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Blood, incompatibility and hearing

Sangre, incompatibilidad y audición

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SUMMARY

This study aims to analyze the relationship between blood incompatibility and hearing, through the severity that occurs in the perinatal period in the fetus and newborn. Systematic descriptive review is subject to the principles adopted by the Cochrane systematic review. This review made it possible to demonstrate the relation between hearing loss and blood incompatibility and the degrees of severity of the pathology in newborns. The ear as one of the most important sense organs for the development and acquisition of the human being in relation to the environment must remain functional. If there are any birth alterations, they would delay the correct development and in turn, would generate problems for the proper acquisition of language. Therefore, it is necessary to have correct gestational control to avoid the associated risk factors that could happen due to hearing loss. It is essential to give continuity to the research proposal because with these contributions we can identify hearing loss at early ages and make a timely intervention.

Keywords: *Blood incompatibility, RH factor, perinatal hemolytic disease, hemolysis, erythroblastosis, jaundice, bilirubin, hyperbilirubinemia, kernicterus.*

RESUMEN

El objetivo de este estudio es analizar la relación entre la incompatibilidad sanguínea y la audición, a través de la gravedad que se presenta en el período perinatal en el feto y recién nacido. Revisión sistemática descriptiva sujeta a los principios adaptados por la revisión sistemática Cochrane. Esta revisión permitió demostrar la relación entre la hipoacusia y la incompatibilidad sanguínea y los grados de severidad

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de la patología en los recién nacidos. El oído como uno de los órganos de los sentidos más importantes para el desarrollo y adquisición del ser humano en relación con el medio ambiente debe permanecer funcional. Si existen alteraciones congénitas, retrasarían el correcto desarrollo y a su vez generarían problemas para la adecuada adquisición del lenguaje. Por lo tanto, es necesario tener un correcto control gestacional para evitar los factores de riesgo asociados que podrían ocurrir por la pérdida auditiva. Es fundamental darle continuidad a la propuesta de investigación ya que con estos aportes podemos identificar la pérdida auditiva en edades tempranas y realizar una intervención oportuna.

Palabras clave: *Incompatibilidad sanguínea, factor RH, enfermedad hemolítica perinatal, hemólisis, eritroblastosis, ictericia, bilirrubina, hiperbilirrubinemia, kernicterus.*

INTRODUCTION

The ear is one of the main sensitive organs, which allows the process of learning, communication, and balance. To perform these functions, it needs the activity of each of the structures, connections, and neural processes related to hearing, and vascularization that comprise the outer, middle, and inner ear. When abnormal characteristics such as decreased hearing sensitivity, vertigo, or dizziness are present, they are due to an alteration that compromises the organ of hearing, which may be associated with genetic, hereditary, or acquired pathologies (1-3).

The vascularization of the ear is mostly found in the otic capsule and membranous labyrinth with the participation of the carotid system and the vertebrobasilar system which are composed of arteries that are responsible for the transport of blood flow (4,5,6). Rh incompatibility is a pathology that is caused by a reaction of the immune system when two incompatible blood groups are found during the gestation period leading to an affectation in the newborn (7-11).

Blood incompatibility is a condition that develops when a pregnant woman is Rh negative and the fetus is Rh positive and triggers the onset of erythroblastosis or hemolytic disease of the newborn (HDN) related to the loss of fetal red blood cells during or after birth (12), This occurs because antibodies produced by the mother cross the placental barrier in response to the passage through the placental circulation of fetal erythrocytes inherited from the father and incompatible with the mother (1,13-15). Such incompatibility encompasses those erythrocyte antigen systems; the one with the highest occurrence is related to the ABO system, however, on many occasions, it has low clinical value. Other minor antigens such as Kell, Duffy, or MNS, generate a lesser degree of EHRN (15-17).

Thus, incompatibility due to the Rh system, made up of more than 50 antigens, is the one that generates the greatest problem, even though it is less common than ABO. The great affectation of the hemolytic process can become very serious, and there are also cases with moderate compromise, which can be considered hyperbilirubinemia, which is an event in which there is an abundance of bilirubin in the blood (18,19). When the blood cells are destroyed, a substance known as bilirubin is formed, which is impossible to get rid of in the newborn. Thus, it accumulates in the blood, tissues, and fluids of the baby's body, which is called hyperbilirubinemia (2,17,18). Bilirubin has a pigment or coloration that causes the skin, eyes and other tissues of the newborn to be affected by yellowish coloration, and the condition receives the name jaundice (13,18,19). During pregnancy, the placenta removes bilirubin from the baby. However, at birth, the newborn's liver must remain in charge of this function.

There are several types of hyperbilirubinemia, which include psychological jaundice, breast milk jaundice, jaundice due to insufficient breastfeeding, jaundice related to inadequate liver function, and, the focus of this research, hemolytic jaundice (20), which occurs when there is a disintegration of red blood cells caused by hemolytic disease of the newborn or by excess red blood cells that disintegrate naturally, producing bilirubin (3,11,21).

The purpose of this research is to provide clinical knowledge to give the audiologist accurate information about the affectation or consequences that may alter their professional field of action in audiological practice and in turn determine the importance of the provision of health services focused on gestational control. Therefore, the following questions have arisen in depth about

blood incompatibility and associated pathologies: How Rh incompatibility can generate hearing loss, how perinatal hemolytic disease can cause hearing loss, what hearing alterations can produce hyperbilirubinemia in the newborn, and what are the consequences of this disease in the newborn?

METHODOLOGY

The methodology developed was applied based on the conceptual foundations adopted by the PRISMA methodology for the active search of scientific articles through the construction of search equations. In addition, the criteria established by the PICO methodology were included for the construction of the clinical question. The review focused on the behavior of blood incompatibility and hearing.

Inclusion criteria

The inclusion criteria for the study were determined to be suitable for those investigations that raised the clinical, preventive, and pathophysiological patterns directly related to the alterations underlying the risk factor.

