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ALOIMUNIZAÇÃO ERITROCITÁRIA: DIAGNÓSTICO E CONDUTA CLÍNICA

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Aloimunização eritrocitária: diagnóstico e conduta clínica

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RESUMO

A aloimunização eritrocitária é uma condição caracterizada pela presença de anticorpos irregulares no soro do paciente, cuja produção é causada pela exposição a antígenos eritrocitários não-próprios. A aloimunização apresenta risco à saúde de pacientes, pois a sua presença pode resultar em reação hemolítica tardia (RHT), em caso de transfusão de concentrado de hemácias ou doença hemolítica perinatal (DHPN), quando em gestações. Assim, a presente revisão bibliográfica tem como objetivos a descrição do diagnóstico e conduta clínica para com pacientes com aloimunização eritrocitária, realizada a partir da literatura existente nas bases de dados Biblioteca de Saúde Virtual, PubMed e Scientific Electronic Library Online, com os descritores “aloimunização”, “transfusão” e “diagnóstico”. O diagnóstico é realizado a partir da pesquisa de anticorpos irregulares e a identificação do anticorpo é feita com o uso do painel de hemácias. Como dito anteriormente, a aloimunização apresenta consequências ao paciente, dessa forma, a conduta clínica abordada para com o paciente é imprescindível para sua qualidade de vida futura. Em casos de transfusões de concentrado de hemácias, o paciente não deve ser exposto ao antígeno ao qual é sensível, sendo necessário, portanto, a transfusão de bolsas fenotipadas de concentrado de hemácias; quanto ao manejo dos casos de RHT, podem ser realizados terapia imunossupressora, otimização da eritropoiese e o cessamento de transfusões. Já para a DHPN, são utilizadas diversas técnicas para o monitoramento de anemia fetal, além de serem verificados os títulos de anticorpo sérico materno, ainda, em casos mais graves, podem ser realizadas transfusões intra uterinas.

Palavras-chave: aloimunização eritrocitária, diagnóstico, conduta clínica, reação hemolítica tardia e doença hemolítica perinatal

INTRODUÇÃO

No início do século XX, Karl Landsteiner fez a descoberta do primeiro grupo sanguíneo, o grupo ABO, amplamente conhecido e de importância imprescindível na medicina transfusional. Desde esse acontecimento, houveram diversas atualizações sobre o tema, incluindo a evidenciação de mais de 30 sistemas de grupos sanguíneos, segundo a Sociedade Internacional de Transfusão de Sangue (International Society of Blood Transfusion -ISBT), dentre eles os sistemas Rh, Kell, Kidd e Duffy.[1]

Cada indivíduo pode apresentar diferentes conjuntos de antígenos eritrocitários, determinados geneticamente. Dessa forma, quando um indivíduo entra em contato com antígenos eritrocitários que não possui, tem o risco de desenvolver anticorpos irregulares. Eles levam esse nome por não serem desenvolvidos naturalmente pelo corpo, somente em situações extraordinárias, como em transfusões de concentrado de hemácias ou gestações, cujo feto possua um ou mais antígenos de origem paterna, que a mãe não apresenta. Essa condição é chamada de aloimunização eritrocitária.[2,3]

As principais consequências atribuídas à aloimunização são as reações hemolíticas tardias (RHT) e a doença hemolítica perinatal (DHPN), em transfusões e gestações, respectivamente. A reação transfusional tardia ocorre devido à hemólise das hemácias recebidas pelos anticorpos irregulares do paciente, podendo causar febre, icterícia, queda dos níveis de hemoglobina e até a morte, em casos severos.[2]

Já a DHPN é causada pela presença de um ou mais antígenos de origem paterna nas hemácias do feto, que a mãe não possui, resultando na hemólise dos eritrócitos fetais. Essa condição ocorre, geralmente, na segunda gestação que apresenta as mesmas condições, já que durante a primeira, os anticorpos IgG (capazes de atravessar a barreira placentária) ainda não estão formados. Dentre as principais consequências da DHPN estão a anemia fetal, hiperbilirrubinemia, kernicterus ou icterícia nuclear (lesão nos gânglios da base e núcleos do tronco cerebral), deficiências neurológicas e morte do feto ou do recém nascido.[4]

O diagnóstico da aloimunização eritrocitária e manejo correto dos pacientes aloimunizados é imprescindível para a saúde e continuação de tratamentos nos casos de pacientes com hemoglobinopatias, por exemplo. Dessa forma, esta revisão tem por objetivos descrever as formas de diagnóstico para a condição, assim como as condutas necessárias para com os pacientes.

