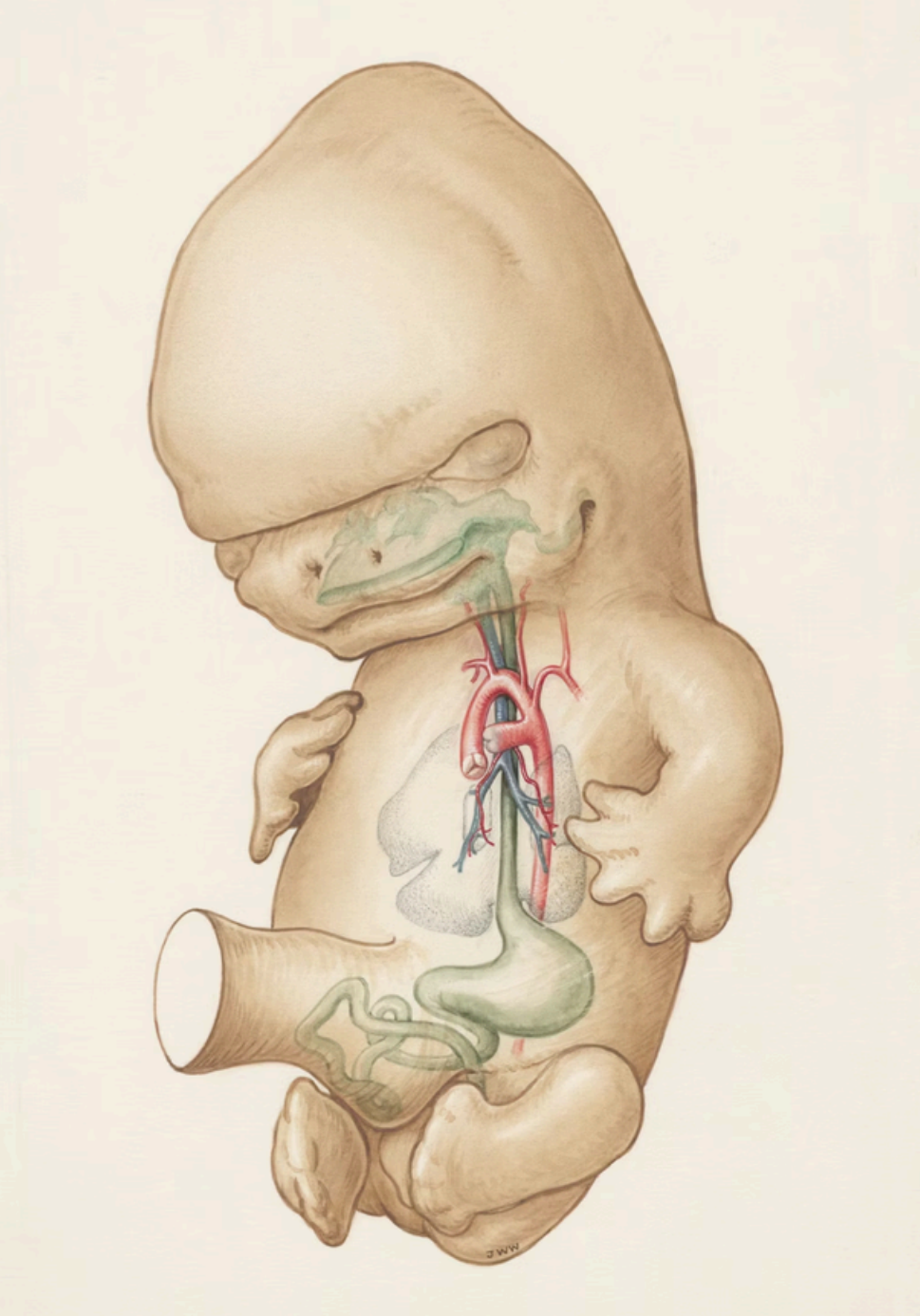
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The journal aims to strengthen the academic, scientific, and professional training of students, medical residents, faculty, and researchers, promoting research, critical thinking, and evidence-based medicine as cornerstones of the development of the health sciences.

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Message from the Editor-in-Chief

Medicine begins with a question.

Why did it happen? What does this discovery mean? Is there a better way to do it? Behind every scientific advance, every surgical technique, and every treatment we now take for granted, there was someone who decided not to settle for the available answer and dared to formulate a new question.

Medical training is not just about acquiring knowledge, but about developing the ability to question, understand, and expand upon it. Research represents precisely that exercise: transforming curiosity into evidence and ideas into opportunities to improve the care of our patients.

The articles in this issue reflect that commitment. Each one arose from a concern, an observation, or a question that someone decided to explore with scientific rigor. Beyond the results obtained, the true value of the process lies in training professionals capable of thinking independently, facing uncertainty, and contributing to the advancement of medicine.

I am deeply grateful to the authors, reviewers, and editors who made this issue possible. Their dedication strengthens an academic community that understands that knowledge is not a destination, but the beginning of new questions.

Because every great answer once began with the courage to ask a question.

Everything is possible for a willing heart.

Miguel A. S. Lecuona
Editor-in-Chief

In this issue

This issue of the Journal of the Physician in Training brings together contributions that reflect the diversity of the health sciences and a commitment to scientific advancement, innovation, and medical education. Through interviews, literature reviews, and reflective articles, readers will find a comprehensive overview of current topics in clinical practice, medical education, public health, and biomedical research.

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Research not only answers questions; it also inspires those yet to be formulated.

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Interview with Gylmar Mariel Cárdenas, M.A.

Carlos Eduardo Aguillón-Narváez[1], Yahir Alejandro Chico-Alcaraz[1].

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ABSTRACT

In this interview, we have the privilege of speaking with ***Gylmar Mariel Cárdenas, M.A.***, Head of the Outreach Division at the Autonomous University of San Luis Potosí, who provided us with a comprehensive overview of his professional career, highlighting important aspects related to his position and its significance and impact on medical students.

Keywords: outreach, opportunities, community service, international.

Could you tell us a little about your career and how you came to hold your current position in the Outreach Division?

I graduated from the Autonomous University of San Luis Potosí, from the Faculty of Engineering; I'm a mechanical and electrical engineer, and I did an internship in the automotive industry, starting at the company "Cummins", where I consider myself lucky because after three months they offered me a position at the plant as a Manufacturing Engineer in the drivetrain department, which was a tiny little room where they bring in tractor-trailer engines and test them to see if they work properly or not. If they don't work properly, they repair them and put them back in to finish the job. After that, I was offered a job in the United States, but they wouldn't let me go, and this is something I believe was my own fault, because I made myself "indispensable". They told me, "No one else does what you do". Honestly, I didn't like that reaction, but now that I think about it in hindsight, I never actually trained anyone who could replace me.

Here's some advice I'll give you right now: always train someone who can take your place, because if a job opportunity ever comes up within the same company, you'll be able to say, "Okay, I can leave, but this person is staying, and with just a little more training, they'll be able to take my place". I think that was my mistake, I never trained anyone who could take my place; at the time, I didn't understand that, and I got really upset. Some time later, I received the same offer again in the United States, and the same thing happened, plus another opportunity at a company called "Valeo" in France. So, I resigned from "Cummins" and moved to France as a Research and Development Engineer.

I returned to Mexico after two years; they made me Research and Development Manager, and later Project Manager, where I was in charge of overseeing a group of projects and ensuring that the alternators were customized for each client. After that, I moved to another company called "Eaton," which specializes in tractor-trailers; at that time, we were manufacturing transmissions and clutches, but I was doing essentially the same work. After that, I joined another company as Engineering Manager for the alternator division, and from there, they offered me the position of Production Manager and later Plant Manager. It's a "bit" of a complicated job and, to be honest, really grueling, but well-paid; I had some disagreements with my boss there, so I decided that was enough.

I was planning to take a sabbatical, and a month later I came here to San Luis Potosí for a management interview. Around that time, a friend contacted me and told me he'd been offered a job with the state government, and he said, "You should go for it". I went to the interview, and to be honest, I did end up joining the government at the Secretariat of Economic Development, working in the industrial infrastructure division, where I stayed for the rest of the six-year term. The administration changed and I left, but I was already working here at the university in the School of Engineering. I applied for a position, won one of them, and now I'm a full-time professor. They put me in charge of the Community Engagement Department because of my government experience, and I brought a lot of investments here to San Luis Potosí.

In May 2016, the dean asked me if I could serve as the Assistant Secretary of Planning for the Faculty of Engineering. In October 2016, the headmaster asked me to assist him with the Community Engagement Division, and now I'm here. Here, we are responsible for community service programs, social service, continuing education, alumni relations, entrepreneurship, and knowledge transfer; the very same areas we've been working on since 2016.

Why is it important for students to do community service?

Imagine if, as students, you had never done any hands-on work. What do you think would happen? How would you feel? In the medical field, for example, you start very early with lab work or clinical practice, and you gradually develop an interest in the theoretical aspects as you apply them in practice.

This isn't unique to medicine or engineering; it applies to all fields of study. When you know what you're getting into and what you'll be doing in the professional world, you develop a deeper love and appreciation for it. The important thing is to see what your work will entail. There are two decisions that I realize are the most important in your life: the first is what you're going to study, because that's how you'll make a living; and the second is who you're going to marry. These are two very important things. If you'd asked me as a kid what I wanted to be, I'd have said an astronaut or something like that. Later, the truth is that my dad was a dentist, my mom had studied biochemical engineering, my wife is a dentist, and my father-in-law is a doctor. I come from a medical background and really liked it, but I was also interested in machines, so I decided to study engineering, and much of the research I do is in biotechnology.

I think it's very important for you to get hands-on experience, to know what you're getting into so you can take a greater interest in it. That's why I believe community service and internships are so important. However, something I strongly encourage is this: if, when you're just starting your degree, you begin to get a feel for what you'll be doing later on, it will spark more interest in what you're learning in class. What I'd say to the people in charge of community service placements is: get the students out there, take them to the workplaces where they'll eventually be, regardless of their major, so they can figure out whether that's what they want to do or not.

Specifically for medical school, how important is it to perform community service in rural areas or by caring for those in need for one's professional development?

I'll answer that with another question. Do you know why the Faculty of Medicine of the Autonomous University of San Luis Potosí is considered one of the best in the country? Because of all the hands-on training. You have four hours of uninterrupted clinical practice every day for two years of your degree program. You have almost no breaks compared to other universities, which have only a third of what you have; even in Europe, where they have only a fifth. So it's very important because of that hands-on experience with experts in the fields who work in those areas every day.

Apart from community service, are there any other options for completing social service in medicine?

You have three types of service: community service, research, and outreach. Which of these is most important? The one you choose, based on what you enjoy doing.

In all of these service options, you'll have different experiences, and it's up to you. We had a program with the Faculty of Medicine called "Social Service in the Productive Sector," in which eight people participated, and seven of them confidently said they learned a lot; but I'll say it again, it depends on what you want. So, which social service option is best? It depends on what you want.

What are the main challenges that students most frequently face during their community service?

When it comes to skills like leadership, teamwork, knowing another language, and being resilient in the face of the complicated situations they encounter, that kind of knowledge comes from within each of you. It depends on each person's personality and how they handle situations. Especially for those of you dealing with a lot of stress, you need to have the strength and character to know how to handle these events. There's a lot of talk about the younger generations being "fragile", but we also need to know how to guide them and help them learn to face these challenges. I'm proud to say that we prepare our students very well, based on my own experience and what I've seen up to now.

Has there been any kind of international program to send students on rotations to other countries?

We haven't explored that option very much, and it would certainly be interesting to do so. We do have a German cultural exchange program where recent graduates can go to work in Germany for approximately 2 to 4 years, but the reality is that they're looking to stay there and work. At the end of the day, these are opportunities, and many know how to make the most of them in their own way.

Are there any other exchange programs available for students in the health sciences in general?

Yes, in fact, we have many programs and agreements with different universities that allow for research exchanges, although these are only available to graduate students and alumni.

For undergraduate students, we offer study abroad opportunities, through which we have more than 600 agreements with universities in many parts of the world.

In the medical school, exchanges to France and Germany are in high demand, and we have also hosted many students from Spain and Colombia. The process is the same for all schools: students must visit the Department of Internationalization to obtain the necessary forms, secure a letter of acceptance from the host university, and determine which courses they will take so that credits can be transferred, among other requirements.

There is also the option for students who wish to do so to complete their community service abroad; so far, I recall three medical students and one engineering student who completed their community service abroad, the first time this was done with interesting results, but this requires an agreement with the university.



Figure 1. From left to right: Yahir Chico, Gylmar Mariel Cárdenas, M.A.; Carlos Aguillón.

In the Faculty of Medicine, as in other schools, there are students with entrepreneurial ideas, whether it's writing books, creating digital resources, or other ventures. What kind of support can the Outreach Division offer all these students?

Yes, it's extremely interesting, some students have even gone on to start their own companies. In the department, we can help them in many ways, both with incubation, if they have a small business already up and running, and with acceleration, through the Office of Technology Transfer and Knowledge to register their trademarks. Let me give you an example: we helped the company Koplik® register its trademark. They came here, sat right where you are now, and began telling us all about their project. We helped them with the registration process, and now the business is up and running. Since then, they've visited us several times to update us on how the venture is going, and we've supported them in applying for various funding opportunities. Right now, we're exploring ways to accelerate their business growth.

Another story is the project led by Dr. Mario Martínez, head of the burn unit at the "*Hospital Central*" [now the "*Hospital Regional de Alta Especialidad 'Dr. Ignacio Morones Prieto'*"]. He began by conducting research on thermography, and after several researchers agreed to establish the company, we teamed up with engineers to determine what equipment we could develop for them. We purchased a thermal imaging camera, and through testing and research, we successfully launched the small business.

All companies go through an investment curve where there are losses at the beginning, but then growth begins, the investment is recouped, and profits start to roll in. We've had several such ventures, and we continue to promote them through various initiatives such as the "Reto San Luis," where various business ideas compete; or "EagleNest", where five entrepreneurs serve as investors and, through donations, a cash prize is awarded to the selected business project, in the style of Shark Tank®, with projects from each faculty competing.

The entrepreneurial spirit of all the contestants does not go unnoticed.

Since 2019, we've been asking ourselves: How can we train students in entrepreneurship if the teachers aren't trained either? So, we began training teachers in partnership with the Wardhwani Foundation, so that they, in turn, could start training students in entrepreneurship.

For you in the healthcare field, a medical consultation is an entrepreneurial venture, one that's more objective than any other. I've noticed that in healthcare degree programs, we're never taught how to bill patients, how to conduct a consultation, how to satisfy your patients, or how to make your practice appealing. These are marketing topics, and the program focuses so heavily on healthcare that when students graduate, they ask themselves, "What do I do now?" and "How do I do it?" It used to be believed that this business was a "Maya business", where you open the business and just wait for clients to come, but that's no longer the case. Competition is very fierce these days, and it's a very valid question: "How do I make my business/practice/clinic/hospital attractive? How do I draw people to me?" Obviously, if you're a very good doctor and treat your patients well, people will talk about you, and you'll gain recognition through word of mouth. But what about in the beginning? No one knows you yet.

Based on the above, do you think it would be essential to add a course on marketing or business administration to the medical school's curriculum?

It's extremely important. I've always said that we all need to be natural salespeople, because, as I tell my students, even if it sounds bad, you have to know how to sell yourself: how you're going to sell your work, your image, your personality, and what you're offering. And what are you offering? Knowledge.

I highly recommend that you follow us on social media, because we offer several free courses, such as "Empréndete", which covers the basics of starting your own business, as well as the "Business Guide" and "The Entrepreneur's Path." You can find us as ***Vinculación UASLP***.

I've always believed that with all the knowledge we acquire in this beautiful art of medicine, there are potential opportunities beyond the clinic, but we lack that entrepreneurial vision, the ability to identify a problem, propose a solution, and create a business. I see this in my colleagues, they all plan to focus exclusively on treating patients, but I believe the field of medicine extends even further than that; we need people who understand human biology in engineering, politics, and other fields.

Even so, I'm impressed by everything you're capable of doing, seeing you all interviewing me, running a medical journal, though I should mention that you're not the first: we once had two medical students in this department who made all the division's promotional videos for me, and I used to wonder, "What is a doctor doing making videos?" They did them perfectly well; I

bought them a green screen, lights, microphones, and stands, and the result was very interesting. I couldn't stop thinking: instead of having a systems engineer, I have doctors doing this work, and they do it very well. That's why I'm impressed by the medical field, because they have so many skills. I've noticed that people in medicine have a very unique profile.

Could you share a final message with all the students reading this?

I think passion is a key factor, if you're passionate about something, go for it. If you have passion, no obstacle will be too big.

I've given many talks on entrepreneurship, and I've often visited graduate programs to answer the question, "How do I fund my projects?" The first thing to ask is: Is the project you're interested in something you're truly passionate about? Do you love it? And if that's the case, you'll really be able to find money even under rocks.

There are four ways to raise money, which I call "the 4 F's": family, friends, funders, and fools (people who believe in your idea). Any of these can fund you, but if you're truly passionate about it, you'll convey that passion, and people will get excited about it right along with you. There are several crowdfunding sites online, and if you check them out, they'll ask you to record a 5-minute video explaining your project and demonstrating your passion for it. Appeal to people's emotions, emotions are what can make a real difference, and you'll succeed.

You'll see this with your patients; if you convey that confidence to them, they'll feel better. You'll see it. Much of what you'll be working on with your patients involves body language, so always be passionate about what you're doing, no matter what it is.

We thank Gylmar Mariel Cárdenas, M.A., for his willingness, time and valuable participation, as well as for sharing his experiences and perspectives for the preparation of this manuscript.



Declarations

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Comparison of the Diagnostic Performance of the ASGE 2019 Criteria and the C-IMP for Choledocholithiasis in Patients Undergoing ERCP

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ABSTRACT

Introduction. Choledocholithiasis is a frequent complication of cholelithiasis (10–20%), and its diagnosis is challenging due to the limited accuracy of initial studies. Endoscopic retrograde cholangiopancreatography (ERCP), the gold standard, is invasive and carries risks; therefore, predictive tools are needed to optimize patient selection.
Objective. To compare the diagnostic performance of the 2019 ASGE criteria versus the Calculator *Ignacio Morones Prieto* (C-IMP) predictive model for identifying choledocholithiasis in patients undergoing ERCP at a tertiary care hospital.
Subjects and methods. A retrospective, cross-sectional, single-center study was conducted, including patients undergoing ERCP at the *Hospital Regional de Alta Especialidad Dr. Ignacio Morones Prieto* between January 2022 and December 2024. Clinical, biochemical, and imaging variables were analyzed, as well as the risk classification according to the 2019 ASGE criteria and the probability estimated by the C-IMP. The presence of choledocholithiasis confirmed by ERCP was used as the reference standard. Sensitivity, specificity, predictive values, and ROC curves were calculated for both models.
Results. Seventy-two patients were included, of whom 49 (68.1%) had choledocholithiasis. Cholangitis was significantly associated with its presence, while pancreatitis was more frequent in patients without stones. The common bile duct diameter and the probability estimated by the C-IMP were greater in patients with choledocholithiasis. The ASGE model showed a sensitivity of 73.5%, a specificity of 43.5%, a positive predictive value of 73.5%, and a negative predictive value of 43.5% (AUC 0.59). The C-IMP model showed a sensitivity of 75.5%, a specificity of 82.6%, a positive predictive value of 90.2%, and a negative predictive value of 61.3% (AUC 0.82), with better reclassification and a lower proportion of false positives.
Conclusions. The 2019 ASGE criteria showed limited discriminatory capacity. The C-IMP model demonstrated better diagnostic performance and could optimize the selection of patients eligible for ERCP, reducing unnecessary procedures.