Exclusion criteria

As exclusion criteria, we took into account the texts on additive hereditary losses in the newborn, minor ABO, and Rh blood group incompatibility (22,23).

In addition, it should be noted that following the PRISMA methodology, the respective filter was applied to the documents found.

Research question

Likewise, from the qualitative perspective, the clinically answerable research question is established according to the criteria established by the PICO methodology where:

P (patient or basic health problem)

I (intervention or risk factor)

C (comparison)

O (outcome)

According to each criterion of the methodology, three questions arise:

Table 1. Research questions

	Question 1	Question 2	Question 3
P	Blood group incompatibility	Perinatal or newborn hemolytic disease.	Consequence of hyperbilirubinemia in the newborn.
I	Hearing loss	Hearing loss.	Hearing loss.
C	Not applicable	Not applicable.	Not applicable.
O	Explicit below	Explicit below.	Explicit below
Ask	How can Rh incompatibility lead to hearing loss?	How can perinatal hemolytic disease cause hearing loss?	What auditory alterations can hyperbilirubinemia produce in the newborn?

Source: Own elaboration

Subsequently, the search equations were elaborated with the descriptors relevant to the study that were the basis for the research, bearing in mind that the databases searched were: PubMed, Scielo, ProQuest, DOAJ, Latindex, Dialnet, and EBSCO.

Table 2. Search equations

Independent Variable	Dependent Variable	Search equations
• HR Incompatibility. • RH blood group system. • Hearing loss. • Congenital hearing loss.	Newborn	("Rh incompatibility" OR "blood group system" OR "hemolytic disease") AND ("newborn") ("Hearing Loss") AND ("Rh Incompatibility") AND ("Newborn")
• Hemolytic disease. • Fetal erythroblastosis. • Isoimmunization. • Hemolysis. • Anemia. • Bilirubin. • Hyperbilirubinemia.		("Erythroblastosis fetalis" OR "isoimmunization" OR "Bilirubin" OR "Hyperbilirubinemia" OR "Hemolysis" OR "anemia" OR) AND ("Hearing loss" OR "hypoacusis") AND ("Newborn")
• Pathological jaundice. • Physiological jaundice.		("pathological jaundice" OR "physiological jaundice") AND ("newborn")

Source: Own elaboration

Once the search equations were constructed, a series of phases were followed to obtain the final sample of the documents that would be the basis of the review. These phases were:

1. *Identification phase:* in this phase, documents are searched in the various databases using the equations constructed.
2. *Selection and elimination phase:* the pertinent filters are made to select the sample so that it meets the selection criteria.
3. *Inclusion phase:* in this phase, the final sample is obtained, analyzed and used to construct the document.

RESULTS

The following identifies the filters used to identify the sample from the search equations.

The following is a diagram of the PRISMA methodology, which describes each of the phases in which the documents were eliminated and/or discarded until the final sample of 70 scientific articles that met all the selection criteria was obtained.

After the inclusion of the articles, a total of 71 scientific articles referred to topics such as Rh incompatibility, hemolytic disease, and hyperbilirubinemia in newborns.

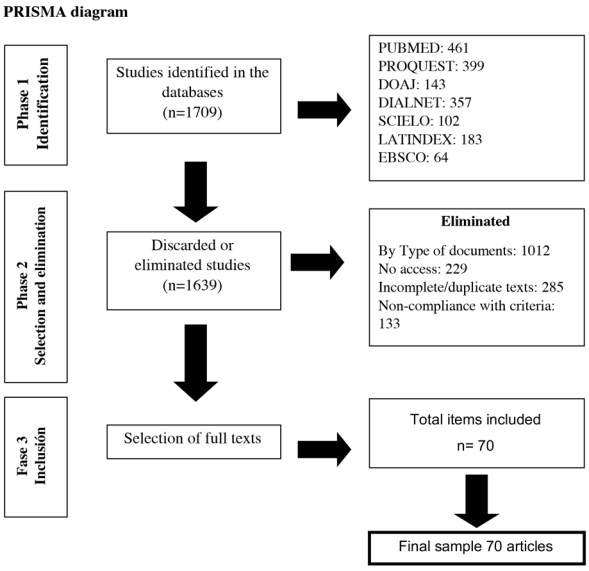
The search allowed us to determine that blood incompatibility can occur in two types, Rh and ABO. The maternal-fetal blood incompatibility that shows a higher rate of affectation at the audiological level is the incompatibility of the Rh blood group system since the mother's blood is Rh negative and the fetus is Rh positive and this shows a higher probability of being born with disabilities. This implies that the mother's body will develop a D antigen or Rh protein that will not affect the first child but the second, since this works as a means of defense that can cause a rupture of red blood cells in the fetus at the moment of direct contact.

Likewise, the behavior of the hemolytic disease in the newborn is highlighted due to the maternal-fetal blood incompatibility, the symptoms present, and the diversity of affectations that could be generated; As in hearing, which consequently develops an auditory neuropathy, non-genetic congenital hearing loss, at the bilateral level of sensorineural type, because, during the disease, the process of hemolysis occurs, interrupting the transport of oxygen and nutrients to organs and body tissues, causing hypoxia due to ischemia that can lead to necrosis, irreversible damage that sometimes is fatal.

