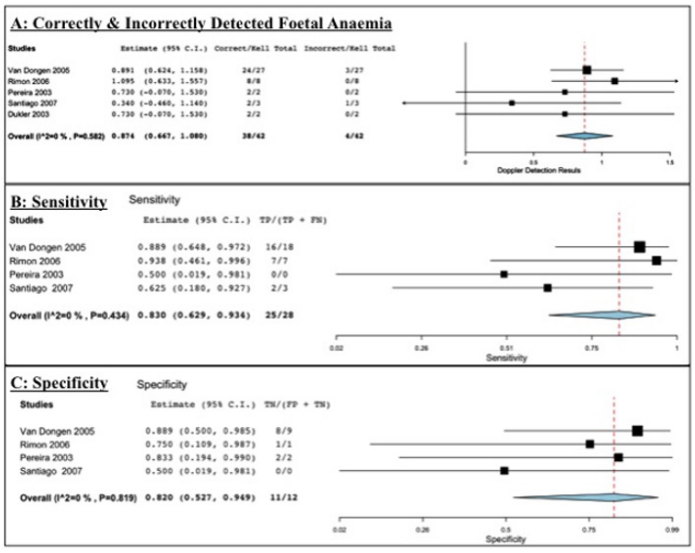

Figure 2: (A-C): Forest plots of meta-analysis. (A) Two-arm proportion on Doppler ultrasound correctly and incorrectly detecting Kell-specific foetal anaemia with Arcsine Risk Difference [ARD], 0.874; 95% Confidence Interval [CI], 0.667-1.080; I2=0%; p-value=<0.001; (B) Sensitivity of the Doppler ultrasound detecting Kell-specific foetal anaemia with 83% sensitivity (CI, 62.9%-93.4%; I2=0%; p-value=0.003); (C) Specificity of the Doppler ultrasound detecting Kell-specific foetal anaemia with 82% specificity (CI, 52.7%-94.9%; I2=0%; p-value=0.035).

DISCUSSION

Key points regarding the Kell blood group system

Past studies investigating the accuracy of the Doppler ultrasound in detecting foetal anaemia have examined a range of antibody specificities, particularly focusing on Anti-D and the overall Rh blood group system. However, it has been discovered that Anti-Kell behaves in a unique way when it comes to HDFN, and therefore common screening procedures for foetal anaemia are often unpredictable in Kell-sensitised pregnancies. Unlike the usual presentations of HDFN, Anti-Kell has demonstrated suppression of erythroid progenitor cells and is often associated with reticulocytopenia and mild hyperbilirubinaemia [5,19]. For this reason, amniotic fluid bilirubin concentration is unreliable in determining the severity of Kell-sensitised foetal anaemia; liver length and spleen perimeter are also unreliable [6-8,15]. While there is still a lot to learn regarding the pathophysiology of the Kell blood group system in HDFN, this systematic review and meta-analysis investigates currently available Kell-specific data relating to the accuracy of the Doppler ultrasound in predicting Kell-sensitised foetal anaemia.

Sensitivity and specificity results

Due to the lack of data available specifically on Kell-sensitised pregnancies, as many studies look at the Doppler ultrasounds accuracy around alloimmunisation as a whole rather than Kell alone, a total of five studies were considered eligible [10,15-18]. One study included two Kell cases within the cohort of sixteen foetuses with a sensitivity and specificity of 100% for the Doppler ultrasound detecting foetal anaemia [15]. However, it could not be included in the meta-analysis for sensitivity and specificity (only included in proportion) as it did not specify whether the Kell cases were anaemic or not; to know whether they were TP or TN [15]. Therefore, the four eligible studies within the meta-analysis regarding the sensitivity and specificity of the Doppler ultrasound detecting Kell-specific foetal anaemia was 83% and 82% respectively [10,16-18]. While these results aren't as high in comparison to some studies findings whom have examined alloimmunisation as a whole with values as high as 100%, the results obtained could still be considered supportive of the Doppler ultrasounds accuracy in predicting foetal anaemia before performing invasive procedures [11,15-21]. In saying this, the limited number of Kell cases within each study in the meta-analysis makes it difficult to propose a reliable and definitive conclusion of the Doppler ultrasounds abilities relating to Anti-Kell.