Keywords: ERCP, choledocholithiasis, ASGE, C-IMP.

INTRODUCTION

Choledocholithiasis, characterized by the presence of stones in the common bile duct (CBD), is a common complication of cholelithiasis, with a prevalence of 10-20% in patients with symptomatic gallstones [1,2]. It can lead to serious complications such as obstructive jaundice, ascending cholangitis, or biliary pancreatitis, with a mortality rate of 3-5% in severe cases [5]. In Mexico, factors such as obesity, high-fat diets, and genetic predisposition increase the incidence of biliary diseases, underscoring their clinical importance [1].

The diagnosis of choledocholithiasis is complex due to nonspecific abnormalities in liver function tests and the limited sensitivity of abdominal ultrasound (20-80%), the latter influenced by the operator's experience and the distal location of the stones [2,3,6]. Endoscopic retrograde cholangiopancreatography (ERCP) is the gold standard for diagnosis and treatment, allowing for stone removal and management of biliary obstructions [7]. However, its invasive nature carries risks such as post-ERCP pancreatitis (5-15%), hemorrhage (1-2%), and perforation (0.6%), highlighting the need for careful patient selection to avoid unnecessary procedures [2,5].

Driven by this need, risk stratification systems have been developed to optimize the indication for ERCP. The American Society for Gastrointestinal Endoscopy (ASGE) has classified the predictors that modulate risk stratification. In 2010, it established "very strong," "strong," and "moderate" predictors (see Table 1) [8], although its accuracy has been limited, with sensitivities of 47-75%, specificities of 73-83%, and negative ERCP rates as high as 20-53% [2,5]. In the context of acute cholecystitis, the high-probability

score has a sensitivity of 89% but a low positive predictive value (PPV) (52% vs. 71-79% in the general population), resulting in 39.3% unnecessary ERCPs, suggesting the need for prior tests such as magnetic resonance cholangiopancreatography (MRCP) or endoscopic ultrasound (EUS) [3,9]. In 2019, the ASGE updated its criteria to include "high-probability" and "intermediate-probability" predictors (see Table 1), removing factors such as pancreatitis and a bilirubin level between 1.8-4 mg/dL due to their low performance [5].

Table 1. ASGE predictors for risk stratification for choledocholithiasis, in their 2010 and 2019 versions.

ASGE 2010	ASGE 2019
"Very high" risk factors: Calculus on ultrasound, cholangitis, total bilirubin >4 mg/dL.	**"High probability":** Calculus on CBC imaging, cholangitis, bilirubin >4 mg/dL plus dilated CBC.
"High" risk factors: Bilirubin 1.8–4 mg/dL, dilated CBC >6 mm.	**"Intermediate probability":** Abnormal liver function tests, age >55 years, dilated CBC without bilirubin >4 mg/dL.
"Moderate" risk factors: Abnormal liver function tests, age >55 years, biliary pancreatitis.	

ASGE = American Society for Gastrointestinal Endoscopy; CBC = common bile duct.

Following this update, several studies have emerged seeking to support the change in these predictors and their actual usefulness in optimizing risk stratification and, therefore, reducing unnecessary procedures. Among these studies, Yousaf *et al.* reported a sensitivity of 96.6%, a specificity of 66.7%, and an AUC of 0.81 for ASGE 2019, although negative ERCPs persisted secondary to suboptimal specificity [2]. Similarly, Wang *et al.* demonstrated that some predictors included in ASGE 2019 have high specificity but low sensitivity, limiting their usefulness in ruling out choledocholithiasis [5]. Other studies validated the performance of the ASGE, ESGE, and SAGES criteria in different populations, reporting high sensitivities but variable specificities and the persistence of unnecessary procedures [13-17].

In parallel, several authors have highlighted the role of complementary tools such as MRCP, EUS, and intraoperative exploration of the common bile duct to optimize the diagnostic and therapeutic approach [10,11,17,23,24]. Likewise, alternative predictive models based on clinical, biochemical, and imaging variables have been developed, including simplified scoring systems and models applied to specific contexts, with discriminative capabilities comparable to or better than ASGE 2019 [18-20]. More recently, machine learning-based studies have reported superior diagnostic performance compared to traditional models, demonstrating the potential of these technologies to optimize the prediction of choledocholithiasis [21,22]. Finally, epidemiological and clinical studies have pointed to population variations and limitations of conventional predictors, suggesting that these may overestimate risk in certain clinical scenarios (Table 2) [4,12]. These findings reinforce the need for predictive tools adapted to specific contexts and highlight the value of integrating diagnostic imaging and predictive models to optimize management.

Table 2. ASGE 2019 Choledocholithiasis Risk Criteria.

Category	Criteria
High risk (>50%)	• Presence of a stone in the common bile duct confirmed by transabdominal ultrasound. • Clinically confirmed ascending cholangitis. • Total bilirubin >4 mg/dL and common bile duct dilation >6 mm (with gallbladder in situ) on ultrasound.
Intermediate risk (10-50%)	• Total bilirubin >4 mg/dL (in isolation). • Common bile duct dilation >6 mm (with gallbladder in situ) on ultrasound. • Abnormal liver function tests (elevated AST, ALT, alkaline phosphatase, or GGT; other than bilirubin >4 mg/dL). • Age >55 years. • Biliary abdominal pain. • Evidence of jaundice.
Low risk (<10%)	• Absence of the above predictors. • Normal liver function tests and ultrasound (without common bile duct dilation).

ASGE = American Society for Gastrointestinal Endoscopy; AST = aspartate aminotransferase; ALT = alanine aminotransferase; GGT = gamma-glutamyl transferase.

In Mexico, a predictive model was developed at the *Hospital Regional de Alta Especialidad Dr. Ignacio Morones Prieto*, based on a cohort of 374 patients and validated in 154. This model, which uses logistic regression with variables such as age, pancreatitis, cholangitis, total bilirubin (log-transformed), and CBC calculation by ultrasound, excluded CBC diameter due to multicollinearity. In validation, it achieved an AUC of 93.81%, with a sensitivity of 80% and a specificity of 87% when the high probability threshold was adjusted to 40%, exceeding the accuracy of ASGE 2010 (<70%) [1]. Compared to ASGE, the Calculator *Ignacio Morones Prieto* (C-IMP) reclassified patients more accurately, reducing false positives. Of 234 patients classified as high-risk by ASGE, only 159 were classified as such by C-IMP, with only 30% of those reclassified as intermediate-risk of having choledocholithiasis [1]. Implemented in an online calculator, this model optimizes patient selection for ERCP in resource-limited settings [1].

The comparison between ASGE 2019 and C-IMP is relevant, as both aim to minimize unnecessary ERCPs, but they differ in approach: ASGE uses categorical criteria, while C-IMP employs a continuous model. Although ASGE 2019 improves specificity compared to 2010, its performance is suboptimal for excluding choledocholithiasis [2], while C-IMP promises greater accuracy in Mexican settings [1]. Validating C-IMP against ASGE 2019 in ERCP patients requires further studies, especially outside of Mexico, justifying local research to optimize management and reduce the burden of invasive procedures. Practically speaking, identifying the most accurate tool will improve patient selection for ERCP in referral hospitals, a procedure that depends on the gastroenterologist's experience and learning curve, thus reducing complications and costs associated with avoidable procedures. From a social perspective, optimizing the management of choledocholithiasis in a country with a high prevalence of biliary diseases will improve the quality of care within the public health system, such as at the *Hospital*

Regional de Alta Especialidad Dr. Ignacio Morones Prieto.

Therefore, this study aims to compare the diagnostic performance of the 2019 ASGE criteria against the C-IMP predictive model for identifying choledocholithiasis in patients undergoing ERCP at a tertiary care hospital, providing evidence to guide clinical decisions, maximizing resources, and benefiting patients with a more accurate diagnosis.

METHODS

- **Study design and subjects**

An observational, analytical, retrospective, and cross-sectional study was conducted, using a cohort of patients from the *Hospital Regional de Alta Especialidad Dr. Ignacio Morones Prieto*, treated between January 1, 2022, and December 31, 2024.

Patients over 18 years of age at the time of ERCP were included. These patients underwent ERCP for clinically suspected or confirmed choledocholithiasis and had complete medical records (including liver function tests with bilirubin and transaminases; abdominal ultrasound report showing the diameter or presence of stones in the common bile duct; relevant clinical history such as pancreatitis, cholangitis, jaundice; and ERCP results indicating the presence or absence of choledocholithiasis).

Patients under 18 years of age, those with an indication for ERCP other than choledocholithiasis, those with incomplete medical records, those with a history of biliary surgery, and those with chronic liver disease or extrahepatic cholestasis unrelated to choledocholithiasis were excluded.

Patients with inconclusive ERCP results, contradictory data, recording errors or duplicate records, and those with failed ERCP were also excluded.

Table 3. Variables analyzed in the study.

Variable	Operational definition	Possible values	Units	Type of variable
Dependent				
Choledocholithiasis	Confirmation of common bile duct stones by ERCP.	Yes / No	Unitless	Dichotomous
Independent				
2019 ASGE Classification	Choledocholithiasis prediction system based on high, intermediate, or low probability criteria, according to the presence of predictors (e.g., stone on CBC, bilirubin >4 mg/dL, cholangitis).	High probability Intermediate probability Low probability	Unitless	Ordinal qualitative
C-IMP	Continuous predictive model for choledocholithiasis based on variables such as age, bilirubin (logarithmic), pancreatitis, and cholangitis, which generates a numerical probability.	0 to 100	Percentage (%)	Ratio quantitative
Control (confounding) variables				
Age	Patient's age at the time of ERCP.	18 to 100	Years	Ratio quantitative
Sex	Patient's biological sex.	Masculine Femenine	Unitless	Nominal qualitative
Cholangitis	Diagnosis of cholangitis based on the 2018 Tokyo criteria.	Yes / No	Unitless	Dichotomous
Post-ERCP pancreatitis	Diagnosis of acute pancreatitis following ERCP, documented in the medical record within 7 days of the procedure, based on clinical criteria (abdominal pain, elevated amylase/lipase >3 times the upper limit of normal) or medical confirmation.	Yes / No	Unitless	Dichotomous
ERCP-related bleeding	Bleeding attributable to ERCP (sphincterotomy, hematoma) documented in the medical record within 7 days of the procedure.	Yes / No	Unitless	Dichotomous

Continuation

Perforation	Perforation of the bile duct, duodenum, or other ERCP-related structure, documented in the medical record within 7 days of the procedure, identified by imaging or surgical intervention.	Yes / No	Unitless	Dichotomous

ERCP = endoscopic retrograde cholangiopancreatography; ASGE = American Society for Gastrointestinal Endoscopy; CBC = common bile duct; C-IMP = Calculator Ignacio Morones Prieto.

- **Statistical analysis**

Data processing and analysis were performed using IBM SPSS Statistics software (IBM Corp., Armonk, NY, USA). Qualitative variables were expressed as absolute frequencies and proportions, while quantitative variables were described using measures of central tendency and dispersion (Table 3).

The comparison of qualitative variables between groups with and without choledocholithiasis confirmed by ERCP was performed using Pearson's chi-square test or Fisher's exact test, depending on the expected frequency size. For quantitative variables, those with a normal distribution were compared using Student's t-test for independent samples, while variables with a non-normal distribution were analyzed using the Mann-Whitney U test.

The evaluation of the diagnostic performance of the 2019 ASGE classification and the C-IMP was performed using ERCP confirmation of choledocholithiasis as the reference standard. For each model, sensitivity, specificity, positive predictive value, and negative predictive value were estimated using 2×2 contingency tables.

Additionally, receiver operating characteristic (ROC) curves were generated for both models to analyze their overall discriminative capacity. The area under the curve (AUC) was calculated along with its 95% confidence interval, standard error, and statistical significance level. Diagnostic performance was compared descriptively using AUC values, with values closer to 1 indicating greater discriminative capacity. A significance level of $p < 0.05$ was established for all statistical tests. The results are presented in tables and figures to facilitate interpretation.

- **Ethical considerations**

The research rigorously adhered to the ethical principles of the Declaration of Helsinki (2013, revised in 2024) and current Mexican regulations. Data protection was guaranteed, ensuring that the use of information from medical records did not allow for patient identification, in compliance with the General Law on the Protection of Personal Data Held by Obligated Entities.

The study was considered low-risk, as it used data from medical records retrospectively, in accordance with Article 17, Section I of the Regulations of the General Health Law on Health Research, and obtained permission from the health institution that holds the records, pursuant to NOM-004-SSA3-2012.

The protocol was evaluated and approved by the Research Committee registered with COFEPRIS 17 CI 24 028 093, and by the Research Ethics Committee registered with CONBIOÉTICA-24-CEI-001-20160427, in accordance with NOM-012-SSA3-2012 and NOM-168-SSA1-1998.

RESULTS

During the period from January 1, 2022 to December 31, 2024, a total of 116 ERCPs were performed at the *Hospital Regional de Alta Especialidad Dr. Ignacio Morones Prieto*, of which 44 records were excluded following the established criteria, leaving a total of 72 patients included in the study (see Figure 1).

The median age of the study population was 45.5 years [IQR: 29.25-65.75], with 72.2% (n = 52) being female.

The age distribution was comparable between the groups, with mean ages of 44.4 (±20.4) and 47 (10-84) for patients without choledocholithiasis and with choledocholithiasis confirmed by ERCP, respectively ($p = 0.38$).

There were no significant differences in the sex distribution between the groups ($p = 0.82$).

A higher frequency of cholangitis was observed in patients with confirmed choledocholithiasis ($p = 0.29$), as well as a lower frequency of pancreatitis ($p = 0.12$). There was no significant difference in the presence of stones in the common bile duct as demonstrated by ultrasound, ASGE classification, or complications between the two groups.

It is worth noting that more than half of the patients without choledocholithiasis were classified as being at high risk for choledocholithiasis (see Table 4).

In the group with confirmed choledocholithiasis, a larger common bile duct diameter ($p < 0.05$) and a higher percentage of C-IMP ($p < 0.05$) were observed. No significant differences were observed in age, total bilirubin, and direct bilirubin between the two groups (see Table 5).

Of the 72 patients, 49 (68.1%) were classified as having a high risk of choledocholithiasis, of which 36 (73.5%) had choledocholithiasis confirmed by ERCP. Our study showed a sensitivity of 73.5%, specificity of 43.5%, positive predictive value of 73.5% and negative predictive value of 43.5% for the classification of high risk of choledocholithiasis according to the ASGE (see Table 6).

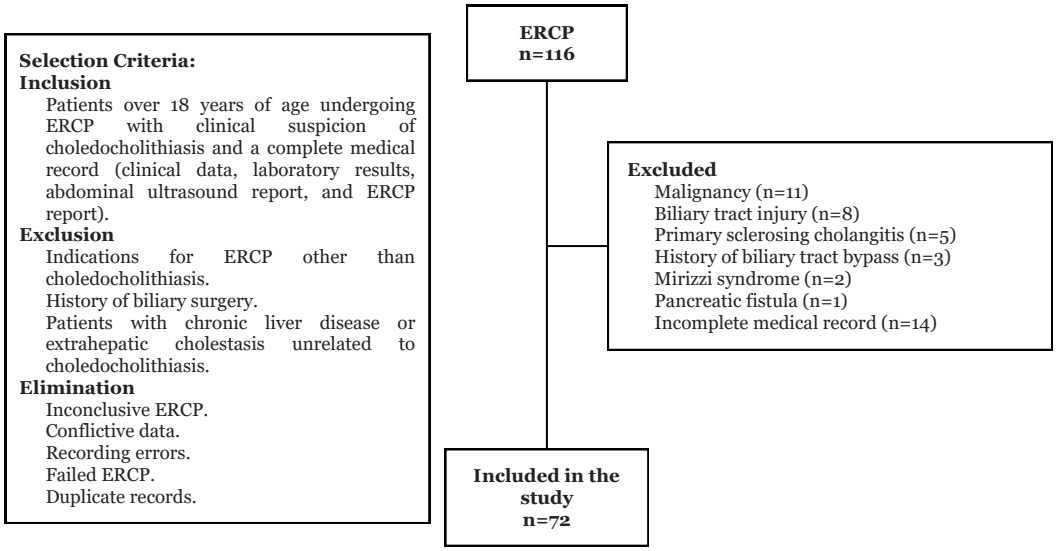


Figure 1. Flowchart for patient selection, with inclusion, exclusion and elimination criteria. *ERCP = endoscopic retrograde cholangiopancreatography.*

Table 4. Analysis of qualitative variables.

Confirmed choledocholithiasis	**No** (n=23)	**Yes** (n=49)	***p value***
Female (%)	17 (73.9%)	35 (71.4%)	.82
Pancreatitis (%)	12 (52.2%)	11 (22.4%)	.012*
Cholangitis (%)	2 (8.7%)	16 (32.6%)	.029*
LCUS (%)	0 (0%)	6 (12.2%)	.09
ASGE (%)			
Low	1 (4.3%)	0	.165
Moderate	9 (39.1%)	13 (26.5%)	
High	13 (56.5%)	36 (73.5%)	
Complications (%)	4 (17.4%)	7 (14.3%)	.48

*The * sign represents statistical significance <.05. LCUS = LCUS: Spanish abbreviation for stone in common bile duct visualized by ultrasound; ASGE = American Society for Gastrointestinal Endoscopy.*

Table 5. Descriptive statistics of the quantitative variables

Confirmed choledocholithiasis	**No** (n=23)	**Yes** (n=49)	***p value***
Age (years)	44.4±20.4	47 (10-84)	.38
Total bilirrubin (mg/dl)	4.2 (2.8-5.6)	5.8 (.4-12.1)	.07
Direct bilirrubin (mg/dl)	3±1.9	4.3 (.1-9.4)	.09
Common bile duct diameter (mm)	6 (4-8)	10.1±4.4	.05*
C-IMP	33.9±20.4	71.7(26.6-116.8)	.05*

*The * sign represents statistical significance <.05. C-IMP = Calculator Ignacio Morones Prieto.*

Table 6. Comparison of patients with and without choledocholithiasis classified according to ASGE.