Table 3. Document filtering

Search equation	Database	Total found	Type of document	Deleted documents: Incomplete/ duplicated texts	Deleted documents: No access criteria	Deleted documents: Non-compliance with variable	Total Sample
	PubMed	98	23	34	23	10	8
("Rh incompatibility" OR	ProQuest	138	99	14	16	7	2
"blood group system" OR	DOAJ	76	64	11	0	0	1
"hemolytic disease")	Dialnet	59	32	11	8	5	3
AND ("newborn")	EBSCO	33	19	9	4	0	1
	PubMed	115	102	4	0	0	9
("Hearing Loss") AND	ProQuest	145	82	26	21	13	3
("HR Incompatibility")	Latindex	156	109	21	19	4	3
AND ("Newborn")	Dialnet	209	178	23	4	2	2
("Erythroblastosis fetalis"	PubMed	146	58	43	27	11	7
OR "isoimmunization" OR	EBSCO	31	12	2	9	4	4
"Bilirubin" OR							
"Hyperbilirubinemia" OR	ProQuest	76	32	6	26	7	5
"Hemolysis" OR "anemia"							
OR) AND ("Hearing loss"	Latindex	27	8	0	13	5	1
OR "hypoacusis") AND							
("Newborn")	Dialnet	89	34	4	32	17	2
("pathological jaundice"	PubMed	102	52	11	23	9	7
OR "physiological	Scielo	102	72	3	15	9	3
jaundice") AND	ProQuest	40	17	4	11	4	4
("newborn")	DOAJ	67	19	3	34	6	5
Total		1 709	1 012	229	285	113	70

Source: Own elaboration



Source: *Own elaboration*

Table 4. Sample ratio

Crossing	Database	Title	Author(s)	Year	Method	Conclusion
("Rh incompatibility" OR "blood group system" OR "hemo-lytic disease") AND ("newborn")	ProQuest	Sangre total reconstituida "vieja", como alternativa de uso en exanguinotransfusión en enfermedad hemolítica del recién nacido.	Caballero-Noguéz, Jiménez, Cahuantzi-Jacobo, Méndez Durán & Caballero-Flores.	2016	Clinical case study	"The prognosis in neo-natal neurodevelop-ment will be profoundly related to serum BST levels" (17).
	PubMed	Molecular study of Cw/Cx antigens and frequency of Rh phenotypes in south-east Brazilian blood donors.	Costa, Souza Silva, Chiba, Cruz, Langhi Junior & Bordin.	2018	Molecular analysis.	" This study showed the prevalence of the RhD+ phenotype in the Brazilian population, and that through the molecular study" (9).
	PubMed	Rhesus factor: management in pregnancy.	Alcocer-Diaz, Preciado-Valencia, Zamora-Llanos & Acebo-Gutiérrez	2021	Descriptive and documentary type.	"The incompatibility of the mother and fetus for the Rh factor could cause the occurrence of the development of pathologies such as erythroblastosis fetalis or hemolytic disease of the newborn" (10).
	PubMed	Enfermedad hemolítica del recién nacido por anti-C y anti-E.	Zavala, Huerta & López.	2011	Case Study	"The presence of anti-c and anti-E antibodies was determined in the mother's serum and glued in the erythrocytes of the newborn" (24).
	PubMed	Enfermedad hemolítica del recién nacido por anticuerpos antieritrocitarios maternos.	Laitano.	2013	Systematic review.	"The implementation of actions for the preven-tion of maternal immunization is necessary to avoid the occurrence of hemolytic pathology of the newborn" (25).
	ProQuest	Criterios de alta hospitalaria del recién nacido a término sano tras el parto.	Rite Gracia, Pérez Muñuzuri, Sanz López, Leante Castellanos, Benavente Fernández, Ruiz Campillo et al. .	2017	Systematic review.	"Infants discharged before 48 h after birth would have to be assessed between the third and fourth day of life"(26).
	PubMed	Metodologías de Evaluación Fonoaudiológica del Componente Pragmático del Lenguaje en Infantes.	Portilla & Mogollon.	2015	Systematic review.	"In the methodologies found, there is no one that allows accounting for the assessment of the illocutive, perlocutive, and locutionary aspects and communicative performance" (27).
	EBSCO	Enfermedad hemolítica del recién nacido por incompatibilidad ABO.	Villegas Cruz, Durán Menéndez, Alfonso Dávila, López De Roux, Cortina, Vilar Carro & Orbeal Aldama.	2007	Clinical case follow-up.	"Phototherapy is the least serious treatment, but one must be alert for an unusual occur-rence of a sign and thus make a relevant and effective action that decreases morbidity" (28).
	DOAJ	Hemolytic disease of the newborn by isoimmu-nization to minor blood groups. A weird case.	Ferrer Montoya, Laurenzo González & Ávila Sánchez.	2016	Clinical case study	" To the attention that with the decline of hemolytic anemia due to Rh incompatibility, it should be taken into account counts jaundice and hemolysis secondary to unusual or minor clusters " (29).
	Dialnet	Tratamiento de la anemia hiporregenerativa tardía de la enfermedad hemolítica del recién nacido con eritropoyetina recombinante.	Donato, Bacciedoni, García, Schvartzman & Vain.	2009	Prospective observational study.	"Erythropoietin is a potentially useful and safe treatment. Its efficacy would have to be confirmed in future randomized studies" (30).
	Dialnet	Hemolytic disease of the newborn blood incompatibility, clinical characteristics, risk factors, and diagnostic methods.	Bohórquez Guerrero, Rocafuerte Alvarado, Mena Villarreal, Saavedra Aguilar & Satama Pereira.	2022	Systematic review.	"The consequences of not predicting HDN can result in acute anemia, brain damage, and cardiac arrest in the neonate" (31).
	PubMed	Protocolo de consenso (SETS/SEGO) del diag-nóstico y prevención de la enfermedad hemolítica del feto y del recién nacido (EHFRN).	Muñiz-Díaz, Oyonarte, Rodríguez-Villanueva, Parra & Santiago.	2010	Practical guide.	"Diagnosis and prevention of hemolytic dis-ease of the fetus and newborn is key to preventing multiple diseases" (32).

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Table 4. Sample ratio (continue from page 836).