METODOLOGIA

A metodologia utilizada neste estudo é de caráter descritivo, com o procedimento de revisão bibliográfica narrativa.

A pesquisa foi realizada a partir da busca de artigos nas bases de dados Biblioteca Virtual em Saúde (BVS), PubMed e Scientific Electronic Library Online (Scielo), no período de 2019 a 2024. As palavras-chave utilizadas foram “aloimunização”, “transfusão” e “diagnóstico” correlacionando-os com o conector “AND”, para resultados mais precisos. Considerou-se elegíveis artigos nas línguas portuguesa, inglesa e espanhola, cujo acesso integral fosse disponibilizado de forma gratuita.

Como fatores de exclusão, desconsiderou-se todos os artigos que abordavam a aloimunização por antígenos não eritrocitários, os antígenos leucocitários humanos (HLA). Dessa forma, foram utilizados os termos “HLA” e “plaquetas” juntamente com as palavras-chave anteriormente mencionadas, porém com o uso do conectivo “AND NOT/NOT”. Além disso, foram retirados os artigos que continham título e resumo que não condiziam com o objetivo do trabalho e que não estavam disponíveis integralmente.

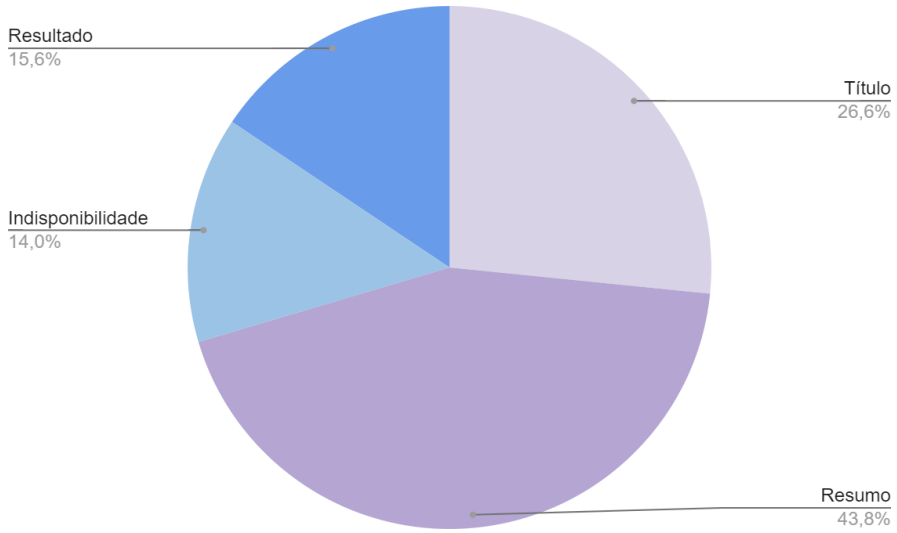
Ainda, foi utilizado o livro “Fundamentos e Técnicas em Banco de Sangue”, de 2014, para a discussão das metodologias dos testes para diagnóstico.

RESULTADOS E DISCUSSÃO

Estratégia de pesquisa e seleção do material bibliográfico

A partir dos termos “aloimunização”, “doença hemolítica perinatal”, “transfusão” e “diagnóstico”, foram encontrados 64 artigos nas bases de dados BVS, PubMed e Scielo. Após a leitura dos títulos, foram descartados 17 artigos, resultando em 47 artigos. A próxima etapa foi composta pela leitura dos resumos, na qual foram excluídos mais 28, por não serem compatíveis com os objetivos da pesquisa. Ainda, 9 foram desconsiderados pela indisponibilidade do artigo na íntegra de forma gratuita. Dessa forma, obtiveram-se 10 artigos para o desenvolvimento da revisão bibliográfica, conforme o Gráfico 1 abaixo, além do livro de Vizzoni.