ASGE Classification	**Negative choledocholithiasis**	**Confirmed choledocholithiasis**
Moderate n=23 (31.9%)	10 (43.5%)	13 (56.5%)
High n=49 (68.1%)	13 (26.5%)	36 (73.5%)

ASGE = American Society for Gastrointestinal Endoscopy.

On the other hand, using the C-IMP, 41 patients (56.9%) were classified as high risk of choledocholithiasis (>50%) of which 37 (90.2%) had the presence of choledocholithiasis confirmed. This represents a sensitivity of 75.5%, specificity of 82.6%, positive predictive value of 90.2% and negative predictive value of 61.3% for the C-IMP high risk classification of choledocholithiasis (see Table 7). Taking this into account, of 49 patients who had been classified as high risk of choledocholithiasis by the ASGE, only 37 of them were reclassified as high risk by the C-IMP (see Table 8).

A ROC curve was performed for the ASGE criteria, obtaining an area under the curve of 0.59, with a standard error of .074 (95% CI: .445-.736; p= .218), indicative of a limited discriminative capacity of the ASGE criteria to identify choledocholithiasis in this population group.

In contrast, the area under the curve for the C-IMP was .82 with a standard error of .048 (95% CI: .73-.92; p <0.001), indicative of a good discriminative capacity of the model to identify choledocholithiasis (see Figure 2).

Table 7. Comparison of patients with and without choledocholithiasis classified by the C-IMP.

C-IMP	Negative choledocholithiasis	Confirmed choledocholithiasis
Moderate n=31 (43.1%)	19 (61.3%)	12 (38.7%)
High n=41 (56.9%)	4 (9.8%)	37 (90.2%)

C-IMP = Calculator Ignacio Morones Prieto.

Table 8. Reclassification to C-IMP of patients with moderate and high risk of choledocholithiasis by the ASGE.

ASGE	Moderate C-IMP	High C-IMP
Moderate n=23	19 (82.6%)	4 (17.4%)
High n=49	12 (24.5%)	37 (75.5%)

ASGE = American Society for Gastrointestinal Endoscopy; C-IMP = Calculator Ignacio Morones Prieto.

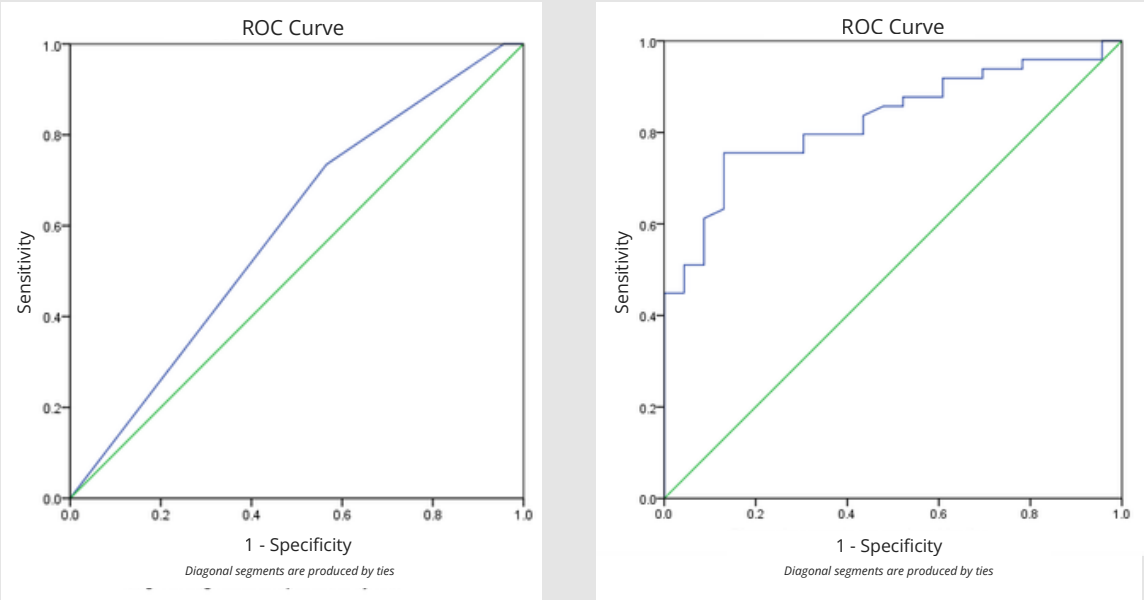


Figure 2. ROC curves for ASGE criteria (left) and C-IMP criteria (right).

DISCUSSION

This study compared the performance of the 2019 ASGE risk stratification criteria for choledocholithiasis with the C-IMP model in a cohort of patients undergoing ERCP at a tertiary care hospital in Mexico. In this population, the ASGE high-risk classification showed limited discriminatory capacity, while the C-IMP model demonstrated superior diagnostic performance, with a better balance between sensitivity and specificity and a reduction in unnecessary ERCP indications.

The prevalence of confirmed choledocholithiasis was high (68.1%), consistent with a population selected for invasive procedures. No differences in age or sex were observed between patients with and without choledocholithiasis, in accordance with the findings reported by Yousaf *et al.* and Hasak *et al.* [2,16], reinforcing the fact that prediction depends primarily on clinical and biochemical variables.

In clinical analysis, cholangitis was significantly associated with the presence of choledocholithiasis, establishing itself as a reliable marker of biliary obstruction. Conversely, pancreatitis was more frequent in patients without common bile duct stones, supporting its limited value as a predictor and its exclusion from the 2019 ASGE criteria [5,14].

From a biochemical standpoint, although bilirubin showed a trend toward higher values in patients with choledocholithiasis, this did not reach statistical significance, confirming its limited diagnostic value when used in isolation [1]. In contrast, the common bile duct diameter was significantly larger in patients with choledocholithiasis, reaffirming its usefulness as an anatomical predictor of biliary obstruction, with high specificity but variable sensitivity [5].

The ASGE score performed suboptimally. Although 68.1% of patients were classified as high-risk, only 73.5% had confirmed choledocholithiasis, resulting in low specificity (43.5%) and a significant proportion of false positives. These findings are consistent with international reports [2,16] and highlight the risk of over-prescribing ERCP when categorical criteria are used in populations with different clinical characteristics.

In contrast, the C-IMP model demonstrated better diagnostic performance. With a cutoff point >50%, it achieved a specificity of 82.6% and a positive predictive value of 90.2%, with sensitivity comparable to ASGE, allowing for more accurate reclassification and a significant reduction in false positives. Importantly, of the 49 patients classified as high-risk by ASGE, only 37 were confirmed by C-IMP, with this subgroup containing the majority of true cases. This behavior is consistent with that described by Huerta-Reyna *et al.* [1].

ROC curve analysis reinforces these findings. The ASGE model showed an AUC of 0.59, indicative of poor discriminative ability and not significantly different from chance, lower than previously reported (~0.80) [2,16]. This discrepancy may be explained by differences in population, sample size, and clinical context, particularly the high proportion of patients with acute cholecystitis and nonspecific biochemical abnormalities [6]. In contrast, the C-IMP model achieved an AUC of 0.82, consistent with its original validation and comparable to other contemporary predictive models, including those based on machine learning [1,21].

From a clinical perspective, ERCP is an effective but not risk-free procedure, making the reduction of unnecessary procedures a priority. In this context, the use of models like C-IMP allows for more precise selection of patients eligible for ERCP, particularly in settings with limited access to MRCP or EUS, favoring decisions based on probability rather than rigid categories.

- **Limitations and perspectives**

This study has inherent limitations due to its retrospective, single-center design and limited sample size, which may affect the generalizability of the results. The exclusive inclusion of patients undergoing ERCP results in a cohort with a high clinical suspicion, which explains the high prevalence observed and may influence the predictive values.

The small sample size limits the precision of the estimates and the analysis by clinical subgroups. Furthermore, the use of ERCP as the gold standard may lead to false negatives due to spontaneous stone migration. Stepwise diagnostic strategies using non-invasive methods, other potentially relevant biochemical markers, and interobserver variability in common bile duct diameter measurements were not evaluated.

Despite these limitations, the results open up important avenues for research. Prospective, multicenter studies are needed to validate the performance of the C-IMP model in different clinical settings and populations, as well as to evaluate its cost-effectiveness. Furthermore, its integration into diagnostic algorithms that incorporate MRCP or EUS could further optimize patient selection for ERCP. Finally, the development of dynamic predictive models based on machine learning represents an opportunity to improve diagnostic accuracy and move towards a more personalized approach.

CONCLUSIONS

The 2019 ASGE criteria remain a widely used tool for the initial stratification of patients with suspected choledocholithiasis; however, in the analyzed population, they showed limited discriminatory capacity, with a significant proportion of false positives and potential over-indication of ERCP. In contrast, the C-IMP model demonstrated a better balance between sensitivity and specificity, as well as a greater capacity to identify patients with a high probability of confirmed choledocholithiasis.

These findings suggest that continuous predictive models based on clinical, biochemical, and imaging variables could represent a more accurate alternative to traditional categorical systems, particularly in populations with clinical characteristics different from

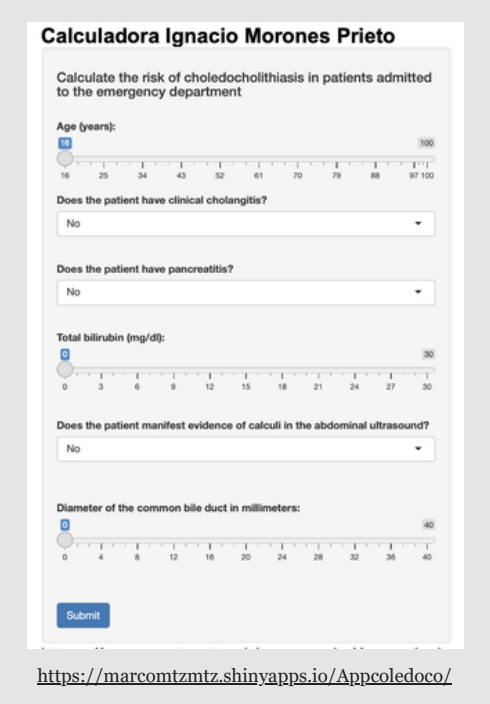
those in which the international guidelines were developed. The ability of C-IMP to reclassify patients initially considered high-risk by ASGE highlights its potential utility for optimizing the selection of ERCP candidates and reducing unnecessary procedures associated with morbidity, costs, and hospital resource utilization.

Furthermore, the observed results support the importance of developing and validating diagnostic tools adapted to the local context, especially in settings where access to complementary methods such as MRCP or EUS may be limited. In this regard, the integration of dynamic predictive models within stepwise diagnostic algorithms could contribute to more individualized and efficient decision-making.

While these results are promising, prospective, multicenter studies with larger sample sizes are needed to confirm the model's performance in different clinical scenarios, evaluate its reproducibility, and determine its impact on clinical outcomes, cost-effectiveness, and the reduction of unnecessary ERCPs.

APPENDICES

Appendix 1. Calculator Dr. Ignacio Morones Prieto (C-IMP)



https://marcomtzmtz.shinyapps.io/Appcoledoco/

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Conflict of interest

The authors declare no conflicts of interest.

Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki (2013, revised in 2024) and current Mexican regulations on health research. This was a risk-free study using information from clinical records retrospectively, guaranteeing the confidentiality and anonymization of the data in compliance with the General Law on the Protection of Personal Data Held by Obligated Entities and NOM-004-SSA3-2012. The protocol was approved by the Research Committee with COFEPRIS registration 17 CI 24 028 093 and by the Research Ethics Committee with CONBIOÉTICA registration-24-CEI-001-20160427, in accordance with NOM-012-SSA3-2012 and NOM-168-SSA1-1998.

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Mental Health in The Digital Age: A Systematic Review of Anxiety and Depression Symptoms Associated with Social Media Use Among Young People

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ABSTRACT

Introduction: The growing use of social media among adolescents coincides with an increase in anxiety and depressive symptoms in this age group. While digital platforms play a central role in adolescent development, continuous exposure to short-form videos and compulsive usage patterns increase the risk of psychological disorders. However, the lack of standardization in the existing literature highlights the need for this review to clarify current knowledge.
Objective: To analyze the scientific evidence on the relationship between the use of digital platforms and anxiety and depressive symptoms in young people, evaluating risk factors such as problematic use of these platforms and current methodological limitations.
Methodology: A qualitative systematic review was conducted by retrieving articles from the PubMed, SciELO, and LILACS databases. The search strategy included observational and review studies published in the last 5 years. After applying the selection criteria, 21 articles were included, of which 9 were primary studies (6 cross-sectional, 2 longitudinal, and 1 prospective cohort study) that formed the basis of the final qualitative synthesis.
Results: The evidence demonstrated a significant correlation between social media use and the development of anxiety and depressive symptoms. It was observed that the deterioration in users' mental health does not depend exclusively on exposure time, but primarily on problematic social media use. The impact of short-form video platforms with variable reward algorithms (e.g., TikTok) was highlighted, as these accelerate users' dependence.
Conclusions: Problematic use of digital media acts as a chronic stressor for young people, calling for interventions to promote healthy use. However, the current evidence has limitations that prevent the establishment of causality due to self-report biases, the presence of mediating variables such as social comparison, and a notable lack of geographic homogeneity in the samples studied.

Keywords: social media, depression, anxiety, young people.

INTRODUCTION

Over the past decade, the use of social media and other digital platforms has steadily increased among adolescents, becoming a central component of social interaction, leisure, and identity formation during critical stages of human development. At the same time, the rise in the prevalence of depressive and anxiety symptoms among young people has sparked growing interest in exploring the possible role of the digital environment in this phenomenon. In this context, a quantitative review of the available evidence has shown that longer exposure to social media is associated with an increased risk of depression in adolescents. A linear dose-response relationship has also been observed, with an increase in risk for each hour of daily use, as well as a stronger association among girls [1].

However, the relationship between social media and mental health does not appear to depend solely on the amount of time spent on social platforms.

Recent evidence indicates that both general social media use and, to a greater extent, problematic social media use—defined as a pattern of use that involves not only the amount of time spent on these platforms but also compulsive and maladaptive behaviour leading to a significant impairment in an individual's daily functioning—is associated with depression, anxiety, sleep disturbances, and reduced well-being in the general population, although the magnitude and consistency of these associations vary [2]. In particular, problematic social media use has shown stronger associations with diverse outcomes, suggesting that the nature of interaction with these digital platforms may be more relevant than the duration of use [1,2]. However, the diversity in operational definitions, measurement instruments, and assessed outcomes limits comparability across studies and makes it difficult to draw uniform conclusions [3].

In recent years, the analysis has shifted toward specific short-form video platforms, which have gained particular relevance due to their structural

characteristics—such as algorithmic personalization, infinite scrolling, and continuous exposure to highly stimulating content. Evidence suggests that these platforms may be associated with an increased problematic use and poorer mental health outcomes, particularly anxiety, stress and depression, although the strength of the findings remains limited by methodological heterogeneity [4,5]. Vulnerability factors such as neuroticism, lower socioeconomic status, and compulsive patterns of digital interaction have also been identified, suggesting that certain usage profiles may pose a greater psychological risk [6].

Despite the growing body of literature, significant limitations remain, including the predominance of observational designs, reliance on self-reported measures, and a lack of standardization in the definition of problematic social media use. Consequently, there remains a need to critically synthesize the available evidence to identify consistent patterns, knowledge gaps, and methodological limitations. Therefore, the objective of this systematic review was to analyze the scientific evidence on the association between social media use and the presence of anxiety and depressive symptoms in young people.

METHODS

A systematic review was conducted to examine the relationship between social media use and symptoms of anxiety and depression in young people. The review was conducted in accordance with the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Due to the considerable heterogeneity among the included studies, no meta-analysis was performed; instead, the data were analyzed narratively.

- **Search strategy**

On December 19, 2025 a bibliographic search was conducted in the following databases: PubMed, SciELO and LILACS. The eligible studies were limited to publications in English and Spanish. The same search strategy was applied to the three databases: *(Adolescent[Mesh] OR "Young Adult"[Mesh] OR youth OR teenagers) AND ("Social Media"[Mesh] OR "Social Networking"[Mesh] OR "Instagram" OR "TikTok") AND (Depression[Mesh] OR Anxiety[Mesh] OR "mental health").*

- **Eligibility and selection criteria**

The studies were considered eligible if: 1) they centered around a population of young people (teenagers and/or young adults, as defined by the original studies, without imposing an age limit); 2) they evaluated social media use (general use and/or use of a specific platform); and 3) they reported results related to symptoms of anxiety and/or depression (or broader mental health indicators that included these outcomes). Studies that did not fulfill these criteria, lacked enough information on outcomes, or were not available on its full version were excluded.

Two reviewers independently assessed the titles and abstracts to determine their eligibility.

Full articles were obtained from the potentially relevant registries and were also independently evaluated by the same two reviewers. Discrepancies were resolved through discussion and consensus.

- **Data extraction and methodological quality**

A standardized data extraction form was used to collect the following data from the articles: authors/years, study design, sample characteristics (sample size and age group), definition and measurement of exposure (social media use and/or problematic social media use), definition and measurement of outcomes (anxiety/depression assessment instruments when specified), and main findings (including measures of association when available). Data extraction was performed by two reviewers.

Three reviewers independently assessed methodological quality and risk of bias using the Joanna Briggs Institute (JBI) critical appraisal tools, selecting the appropriate checklist based on the study design. Cross-sectional studies were assessed using the JBI critical appraisal checklist for analytical cross-sectional studies. Longitudinal observational studies and prospective cohort studies were assessed using the JBI critical appraisal checklist for cohort studies. Meanwhile, the methodological quality of the systematic reviews and meta-analyses included to contextualize the literature was assessed using the JBI Critical Appraisal Checklist for Systematic Reviews and Research Syntheses. Each item was rated as “yes”, “no”, “unclear”, or “not applicable.” Bias assessments were reported at the item level and summarized at the study level as low, moderate, or high risk of bias, based on predefined thresholds for the proportion of items rated “yes” (low ≥70%, moderate 50-69%, high <50%).

- **Data synthesis**

Because the included studies varied in terms of study design, definitions of exposure (e.g., time-based use versus problematic use), and outcome measures, the findings were synthesized narratively. The results were summarized by outcome measure (anxiety and/or depression) and, when possible, by type of exposure and platform.