Crossing	Database	Title	Author(s)	Year	Method	Conclusion
	PubMed	Enfermedad hemolítica perinatal: manejo de la embarazada RhD negative.	Insunza, Behnke, Carrillo.	2011	Meta analysis.	"HPE due to RhD iso-immunization has decreased markedly, however, it will remain a possibility in perinatology" (33).
	Dialnet	Ayudas para la marcha en la pa-rálisis cerebral infantil/Help for the March in the Child Cerebral Palsy.	Bermejo Franco.	2012	Systematic review.	"Proven effectiveness of orthopedic treatment on the handicaps and individualities of each child" (34).
	PubMed	La encefalopatía hipóxico isquémica en una unidad de cuidados intensivos.	Franco Argote, Coca Álvarez, Domínguez Dieppa, Amador & Almeida.	2017	Descriptive, longitudinal investigation in 46 neonates.	"Among neonates with hypoxic encephalopathy, those born at term predominate" (35).
	Dialnet	Incompatibilidad Rh en el embarazo.	Vizueta, López, Balon & Zam-brano	2019	Case study	"Rh incompatibility in pregnancy occurs in Rh-negative patients whose father is Rh-positive, resulting in a blood incompatibility disorder in the product that causes hemolytic disease in the fetus" (1).
	PubMed	Cumplimiento de la normatividad vigente para la detección temprana de la hipoacusia neonatal.	Rojas Godoy, Rivas Muñoz. & Gómez Gómez	2014	Cross-sectional study, the medical records of all children born in a certain period of time were reviewed.	"None of the children were screened for neonatal hearing loss because according to their characteristics it was not necessary" (4).
	PubMed	Neuropatía auditiva, diagnóstico y manejo audiológico.	Cañete.	2008	Meta-analysis.	"Clinical conditions associated with NA/DA include hyperbilirubinemia, neurovegetative diseases" (5).
	PubMed	Prevalencia de hipoacusia y factores de riesgo asociados en recién nacidos del estado de Colima, México.	Gómez Pichardo, Martinez Contreras, Ochoa Brust & Vásquez.	2013	Cross-sectional study with patients.	"Otoacoustic emissions are an appropriate test for hearing screening in newborns" (36).
("Hearing Loss") AND ("HR Incom-patibility") AND ("Newborn")	PubMed	Hipoacusia: identificación e intervención precoces.	Benito Orejas & Silva Rico.	2017	Meta analysis.	"The causes of childhood hearing loss are numerous, and knowledge of them is evolving as genetics develops" (37).
	PubMed	Prevalencia de hipoacusia en recién nacidos sanos en un hospital de tercer nivel de atención. Detección mediante tamiz auditivo neonatal.	Peña-Alejandro & Contreras-Rivas.	2018	Hearing screening.	"It is estimated that approximately 61% of the population suffers from hearing loss from birth" (38).
	Dialnet	Hipoxia perinatal y su impacto en el neurodesarrollo.	Flores Compadre, Cruz, Orozco & Vélez.	2013	Meta analysis.	"The existence of secondary neuronal dam-age ranging from days to weeks after the hypoxic event highlights the importance of early assessment and intervention to prevent the sequelae of this brain insult" (39).
	ProQuest	Tamizaje auditivo neonatal en pacientes de alto riesgo con otoemisiones acústicas: evaluación de resultados.	Ordóñez, Díaz Patiño, González-Marín, Rueda, Silva, Ramírez et al.	2018	Clinical case follow-up.	"Congenital infection as a risk factor was present in 2.4% only with the presence of Toxo-plasmosis, of which 2 ears presented cofosis"(40).
	PubMed	Enfermedad hemolítica por incompatibilidad de Rh: presentación de un caso.	Pérez Escalante & González.	2017	Case study.	"Generalized cutaneous mucosal jaundice and improvement after phototherapy and exchange transfusion" (41).
	Latindex	Association of family history and consanguinity with permanent hearing impairment	Selvarajan, Arunachalam, Bellur , Mandke & Nagarajan.	2022	Neonatal screening.	" Family history and consanguinity seem to be an important risk factor of hearing impairment both in isolation and in combination" (42).

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Table 4. Sample ratio (continue from page 837).

Crossing	Database	Title	Author(s)	Year	Method	Conclusion
	Latindex	La discapacidad auditiva. Principales modelos y ayudas técnicas para la intervención.	Carrascosa García	2015	Systematic review.	"Hearing impairment makes it possible to get to know minors better" (43).
	Latindex	Detección precoz de la hipoacusia infantil.	Delgado Domínguez.	2011	Meta analysis.	"Early detection of childhood hearing loss" (44).
	PubMed	Comportamiento de la hipoacusia no sindrómica en una familia del municipio de Urbano Noris.	Noris Holguín, Márquez Ibáñez & Santana Hernández.	2017	Case studies.	"The great clinical heterogeneity described for hypoacusis was corroborated" (45).
	PubMed	Recomendaciones CODEPEH 2014 para la detección precoz de la hipoacusia diferida.	Núñez-Batalla, Jáudenes-Casaubón, Sequí-Canet, Vivanco-Allende & Zubicaray-Ugarteche.	2016	Systematic review.	"Early identification of deferred disorders requires special attention and expertise among all professionals who care for children during their childhood" (46).
	PubMed	Atención del recién nacido sano.	Pezzotti Rentería, Alvarado Vega, Segura Roldán, Fernández Lafontaine, de Sarasqueta &Vincent.	1981	Case study.	"Early detection of conditions not evident at the newborn stage would be a major biological disadvantage" (47).
	ProQuest	Tamizaje universal de hipoacusia en el recién nacido.	Alvo, Der & Délano.	2010	Screening study.	"The need for a universal screening program for children with hearing loss is becoming increasingly evident" (48).
	ProQuest	Hipoacusia mediante emisiones otoacústicas en el recién nacido de la UCIN.	Castellanos-Coutiño, Santamaría-Muñoz & Escobar-Carrillo.	2012	Prospective study .	"Otoacoustic emissions proved to be a useful tool in screening for cochlear damage in the high-risk newborn in the NICU" (49).
("Erythroblastosis fetalis" OR "isoimmunization" OR "Bilirubin" OR "Hyperbilirubinemia" OR "Hemolysis" OR "anemia" OR) AND ("Hearing loss" OR "hypoacusis") AND ("Newborn")	PubMed	Manejo de la embarazada con isoinmunización por anticuerpos irregulars.	Javiera Fuenzalida & Jorge Carvajal	2014	Meta-analysis.	"Feto-maternal isoimmunization can lead to EHP disease. The main cause remains ABO incompatibility, followed by RhD isoimmunization" (2).
	ProQuest	Hiperbilirrubinemia neonatal agravada.	González, Uría, Morán, López, Aguilar & Pérez.	2010	Descriptive and retrospective study of 173 newborns.	"Aggravated neonatal hyperbilirubinemia constitutes a health problem. Aggravating factors are prematurity and low birth weight"(3).
	Dialnet	Transfusión intrauterina: tratamiento de anemia fetal severa en el Centro de Referencia Perinatal Oriente.	Trinidad Pinochet, Susana Aguilera, Daniela Cisternas, Rodrigo Terra, Sergio De La Fuente & Juan Guillermo Rodríguez.	2019	A retrospective descriptive analysis of the cases of fetal anemia requiring transfusion in the hospital was performed.	"A mortality rate of 3.7% associated with the procedure was reported" (7).
	EBSCO	The neurological sequelae of neonatal hyperbilirubinemia: definitions, diagnosis, and treatment of the kernicterus spectrum disorders (KSDs).	Shapiro, Le Pichon, Riordan & Watchkoe.	2017	Systematic nomenclature based on pathophysiological and clinical criteria.	"The adoption of a systematic nomencla-ture for the spectrum of clinical consequences of hyperbilirubinemia will help to unify the field and promote more effective research" (11).
	ProQuest	Isoinmunización ABO en recién nacidos en Pinar del Río.	Hernández Castro, Iglesias Castro & Abascal González.	2017	Observational, descriptive, and cross-sectional research.	"ABO isoimmunization is a frequent cause of severe hyperbilirubinemia between the second and seventh day of life, indirect bilirubin determined between 24 and 36 hours of life allows us to identify newborns with the possibility of developing severe hyperbilirubinemia" (12).