Two-arm proportion meta-analysis

The meta-analysis for two-arm proportion using five eligible studies shows with the pooled effect that the Doppler ultrasound correctly identifies foetal anaemia in 87.4% of Kell cases. 10, 15-18 with a p-value of <0.001 this data is highly statistically significant and could be said to support the Doppler ultrasounds ability to predict foetal anaemia in Kell-sensitised pregnancies. However as mentioned above, the study sizes for Kell cases within this meta-analysis are limited and therefore a much larger population needs to be assessed in order to provide a more reliable conclusion. Nevertheless, this analysis has provided a brief insight into the Doppler ultrasounds use specifically in Kell-sensitised pregnancies. The heterogeneity across the studies was insignificant with a p-value of 0.582 and an I2 value of 0% indicating all variability is due to sampling error within the studies which correlates with the small study sizes.

Limitations of the review

HDFN is a rare disease occurring in approximately 3/100,000 to 80/100,000 patients in the United States per year [22]. According to the Australian Red Cross Lifeblood 0.5% of pregnancies have an IgG antibody against Rh CcEe, Duffy or Kell, signifying the rarity of Anti-Kell in an already rare disease [23]. The phenotype K-k+ is also prevalent in 91% of caucasians meaning the possibility of a foetus being Kell-positive and therefore at risk of foetal anaemia is low.4 For this reason it is difficult to acquire a large number of Kell-sensitised pregnancies with Kell-postitive foetuses at risk to truely assess the Doppler ultrasounds ability to predict foetal anaemia specifically in Kell-sensitised pregnancies. Therefore, the number of studies available as well as the number of Kell cases within these studies was a limitation of this systematic review. There were two case reports with Kell specific data unable to be included in the study due to assessing less than two cases, one of which found the Doppler ultrasound unable to detect foetal anaemia [7]. An additional challenge was gaining access to articles with appropriate data; four studies had to be excluded for this reason. Three of the studies included were of retrospective design (one study was both retrospective and prospective) which could introduce selection bias and relies on the accuracy of the transcribing. Furthermore, none of the studies included blinding of patients or examiners which could also introduce bias into the results used in the review.

False negative case in Santiago et al. study

The incidence of the Doppler ultrasound correctly detecting the presence or absence of Kell-specific foetal anaemia was 38 out of 42 cases. However, in three cases the Doppler ultrasound did not detect anaemia in foetuses whom were in Fact Anemic (FN) at birth or through Foetal Blood Sampling (FBS). In the study conducted by Santiago et al. case 3's Doppler results were repeatedly at or below the normal range throughout the pregnancy [17]. An example of this was a Hb of 0.55 Multiples of the Median (MoM) at 31 weeks gestation indicating severe anaemia however they measured below the reference range for GA with the Doppler ultrasound. It was stated that this woman had no history of a blood transfusion and had one previous pregnancy with no significant issues. There was no reasoning given within the study as to why this result was repeatedly low despite the foetus being anaemic; the neonate received a blood transfusion at day 10 post-delivery however their Hb was above 80 g/L.

False positive case in Van Dongen et al. study

In the study by Dongen et al. there was one case that had a MCA-PSV >1.5 MoM measured by the Doppler ultrasound, indicating severe anaemia, however the FBS detected moderate anaemia (i.e., FP) with a haemoglobin of 89 g/L [11]. While the foetus was moderately anaemic rather than severely, according to the study by Mari et al. (not included in this meta-anaylsis) cordocentesis is performed in foetuses with moderate-to-severe anaemia as they may require an IUT [11]. Therefore, this foetuses management would be likely to remain the same even though they were detected incorrectly. Furthermore, in the study by Pereira et al. an IUT is performed in foetuses with a Hb <90 g/L, so this foetus could also qualify for a transfusion [16].