RESULTS

- **Selection of studies**

The initial database search yielded a total of 1,414 articles (PubMed: n=1,331; LILACS: n=77; SciELO: n=6). Subsequently, automated filters were applied to the databases, limiting the results to the last 5 years, the languages English and Spanish, and study types (meta-analysis, observational study, review, and systematic review), which reduced the sample to a total of 127 articles.

During the screening phase, 1 duplicate article was discarded, and 84 articles were excluded after reviewing the title and abstract. The remaining 42 articles were retrieved in full text to determine their eligibility.

Following this thorough review, an additional 21 articles were excluded for failing to meet the required methodological quality or for presenting insufficient data.

Finally, the review included a total of 21 articles. Of these, 12 were systematic reviews and meta-analyses that were used exclusively to contextualize the literature and enrich the frame of reference. The remaining 9 studies provided primary data and were the only ones included in the final qualitative synthesis for the extraction of results. These 9 primary studies are broken down as follows: cross-sectional studies (n = 6), longitudinal observational studies (n = 2), and one prospective cohort study (n = 1) (Figure 1).

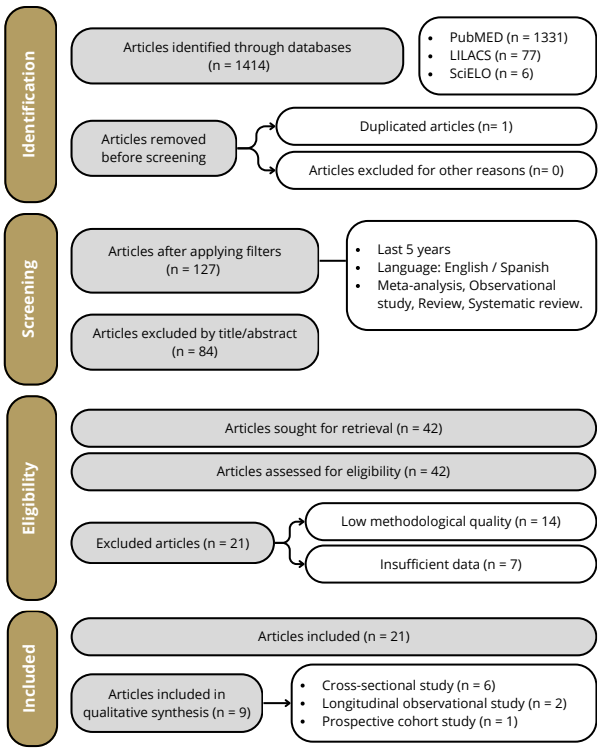


Figure 1. PRISMA Flowchart.

- **Characteristics of the included studies**

A total of 9 studies were included, all of which were published between 2021 and 2025. Cross-sectional studies predominated [7-12], along with longitudinal studies [13,14] and one prospective cohort study [15] (Table 1). These studies were conducted in various geographic settings, including the Dominican Republic [7], Brazil [8,12], Peru [9,10], Ecuador [11], the United Kingdom [13,14], and the United States [15]. Overall, the study population consisted of adolescents and young adults.

Sample sizes varied across studies. The smallest samples consisted of medical students in the Dominican Republic (n = 201) [7], while the largest included 15,836 participants in the United Kingdom [14]. Heterogeneity was observed in the methods used to measure exposure. Some studies assessed internet addiction or problematic internet use using scales such as the Internet Addiction Test (IAT) [8,10,12], while others analyzed smartphone addiction [7,9], and the most recent longitudinal studies focused specifically on social media use, even differentiating between passive viewing, active posting, or self-reported problematic use [13,14,15].

As for the outcomes, the main ones were symptoms of depression, anxiety, stress, insomnia, loneliness, and general psychological distress, measured using validated instruments such as the Patient Health Questionnaire (PHQ-9), the Generalized Anxiety Disorder Scale (GAD-7), the Depression, Anxiety, and Stress Scale (DASS-21), the General Health Questionnaire (GHQ-12), the Schedule for Depression, Anxiety, and Stress (SDQ), and other clinical scales depending on each study [7,8,10,13,14,15].

- **Risk of bias and methodological quality**

The assessment of the methodological quality of the 9 primary studies revealed that the overall quality was acceptable, allowing for a methodologically sound narrative synthesis of the evidence (Table 2). In general, most studies had a low to moderate risk of bias, with no studies identified as having a high risk of bias. Of the 6 cross-sectional studies assessed using the 8-item JBI tool for analytical cross-sectional studies, 3 studies had a low risk of bias, while the remaining 3 had a moderate risk. The main methodological limitations in this group were related to the lack of identification and statistical control of confounding variables (items 5 and 6), as well as the self-reported measurement of digital exposure—including internet use, smartphone use, or social media use—in some cases using adapted instruments or simplified measures, which may have affected the validity of the measurement (item 3).

Meanwhile, the three studies with a longitudinal, prospective cohort design, which were assessed using the 11-item JBI checklist for cohorts, showed relatively better methodological quality, with two studies classified as having a low risk of bias and one with a moderate risk. These studies stood out for their use of large samples and the application of validated clinical instruments to measure anxiety and depression outcomes (item 7). However, methodological limitations persisted in this group, primarily related to self-reported or simplified measurement of exposure, the duration or adequacy of follow-up (item 8), and an incomplete description of strategies for managing losses to follow-up (item 10). In the prospective cohort study with voluntary intervention, furthermore, the absence of randomization and participant self-selection increased the risk of bias.

No primary studies were excluded at this stage due to a high risk of bias (<50%); therefore, all included studies were considered methodologically acceptable for the narrative synthesis. However, these limitations should be taken into account when interpreting the findings, especially regarding causal inference and the magnitude of the observed associations.

- **Association between problematic digital media use and anxiety or depression symptoms**

Overall, the included studies showed a predominance of positive associations between problematic use of the internet, social media, or smartphones and the presence of anxiety and depression symptoms in

Table 1. Analysis of the scientific evidence on the impact of digital technologies on mental health.

Article	Study design	Prevalence	Correlation	Key finding
Prevalencia de adicción a teléfonos inteligentes en estudiantes de medicina[7]	Cross-sectional	Prevalence of smartphone addiction: 48.8%	Significant association with depressive symptoms ($\chi 2$, p=0.007) and anxiety ($\chi 2$, p< 0.001)	No significant association was identified between smartphone addiction and sleep quality (p = 0.856).
Internet addiction, sleeping habits and psychological distress in Brazilian adolescents and young adults[8]	Cross-sectional	Prevalence of moderate internet addiction of 48.1%	Moderate positive correlations between internet addiction and depression (r≈0.43), anxiety (r≈0.31) and stress (r≈ 0.37)	Problematic use showed significant associations with psychiatric symptoms, being independent predictors of sleep problems.
Adicción a los teléfonos inteligentes en adolescentes tras la pandemia por la COVID-19[9]	Cross-sectional	The prevalence of smartphone addiction was 21.7%.	Associated factors: family conflicts (aRP=1.4) and feelings of shame (aRP=1.44).	No significant association was found with feelings of sadness, anxiety, depression, or social rejection.
Internet addiction and mental health disorders in high school students in a Peruvian region: a cross-sectional study.[10]	Cross-sectional	Internet addiction prevalence of 25.9%	Severe addiction was strongly associated with anxiety (PR=2.96).	No statistically significant difference was found between internet addiction and depression.
Uso de internet y su relación con depresión, insomnio y autoestima en estudiantes de bachillerato, Quito (Ecuador)[11]	Cross-sectional	The prevalence of risk of internet addiction was 46%.	Significant risk factor for depression (OR=3.82) and insomnia (OR=2.59).	There was no statistically significant association between the risk of internet addiction and low self-esteem.
Problematic Internet use, emotional problems and quality of life among adolescents[12]	Cross-sectional	Prevalence of problematic internet use of 17%	There was no significant difference in the intensity of depressive symptoms or stress between users.	The perception of their internet use negatively affected their daily activities and quality of life domains.
The Longitudinal Impact of Social Media Use on UK Adolescents' Mental Health: Longitudinal Observational Study[13]	Longitudinal observational	The study does not mention prevalence.	Spending more time actively using drugs between the ages of 12-13 was not associated with mental health problems at ages 14-15.	Passive use is associated with envy and social comparison; parental support mitigates the negative impact.
The Impact of Different Types of Social Media Use on the Mental Health of UK Adults: Longitudinal Observational Study[14]	Longitudinal observational	55.3% of participants view social media every day.	Daily posting slightly increased psychological distress (+0.35 points on the GHQ-12).	Passively viewing content showed no association with long-term mental health problems.
Social Media Detox and Youth Mental Health[15]	Prospective cohort	The prevalence of network use was 93.8%.	Reduction of symptoms: depression (24.8%), anxiety (16.1%) and insomnia (14.5%).	No statistically significant change was observed in the feeling of loneliness after the detox period.

χ^2: chi-square; r: correlation coefficient; aRP: adjusted prevalence ratio; PR: prevalence ratio; OR: odds ratio; GHQ-12: General Health Questionnaire-12; COVID-19: coronavirus disease 2019.

Table 2. Assessment of risk of bias and methodological quality of the included primary studies.

Article	Study design	JBI Checklist	JBI Score	Overall bias risk	Main methodological shortcomings
Prevalencia de adicción a teléfonos inteligentes en estudiantes de medicina[7]	Cross-sectional	JBI for analytical cross-sectional studies	62.5% (5/8)	Moderate	This is a descriptive cross-sectional study, so it does not allow for establishing a causal direction; it used convenience sampling, which increases selection bias; the population comes from a single university campus, which restricts extrapolation; although it uses known instruments, everything is based on self-reporting, with a risk of recall bias and social desirability bias; methodologically, the association was analyzed only with Chi-square and bivariate comparisons, without multivariate adjustment, so it does not control for confounders; therefore, the associations found with depression and anxiety should be interpreted with caution, because they could be explained by unmeasured variables such as academic workload, stress, sleep habits, or psychological history.
Internet addiction, sleeping habits and psychological distress in Brazilian adolescents and young adults[8]	Cross-sectional	JBI for analytical cross-sectional studies	62.5% (5/8)	Moderate	This cross-sectional study used a non-probability convenience sample, which limits representativeness and generalizability. It includes a broad age range (15–36 years), mixing adolescents and young adults, introducing clinical and behavioral heterogeneity. Exposure and outcomes depend on self-reporting via online forms, with risks of information bias and social desirability bias. Although logistic regression was performed, residual confounding may persist, and a temporal relationship between internet addiction, poor sleep, and psychological distress could not be established.
Adicción a los teléfonos inteligentes en adolescentes tras la pandemia por la COVID-19[9]	Cross-sectional	JBI for analytical cross-sectional studies	75% (6/8)	Low	This is a cross-sectional study, so it does not establish temporality or causality; the main outcome was measured with a modified version of the SAS-SV, adapted by the authors for Peru, with piloting and CFA, but without prior formal external validation in that population; several associated factors were collected with self-reported dichotomous questions, which increases information bias; the sample is restricted to women from a single educational institution, reducing generalizability; in addition, the authors themselves acknowledge that psychiatric comorbidities were not ruled out and that exposure to other screens was not evaluated, which leaves room for residual confounding.
Internet addiction and mental health disorders in high school students in a Peruvian region: a cross-sectional study.[10]	Cross-sectional	JBI for analytical cross-sectional studies	75% (6/8)	Low	This is a cross-sectional study, so causality cannot be inferred; the sample was recruited using non-probability snowball sampling, which compromises representativeness and introduces selection bias; the study was conducted in two private schools in a Peruvian region, which limits external validity; many variables, including the main exposure, depend on self-reporting in online questionnaires; in addition, the authors acknowledge that they did not measure several relevant confounders such as stress, family communication, sleep duration, homework, parental education, and family functioning.
Uso de internet y su relación con depresión, insomnio y autoestima en estudiantes de bachillerato, Quito (Ecuador)[11]	Cross-sectional	JBI for analytical cross-sectional studies	75% (6/8)	Low	This is a cross-sectional study, so it does not demonstrate causality. The association analysis was based primarily on bivariate odds ratios, without extensive multivariate adjustment for potential confounders. The measurement relies on self-reporting, especially regarding emotional symptoms and internet use. The sample comes from two institutions in Quito, which limits generalizability. There is also conceptual ambiguity because the methods section describes it as a "cross-sectional cohort," although methodologically it corresponds to an observational cross-sectional study.
Problematic Internet use, emotional problems and quality of life among adolescents[12]	Cross-sectional	JBI for analytical cross-sectional studies	62.5% (5/8)	Moderate	The study employed a cross-sectional design, thus precluding inferences of causality. Although schools were selected within a broader program, data were collected in a single city, limiting external validity. Emotional problems and problematic internet use were measured using self-reported questionnaires, without clinical confirmation. The authors themselves acknowledge potential confounding factors such as smartphone use, which was not thoroughly assessed. Furthermore, several associations were explored primarily through bivariate analyses, without robust control for all potential confounders.
The Longitudinal Impact of Social Media Use on UK Adolescents' Mental Health: Longitudinal Observational Study[13]	Longitudinal observacional	JBI for cohort studies	81.8% (9/11)	Low	It only assesses hours of "chatting or interacting" on social networks and uses examples from outdated platforms, which may affect its validity. There is significant data loss in the analysis of complete cases, even though multiple imputation was used as a sensitivity measure. The measurement of social network use is self-reported, not objective. Furthermore, the mediation by self-esteem and social connection relies on simplified constructs that may not fully capture these phenomena.
The Impact of Different Types of Social Media Use on the Mental Health of UK Adults: Longitudinal Observational Study[14]	Longitudinal observacional	JBI for cohort studies	81.8% (9/11)	Low	Exposure is self-reported and relatively limited: the frequency of "viewing" and "posting" does not capture the quality, content, or context of use. Data were collected during the COVID-19 pandemic, which may have affected both digital behavior and mental health and limit extrapolation to other contexts. There is a significant proportion of missing data in education, which was addressed through imputation. Furthermore, the follow-up was essentially from one wave to the next, so it does not explore long-term trajectories.
Social Media Detox and Youth Mental Health[15]	Prospective cohort	JBI for cohort studies	63.6% (7/11)	Moderate	The detox was voluntary and non-randomized, introducing self-selection bias; there was no randomized control group, so the improvement could be partly explained by motivation, expectation, or regression to the mean; the follow-up of the effect was very short (only 1 week of detox), insufficient to assess durability; the outcomes were not completely absent at the beginning, as the participants had variable baseline symptoms; in addition, there are missing data in passive sensing, resolved with MICE under the assumption of missing at random, an assumption that the authors themselves admit may not be met; the sample was also very homogeneous (predominantly female, university students), which reduces generalizability.

JBI: Joanna Briggs Institute; OR: odds ratio; CI 95%: 95% confidence interval; SAS-SV: Smartphone Addiction Scale–Short Version; CFA: confirmatory factor analysis; MICE: multiple imputation by chained equations; COVID-19: coronavirus disease 2019

adolescents. This relationship was consistently observed, and it was even reported that a one-week social media detox was associated with a reduction in symptoms of anxiety and depression [15]. Similarly, a higher frequency of social media posting was linked to poorer mental health in longitudinal follow-up studies [14]. Similarly, the risk of internet addiction was reported to be associated with depression, although the relationship was clearer for severe anxiety, and some studies reported positive correlations between internet addiction, depression, anxiety, and stress [8,10,11].

In Latin American cross-sectional studies, the association between problematic digital exposure and emotional symptoms was common. In Quito, the risk of internet addiction was significantly associated with depression and insomnia, showing a prevalence of 46% for internet addiction, 62% for depression, and 42% for insomnia; furthermore, the risk of internet addiction constituted a risk factor for depression (OR = 3.82; 95% CI: 2.36–6.18) and insomnia (OR = 2.59; 95% CI: 1.66–4.04) [11].

A link between internet addiction disorder and symptoms of anxiety and depression was documented among Peruvian adolescents. In this study, 22.2% had mild internet addiction, 3.2% had moderate internet addiction, and 0.6% had severe internet addiction; moderate or severe anxiety was present in a significant proportion of students, as were depressive symptoms. In the unadjusted analysis, internet addiction was associated with a higher prevalence of depression; however, after multivariate adjustment, this association did not hold. In contrast, the association with anxiety persists in cases of severe addiction, where the prevalence of anxiety increased markedly [10].

Another study reported a 21.7% prevalence of smartphone addiction and a 48.7% risk of dependence. In the adjusted analysis, this addiction was associated with family conflicts at home and feelings of shame, while feelings of sadness, anxiety, or depression and the perception of social rejection showed an association only in the unadjusted analysis [9].

In Brazil, it was found that 48.1% of participants had moderate internet addiction and 0.8% had severe addiction. Positive correlations were described between internet addiction and depression, anxiety, and stress, showing that both internet addiction and overall psychological distress predicted sleep difficulties [8]. This reinforced the idea of an interaction between excessive internet use and the prevalence of emotional disorders.

In the Dominican Republic, smartphone addiction was found in 48.8% of the sample and was significantly associated with symptoms of depression ($p = 0.007$) and anxiety ($p < 0.001$) [7]. Although no significant association was found with sleep quality, it was documented that those with smartphone addiction exhibited a considerable proportion of emotional symptoms, suggesting an adverse relationship between technology dependence and mental health.

Not all studies consistently showed a significant association between problematic digital use and symptoms of anxiety or depression.

Among Brazilian adolescents, problematic internet use was present in 17% of the sample; however, no statistically significant differences were found between problematic and non-problematic users in terms of depression, anxiety, stress, or quality of life. Even so, 40.1% of adolescents reported that the internet negatively affected their daily activities, with this group showing higher dependency scores and greater levels of stress [12]. Therefore, although the direct association with anxiety and depression was not significant, a pattern of greater subjective distress and stress was identified, suggesting that the mere duration or frequency of use does not always, on its own, explain psychological distress.

Studies such as the one conducted in the United Kingdom revealed a more nuanced picture. The analysis distinguished between viewing and posting content on social media. No evidence of an association was found between the frequency of viewing and worse mental health problems after full adjustment. In contrast, posting daily was associated with greater subsequent psychological distress, with a 0.35-point increase in the GHQ score compared to those who never post anything. Furthermore, those who combined high viewing frequency with high posting frequency had worse mental health scores than those with low frequency in both behaviors [14].

- **Social media detox**

A cohort study conducted in the United States provided additional evidence by evaluating a one-week social media detox among young adults. Of the 373 participants who completed the baseline assessment, 295 agreed to participate in the intervention. After one week of reduced social media use, significant decreases were observed in anxiety (-16.1%), depression (-24.8%), and insomnia (-14.5%), with no significant changes in loneliness [15].