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Table 4. Sample ratio (continue from page 839).

Crossing	Database	Title	Author(s)	Year	Method	Conclusion
	EBSCO	Hemolytic disease in fetuses and newborns due to antibodies against the M-antigen.	Páez, Jiménez & Corredor.	2021	Case study.	"Although anti-M antibodies do not usually play a significant role in HDFN, it highlights the importance of identifying the presence of antibodies that may be crucial in preventing HDFN and lead to new recommendations for screening and timely treatment of hemolysis in newborns" (13).
	EBSCO	Anti-E alloimmunization in a pregnancy with a low antibody titer E.	Nakanishi, Oishi, Nakamura, Murakami, Ono, Nozawa, Kitamura &. Sengoku.	2020	Case study.	" The potential risk of hemolytic disease should be considered in cases with such low titers " (14).
	Latindex	Disfunción neurológica inducida por bilirrubina.	Campistol, Galvez, Cazorla, Málaga, Iriondo & Cusí.	2012	Case study.	"All patients presented clinical manifestations in the neonatal period, and more or less severe neurological sequelae in all 6 survivors" (15).
	ProQuest	Efectividad de la fototerapia en la hiperbilirrubinemia neonatal.	Durán, García & Sánchez.	2015	Systematic review.	"The most effective light therapy is LEDS, white sheets increase the effectiveness of light therapy, and the neonate's diaper can be removed when bilirubin has increased" (16).
	PubMed	Encefalopatía por Kernicterus: Serie clínica.	Hernandez, Schmidt & Huete.	2013	Clinical case.	"Kernicterus is a devastating disease that is still present in the national reality" (18).
	PubMed	The role of recombinant Human erythropoietin in neonatal anemia.	El-Lahony, Saleh, Habib, Shehata & El-Hawy a.	2020	Clinical case.	" PO therapy in conjunction with iron, vitamin E, and folic acid, stimulated erythropoiesis and significantly reduced the need for blood transfusion in AOP" (22).
	PubMed	Guia de manejo obstétrico e neonatal em mães aloimunizadas.	Rivas, Marcalain, Recouso, Silveira, Bentos, Alonso, et al.	2021	Meta analysis.	" It's fundamental that the immunohematology laboratories of the haemotherapy and transfusion medicine services be in charge of diagnostic studies of erythrocyte alloimmun-ization"(23).
	EBSCO	Pigmentación intrínseca verde en dentición temporal asociada a hiperbilirrubinemia neonatal: Reporte de un caso.	Gabriela, Aportela, Angélica, Mendoza, Domínguez & Javier.	2015	Clinical case study.	" The case presented, a child of two years ten months age with a history of hyperbilirubinemia that was the primary dentition green as a result of the deposit of bilirubin in the dental tissues" (21).
	PubMed	Implicaciones clínicas de incompatibilidad RH entre feto-madre, riesgos y tratamiento.	López Carvajal, Viteri Luzuriaga, Frías Ponce & Quinto Mina.	2021	Systematic review.	"Rh incompatibility is a maternal condition that warrants sequential follow-up to favor perinatal outcomes"(50).
	PubMed	Factores asociados a hipoacusia basados en el programa Tamiz Auditivo Neonatal e Intervención Temprana.	González-Jiménez, Delgado-Mendoza, Rojano-González, Valdez-Izaguirre, Gutiérrez-Aguilar, Márquez-Celedonio & González-Santes.	2017	Analytical, cross-sectional study with neonates.	"The incidence of hearing impairment in newborns diagnosed was (5/234 newborns)" (51).
	PubMed	Guías para la transfusión de sangre y sus componentes.	Salazar.	2003	Meta-analysis.	"Transfusion therapy has reduced mortality and prolonged and improved quality of life" (52).
	ProQuest	Factores promotores de la hiperbilirrubinemia neonatal no hemolítica, en una unidad de cuidados intermedios del recién nacido.	Villalobos-Alcázar, Guzmán-Bárcenas, González-Pérez & Rojas-Hernández.	2001	Retrospective, case-control study.	"The promoter factors identified in both groups were sepsis and fasting" (53).
	ProQuest	Anemias hemolíticas autoinmunes.	Mejía-Arregui	2005	Systematic review.	"Isoimmune hemolysis occurs as a conse-quence of a conflict between red blood cells and antibodies when one of these two fac-tors is exogenous" (54)

(continue in page 840…).