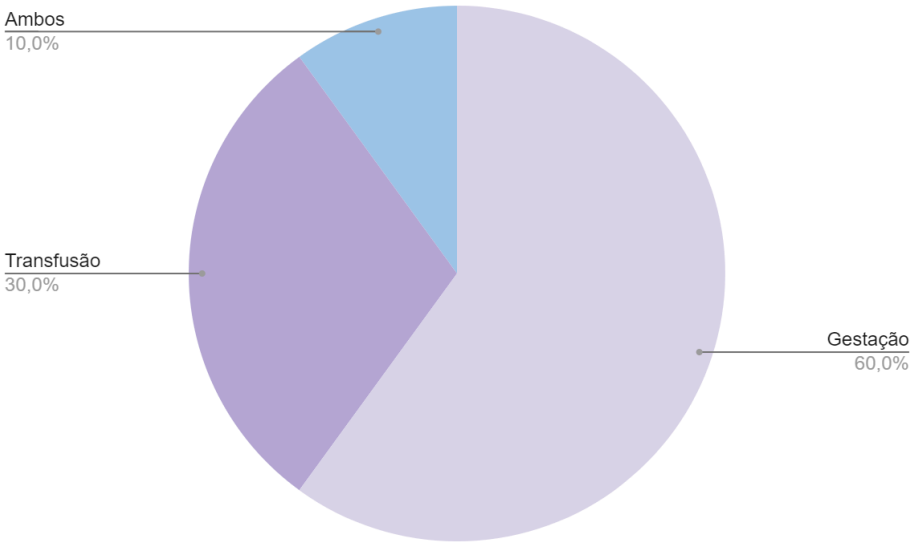
Gráfico 1. Critérios de exclusão utilizados para a seleção dos artigos.



Fonte: Autora (2024).

Dos 10 resultantes, 100% estão disponíveis em língua inglesa, não foram encontrados artigos nas línguas portuguesas ou espanholas que compreendessem o objetivo desta revisão. Quanto ao assunto, três deles referem-se a complicações devido a transfusões de concentrado de hemácias, seis devido à gestação e um a ambos, conforme representado no Gráfico 2.

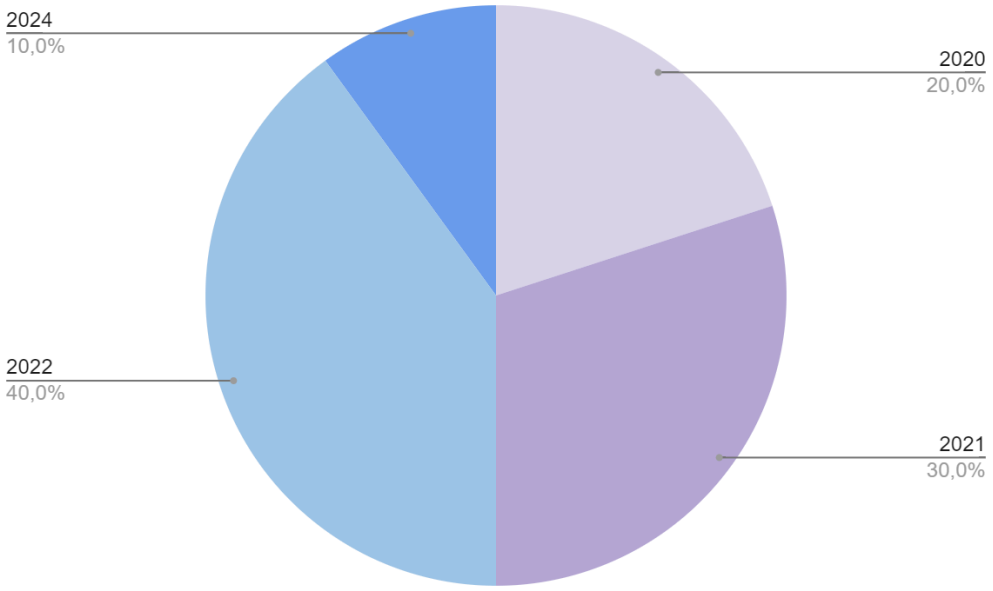
Gráfico 2. Temas dos artigos selecionados.



Fonte: Autora (2024).

Ainda, conforme dito anteriormente, o critério utilizado para inclusão de artigos quanto ao ano de publicação comporta os anos de 2019 a 2024. Ao final da pesquisa, foram selecionados dois artigos de 2020, três de 2021, quatro de 2022 e um de 2024, representado no Gráfico 3.