Furthermore, multivariate analyses showed that self-reported problematic social media use was consistently associated with greater severity of depression, anxiety, loneliness, and insomnia, whereas objective measures of use showed little or no association [15]. These findings suggest that it is not merely the amount of social media use that matters, but rather the problematic or emotionally dysfunctional nature of that use.

- **Overall synthesis of findings**

Overall, the results of the articles analyzed in this review showed that the association between problematic use of the internet, social media, or smartphones and anxiety or depressive symptoms was predominantly positive, although not uniformly so. The evidence was more consistent in studies that assessed addiction, dependence, or problematic use, while studies focusing solely on usage time or general frequency tended to show weaker or more inconsistent results. Similarly, longitudinal studies suggested that the effect may depend on the type of use, with active or problematic use having a greater impact than simple passive exposure. Finally, the available evidence suggested that a brief reduction in social media use could be associated with an improvement in anxiety and depressive symptoms [10,11,12,14,15].

DISCUSSION

It is crucial to distinguish between time spent on social media and use considered problematic, since various cited studies agreed that problematic use poses significantly greater risks to the mental health of adolescents and young adults.

The reviewed articles concluded that excessive time spent on social media during the COVID-19 pandemic is specifically associated with a higher likelihood of experiencing symptoms of anxiety (OR 1.55) and depression (OR 1.43), thus establishing that prolonged use is described as a "double-edged sword" since the content consumed on various social media platforms can provide a sense of relief from isolation, but also exposes users to misinformation and content that exacerbates behaviors such as desensitization, irritability, low frustration tolerance, sadness, and annoyance, among others [16].

Consider, then, that since the COVID-19 pandemic, there has been a significant increase in these symptoms among both young adults and adolescents. What is happening to adolescents? How does this problematic use affect them? Well, community-based clinical studies have highlighted that adolescents with certain medical conditions may be more affected because social comparison—based on the number of "likes" and the fear of negative evaluation—is more prevalent, significantly altering the way adolescents interact digitally [17]. When we talk about the fear of negative evaluation, we are referring to feelings of comparison with other adolescents regarding physical appearance, which is more common in this age group. However, it also impacts socialization, as face-to-face interactions have become increasingly rare, thereby reducing socio-emotional skills.

This face-to-face interaction decreased considerably during the COVID-19 pandemic; however, after this period, such interaction struggled to become a natural tool for human socialization. Consequently, during the first year of the pandemic, it was noted that more active and prolonged use of social media was associated with a predominantly negative impact, directly affecting sleep and increasing family conflicts. In addition, increased stress led to social media addiction and psychological distress as a form of immediate reward [18].

Returning to the concept of face-to-face social interactions, some studies have focused on social connection interventions, noting that platforms have evolved toward formats that encourage one-way, non-interactive engagement (such as passive scrolling), which differs from healthy connection with others as well as from one's attention span. This leads to a sense of loneliness, which is a pattern that predicts signs of depression in young adults [19].

Previous studies have shown a positive association between social media use and mental health problems. They highlighted that risk-based measures (such as addiction or Facebook intrusion) have a more consistent association with psychiatric symptoms than measures based solely on frequency and duration of use [20].

Finally, as mentioned at the beginning, distinguishing between duration of use and problematic use is linked to other risky behaviors or experiences, such as cyberbullying and digital hoarding, which are associated with symptoms of anxiety, depression, and even hypersexualization and self-harming behaviors—especially among young people with preexisting vulnerabilities such as ADHD or eating disorders. The global prevalence of this problematic use is estimated to be approximately 7% [21].

Among other mechanisms revealed in the studies, FOMO (Fear of Missing Out) was discussed as a compulsive behavior stemming from the fear of being excluded from social dynamics or trends, which compels individuals to impulsively check social media, leading to an addiction to these platforms [1,20]. FOMO also influences algorithms and the flow experience, especially on short-form video platforms like TikTok, which use advanced recommendation algorithms to create a personalized "feed" that generates this flow experience characterized by intense concentration while enjoying the content and a distorted perception of time [4], that is to say; the more they scroll, the more their attention is captured, preventing them from noticing how much time they are spending on the platform.

Given the growing problem among adolescents, the emotional, physical, and psychological consequences are evident in education. For example, due to social media addiction and overstimulation, adolescents are unable to concentrate for long periods of time and tend to procrastinate more, leading to lower academic achievement and greater distraction from academic responsibilities [5,6,7,10]. The academic community can begin to implement certain strategies related to school curricula [6], which include topics on how the brain works and what happens when there is overstimulation caused by social media due to addiction, as well as teaching habits related to managing screen time and promoting face-to-face interactions, avoiding the use of electronic devices or platforms [5,6].

It is therefore essential that teachers be able to detect when students show signs of isolation or compulsive use of electronic devices during class or at lunch. Identifying these signs and incorporating relevant topics and interactive activities serve as an intervention that fosters students' social development [8]. Such interventions are related to "digital detoxes," which serve as an effective tool for significantly reducing psychological distress and improving well-being in just one week [6,15]. These activities and adjustments to the curriculum can have a positive impact not only on adolescents' social-emotional development but also on the development of their identity and self-esteem. Ultimately, the discussion also touched on the responsibility of social media companies—namely, to design apps with fewer addictive features—and the need for laws that limit minors' access and screen time [6].

Other authorities, such as the World Health Organization (WHO), recommend establishing clear usage guidelines to prevent behavioral issues exacerbated by the COVID-19 pandemic [7]. These

guidelines and new well-being initiatives require a collaborative effort among society, the government, and parents. Society and the government have tools with a broader reach, such as workshops open to the general public, promoting new community activities, addressing the stigma associated with acknowledging the need for help, and encouraging visits to a mental health professional. In the specific case of parents, their support and active involvement are key, as they serve as protective factors to mitigate the risk of addiction, not only in terms of emotional and psychological consequences but also physical ones (by preventing a sedentary lifestyle) [5].

The study had some limitations regarding generalizability and geographic bias, since most of the data comes from high-income populations, which does not allow for an explanation of social media use among families with different structures or income levels, factors that give rise to different social dynamics and forms of interaction, as is the case, for example, in Latin America, as it appears that cultural norms influence what may be considered problematic use across different countries (Table 3).

Moreover, it is difficult to establish a definitive cause-and-effect relationship between social media use and symptoms of distress, given the possibility that young people with pre-existing symptoms may use digital platforms more as maladaptive coping mechanisms, rather than social media and its problematic use being the primary cause of the problem. In addition, there is a bias in data collection because the data are obtained through self-reporting, primarily using self-administered digital questionnaires, which lack in-person clinical validation. Therefore, the results reflect only the respondent's subjective perception, which may lead to an overestimation of the results and the actual prevalence of the mental disorders studied.

This study may pave the way for novel lines of research, such as conducting cohort studies and experimental designs (controlled trials) to understand how the relationship between technology and well-being evolves over time and the persistence of the observed symptoms. In addition, it could help monitor the effects of a digital detox and assess its impact on cognitive functions—such as attention and memory—which appear to be most affected by overstimulation and problematic social media use.

Of course, it is also essential that, rather than analyzing screen time, future research could focus on distinguishing variations in the architecture of different platforms, as well as analyzing variations among existing algorithms and interaction dynamics, all while taking into account how these factors impact users' cognition and their interactions with friends and family. Along these lines, it is necessary to distinguish between active use (creating content and interacting) and passive use (endless scrolling), as well as to investigate the nature of the content consumed (whether it is educational or for entertainment) and the impact of this consumption on users.

Finally, vulnerable groups should not be excluded based on factors such as race, ethnicity, and socioeconomic status, as these variables moderate and provide new insights into the actual impact of social media on mental health. In this regard, it is also important to emphasize the need for research in other regions, such as Latin America and Africa, to enable comparisons between different countries, taking into account whether they are high- or low-income nations. It is also necessary to include holistic perspectives that highlight potential benefits (social support, connection with peers) in order to develop new solutions to this problem, such as digital detox and the implementation of activities by communities and the government.

Table 3. Critical analysis and methodological limitations of the reviewed literature on social media use.

Analysis	Findings	Limitations
Homogeneity and geographical bias	Data saturation is observed among high-income populations: the United Kingdom[13] and Korea[5,16]. Evidence in Latin America is emerging but is still limited to local samples in places like Ecuador[11] and Peru[10].	There is a limitation to generalization: Problematic social media use is mediated by cultural norms. Western results do not explain the impact on young people with different family structures or social dynamics.
Disparity in standardization	There are multiple diagnostic criteria applied, including smartphone addiction scales (SAS.SV), internet addiction test (IAT) and clinical symptom scales such as PHQ-9 for depression and GAD-7 for anxiety.	There is a lack of standardized measurement. There is a lack of consensus on whether the damage to mental health stems from the duration of the interaction or its nature, leading to inconsistent diagnoses across studies.
Nature of data collection	Most studies use self-administered digital questionnaires such as IAT, or SAS-SV, which are distributed through social networks or survey platforms.	There is a self-reporting bias, since in most cases in-person clinical validation is not available. The results reflect the user's subjective perception, which may overestimate or underestimate the true prevalence of these mental disorders.[17]
Stress isolation (Mediating variables)	No direct impact on the mental health of users is indicated; there are other variables such as body dissatisfaction[5] and social comparison that act as critical bridges for the development of anxious-depressive symptoms[1,13,18,19,20]	It is difficult to determine causality, that is, whether social networks cause the symptoms of distress or whether young people with previous symptoms use social networks as a maladaptive coping mechanism.
Interface Dynamics and Algorithms	Research on platforms with short video formats such as TikTok has shown that the algorithm's "variable reward" design accelerates user dependence compared to static social networks.[21]	There is a technological gap between research and updates to digital social media platforms, making it difficult to create intervention protocols that are up-to-date for these new interfaces.

IAT: Internet Addiction Test; PHQ-9: Patient Health Questionnaire-9; GAD-7: Generalized Anxiety Disorder-7; DASS-21: Depression, Anxiety and Stress Scale-21; GHQ-12: General Health Questionnaire-12; SDQ: Strengths and Difficulties Questionnaire; SAS-SV: Smartphone Addiction Scale-Short Versión.

CONCLUSIONS

The evidence analyzed suggests that there is an association between problematic social media use and the presence of anxiety and depressive symptoms in adolescents, with this association being more consistent when digital exposure was defined as addiction, problematic use, or compulsive interaction. In particular, anxiety, stress, and sleep disturbances showed more frequent associations, while the findings regarding depression were less consistent.

However, these results should be interpreted with caution. The included literature revealed significant heterogeneity in methodological designs, study populations, the instruments used to measure both digital exposure and emotional outcomes, and the statistical strategies employed. Furthermore, the predominance of cross-sectional studies limits the ability to establish causal relationships and to clearly differentiate between association, bidirectionality, and temporal effects.

Overall, the findings presented support the need to consider problematic use of digital technologies as a potential factor associated with emotional distress in young people, although longitudinal studies with standardized measurements and greater methodological rigor are still needed to more precisely define the magnitude, direction, and mechanisms of this association.

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Conflict of interest

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Ethical considerations

This study did not involve the participation of humans or animals, nor the collection of primary data; therefore, it did not require approval from a research ethics committee. All data used were obtained from previously published and publicly accessible secondary sources.

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Amiodarone: Adverse Effects and the Clinical Picture of Torsades de Pointes. A Narrative Review

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ABSTRACT

Introduction: Amiodarone is a Class III antiarrhythmic drug widely used in the treatment of supraventricular and ventricular arrhythmias. However, its pharmacokinetic profile is associated with a wide range of adverse effects, including QT interval prolongation, a condition that predisposes patients to the development of *Torsades de Pointes* (TdP), a potentially fatal ventricular arrhythmia.
Objective: To analyze the adverse effects associated with the use of amiodarone and their relationship to the development of TdP, highlighting risk factors and drug interactions.
Methods: A narrative review was conducted by searching databases such as PubMed, Cochrane, LILACS, and SciELO, including studies published between 2010 and 2026 in English, Spanish, and Portuguese. Observational studies, systematic reviews, and case reports were included, while studies not available via open access and those involving pediatric and animal populations were excluded.
Results: Amiodarone acts primarily by blocking HERG-type potassium channels, prolonging cardiac repolarization. Its use is associated with multiple systemic adverse effects and significant drug interactions. QT interval prolongation was identified as the main mechanism associated with the development of TdP, especially in the presence of risk factors such as electrolyte imbalances, comorbidities, and concomitant use of QT-prolonging drugs.
Conclusions: Although the incidence of amiodarone-associated TdP is low, its potential severity makes early identification of risk factors, clinical and electrocardiographic monitoring, and appropriate management of drug interactions essential in order to prevent major adverse events.

Keywords: amiodarone, torsades de pointes, QT prolongation, drug interactions.

INTRODUCTION

Amiodarone is used to treat supraventricular and ventricular arrhythmias [1,2]. Its adverse effects (AEs) include liver, thyroid, pulmonary, dermatological, ocular, neurological, and even cardiac complications [3,4,5]. Although rare, it is associated with QT interval prolongation on the electrocardiogram (EKG), causing *Torsades de Pointes* (TdP), a polymorphic ventricular arrhythmia that carries a risk of sudden cardiac death [6,7]. To prevent the potential proarrhythmic effects of amiodarone, it is necessary to monitor underlying diseases, cardiac and extracardiac adverse events, the route of administration, and the concomitant use of drugs that also prolong the QT interval [2,5,8,9].

METHODS

A search was conducted in the PubMed, Cochrane, LILACS, and SciELO databases, and studies published in English, Spanish, and Portuguese between 2010 and 2026 were included using the terms “amiodarone”, “adverse effects”, “QT prolongation”, “Torsades de Pointes”, among others, with the Boolean operators AND and OR.

Cohort studies, systematic reviews, case reports, case-control studies, narrative reviews, translational studies, and observational studies were considered; studies that were not open access, as well as those involving pediatric and animal populations, were excluded. Additionally, a manual search of scientific journals and a review of the references in relevant articles were conducted to identify additional literature.

RESULTS

1. Amiodarone

Amiodarone is a Class III antiarrhythmic drug, a derivative of iodinated benzofuran; its mechanism of action involves blocking HERG-type potassium channels (KCNH2), which are responsible for the IKr current (rapid delayed rectifying current) involved in the repolarization phase of the cardiac action potential, thereby prolonging its duration [10,11].

A clinically relevant aspect of amiodarone lies in its broad spectrum of action, as it also inhibits, to a lesser extent, cardiac Na+ (Class I) and Ca2+ (Class IV) channels and even acts as a beta-adrenergic receptor antagonist (Class II) [11,12].

Regarding its pharmacokinetics, it is highly lipophilic and is absorbed slowly, characterized by a bioavailability ranging from 30% to 80% [10], with

significant distribution in highly perfused tissues and muscle, and a tendency to accumulate in adipose tissue [12]. Additionally, it has a protein binding rate of over 95%. The onset of action varies depending on the route of administration; when administered orally, it ranges from 2 to 3 days and may be prolonged up to 3 weeks, whereas when administered intravenously (IV), it occurs within 1 to 2 hours, with a peak concentration reached after 12 to 24 hours [10,12]. It has a long half-life, ranging from 60 to 100 days [10], which can extend to 142 days during chronic treatment [13,14].

It acts as a cytochrome P450 inhibitor, which causes drug interactions with medications that rely on this system for their metabolism; such is the case with warfarin, an anticoagulant that, when administered with amiodarone, increases the risk of bleeding. It is metabolized by the CYP3A4 enzyme and produces an active metabolite, desethylamiodarone, which has an even longer half-life than the original drug, although the exact magnitude of its antiarrhythmic effect is unknown. This explains the occurrence of toxic effects following chronic use. It is excreted primarily via the bile and, to a lesser extent, via the kidneys. Therefore, no dose adjustment is required in patients with renal insufficiency [2,10,11,12,13].

The clinical use approved by the Food and Drug Administration (FDA) is for recurrent ventricular fibrillation and ventricular tachycardias in high-risk patients in whom other drugs are ineffective; although it is also used off-label for the treatment of supraventricular tachyarrhythmias, prevention of ventricular tachyarrhythmias, drug-induced arrhythmias, postoperative tachyarrhythmias, and atrial fibrillation [5,11,14,15].

2. Adverse effects of amiodarone

Although effective, amiodarone has been shown to be associated with adverse effects in 15% of patients after one year of treatment, and in up to 50% during chronic use. Doses exceeding 400 mg carry a higher risk of complications [13,16]. Continuous patient follow-up and monitoring of any adverse effects that develop are essential, as are careful management and laboratory testing. Fortunately, most adverse effects tend to improve upon discontinuation of the drug, and in 20% of cases, they are associated with a clinically relevant risk [17]. The main adverse effects are listed below.

2.1. Cardiac

Cardiac adverse effects primarily include sinus bradycardia (12%) and atrioventricular block. In cases of atrioventricular block with a risk of worsening conduction, symptoms typically resolve when the dose is reduced; if this is not the case, a pacemaker is implanted. In addition, an increase in the pacing threshold of monophasic and biphasic defibrillators of up to 62% has been reported. Hypotension is the main adverse event following IV administration of amiodarone after the first few hours; as a preventive measure, it is recommended that initial infusion rates not exceed 30 mg/min [5,12]. QT interval prolongation, defined as a value greater than 460 ms, and TdP, a potentially fatal arrhythmia with a prevalence of less than 1%, are the main focus of this manuscript and will be discussed later [18].

2.2. Thyroid

Amiodarone consists of 37.5% iodine, a dose that exceeds the maximum daily intake; it also bears a resemblance to the thyroid hormones triiodothyronine (T3) and thyroxine (T4). As a result, the prevalence of thyroid disorders is 15-20% [19]. Amiodarone-induced thyrotoxicosis (AIT) is classified into two categories. Type 1 AIT is due to increased synthesis of thyroid hormones, generally in patients with pre-existing thyroid disease, whereas Type 2 AIT occurs more frequently in patients without prior thyroid dysfunction and results from drug-induced cytotoxicity [20,21]. On the other hand, hypothyroidism and hyperthyroidism are caused by a decrease in T3 and an increase in inactive T3, effects preceded by the inhibition of the conversion of T4 to T3. Hypothyroidism (1-32%) is associated with iodine-sufficient areas, in women, and in patients with positive antiperoxidase antibodies. Hyperthyroidism (1-23%) is found in iodine-deficient areas. To prevent the patient's condition from worsening, monitoring of T3 and T4 is recommended before and 6 months after treatment with amiodarone [5,21,22].