Table 4. Sample ratio (continue from page 839),

Crossing	Database	Title	Author(s)	Year	Method	Conclusion
	Dialnet	Relación entre hiperbilirrubinemia neonatal e hipoacusia neurosensorial.	Corujo-Santana, Falcón-González, Borkoski-Barreiro, Pérez-Plasencia & Ramos-Macías.	2015	Retrospective study.	"The percentage of infants with a diagnosis of sensorineural hearing loss among newborns with hyperbilirubinemia at birth is higher than expected in the general population" (55).
	ProQuest	Factores predisponentes para ictericia neonatal en los pacientes egresados de la UCIneonatal, Hospital Infantil los Ángeles de Pasto.	Galíndez-González, Carrera-Benavides, Díaz-Jiménez & Martínez-Burbano.	2017	Observational, descriptive, retrospective, and quantitative study.	"Neonatal jaundice is associated with both modifiable and non-modifiable maternal and neonatal factors, which can be addressed with appropriate strategies to reduce the burden of disease"(6).
	ProQuest	Prevalencia de ictericia neonatal y factores asociados en recién nacidos a término.	Ñacari Vera.	2019	Systematic review.	"The prevalence of neonatal jaundice is variable worldwide" (8).
("pathological jaundice" OR "physiological jaundice") AND ("newborn")	DOAJ	Hiperbilirrubinemias hereditarias: Un diagnóstico diferencial a considerar en ictericia.	Díaz Gutiérrez, García Sáenz & Ortiz Orrego	2019	Systematic review.	"The knowledge of these syndromes is important given the high index of suspicion required for its diagnosis and its differentiation from other hepato-biliary pathologies of greater risk and severity."(19).
	DOAJ	Factores maternos y neonatales asociados a la ictericia del recién nacido en el hospital regional Moquegua. 2014-2015.	Quintanilla Flores.V	2016	Observational study,	"Maternal age and type of delivery are maternal factors associated with jaundice; associated neonatal factors are ABO group incompatibility, breastfeeding, and early contact" (20).
	Scielo	Conducting systematic reviews of association (etiology): the Joanna Briggs Institute's approach.	Moola, Munn, Sears, Sfetcu, Currie, Lisy, Mu.	2015	Descriptive study.	"Systematic evidence review is the research method that underpins the traditional evidence-based approach to healthcare" (56).
	PubMed	El sistema inmune neonatal y su relación con la infección.	Herrera Aguirre, Rodríguez Tapia, Suarez Aceves and Hernández Bautista.	2013	Systematic review.	"It is necessary to be alert to the recognition of neonatal risk factors"(57).
	DOAJ	Neonatal hyperbilirubinemia, acute bilirubin encephalopathy, and Kernicterus: The continuum is still valid in the 21st century.	Mesquita & Casartelli.	2017	Meta-analysis.	"Hyperbilirubinemia continues to be a neonatal health problem today" (58).
	DOAJ	Prevalencia de ictericia en el período neonatal en un hospital público de la ciudad de Buenos Aires.	Aspres, Boccaccio, Tovo, Molina, Ferreira.	2011	Neonatal screening-Case follow-up.	"Neonatal jaundice in infants ≥ 35 weeks' GA attended in Pediatric ICU continues to be a problem for the health care team and their families" (59).
	PubMed	Hipoacusia neonatal, secundaria a hiperbilirrubinemia.	Garay-Mendoza & Murillo-Hernández.	2007	Thirty newborns with jaundice and hyperbiliru-binemia were studied with PEATc.	"Bilirubin level between 16 mg/dL in a jaundiced neonate is sufficient to study possible central nervous system damage" (60).
	ProQuest	La ecografía clínica permite visualizar la causa de la ictericia patológica en lactantes y niños.	Kippes.	2015	Descriptive study.	"Ultrasonography plays an indispensable role in the evaluation and follow-up of infants and children with jaundice" (61).
	DOAJ	Guidelines for the prevention, detection, and management of hyperbiliru-binemia in newborns of 35 or more weeks of gestation.	Sánchez-Redondo, Leante Castellanos, Benavente Fernández, Pérez Muñuzuri, Rite Gracia & Ruiz Campillo.	2017	Meta-analysis.	"Hyperbilirubinemia is one of the most frequent causes of hospital readmission during the first week of life"(62).
	Scielo	Trastorno Específico del Desarrollo del Lenguaje en una población infantil colombiana.	Hincapié, Giraldo, Lopera, Pineda, Castro, Lopera, Mendieta, Jaramillo, Arboleda & Aguirre.	2008	Case study.	"The great clinical heterogeneity described for hypoacusis was corroborated" (63).

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Table 4. Sample ratio (continue from page 840).