Gráfico 3. Ano de publicação dos artigos selecionados.



Fonte: Autora (2024).

Diagnóstico laboratorial de aloimunização eritrocitária

A reação hemolítica tardia (RHT) e a doença hemolítica perinatal (DHPN) são as principais consequências em casos de aloimunização eritrocitária, como previamente mencionado. Dessa forma, devido ao risco à saúde dos pacientes nessas situações, torna-se imprescindível o diagnóstico da condição.[2,3]

O principal teste realizado para o diagnóstico é através da pesquisa de anticorpos presentes no soro do paciente contra antígenos eritrocitários não-próprios, chamado de pesquisa de anticorpos irregulares (PAI) ou Coombs indireto.[6] O exame é realizado a partir do uso de hemácias comerciais fenotipadas, que apresentam antígenos conhecidos em suas superfícies. O material biológico utilizado é o soro ou plasma do paciente, que reage com as hemácias comerciais, caso haja anticorpos irregulares na amostra. Em situações cujo o teste

apresenta-se reagente, é recomendado o uso do painel de hemácias para a identificação do anticorpo presente.[5]

No teste Coombs indireto, também podem ser utilizados potencializadores da reação antígeno-anticorpo, como o polietilenoglicol (PEG). Essas substâncias favorecem a identificação de anticorpos irregulares, devido ao aumento da sensibilidade do teste. Ainda, é possível a realização do teste para a quantificação dos níveis de concentração dos anticorpos presentes no soro do paciente, para melhor avaliação do caso.[1,6]

O painel de hemácias é composto por diversos eritrócitos com fenótipos conhecidos, cuja quantidade varia de acordo com a marca do teste. O teste é realizado pela metodologia de aglutinação, que ocorre quando o anticorpo irregular presente no soro do paciente reage com o antígeno presente na hemácia comercial fenotipada, assim como a pesquisa de anticorpos irregulares. Cada eritrócito possui antígenos conhecidos, assim, a identificação do anticorpo irregular é realizada a partir da comparação das hemácias em que há reação com aquelas em que não há reação, excluindo-se os antígenos (possíveis causadores da aloimunização) que estão presentes somente em hemácias com resultados não-reagentes, em um processo de eliminação. Ainda, é utilizado também o painel de hemácias papainizadas, que podem aumentar a reatividade ou destruir determinados antígenos, como representado na Tabela 1.[5]

Tabela 1. Representação das hemácias fenotipadas geralmente utilizadas no painel de hemácias.

Sistemas		Rh					Kell		MNS				Kidd		Duffy		Lewis		P	Lutheran	
Antígenos		D	C	E	c	e	K	k	M	N	S	s	Jk^a	Jk^b	Fy^a	Fy^b	Le^a	Le^b	p^1	Lu^a	Lu^b
Hemácias	1	+	+	0	0	+	0	+	+	+	+	+	+	+	0	+	0	+	+	+	+
	2	+	+	0	0	+	0	+	0	0	0	+	+	0	+	+	+	+	+	0	+
	3	+	0	+	+	0	0	+	+	+	+	+	+	0	+	0	0	+	0	0	+
	4	0	+	0	+	+	0	+	+	+	0	+	+	+	+	+	0	+	+	0	+
	5	0	0	+	+	+	0	+	0	+	+	+	+	+	+	+	0	+	0	0	+
	6	0	0	0	+	+	+	+	+	+	0	+	+	+	0	+	0	0	0	0	+
	7	0	0	0	+	+	0	+	0	+	+	+	+	0	+	0	+	0	+	0	+
	8	+	0	0	+	+	0	+	+	0	0	+	+	0	0	0	+	0	+	0	+
	9	0	0	0	+	+	0	+	+	0	+	0	0	+	+	+	0	+	0	0	+
	10	+	0	+	+	0	0	+	0	+	0	+	0	+	0	+	0	+	0	0	+
	11	+	+	+	0	+	+	+	+	+	+	0	+	+	+	+	+	0	+	0	+

Legenda: +: Presença do antígeno; 0: Ausência do antígeno; : podem ser destruídos pelo tratamento enzimático.

Fonte: Adaptado de Vizzoni, 2016.