2.3. Pulmonary

Clinically, pulmonary toxicity and pulmonary fibrosis are the most concerning adverse events due to their potentially life-threatening severity. Pulmonary toxicity, with an incidence of 4-17%, can manifest as organized pneumonia that responds favorably to corticosteroids, chronic interstitial pneumonia, pulmonary nodules, and eosinophilic pneumonia; the latter is considered the primary radiographic finding of this AEs. The progression of pulmonary toxicity can even lead to acute respiratory distress syndrome [5,10,23,24,25]. Pulmonary fibrosis is reported in 1 out of every 1,000 patients following IV administration of amiodarone and is a serious condition, as it can occur within the first 3 months after the start of amiodarone treatment. The progression of pulmonary fibrosis is alarming, as there is a risk of developing respiratory failure and, in fatal cases, death. In such cases, discontinuation of the drug should be considered [5,10,26].

2.4. Liver-related

Amiodarone can cause elevated levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in 25% of cases, although these levels tend to decrease when the drug is discontinued. In addition, it can cause liver damage and steatosis, as its continuous administration places stress on the endoplasmic reticulum in the liver and adipocytes, leading to lipid accumulation, reduced lipogenesis, and induced lipolysis. Hepatotoxicity manifests in 15-20% of cases in two forms: severe acute hepatitis, occurring 24 hours after IV administration of amiodarone; and chronic toxicity resulting from prolonged oral therapy, with a marked increase in AST and ALT. In severe cases with multiple comorbidities, it may even progress to liver failure. As previously mentioned, reducing or discontinuing amiodarone is the recommended course of action in these cases [5,10,27,28].

2.5. Ocular

Among the adverse effects, ocular adverse effects are recognized as a key manifestation. More than 90% of patients treated with amiodarone develop corneal

microdeposits, which constitute the primary sign of ophthalmic toxicity. In 10% of cases, this may occur alongside visual halos. Optic neuritis is considered one of the most severe complications, as it causes unilateral or bilateral vision loss, with a recurrence rate of less than 1-2%; it usually resolves upon reduction of the drug, although in a minority of these cases it may be permanent. Discontinuation of the drug should be considered [5,29,30,31].

2.6. Dermatological

At the skin level, "blue man syndrome", which, as its name suggests, is characterized by a bluish-gray discoloration of the skin, has been documented in less than 3% of cases, while the yellowish-brown variant has a prevalence of 10%. These manifestations result from the accumulation of amiodarone, and although they may cause cosmetic concerns, both are benign. The use of protective creams is recommended, and in some cases, treatment may even be suspended [5,32,33].

3. QT interval prolongation

QT prolongation is defined as a corrected QT (QTc) interval greater than 460 ms in women and 450 ms in men. The Bazett formula is the most commonly used in clinical practice to determine the QTc based on heart rate,

$$(QTc = QT/\sqrt{RR})$$

where RR is the interval between two consecutive R waves and QT is the interval between a Q wave and a T wave.

There are various causes; however, in the case of amiodarone administration, this prolonged QTc is due to the inhibition of potassium ion channels, which are responsible for cardiac repolarization. These values vary depending on the patient's age and sex. High doses of amiodarone, associated comorbidities, electrolyte imbalances, and the coadministration of other drugs that also prolong the QT interval, among other factors, tend to increase the likelihood of developing TdP. QT interval prolongation creates an electrophysiological environment that promotes the onset of polymorphic ventricular arrhythmia due to an abnormal ventricular complex that triggers it (Figure 1) [34,35,36,37].

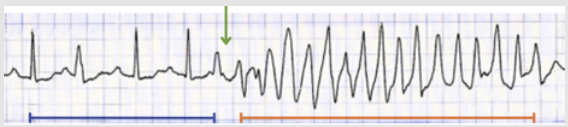


Figure 1. Transition from QT interval prolongation to the onset of Torsades de Pointes. The blue line represents the preliminary phase with QT interval prolongation. The green arrow highlights the onset of Torsades de Pointes, corresponding to the first abnormal ventricular complex. The orange line delineates the polymorphic ventricular tachycardia. *Adapted from: Lee B et al. Rare case of Torsades de Pointes in severe hypothyroidism: literature review and challenges in management. Int J Emerg Med. 2022;15(1):11.*

4. *Torsades de Pointes*

TdP is recognized as a polymorphic ventricular arrhythmia that manifests as oscillations in the amplitude of the QRS complexes around the isoelectric line, associated with QT interval prolongation (Figure 2); a QTc interval greater than 500 ms increases the risk of developing TdP. This arrhythmia may resolve or progress to ventricular fibrillation.

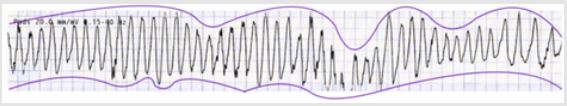


Figure 2. Characteristic twisting pattern of *Torsades de Pointes*. The upper and lower purple envelope lines highlight the tachycardia and the cyclic variation in the amplitude of the QRS complexes, creating the twisting appearance around the isoelectric line characteristic of *Torsades de Pointes* ("twisting of the tips"). *Adapted from: Lee B et al. Rare case of Torsades de Pointes in severe hypothyroidism: literature review and challenges in management. Int J Emerg Med. 2022;15(1):11.*

Fifty percent of patients who develop TdP are asymptomatic, although reported symptoms include syncope, palpitations, and dizziness. Fortunately, in the context of amiodarone therapy, the incidence is less than 1% of cases. Approximately 10% of TdP cases result in sudden cardiac death. Prevention of this arrhythmia involves correcting modifiable risk factors, such as discontinuing the coadministration of drugs that prolong the QTc interval and maintaining the patient's electrolyte balance. The primary treatment for TdP is IV magnesium, as it stabilizes the cardiomyocyte membrane and corrects hypokalemia. Because TdP is bradycardia-dependent, another option is to increase the heart rate, typically with drugs such as isoproterenol or by implanting a pacemaker [39,40,41].

5. Risk factors associated with amiodarone treatment

In light of the above, the risk factors include the following (Table 1).

Table 1. Risk factors for TdP during amiodarone therapy.

Factors	Examples
Electrocardiographic	• QTc prolongation greater than 460 in women and 450 in men • Bradycardia
Electrolyte-related	• Hypokalemia • Hypomagnesemia • Hypocalcemia
Patient related	• Patient's age (>65 years) • Female gender • Liver dysfunction • Renal dysfunction • Duration of treatment • Underlying heart conditions (congenital long QT syndrome, heart failure, left ventricular hypertrophy, acute myocardial infarction) • Obesity • Impaired hepatic metabolism
Pharmacological	• Treatment with diuretics • Concomitant use with drugs that prolong the QT interval • IV administration (15%)

Distribution of factors that contribute to the development of this polymorphic ventricular arrhythmia during amiodarone administration [5,36]. TdP = torsade de pointes; QTc = corrected QT interval; IV = intravenous.

6. Drug interactions

With regard to drug interactions, we analyzed the drugs that interact with amiodarone and verified that they are currently available in Mexico (Table 2).

Table 2. Drugs available in Mexico that are associated with an increased risk of TdP when coadministered with amiodarone.

Group	Drugs	
Antibiotics	• Erythromycin • Azithromycin • Clarithromycin • Ciprofloxacin • Trimethoprim/sulfamethoxazole	• Levofloxacin • Moxifloxacin • Gatifloxacin • Metronidazole
Antifungals	• Fluconazole • Itraconazole	• Ketoconazole
Cardiovascular	• Dronedarone • Ivabradine	• Ranolazine
Antipsychotics	• Haloperidol • Chlorpromazine • Olanzapine	• Risperidone • Aripiprazole • Clozapine
Antidepressants	• Fluoxetine • Paroxetine • Citalopram • Escitalopram	• Imipramine • Amitriptyline • Mirtazapine • Trazodone
Dementia	• Donepezil	• Galantamine
Antineoplastic	• Lapatinib • Lenvatinib • Sorafenib • Sunitinib • Osimertinib • Arsenic trioxide	• Vandetanib • Crizotinib • Dabrafenib • Dasatinib • Tamoxifen
Antimalarials	• Chloroquine • Hydroxychloroquine	
Antihistamines	• Loratadine	• Hydroxyzine
Urological	• Solifenacin • Tolterodine	• Alfuzosin
Muscle relaxants	• Cyclobenzaprine	
Inhaled anesthetics	• Isoflurane	• Sevoflurane
Migraine	• Zolmitriptan	
Antiparkinsonian	• Apomorphine	
Laxatives	• Sodium phosphate (mono/dibasic)	
Bronchodilators	• Formoterol	• Vilanterol
Antiemetics	• Ondansetron	• Granisetron
Antiretrovirals	• Efavirenz	• Atazanavir
Anti-ulcer	• Famotidine	

This table lists the main drugs that have a valid marketing authorization from COFEPRIS and increase the risk of TdP following administration of amiodarone [5,42]. TdP = torsade de pointes.

DISCUSSION

Amiodarone is a Class III antiarrhythmic drug used in the treatment of ventricular and supraventricular arrhythmias; however, its pharmacokinetic and pharmacodynamic profile is associated with a wide range of adverse effects and drug interactions. Its primary mechanism of action involves the inhibition of HERG-type potassium channels, which are responsible for the repolarization of the cardiac potential, leading to QT interval prolongation. This phenomenon, in and of itself, represents a risk factor for the development of early post-depolarizations and, in the presence of comorbidities and other predisposing factors, may contribute to the onset of TdP, a potentially fatal polymorphic ventricular arrhythmia, with an incidence of less than 1%.

Despite its low frequency, amiodarone-associated TdP has significant clinical implications, as adverse effects and drug interactions may necessitate adjusting, reducing, or discontinuing treatment. In this context, early detection via electrocardiogram, as well as the identification and correction of risk factors, are essential for preventing adverse outcomes. Furthermore, it is essential to avoid the coadministration of drugs that prolong the QT interval and to perform an individualized risk assessment for each patient.

Among the main limitations of this study are the scarcity of evidence in the Mexican population, as well as the lack of specific records on amiodarone-induced TdP in this context. Consequently, future studies should focus on developing therapeutic alternatives with an effective antiarrhythmic profile and a lower incidence of adverse effects, with the goal of reducing the risk of QT prolongation and the development of TdP [10,11,36].

CONCLUSION

Amiodarone therapy and the development of TdP pose a relatively low risk compared to other antiarrhythmic drugs in the same class; however, this risk is not negligible. Furthermore, the presence of comorbidities in the patient increases this risk. It is essential to identify risk factors early; to identify drugs that interact with amiodarone; to perform the laboratory tests deemed necessary by the cardiologist before and during administration of the drug; to identify and manage adverse events; and, if necessary, to reduce or discontinue the amiodarone dose.

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Conflict of interest

The author declares no conflicts of interest.

Ethical considerations

This study did not involve the participation of humans or animals, nor the collection of primary data; therefore, it did not require approval from a research ethics committee. All data used were obtained from previously published and publicly accessible secondary sources.

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Early Detection of Neonatal Hearing Loss: Screening Algorithm

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ABSTRACT

A screening test is used to detect a group of relevant diseases in the neonatal period, including hearing loss, which is defined as the decrease or absence of the ability to perceive and interpret sound waves. Untreated hearing loss constitutes a serious obstacle to the development of oral language, writing, and cognition, as well as to the child's education and social integration.

The neonatal hearing screening (NHS) is performed using two tools: Otoacoustic Emissions (OAE) and Auditory Brainstem Response (ABR), which complement each other for the timely detection and treatment of hearing loss.

An algorithm is proposed to optimize the understanding, application, and follow-up of the neonatal hearing screening (NHS). Based on risk factors and the results of otoacoustic emissions (OAE) as the first universal test, the need to perform auditory brainstem response (ABR) is determined, and the corresponding follow-up plan is established.

Keywords: newborn hearing screening, newborn hearing loss, auditory brainstem response.

INTRODUCTION

Human beings relate to one another through their senses, forming alliances, experiencing emotions, and establishing ethical and social norms. Therefore, untreated hearing loss constitutes a serious obstacle to development, education, and social integration in childhood. This condition isolates the individual from information about their environment, hindering the acquisition of spoken language, writing, and cognitive development. In Mexico, it is estimated that 10 million people suffer from some type of hearing loss, of whom between 200,000 and 400,000 are completely deaf. Furthermore, it is estimated that between 2,000 and 6,000 children are born each year with congenital deafness; therefore, hearing loss is considered a public health problem [1].

A determining factor in this condition is the age at which intervention begins. Children whose hearing loss is detected early and who receive prompt and appropriate rehabilitation achieve better results and greater progress than those whose hearing loss is detected late. Therefore, it is crucial to recognize that hearing impairments can be detected in the first hours after birth. Intervention during the maturation and modeling stages of cortical structures is essential, as this critical period defines the prognosis and future development of newborns with deafness or profound hearing loss born each year in our country [2].

In the practice of medicine, the ultimate goal is disease prevention. For this reason, newborn hearing screening and follow-up are vital, given that hearing loss is often asymptomatic and usually goes unnoticed. Screening should be universal, applied to all newborns regardless of whether they present risk factors. Furthermore, it is essential that this strategy be known not only by medical personnel, but also by parents or guardians, thus ensuring timely intervention that promotes development and cognition appropriate for the child's age.

NEWBORN HEARING SCREENING

A “screen” refers to “...the act of examining, carefully selecting, or refining and choosing with care and thoroughness...”, according to the Royal Spanish Academy (RAE) [2]. In other words, a screen is used to detect a group of relevant diseases in the neonatal stage, including hearing loss.

Hearing loss is the decrease or absence of the ability to perceive and interpret sound waves and, therefore, auditory sensations. Different degrees of hearing loss can be classified:

- **Mild hearing loss:** threshold between 30 and 40 dB.
- **Moderate hearing loss:** hearing threshold between 41 and 60 dB.
- **Severe hearing loss:** threshold between 61 and 90 dB.
- **Profound hearing loss:** threshold above 90 dB.

Newborn hearing screening (NHS) can be performed in one or two steps using Otoacoustic Emissions (OAEs) and/or Auditory Brainstem Response (ABR) testing. OAEs are performed on all newborns without exception, and if the result is abnormal or if the newborn has risk factors, an ABR test should be performed at three months of corrected age to avoid false negatives that could occur with OAEs. OAEs have a sensitivity >80% in healthy newborns; however, in newborns with risk factors, the sensitivity decreases to less than 60% [1].

PHYSIOLOGY OF HEARING

The cochlea is divided into three compartments: the vestibular scala, the tympanic scala, and the middle compartment or scala media; the latter contains the organ of Corti and is separated from the first two by Reissner's membrane and the basilar membrane, respectively. This entire system is distributed along the cochlear modiolus, from the base to the apex. (Figure 1) [3].

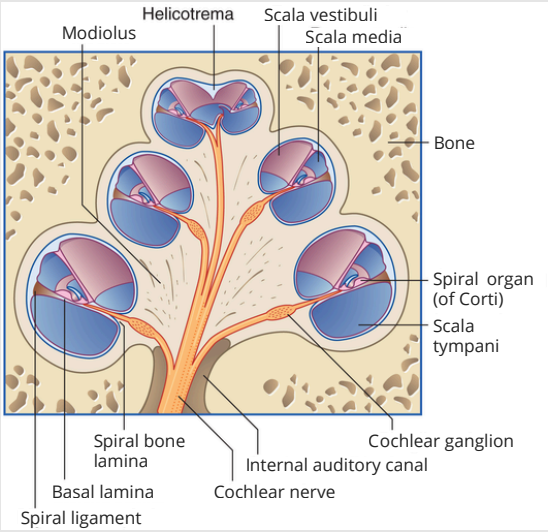


Figure 1. Cross-sectional anatomy of the cochlea. *Mtui E, Fitzgerald T. Clinical Neuroanatomy and Neuroscience. 8th ed. Elsevier; 2022.*

The hair cells (Figure 2) are interconnected by the cytoarchitecture of the organ of Corti; thus, when several cells move in synchrony, their mechanical responses can be summed. Therefore, this activation of large numbers of coordinated cells can change the mechanical response of the cochlea. The outer hair cells mechanically influence the responses of the inner hair cells [3].

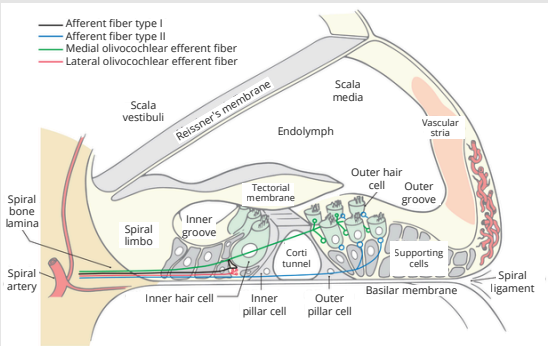


Figure 2. Cross-section of a typical turn of the cochlear labyrinth. *Haines DE. Principles of Neuroscience: Basic and Clinical Applications. 5th ed. Elsevier; 2019.*

The inner hair cells transmit the auditory message to the brain, while the outer hair cells provide high sensitivity and frequency selectivity to the cochlea (Figure 2). Cochlear hearing loss is sometimes associated with hair cell damage. Occasionally, the inner hair cells may be non-functional or absent, meaning that the auditory nerve innervation in these areas may not be functioning or may have degenerated [3].

OTOACOUSTIC EMISSIONS

Otoacoustic emissions are mechanical vibrations generated in the cochlea, which are transmitted through the lymphatic fluid and through the middle ear to the external auditory canal, where faint sounds can be recorded with a microphone (Figure 3) [3].

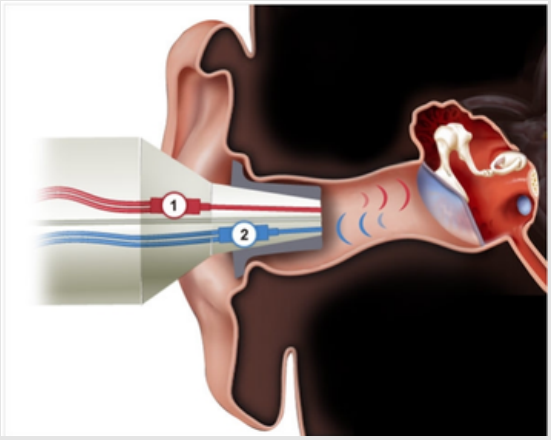


Figure 3. Diagram of otoacoustic emissions. 1 = probe emitting the stimulus sound; 2 = microphone picking up the sound emitted by the hair cells. *Taken from: Puel J-L. Otoemissions [online]. https://www.cochlea.eu/es/exploracion-funcional/metodos-objetivos/otoemisiones*

The organ of Corti receives sounds, processes them, and sends them via the auditory pathway to the brain; at the same time, it produces and emits spontaneous sounds through the activity of its structures. This is known as spontaneous otoacoustic emissions [3].

Transient otoacoustic emissions are frequency responses that arise in the cochlea and can be measured in the external auditory canal after a brief acoustic stimulus, such as a click or a burst tone. These emissions are present in all individuals with normal hearing and are an expression of normal cochlear function [3].