Crossing	Database	Title	Author(s)	Year	Method	Conclusion
	PubMed	Etiología de ictericia neonatal en niños ingresados para tratamiento con fototerapia.	Rebollar-Rangel, Escobedo-Torres & Flores-Nava.	2017	Review of files.	"The main cause of admission for neonatal jaundice was due to ABO group incompatibility followed by phys-iological jaundice, sepsis, and low birth weight"(64).
	PubMed	Inmunoglobulina endovenosa como una opción en el manejo de la ictericia neonatal por incompatibilidad ABO.	Arenas & Pradil-la.	2015	Meta-analysis.	"Jaundice remains a frequent entity in the neonatal stage and implies a high risk of mainly short- and long-term neurological complications" (65).
	PubMed	Prevalencia de ictericia neonatal patológica en el servicio de Neonatología del hospital universitario Dr. Ángel Larralde, Valencia estado Carabobo. Venezuela.	Rodríguez, Rojas, Ruiz, Peñuela & Naguanagua.	2012	Prospective study.	"The majority of cases were attributable to ABO incompatibility"(66).
	PubMed	Evaluation of neonatal hemolytic jaundice: clinical and laboratory parameters.	Cherepnalkovski, Krzelj, Zafi-rovska-Ivanovska, Gruev, Markic, Aluloska & Piperkovska.	2015	Case Study	"The laboratory profile in cases of ABO/Rh isoimmunization shows the hemolytic mechanism of jaundice"(67).
	Scielo	Neuropatía auditiva y cribados neonatales.	Trinidad Ramos & Trinidad Ruiz.	2015	Review of files.	"Auditory neuropathy may go undetected in programs based on the use of otoemissions as the first level of screening" (68).
	ProQuest	Caracterización casos de ictericia neonatal desde una perspectiva de enfermería.	Bello Carrasco, García Delgado, Santos Álvarez & Rio Frio	2018	Quasi-experimental	"We can say that the implementation of educational strategy contributes to improving the level of knowledge. And thus provide a quality service and warmth" (69).
	PubMed	Neuropatía auditiva en México: la importancia de realizar potenciales auditivos de tallo.	Rubio-Partida, Celis-Aguilar, Verdiales-Lugo, Castro-Urquizo, De la Mora-Fernández & Coutinho-de Toledo	2020	Narrative literature review.	"The importance of performing otoacoustic emissions and auditory evoked potentials in the population lies in the improvement of the quality of life of people" (70).

Source: Own elaboration.

ANALYSIS AND DISCUSSION

The ear is one of the main organs that gives us direct access to language and human communication. To achieve its functioning, interdisciplinary work must be carried out in which different structures are involved, such as anatomical structures, irrigation, and brain function (23,25).

Hearing loss very early in life can have multiple deleterious effects on the newborn, most commonly related to speech and language attainment (13,33,56).

During pregnancy, it is possible to contract or acquire diseases that can affect the baby and its development. Therefore, it is important to perform each of the tests or routine analyses that help us to rule out a high-risk pregnancy, the hemogram is a clinical examination that provides information on the presence of red blood cells, white blood cells, platelets, hemoglobin status, and hematocrit, as well as blood group and Rh factor (20).

The Rh factor is a protein found in red blood cells and is present in Rh-positive individuals, i.e. Rh-negative individuals do not carry this protein. When the father and mother are not Rh similar, i.e. Rh negative or Rh positive, it is called Rh incompatibility (17,28).

Blood incompatibility is an affectation in the blood that can cause changes or alterations in the organism that lead to pathologies that can compromise organs or structures of the human body that fulfill one or several functions (29). In this case, the ear is one of the organs that due to its irrigation and function can have an affectation.

The diagnostic analysis of the fetal problem due to Rh (D) conflict should be performed progressively based on clinical and complementary tests. In the case of an Rh (D) negative pregnancy, a study of the paternal group and factor is required to identify the risk of Rh incompatibility. If the father is Rh (D) negative, normal prenatal care is continued, since there is no risk of developing Rh (D) incompatibility. If, on the contrary, it is positive, it is necessary to check the mother for the appearance of immune antibodies using the indirect Coombs' test, to establish whether or not she is sensitized (7,30,31,33).

Sensitization occurs in Rh-negative women due to the passage of Rh-positive fetal blood into the maternal circulation, which can be spontaneous or due to feto-maternal hemorrhage. The origin of the occurrence of passage of fetal blood occurs when the placenta separates at the time of delivery, which is why it is necessary to administer anti-D immunoglobulin within 72 hours of this event (15).

At the moment of the blood transfusion, the D antigen is produced in the mother that will directly affect the second child at the moment of the delivery or if a hemorrhage or miscarriage occurs, this antigen reacts to the Rh positive factor as a means of defense against the red blood cells of the fetus considered a foreign agent, This results in a lack of irrigation or passage of the bloodstream to the medulla oblongata and produces an affectation in the ventral nuclei and, therefore, the decussation or synapsis of the auditory impulse will not take place (36,39).

Rh incompatibility results in PNHD (perinatal hemolytic disease), as a result of the degree of hemolysis and compensatory erythrocyte production generated by the fetus (11,29,34). In 1932, Diamond, Blackfan, and Batty described Erytroblastosis foetalis. Smith called this entity a hemolytic disease of the fetus and newborn and today due to new knowledge about it were named perinatal hemolytic disease (PNHD) (15,35). Hemolytic disease of the fetus and newborn is an autoimmune immunological pathology, where there is a relationship with the destruction of fetal erythrocytes (red blood cells) at or after birth, caused by maternal antibodies that cross the placental barrier, which occurs in response to the passage of fetal erythrocytes inherited from the father and incompatible with the mother into the placental circulation; it can generally affect the second or subsequent pregnancies, after the sensitization of the mother (38,69). To establish the onset of the disease, the following conditions must be present: the mother must develop an immune response against the fetal red blood cell antigen, the maternal antibody must be able to cross the placental barrier and it must enter the fetal circulation (36-38).

When this attack on the red blood cells occurs, they are broken down and destroyed. This process is called hemolysis and results in anemia, which is highly dangerous because it limits the ability of

the blood to carry oxygen to the organs and tissues of the fetus or newborn. In response, the fetus tries to generate more red blood cells rapidly in the bone marrow, liver, and spleen; these new red blood cells are called erythroblasts, characterized by their immaturity and, as the red blood cells break down, a substance called bilirubin is formed which the fetus cannot easily get rid of and in which the placenta intervenes helping to eliminate it but at low rates. The remainder may accumulate in the blood and other tissues and fluids of the body (39-41).