Ainda, nos casos de aloimunização eritrocitária com risco de DHPN, é possível a realização da determinação do fenótipo paterno, que, caso seja homozigoto para um determinado antígeno, que a mãe não possui, automaticamente demonstra risco para o feto; já nos casos em que o pai é heterozigoto, o fenótipo fetal pode ser realizado de maneira não invasiva, que consiste na amplificação do DNA fetal presente no plasma materno, utilizando técnicas de Reação em Cadeia da Polimerase (PCR).[4]

Tanto em transfusões de sangue quanto na gestação, a pesquisa de anticorpos irregulares é essencial, pois é um teste com a capacidade de evitar transfusões incompatíveis, além de ser capaz de impedir a aloimunização eritrocitária quando o risco é identificado na primeira gestação, ou ser responsável pelo acompanhamento do feto e da mãe quando há gestações com mães sensibilizadas.[7,4]

Em casos de complicações, é utilizado também o teste de antiglobulina direta (TAD) ou Coombs direto, que identifica a presença de hemácias sensibilizadas por anticorpos irregulares no soro do paciente, que comprova aloimunização eritrocitária ativamente. Ainda, outros exames laboratoriais rotineiros ajudam a determinar a ocorrência de reações hemolíticas tardias nos pacientes, quando correlacionado com o quadro clínico, como o aumento do lactato desidrogenase (LDH), a diminuição da hemoglobina e o aumento na contagem de reticulócitos.[2,11]

Conduta clínica em aloimunização eritrocitária causada por transfusão de concentrado de hemácias

Como mencionado anteriormente, em casos de transfusões de concentrados de hemácias, a aloimunização é responsável pelo desenvolvimento de reações hemolíticas tardias. Essa condição pode apresentar um grande risco à saúde do paciente, portanto deve ser identificada, diagnosticada e tratada rapidamente.[2]

A RHT é caracterizada pela hemólise dos eritrócitos recebidos através de uma transfusão de concentrado de hemácias por anticorpos irregulares presentes no soro do receptor, que tem como consequência a anemia, cuja gravidade é variável. A RHT tardia ocorre entre 24 horas até 21 dias após a transfusão de concentrado de hemácias e apresenta os seguintes sintomas: febre, dor, urina escura, icterícia e queda nos níveis de hemoglobina.[7]

Um estudo de coorte realizado por Gerritsma *et al* durante 9 anos, entre 2011 e 2020, relata que, das 508 transfusões de concentrado de hemácias realizadas nesse período, 68 (12%) resultaram em sintomas compatíveis com a RHT. Porém, somente 6 dessas tiveram o diagnóstico de RHT, já que em 46 delas chegou-se a um diagnóstico alternativo. Nos 16 restantes a condição foi suspeitada, dos quais 4 foram tardiamente diagnosticados como RHT, também.

Os anticorpos irregulares mais comuns na aloimunização eritrocitária causada pela transfusão de concentrado de hemácias são aqueles contra os antígenos dos sistemas Rh, Kidd, Kell e MNS.[7]

Pacientes politransfundidos, ou seja, aqueles que são submetidos a diversas transfusões, possuem maiores incidências de desenvolvimento de aloimunização eritrocitária. Também, há a hipótese que as transfusões de concentrados de hemácias realizadas em pacientes apresentando condições inflamatórias estão mais associadas ao desenvolvimento da aloimunização.[2]

Pacientes com anemia falciforme tendem a apresentar aloimunização eritrocitária com mais frequência que pacientes sem hemoglobinopatias, devido a alta quantidade de bolsas de concentrados de hemácias que são transfundidas ao longo de suas vidas. Porém, além da maior incidência, muitas vezes a RHT não é diagnosticada corretamente nesses pacientes devido à similaridade dos sintomas com a crise vaso-oclusiva, que é um sintoma recorrente em pacientes com anemia falciforme, demonstrando risco à saúde do paciente.[2]

Estima-se que cerca de 30 a 50% dos pacientes com anemia falciforme desenvolvem aloimunização eritrocitária e que até 13,52% sofrem por RHT, que é fatal em cerca de 11,5% dos casos.[2]

Em casos de RHT, apesar de não haver uma conduta específica estabelecida, o mais indicado é a terapia imunossupressora, aumento da eritropoiese, cessamento de transfusões, além de imunoglobulina intravenosa (intravenous immunoglobulins - IVIG). O fármaco mais utilizado é a Prednisolona, que age como um anti-inflamatório e imunossupressor, também é utilizado rituximab, um anticorpo monoclonal quimérico e inibidores de C1 esterase.[7]

Como dito anteriormente, a aloimunização eritrocitária é um grande risco para o desenvolvimento da RHT, portanto a identificação de anticorpos irregulares antes de transfusões, assim como a prova de compatibilidade entre a bolsa de sangue e o paciente e o uso de bolsas fenotipadas são essenciais para a prevenção e monitoramento de complicações em pacientes politransfundidos.