Most hearing losses are associated with lesions in the external ear, middle ear, or cochlea, specifically affecting the outer hair cells; these can be detected using otoacoustic emissions. On the other hand, emissions tests are unable to detect lesions beyond the outer hair cells; therefore, they do not detect retrocochlear hearing loss. Auditory brainstem response (ABR) are more specific and sensitive for detecting hearing loss due to auditory neuropathy. For this reason, hearing screenings have been adopted that include evaluation with both otoacoustic emissions (OAEs) and ABR [4,5].

AUDITORY BRAINSTEM RESPONSE

In pediatric audiology, auditory brainstem response (ABR) testing provides an objective assessment of hearing, the severity of hearing loss, and the location of the lesion. This is because it is a qualitative and

quantitative method for recording the activity generated by the central auditory nervous system in the brainstem in response to acoustic stimulation. The test involves stimulating the auditory pathway with a click (which stimulates most of the cochlea). This mechanical stimulus is transformed in the organ of Corti into an electrical stimulus that travels along the auditory pathway to the auditory cortex.

ABR testing is a fundamental tool in screening programs for cochlear and retrocochlear hearing loss, especially in young children and in cases where audiometry results are difficult to obtain.

The test is performed by placing one electrode on each mastoid process and another active electrode on the forehead. These are coupled with transducer paste, which facilitates the transmission of electrical activity, and are fixed to the skin with self-adhesive patches (Figure 4). The sound stimulus is delivered through conventional headphones, in-canal headphones, or a bone vibrator, by previously setting the number of clicks per second, as well as the morphology, duration, and intensity of the stimulus.



Figure 4. Auditory brainstem response application. (1) Active electrode (-) mastoid. (2) Air conduction transducer, hearing aid. (3) Midline electrode (ground). (4) Reference electrode (+). *Senced. Auditory evoked potentials: limitations and advantages [online]. https://audiopacks.es/es/blog-audiosocial/2013/01/27/potenciales-evocados-limitaciones-y-ventajas*

Subsequently, a 5-wave pattern will be reflected, which will guide us to the patient's auditory state (Figure 5).

- **Wave I:** Electrical activity of the spiral ganglion.
- **Wave II:** Posterior portion of the anteroventral cochlear nucleus and anterior portion of the posteroventral cochlear nucleus.
- **Wave III:** Anterior portion of the ipsilateral anteroventral cochlear nucleus and contralateral medial nucleus of the trapezoid body.
- **Wave IV:** Isolator and contralateral cells of the superior medial olive.
- **Wave V:** Cells of the lateral lemniscus and/or inferior colliculus.

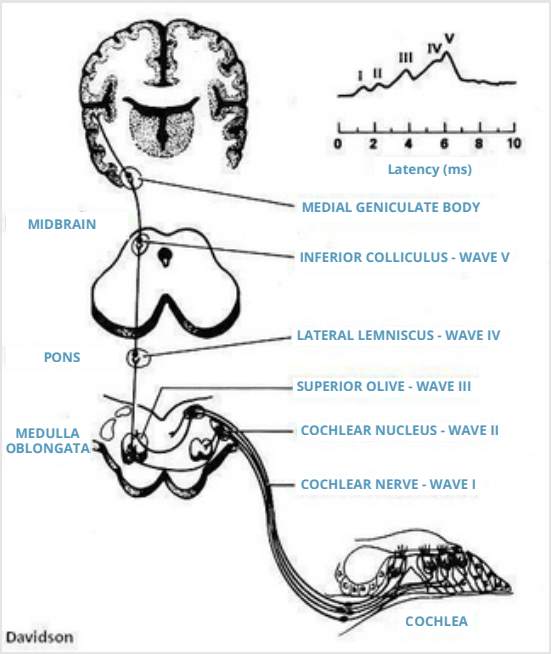


Figure 5. Waves through the auditory pathway. Schematic representation of the anatomical generators of the auditory brainstem evoked response (ABR) waves (I–V) along the auditory pathway, from the cochlea to the midbrain. *Taken from: Lafuente DA. Auditory brainstem evoked potentials (ABRs) [online]. https://www.sorderayvertigo.com/sordera/pruebas//*

Quantitative diagnosis is performed by identifying wave V, which is the last to disappear and the easiest to visualize.

It is of great importance to perform ABR tests, especially in patients with risk factors for developing hearing loss, since, in addition to guiding us toward early detection, it is a non-invasive test that allows for a fairly accurate diagnosis of hearing impairment.

PROPOSED ALGORITHM FOR NEWBORN HEARING SCREENING

The WHO recommendations suggest a hearing screening protocol with the "1-3-6" principle, which serves as a mnemonic for:

- **1** - All children should undergo hearing screening within the first month of life.
- **3** - All children with initial and subsequent screening who require diagnostic testing should receive an appropriate hearing evaluation within the first three months of life to confirm their hearing status.
- **6** - Once hearing loss is diagnosed, the child and family should have immediate access to intervention strategies. This should begin as soon as possible after the diagnosis and no later than six months of age.

A study was conducted on newborns at the *Hospital Regional de Alta Especialidad "Dr. Ignacio Morones Prieto"* to determine the diagnostic validity of OAEs in high-risk patients (Table 1). The study showed that, of the 134 patients in the sample, OAEs yielded a "no problem" result in 7, while the remaining 127 passed.

Subsequently, when the same group underwent the ABR test, 115 newborns showed normal hearing, while 19 showed abnormal results [1].

Table 1. Risk factors for developing hearing loss.

Risk factors
• In utero infection
• Intraventricular hemorrhage
• NICU stay >24 hours
• Severe perinatal asphyxia
• Weight less than 1500 g
• Ototoxic medications
• Craniofacial abnormalities
• Early and late sepsis
• Mechanical ventilation

NICU = Neonatal Intensive Care Unit. Table compiled by the author, with information obtained from: González-Amaro C. Validity of otoacoustic emissions to detect hearing loss in high-risk neonates. Pediatr Mex. 2013;15(3):80-83

Currently, based on studies that have been carried out and recommendations from the WHO, the screening and diagnosis of hearing problems is carried out as follows (Figure 6):

1. Screening is performed using OAEs within the first month of life (preferably before hospital discharge) [5]. This screening can have two results:
   a. Pass: correct cochlear conduction of the auditory stimulus.
   b. Fail: alterations in the conduction and/or reception of the auditory stimulus.

2. Once the results are obtained, different paths can be followed:
   a. "Pass" result in both ears, without risk factors: Discharge and follow-up in primary care, due to the low risk [6].
   b. "Pass" result in both ears, with risk factors: ABR at 3 months of corrected age, due to the risk [5,6].
   c. "Fail" result in one or both ears, without risk factors: Repeat the OAEs.
      i. "Pass" result: follow-up in early intervention and monitoring.
      ii. "Fail" result: perform ABR within the first 3 months of corrected age [5,6].
   d. "Fail" result in one or both ears, with risk factors: ABR at 3 months of corrected age [6].

In all cases, follow-up should be performed at one, three, and six years of age, as late-onset hearing loss may occur; although this condition is less frequent, this protocol helps prevent it from being overlooked.

Depending on an unfavorable result of the ABR test, the decision will be made regarding further studies to determine the cause and follow-up of the hearing loss. This follow-up is carried out by audiologists or otolaryngologists. [5,6]

CONCLUSIONS

It is of great importance for medical personnel to be knowledgeable about the Newborn Hearing Screening algorithm in order to detect hearing loss and deafness early.

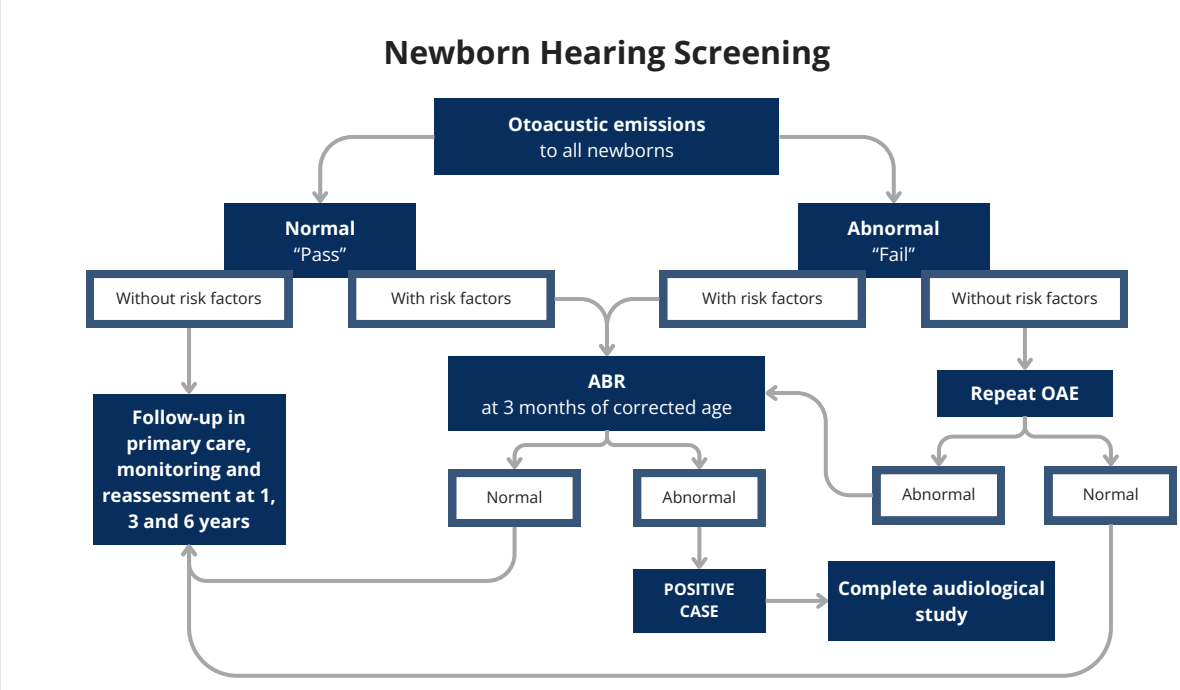


Figure 6. Algorithm for neonatal hearing screening and follow-up. *Diagram compiled by the author, with information obtained from: World Health Organization. Hearing screening: considerations for implementation. Geneva: World Health Organization; 2021. ABR = auditory brainstem response; OAE = otoacoustic emissions.*

As primary care physicians, it is relevant to promote the correct follow-up of the Newborn Hearing Screening algorithm among the parents and guardians of the newborn for the benefit of their well-being.

In conclusion, newborn hearing screening is a fundamental tool for detecting potential hearing problems in newborns early, enabling early interventions that promote their linguistic, cognitive, and social development, significantly improving their long-term quality of life.

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Conflict of interest

The authors declare no conflicts of interest.

Ethical considerations

This work did not involve the participation of human subjects or animals, nor the collection of primary data; therefore, it did not require approval from a research ethics committee. All data used were obtained from previously published and publicly accessible secondary sources.

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The Use of Clinical Simulation in Medical Education

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ABSTRACT

Clinical simulation has become established as one of the most relevant pedagogical strategies in contemporary medical education due to its ability to strengthen clinical competencies in safe and controlled environments. This essay critically analyzes the role of clinical simulation in the training of healthcare professionals, emphasizing its pedagogical foundations, implementation methods, documented benefits, and main challenges. Drawing on recent scientific literature, it examines theories such as experiential learning, deliberate practice, and cognitive load theory, as well as the importance of debriefing as the core of reflective learning. It also describes the different levels and models of simulation, including low- and high-fidelity simulators, standardized patients, virtual reality, and hybrid simulation, highlighting the importance of its longitudinal curricular integration. The reviewed evidence demonstrates that simulation promotes the acquisition and retention of technical and non-technical skills, improves teamwork, and contributes to patient safety by allowing training in highly complex scenarios without real risk. However, its effectiveness depends on pedagogical rigor, teacher training, and proper integration with supervised clinical practice. Finally, the need to conceive of simulation as a means for the comprehensive and ethical training of future healthcare professionals, and not merely as a technological innovation, is discussed.

Keywords: clinical simulation, medical education, competencies.

INTRODUCTION

Contemporary medicine faces a formative paradox that few disciplines share with the same intensity: to learn to heal, the student needs to practice on someone who may be affected by that practice. For decades, the hospital-based learning model based on observation and the progressive repetition of procedures on real patients was the norm. However, the growing complexity of clinical practice, expanding ethical standards, and accumulated evidence on preventable medical errors have demanded a rethinking of the foundations of medical education [1].

It was in this context that clinical simulation emerged as a systematic alternative that allows students to approach clinical reality without compromising patient safety. Its development has been driven by the confluence of pedagogical frameworks centered on active learning, the technological revolution in simulation devices, and a global health safety agenda that places medical error as a priority public health problem. Over the past two decades, the use of simulation has grown exponentially, and it currently constitutes the leading practical training strategy in multiple health sciences programs worldwide [2].

Clinical simulation can be defined as a pedagogical technique that uses designed scenarios to replace or expand real experiences in order to interactively evoke substantive aspects of the clinical world. Simulation aligns with new paradigms in education and is consistent with theories of experiential learning, as it promotes the development of psychomotor skills and strengthens executive functions in a controlled environment [1].

Its relevance in contemporary medical education is multifaceted. From an ethical perspective, it allows error to occur in a safe environment, with no real consequences for any patient. From a pedagogical perspective, it offers deliberate repetition, immediate feedback, and gradual control of scenario complexity. From an institutional perspective, it facilitates the objective evaluation of competencies and contributes to the standardization of training processes, which is especially valuable in health systems with high variability in the quality of clinical education [3].

Despite its growing adoption, clinical simulation is not free of criticism and limitations. Its implementation demands considerable financial investment, requires faculty with specific pedagogical competencies, and carries the risk of becoming an end in itself, disconnected from real clinical practice. Moreover, its incorporation into the medical curriculum is far from homogeneous: while some institutions have integrated it longitudinally and coherently, others employ it sporadically and disjointedly, thereby compromising its formative potential. This landscape raises a question that organizes the present essay:

To what extent does clinical simulation, when implemented with pedagogical rigor and curricular integration, contribute to the training of more competent and safer health professionals?

Therefore, the objective of this essay is to analyze, from a critical perspective and grounded in recent scientific literature, the role of clinical simulation as a pedagogical tool in undergraduate and graduate medical education. To this end, its theoretical foundations, the different models and technologies

available, the documented benefits, and the challenges that condition its effectiveness are examined. This work is aimed at students and health professionals interested in educational innovation and the continuous improvement of quality in clinical training, and is written from the perspective of a medical student who has gone through simulation experiences at different stages of her training.

PEDAGOGICAL FOUNDATIONS OF CLINICAL SIMULATION

- **Experiential learning**

The most widely cited theoretical foundation for clinical simulation is David Kolb's experiential learning model, which posits that knowledge is generated through a four-stage cycle: concrete experience, reflective observation, abstract conceptualization, and active experimentation. Simulation offers an ideal setting for navigating this cycle in a controlled and repeatable manner. Herrera-Aliaga and Estrada draw on Kolb to point out that when students experience simulated situations, they must reflect on what they have experienced, construct abstract concepts, and test what they have learned in new situations; in this sense, debriefing—which will be discussed later—acts as the mechanism that transforms the experience into genuine learning [2].

This alignment between Kolb's cycle and the operational characteristics of well-implemented simulation explains why this strategy has gained so much ground in contemporary medical education. Alonso-Peña and Álvarez-Álvarez reviewed 43 studies on simulation in health sciences education and confirmed that programs incorporating structured feedback, repetitive practice, and progressive variation in difficulty—all dimensions of the experiential cycle—produce the most consistent and lasting learning outcomes [4].

- **Deliberate practice**

Ericsson's theory of deliberate practice suggests that expertise does not result simply from repeated exposure to a task, but rather from conscious practice that is goal-oriented and accompanied by high-quality feedback. Felix and Schertzer describe mastery learning as the direct application of this principle to medical simulation: in this approach, progress depends not on the amount of time elapsed but on the level of performance demonstrated, and the student repeats the scenario until reaching a previously established minimum standard of competence [5].



Figure 1. Dr. Mary D. Patterson trains medical students using a human patient simulator at UF's Center for Experiential Learning and Simulation.

> *"The simulation environment represents an ideal opportunity for the deliberate practice of complex skills to the point of mastery, both in routine procedures and in low-frequency, high-severity situations." (Felix & Schertzer, 2022, p. 1)*

The results of this approach are especially significant in invasive procedures and emergency situations. Mitzman and colleagues implemented a simulation-based mastery curriculum for pediatric emergency medicine residents and found substantial improvements in the execution of high-risk procedures, with a documented reduction in performance variability among participants, supporting the usefulness of this approach in reducing formative inequity within a single program [6].



Figure 2. A group of students observes the execution of a simulated procedure through screens, while an instructor directs the session from a central console.

- **Cognitive load theory**

Cognitive load theory distinguishes between intrinsic load, determined by the complexity of the material; extrinsic load, generated by instructional design; and relevant load, which is directed toward effective learning. In a real clinical setting, the total cognitive load can be so high that novice students devote most of their cognitive resources to avoiding serious errors, leaving little room for reflection and consolidation of learning. Simulation can reduce extrinsic load by eliminating the uncertainty of real-world consequences and adjusting the complexity of the scenario to the learner's level.

This principle has direct implications for the design of simulation programs: a gradual progression in complexity is not only pedagogically desirable but also cognitively necessary. Tokuno and colleagues applied cognitive load theory to the analysis of virtual reality simulation programs for invasive procedures and confirmed that the cognitive load perceived by students decreases progressively with practice, freeing

up attentional resources that are then redirected toward clinical decision-making [7]. This finding supports the design of tiered curricula that begin with low-complexity scenarios before introducing high-fidelity, time-pressured situations.

- **Debriefing as a pedagogical core**

If there is one element that distinguishes pedagogically rigorous clinical simulation from mere exposure to a scenario, it is debriefing. Abulebda *et al.* define it as the intentional discussion following the simulation that allows participants to clearly understand their actions and thought processes in order to promote learning and improve future clinical performance [8]. Without a structured debriefing, simulation can lead to errors or reinforce inappropriate behaviors without the student realizing it.

> *"Debriefing after simulation is one of the most effective components of simulation-based education and the cornerstone of the learning experience in the medical simulation setting." (Abulebda et al., 2022, para. 1)*

Duff and colleagues conducted a systematic review that included 70 studies on debriefing methods in health simulation and found that, while there is a wide variety of models and techniques, the most effective frameworks share characteristics such as exploring the student's mental model, using open-ended questions, and explicitly linking the simulated experience to real-world clinical practice [9]. This review also notes that the empirical evidence is still insufficient to recommend a single debriefing model over others, underscoring the need for further research in this field.