Advanced gestational age in relation to the Doppler

In terms of the two false negative cases by Dongen et al., one was detected at 27 weeks gestation with the study not addressing a possible cause. The second was severely anaemic at birth despite normal

Doppler results at 36 weeks [18]. However, it was suggested this may be explained by the 2-week interval between the delivery and the last ultrasound. Moreover, the advanced gestational age of 36 weeks was also a possible explanation due to findings that the Doppler ultrasound may be less reliable after 35 weeks gestation [20]. The study by Zimmermann et al. (not included in this meta-analysis) supported this phenomenon as it found that seven foetuses >35 weeks gestation developed abnormal MCA-PSVs measured by the Doppler ultrasound and upon inducing labour all seven cases were not anaemic.20 The study found the sensitivity of the Doppler to detect moderate-to-severe anaemia before 35 weeks gestation was 88% and the specificity was 87% [20]. Furthermore, the prospective study by Lubuský et al. (not included in this meta-anaylsis) with a total of 331 Doppler examinations across 81 pregnancies had a total of one false positive case (100% sensitivity, 92% specificity) which was identified in a foetus >35 weeks gestation [21].

Measures that may affect the Doppler ultrasound and future research

There have been questions surrounding the most appropriate cut off in MoM for the Doppler ultrasound to detect foetal anaemia and avoid introducing risk with invasive procedures for those who are in fact not anemic; without reducing the sensitivity and specificity of the ultrasound. Additionally, how accurate the Doppler is after IUT's have been performed has been further questioned. The study by Oakes et al. examined both of these concepts suggesting in those with recurrent moderate-to-severe anaemia, raising the cut off to ≥ 1.74 MoM after one IUT would reduce unnecessary procedures [24]. However, there have been many studies with differing conclusions, some inconclusive, so this is something that needs further research. A limitation with the Doppler ultrasound is that it requires a highly experienced sonographer to perform the scan to obtain accurate results and even then there can be variability based on the technologist, machine and individual patient. Lui et al. studied human factors that can be a source of error regarding the Doppler ultrasound and concluded factors such as inaccurate angle and sample volume placement, the presence of stenosis, and the gain settings set on the machine were all major contributing factors to variability with peak velocity measurements [25]. This emphasises the need for highly trained sonographers to understand the machine and how to appropriately adjust procedure based on individual cases. Lastly, the study by Rimon et al. raised the question regarding Kell-sensitised pregnancies as to whether weekly assessments of MCA-PSV is optimal for the detection of foetal anemia or if it should be performed more regularly due to the severity and rapid decline of Hct in Kell-positive fetuses [10]. It was also mentioned that predicting a foetus is going to become severely anaemic, particularly with Kell, before it occurs would greatly reduce the risk of hydrops. The study by Detti et al. found that the use of the MCA-PSV slope was an excellent tool for identifying this. This research would expand the use of the Doppler ultrasound in clinical application to not only accurately detect anaemic foetuses but predict foetuses whom will become severely anaemic to ensure close monitoring for the best possible outcome.

CONCLUSION

While this systematic review and meta-analysis shows promising results regarding the Doppler ultrasounds ability to detect foetal anaemia specifically for Kell-sensitised pregnancies, the small cohort of studies within the analysis means more data is required to provide a strong and reliable conclusion. In order to do this, more studies using the Doppler for Anti-Kell cases need to be conducted and published for analysis. However, it can be said that the Doppler ultrasound shows evidence of being less reliable after 35 weeks gestation. It is also important that women who are Kell-sensitised are educated on the clinical significance of Anti-Kell and seek monitoring should they experience reduced foetal movement. In addition, further research is needed around appropriate cut-offs, the reliability after IUT's and optimal intervals between scans.

DECLARATION

Conflict of interest

Authors declare no conflict of interest.

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