Conduta clínica em aloimunização eritrocitária causada por gestação

Em casos de gestações, a principal consequência da aloimunização eritrocitária é o desenvolvimento da DHPN, que apresenta grande risco à saúde do bebê. É causada pela hemólise das hemácias fetais, que possuem um ou mais antígenos de origem paterna, por anticorpos irregulares de classe IgG presentes no soro materno, que atravessam a barreira placentária. Como consequência, o feto e/ou recém-nascido pode apresentar anemia, que se não for devidamente tratada é capaz de originar hiperbilirrubinemia, cardiomegalia, hidropsia fetal, kernicterus, surdez, deficiências neurológicas e até a morte.[4]

O estudo de Liu *et al*, de 2021, demonstrou que cerca de 64% das gestações com risco de DHPN tiveram anticorpos irregulares inicialmente detectados no primeiro trimestre, enquanto 16% foram identificados no segundo e, por fim, 19% no terceiro trimestre. A pesquisa inclui todas as gestações com aloimunização, que apresentavam riscos de desenvolvimento de DHPN, entre os anos de 1990 e 2016 da região de Estocolmo. Ainda, a análise dentre as 1079 gestações incluídas ao estudo, demonstra que os principais antígenos eritrocitários envolvidos na aloimunização em gestantes são o D, com aproximadamente 46% de incidência, seguido pelo E (12,5%), c (12%), Fya (4%) e K (3%), porém ainda foram encontrados anticorpos considerados de baixo risco para DHPN em 19% das gestações, que incluem aqueles contra os antígenos k, C, U, Cw, f, Jka, Jkb, M, S, s, Fyb, Lua, Lub, Kpa, Kpb, Yta, Coa, Cob, Ge2 e Ge3.

Dessa forma, é recomendado que durante o primeiro e o terceiro trimestre de gestação sejam realizados os testes para tipagem sanguínea dos grupos ABO e Rh, além da pesquisa de anticorpos irregulares no soro da mãe. A prática promove a identificação precoce de aloimunização eritrocitária materna e, consequentemente, possíveis complicações, como a DHPN.[4]

É observado que alguns anticorpos irregulares representam um maior risco para a gestação e para o desenvolvimento de DHPN do que outros, como o anti-D e o anti-K, que tanto representaram a maior incidência de partos prematuros , principalmente em gestações nas quais ambos anticorpos estavam presentes. Também, gestações com a presença de anti-D demonstraram maior necessidade de transfusões intrauterinas, seguida pelo grupo com anti-K.[8]

Nos casos de possível aloimunização eritrocitária, ou seja, na primeira gestação em que há incompatibilidade do antígeno eritrocitário RhD entre a mãe e o feto, é realizada a injeção com anticorpos IgG anti-RhD em até 72 horas após o nascimento do bebê, evitando o

desenvolvimento desses anticorpos pela mãe e, consequentemente, prevenindo um caso de possível DHPN em uma gestação futura em mesmas condições.[9]

A hemorragia feto-materna é um evento que pode ocorrer naturalmente durante a gestação e parto, no qual as hemácias fetais estão presentes na circulação sanguínea materna. Assim, testes para detecção de hemorragia feto materna afirmam a exposição materna aos eritrócitos fetais ao determinar a porcentagem e o volume de eritrócitos fetais que estão presentes na circulação materna.[10]

É considerado um teste bastante importante, principalmente nos casos em que a mãe é RhD negativo e o feto RhD positivo, já que ajuda a determinar o risco de aloimunização materna e é utilizado como base para a dosagem da profilaxia com anticorpos de classe IgG anti-RhD, com o objetivo de impedir o desenvolvimento da aloimunização materna. Geralmente, a dosagem aplicada é de 300 μg de anticorpo, porém, se o volume de sangue fetal ao qual a mãe foi exposta for superior a 30 mL, o que ocorre em cerca de 0,3% dos casos, é necessária uma concentração maior de anti-RhD.[10]