Subsequently, complications may vary from mild to severe; during pregnancy, mild to severe stages of anemia may occur, affecting other organs. Hydrops fetalis, which carries a higher risk, may develop. In this condition, the heart fails and large amounts of fluid accumulate in the tissues and organs of the fetus, running the risk of intrauterine death (13,22,42). If the fetus is born, complications remain at high risk with severe jaundice (53). And its relationship with hearing loss is directly associated with the vertebrobasilar system responsible for blood supply, irrigating most of the inner ear (43,44), and also with the basilar membrane. These cells interpret the information and secrete a chemical substance that will be transformed into electrical impulses that the auditory nerves will carry to the brain, in the presence of the pathology the membrane will not have any functionality, remaining static, without generating any movement and pressure on the cells, causing a cochlear alteration of neurosensory type (46,57). Several investigations refer that there are many causes of congenital or neonatal hearing loss; classified within the non-genetic congenital and bilateral types in which the behavior of the pathophysiological agent occurs simultaneously in the ears in prematurity, especially when it is related to fetal erythroblastosis and hypoxia (42,43).

Hyperbilirubinemia is a condition in which there is too much bilirubin in the newborn's blood (47,48). It occurs when red blood cells break down, and a substance called bilirubin is formed, at which time the newborn cannot get rid of it and it accumulates in the blood and other tissues and body fluids of the newborn, this is called hyperbilirubinemia. Although low bilirubin levels are not a problem, it is considered physiological jaundice since it is very frequent in 60 % of term newborns, characterized by low bilirubin levels, its time of appearance is after 24 hours of life and it is considered a benign condition. However, large amounts of bilirubin can circulate to the tissues in the brain and cause seizures and brain damage; this is considered pathological jaundice, which is characterized by high levels of bilirubin before 24 hours of birth and is considered a high-risk condition capable of producing complications in the newborn (61).

Hyperbilirubinemia is considered one of the pathological conditions in newborns (33,34,48), especially in children with other risk factors. The effects include neurological problems such as Kernicterus, in which there is generalized encephalopathy that refers to a syndrome of brain dysfunction and sensorineural deafness (39), due to the frequency of jaundice in the newborn, studies confirm that it can generate sensory hearing loss (59). The Joint Committee on Infant Hearing shows that taking into account that sensorineural hearing loss or deafness can be caused by high levels of bilirubin causing hyperbilirubinemia and Ictericia, as long as jaundice is considered high risk, i.e., pathological jaundice (49,61).

In a study at INPER (Instituto Nacional de Perinatología) in Mexico City with 5,109 newborns in 2013, hyperbilirubinemia was more frequent in male newborns (15,57). The most frequent etiology was Rh incompatibility, in relation to the gestational time the most frequent hypoacusis occurs in preterm newborns, the minimum and maximum range of hyperbilirubinemia with which hypoacusis was diagnosed was 18.7- 22.2 mg/dL, presenting 10 % of auditory neuropathy; which contrasted with our findings. However, no study correlates the bilirubin level with the degree of hypoacusis, so a comparison is not possible (5,44,66).

Some studies contradict the INPER research, such as the study by Suresh and Lucey (2015) who state that they did not find any case of hearing loss despite prolonged exposure to high bilirubin values, which led them to indicate that bilirubin is not as toxic to the auditory system as it is supposed to be (46,52,57). On the other hand Parodi (2013) with his research on "causes of auditory neuropathy" reaches a point where he states that the auditory pathway is vulnerable due to the high levels of bilirubin in the newborn,

being the cause of AN (34,35,67). This analysis leads us to believe that although the inner ear is interrupted due to its irrigation by high levels of bilirubin in the blood, there are very few studies on the hyperbilirubinization of the auditory system. There are very few studies on hyperbilirubinemia in relation to hearing loss in newborns, but this does not mean that most of the evidence found does not lead us to the relationship that hyperbilirubinemia has with hearing loss in newborns, since neurosensory impairment appears as a result of increased bilirubin in the circulation, but it has not been shown that there is a proportional relationship between studies that lead to an exact criterion with (52,53,66,67). The present study, with an appropriate methodological design, finds important factors and various pathologies related to bilirubin and its strong relationship with hearing loss that could be of great importance for future studies.

CONCLUSIONS

In the exhaustive search of the bibliography for the systematic review, minimal information was found on the affectation that Rh incompatibility has on hearing; in addition, blood incompatibility is a relevant pathology since means of immunoglobulin prevents the activation of anti-D that can cause an affectation to the fetus at the moment that a blood transfusion occurs. Likewise, Rh incompatibility presents a retrocochlear affectation directly affecting the ventral nuclei found in the medulla oblongata leading to non-genetic congenital deafness.

In Colombia, Resolution 412 of 2000 is mandatory, which refers to the audiological assessment for early detection of neonatal hearing loss by referring newborns to the performance of evoked auditory potentials that are irrigated under high-risk criteria. In the field of Speech-language pathologist, it is important to implement promotion and prevention, as well as to be part of the interdisciplinary work for maternal-fetal care with a high-risk index.

Likewise, it was observed that the most affected by hyperbilirubinemia in newborns are males with high levels of bilirubin in the blood. This allows us to conclude from the research that the study of hyperbilirubinemia was based on the picture of pathological jaundice since it presents high degrees of danger at the cerebral level. Therefore, it is necessary to continue with future proposals in relation to the investigated subject.

It should be noted that, due to its ambiguity, not much scientific evidence was found in relation to hyperbilirubinemia and its auditory affectation. However, the perinatal hemolytic disease continues to prove to be a risk factor for both the fetus and the mother, which is why it should be prioritized at two points in time, during the gestational period and delivery.

Finally, it was found that perinatal hemolytic disease produces a bilateral sensorineural hearing loss, but without specifying the degree of severity in the newborn, which would lead to alterations in its development. In clinical practice, the participation of the speech therapist and/or specialist audiologist within the interdisciplinary team led by the obstetrician is essential, considering the risk factor to which the newborn is exposed and the consequences that would be generated.

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