É importante salientar que, devido à grande disponibilidade da profilaxia com IgG anti-RhD, o número de gestações com aloimunização eritrocitária causadas pelo antígeno RhD apresentou um grande declínio, porém ainda torna-se necessário o monitoramento e a pesquisa visando à profilaxia contra os anticorpos irregulares não-RhD, que atualmente são os principais anticorpos causadores de DHPN.[3]

Enquanto nas gestações em que há a presença de anticorpos irregulares, é realizado o acompanhamento médico quanto à concentração do anticorpo no soro da paciente e/ou a citotoxicidade mediada por anticorpo (CMA), cujo título de referência normalmente é estabelecido como 1:16, para monitoramento e avaliação do quadro clínico, apesar de demonstrar uma taxa de 77% de falsos positivos para a identificação de anemia fetal. O título estabelecido depende da técnica utilizada pelo laboratório, que pode variar entre 8 e 32, e do anticorpo pesquisado, devido aos diferentes riscos que cada anticorpo apresenta, como dito anteriormente.[4]

Nas gestações consideradas em risco de DHPN também são monitoradas a partir de ultrassonografias e/ou exames de Doppler (como a velocidade do pico sistólico da artéria cerebral média) recorrentes, com o objetivo de detectar possíveis anemias fetais. O teste da velocidade do pico sistólico da artéria cerebral média apresenta sensibilidade que varia entre 75,5 a 95% e 10 a 12% de falsos positivos; porém, é reportado que, ao longo da realização de transfusões intrauterinas, há um aumento considerável de falsos positivos, podendo alcançar

90% após a terceira transfusão, em casos de anemia severa. Dessa forma, não é recomendado o uso desse teste para o monitoramento da anemia fetal após esses procedimentos.[9,10]

O tratamento da DHPN depende da gravidade do quadro clínico, considerando os níveis de bilirrubina e a possível anemia. A conduta clínica é iniciada durante a gestação, que pode envolver procedimentos como transfusões intra uterinas, troca plasmática terapêutica, fototerapias e a administração de imunoglobulina intravenosa ou imunossupressores. [1,4]

Já a conduta pós natal é composta por fototerapia, transfusões de concentrado de hemácias e troca total do volume hemático dos neonatos por aférese, com objetivo do tratamento de anemias e diminuição dos níveis de bilirrubina do recém-nascido.[1]

CONCLUSÃO

A aloimunização eritrocitária é uma condição importante que tem o potencial de causar consequências significativas na saúde de pacientes, como é o caso da reação hemolítica tardia e a doença hemolítica perinatal. Porém, com frequência não é devidamente identificada e diagnosticada, o que resulta nas complicações mencionadas. Portanto, torna-se necessário o cuidado para com os pacientes que apresentam riscos de desenvolvimento de aloimunização e a conduta correta com aqueles que já apresentam a condição.

CONFLITOS DE INTERESSE

A autora declara não haver conflitos de interesse na elaboração do artigo.

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• **Books:** Chalmers J. Clinician’s manual on blood pressure and stroke prevention. 3rd ed. London: Science Press; 2002. 70 p.

Richardson MD, Warnock DW. Fungal Infection Diagnosis and Management. 2nd ed. Oxford: Blackwell Science Ltd; 1997.249 p.

•**Book chapters:** F. Reyes. Lymphocyte differentiation. In P Solal-Céligny, N Brousse, F Reyes, C Gisselbrecht, B Coiffier. Non-Hodgkin`s Lymphomas. Paris: Éditions Frison-Roche; 1993. p.19-29.

•**Annals:** Souza AM, Vaz RS, Carvalho MB, Arai Y, Hamerschilak B. Prevalência de testes sorológicos relacionados à hepatitis B e não-A, não-B em doadores de sangue. In: 190 Congresso Brasileiro de Hematologia e Hemoterapia / 260 Congresso da Sociedade Brasileira de Hematologia e Hemoterapia; 2003 Ago 6-9; São Paulo, 2003. Anais. p.103.

•**Theses:** Sandes AF. Caracterização imunofenotípica da diferenciação eritrocitária, granulocítica e megacariótica em pacientes com síndromes mielodisplásicas [thesis]. São Paulo: Universidade Federal de São Paulo; 2009. 126p.

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