TYPES, LEVELS, AND CURRICULAR INTEGRATION

- **Low-fidelity simulators**

Low-fidelity simulators include static anatomical models, arms for venous access, suture pelvises, or basic cardiopulmonary resuscitation manikins. Their main advantage is their low cost and accessibility, characteristics that make them particularly useful for teaching specific procedural skills in the early stages of training. Elendu *et al.* argue that the choice of fidelity level should be guided by learning objectives rather than by the availability of technology, since high fidelity does not in itself guarantee superior results when the goal is the acquisition of an isolated technical skill [2].

This distinction is particularly relevant in resource-limited settings. Alonso-Peña and Álvarez-Álvarez report that in Latin American institutions with limited access to high-fidelity technology, low-fidelity models—when combined with deliberate practice and structured feedback—produce learning outcomes comparable to those obtained with more sophisticated devices in the acquisition of basic procedural skills [4]. This evidence challenges technological determinism in medical education and suggests that pedagogical rigor is a more decisive factor than investment in equipment.



Figure 3. Close-up of an intravenous catheter being inserted into the arm of a training manikin, with a tourniquet and gauze pads placed on the surface.

- **High-fidelity simulators**

High-fidelity simulators are computerized manikins capable of replicating complex physiological responses: a palpable pulse, spontaneous breathing, reactive pupil dilation, crying, and responses to medications. Their use focuses on simulating emergency scenarios, highly complex situations, and training multidisciplinary teams. Elendu *et al.* note that high-fidelity simulation significantly improves clinical decision-making, team communication, and safety during invasive procedures, particularly in low-frequency, high-severity scenarios that residents may not encounter frequently enough during their hospital training [2].

However, high technological fidelity does not automatically guarantee superior learning. The concept of functional fidelity, which is gaining acceptance in the literature, proposes that what truly matters is not how closely the simulator resembles a real patient, but rather the extent to which the scenario triggers the same cognitive and decision-making processes as a real clinical situation. A well-designed scenario using a medium-fidelity simulator can be more educational than a poorly structured one using state-of-the-art technology.

- **Standardized patients**

Standardized patients (SPs) are individuals trained to consistently and reproducibly portray patients with specific clinical conditions. Their use is particularly valuable in teaching and assessing communication skills, clinical interviews, physical examinations, and the management of emotionally complex situations, such as delivering bad news. Unlike mannequin simulators, SPs offer genuine human interaction that triggers the same emotional and communicative responses as a real clinical encounter, which is irreplaceable for training so-called "soft skills" or relational competencies.

Herrera-Aliaga and Estrada highlight that simulation with standardized patients is one of the most widely used methods in undergraduate programs for assessing communication competencies through objective

structured clinical examinations (OSCE) [1]. Its pedagogical advantage lies in the ability to reproduce identical scenarios for multiple students, ensuring equitable assessment conditions—something that is difficult to achieve in a real clinical setting, where patient cases are inherently variable.



Figure 4. A clinical team performs a procedure on a pediatric mannequin in a simulated operating room setting. Imaging studies can be seen in the background.

- **Virtual reality and hybrid simulation**

Virtual reality (VR) and augmented reality technologies represent the latest frontier in medical simulation. Han *et al.* conducted a systematic review with a meta-analysis that included 45 randomized controlled trials on the use of VR in health education and found significant improvements in knowledge, skills, and attitudes, with a moderate-to-large effect size compared to traditional methods [10]. Moll-Khosrawi *et al.* demonstrated in a randomized controlled trial that first-year medical students trained in basic life support using VR performed cardiopulmonary resuscitation maneuvers with higher quality compared to those who received exclusively online training [11].

Birrenbach *et al.* published a randomized trial on the use of VR for Advanced Trauma Life Support (ATLS) training and found that the VR-trained group performed significantly better in post-training assessment scenarios, with shorter response times in managing treatment priorities [12]. Hybrid simulation, which combines SPs with partial manikins or VR environments, represents the highest level of simulated integration available and offers scenarios that replicate the multidimensional complexity of real clinical encounters, although its cost and logistical complexity are considerable.

- **Integrated curriculum**

The effectiveness of any simulation modality depends on how it is integrated into the medical curriculum. Alonso-Peña and Álvarez-Álvarez found that programs that incorporate simulation in a longitudinal manner and integrate it with theoretical content and clinical practice produce significantly better results than those that use it in isolation or on an episodic basis [4].

Curricular integration means that simulation scenarios are aligned with the learning objectives of each stage of training, that there is a progression in complexity, and that performance in simulation has implications for student evaluation.

Elendu *et al.* propose that simulation should be part of a broader and more coherent training system, in which the simulated experience prepares the student for the real clinical encounter and vice versa: supervised clinical practice informs the design of simulation scenarios [2]. This two-way interaction between the simulation lab and the clinical setting is the feature that distinguishes truly integrated simulation programs from those that merely incorporate technological devices without transforming the curricular framework.

EVIDENCE-BASED BENEFITS

- **Technical competencies**

The strongest evidence in favor of clinical simulation comes from the area of technical skills. Ajemba *et al.*, in a systematic review that analyzed randomized controlled trials and quasi-experimental studies published between 2008 and 2023, concluded that simulation-based training is an effective educational strategy for the acquisition and retention of clinical skills, with outcomes superior to no intervention and, in several studies, to traditional training methods [3]. The review identifies program duration, frequency of practice, and the quality of debriefing as moderating factors.

Comparable results have been reported in specific contexts. McInerney *et al.*, in a systematic review on the effect of simulation training on medical students' performance, confirmed consistent improvements in procedural skills, with learning retention documented up to twelve months after training when the program included reinforcement sessions [13]. This finding has relevant practical implications: well-designed simulation not only teaches but also ensures that what is learned persists long enough to be transferred to actual clinical practice.

- **Non-technical skills**

Non-technical skills, such as communication, teamwork, situational leadership, stress management, and decision-making under pressure, can also be trained through clinical simulation, although measuring them is methodologically more complex. Sezgin and Bektas conducted a systematic review with a meta-analysis that included eight randomized controlled trials with 819 participants and found that interprofessional simulation programs significantly improve teamwork (Hedges' $g = 0.41$; $p < 0.001$) and communication ($g = 0.54$; $p < 0.001$) among students from different health disciplines [14].

Pitiris *et al.*, in a systematic review of the literature published between 2013 and 2023, analyzed 22 studies on the development of nontechnical skills in interprofessional teams through simulation experiences and found that teamwork and cooperation

were included as learning objectives in all of the included studies [15]. This consensus reflects the growing recognition that nontechnical skills are just as critical to patient safety as technical skills, and that simulation offers an ideal setting for their systematic training.

- **Patient safety**

The most significant contribution of clinical simulation to contemporary medical education is, without a doubt, its impact on patient safety. By allowing errors to occur and be analyzed outside of a real-world context, simulation makes it possible to identify and correct behaviors before they cause harm. Bennion and Mansell analyzed the role of simulation-based education in the management of deteriorating patients and concluded that well-structured simulation programs improve early recognition of clinical deterioration and timely team response—two competencies directly linked to the reduction of serious adverse events [16].

This evidence takes on special significance in low-frequency, high-severity situations—such as cardiopulmonary arrest, anaphylaxis, and obstetric hemorrhage, among others—which residents may not encounter frequently enough during their hospital training. For these scenarios, simulation does not merely complement clinical experience; it necessarily replaces it. The scoping review by Kubin *et al.* on the influence of simulation on patient outcomes and nursing safety confirmed that simulation has a positive impact on clinical performance, patient safety, and care outcomes, although it highlights the need for further research with rigorous designs to more accurately quantify the effect size [17].

- **Educational equity**

A less-explored but increasingly important benefit is simulation's contribution to equity in medical education. In the traditional hospital-based learning model, opportunities for hands-on practice are unequal: they depend on the caseload of the department, the preferences of the supervising physician, and the student's availability at key moments. Simulation, by replicating scenarios in a standardized manner, ensures that all students have access to the same training experiences, regardless of the department in which they rotate or the hospital where they are trained.



Figure 5. A standardized patient is examined with an otoscope by a health professional, while a second observer witnesses the interaction.

This aspect is particularly relevant in health systems with high variability in the quality of clinical training, such as those prevalent in Latin America. Ajemba *et al.* note that standardizing simulation experiences can help reduce competency gaps among students from different training centers, provided that programs are designed with accessibility in mind and are aligned with standardized assessment processes [3]. In this sense, simulation can serve as a powerful equalizer of educational opportunities.



Figure 6. A student uses a virtual reality headset and a robotic device connected to a screen to practice spinal surgical intervention for scoliosis. An experienced physician guides the simulation.

CHALLENGES AND LIMITATIONS

- **Implementation costs**

The main barrier to the widespread adoption of clinical simulation is its cost. High-fidelity simulators can cost more than 50,000 dollars per unit, and their maintenance, calibration, and updating require significant ongoing investments. Added to this is the cost of the necessary infrastructure, including simulation centers, debriefing rooms, video recording systems, and specialized technical staff. For many medical schools in low- and middle-income countries, these figures are prohibitive [2].

However, this argument must be put into perspective. On the one hand, low-fidelity simulators are equally effective for many learning objectives. On the other hand, available cost-effectiveness analyses suggest that the reduction in complications and adverse events associated with simulation training can generate hospital savings that justify the initial investment. The discussion about the cost of simulation cannot be separated from the human, institutional, and economic costs of clinical errors that could have been prevented.

- **Facilitator training**

Clinical simulation requires facilitators to possess specific pedagogical skills that go beyond expert

clinical knowledge. Scenario design, debriefing facilitation, formative assessment, and curriculum integration are skills that are not acquired automatically simply by being an experienced physician. Al-Khayat *et al.* implemented the DASH (Debriefing Assessment for Simulation in Healthcare) tool to train simulation instructors and found that most of the physicians evaluated demonstrated deficiencies in conducting debriefings before receiving formal training, with significant improvements following the intervention [18].

Ajemba *et al.* agree that the quality of the facilitator is one of the most important determinants of simulation's educational impact and that a lack of instructor training is one of the most common reasons why programs fail to produce the expected results [3]. This implies that any institutional investment in simulation should include, as a necessary condition, a systematic program for training and continuing education of its facilitators.

- **The risk of oversimulation**

A less-discussed but equally relevant risk is that of "oversimulation": the tendency to excessively substitute real clinical experience with simulated scenarios. While simulation can prepare students for practice, it cannot fully replace it. Encountering genuine uncertainty, individual patient variability, and the emotional burden of real human suffering are dimensions of medical training that simulation cannot and should not attempt to fully replicate.

Elendu *et al.* note that there are legitimate concerns about the realism of simulations and the transferability of acquired skills to the real clinical context [2]. Some programs that have disproportionately increased the number of simulation hours at the expense of supervised clinical practice have reported that graduates, although technically competent, show a reduced ability to handle the unpredictability and emotional complexity of real clinical encounters. The balance between simulation and genuine clinical practice must be an explicit and thoughtful criterion in curriculum design.

- **Transfer of skills to the real-world context**

The central question surrounding clinical simulation—whether what is learned in the simulator is effectively transferred to real-world practice—remains a subject of debate. Transfer is neither automatic nor guaranteed: it depends on the functional fidelity of the scenario, the quality of the debriefing, the opportunity to practice the acquired skills in a real-world context, and longitudinal performance monitoring. Ajemba *et al.* [3] note that the available evidence, while positive, remains heterogeneous in methodological quality, which limits the ability to draw definitive conclusions about the magnitude of the transfer effect.

This limitation does not invalidate the use of simulation, but it does require epistemological humility: simulation is a powerful tool within a broader educational system, not a self-sufficient solution. Its effectiveness depends on the coherence of the instructional design, the competence of the facilitator, and, fundamentally, its integration with the subsequent supervised clinical practice.



Figure 7. A team of medical professionals works together to provide emergency medical care to a simulated patient at the 88th Medical Group's simulation center.

REFLECTION

- **Simulation as a means, not an end**

As medical students who have participated in clinical simulation experiences at various stages of our training, we share a view supported by the academic literature: simulation transforms learning only when those who design and implement it view it as a means to achieve real clinical competencies, not as an end in itself. The danger of fetishizing technology—of valuing the simulator for its sophistication rather than its educational utility—is a trap into which both institutions and instructors can fall.

We have participated in simulation sessions where the time spent operating the equipment or "acting out the scenario" far exceeded the time allocated for subsequent reflection. The result was an intense but scarcely educational experience. We contrasted these experiences with others in which a relatively simple scenario—such as communicating an unexpected diagnosis to a standardized patient—was followed by an in-depth debriefing that confronted us with our communication biases and our automatic response patterns in the face of clinical uncertainty. In those moments, simulation fulfilled its pedagogical promise. This distinction between simulation as an experience and simulation as learning is precisely what Herrera-Aliaga and Estrada identify as the differentiating factor between effective programs and those that merely incorporate technology without transforming pedagogy [1].

- **Debriefing as the core of learning**

A review of the literature and our own experience as students converge on one point: debriefing is the element that most consistently determines the educational quality of a simulation session. When the facilitator skillfully leads the debriefing—exploring the student's mental framework, validating emotions without ignoring mistakes, and linking the simulated experience to future practice—the simulation transcends a technical exercise and becomes a genuine space for building professional identity.

The evidence from Duff *et al.* on the critical importance of debriefing, along with the observation that many facilitators "learn by doing" without formal training in

this skill, directly challenges us as stakeholders in the educational system [9]. Training instructors in the art and science of debriefing should be a top institutional priority, at least as important as acquiring simulation equipment. Without this investment in the pedagogical capital of facilitators, investment in technology loses much of its transformative potential.



Figure 8. Students practice with pediatric simulators to understand the treatment protocols that prevent pediatric emergencies.

- **The importance of curricular integration**

Finally, we reflect on the need for simulation to occupy an explicit and integrated place in the medical curriculum—not as an extracurricular activity or an optional supplement available only to those who have the time and motivation to take advantage of it. The curricular fragmentation that characterizes many medical programs—in which simulation appears as an isolated event, disconnected from theoretical content and clinical practice—drastically reduces its educational potential.

An integrated simulation curriculum, as proposed by Alonso-Peña and Álvarez-Álvarez, requires coordination among faculty members from different disciplines, agreement on learning objectives for each stage of training, and an assessment system that recognizes performance in simulation as a legitimate indicator of competence [4]. This implies a cultural shift within the institution that goes far beyond the acquisition of manikins or access to virtual reality platforms. Ultimately, it involves a collective decision regarding the type of physicians we wish to train and the conditions we must provide to achieve this goal.

CONCLUSIONS

Clinical simulation has proven to be a highly valuable educational tool in the training of healthcare professionals, with a documented positive impact on the acquisition of technical and non-technical competencies, and a significant contribution to patient safety. Its foundation in sound pedagogical theories—such as experiential learning, deliberate practice, cognitive load theory, and reflective debriefing—and its ability to provide reproducible, standardized, and safe experiences position it as an essential component of contemporary medical education.

However, its effectiveness does not stem from the technological device used, but rather from the pedagogical rigor with which it is designed and implemented. A simulation without structured debriefing, without curricular integration, and without trained facilitators is, at best, a memorable experience; at worst, an opportunity to reinforce errors without reflection. An institution that invests in simulators without simultaneously investing in the training of its faculty and the coherence of its curriculum is purchasing technology without pedagogy.

The future of clinical simulation points in three particularly significant directions. The first is interprofessional simulation, which brings together students of medicine, nursing, pharmacy, and other disciplines in a single scenario to train the collaborative skills required by contemporary models of health care [14]. The second is the integration of artificial intelligence for automated performance analysis, personalized feedback, and dynamic adjustment of the scenario's complexity [2]. The third is telesimulation, which allows for the remote replication of training experiences and can help democratize access to this educational modality in contexts of high geographic dispersion or limited resources [10].

As medical students, we conclude with a message that speaks directly to us: simulation offers us the privilege of learning to care for others without anyone paying the price for our learning. This opportunity carries an ethical responsibility that falls on all of us—students, faculty, and institutions alike—to make the most of it with commitment, rigor, and a willingness to confront our own mistakes before they affect a real patient. Ultimately, clinical simulation is not just an educational tool; it is a statement of values about the kind of physicians we want to become.



Figure 9. Professionals at Sant Joan de Déu Barcelona Hospital conducting a clinical simulation session with SIMTest to detect risks in the medical procedure.



Figure 10. Tulane School of Medicine faculty lead a high-stakes simulation training session from the control room, assessing the competencies demonstrated by the students.

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Conflict of interest

The author declares no conflicts of interest.

Ethical considerations

This work did not involve the participation of human beings or animals, nor the collection of primary data, and therefore did not require approval by a research ethics committee. All data used come from previously published secondary sources that are publicly accessible.

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Artificial Uterus in Extremely Preterm Birth: Current Advances and Future Prospects. A Narrative Review

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ABSTRACT

Extreme prematurity remains one of the leading causes of neonatal morbidity and mortality and is associated with long-term respiratory, neurological, and neurodevelopmental complications. Although advances in neonatal intensive care have improved survival rates for these patients, conventional strategies, such as mechanical ventilation, force the immature fetal organism to undergo a premature transition to neonatal physiology, exposing the lungs, cardiovascular system, and brain to conditions for which they are not yet prepared. In this context, the artificial uterus and extrauterine fetal support systems have emerged as an experimental alternative aimed at temporarily preserving fetal physiology outside the maternal uterus.

The objective of this narrative review was to analyze the physiological basis, historical development, major contemporary models, experimental results, and transnational and ethical challenges related to these technologies. The available literature shows that platforms such as EXTEND/Biobag have succeeded in maintaining, in extremely preterm animal models, a closed liquid environment, functional umbilical circulation, extracorporeal gas exchange, and prolonged hemodynamic stability, thereby promoting lung maturation and partially preserving conditions associated with fetal neurodevelopment. Unlike conventional neonatal care, these systems do not aim to rapidly adapt the preterm infant to extrauterine life, but rather to prolong the fetal physiological state in a controlled manner during a critical stage of organ maturation. However, their clinical application in humans remains limited by challenges related to anticoagulation, circuit miniaturization, umbilical cannulation, infection control, neurological safety, candidate selection, and bioethical considerations regarding viability and medical intervention.

Overall, the artificial uterus represents a promising preclinical technology and a paradigm shift in the management of extreme prematurity, whose future value will depend not only on prolonging survival but also on improving functional survival and reducing long-term sequelae.

Keywords: artificial uterus, extreme prematurity, extrauterine fetal support, artificial placenta, ectogenesis.

INTRODUCTION

Extreme prematurity remains one of the leading causes of neonatal morbidity and mortality worldwide. It is estimated that approximately 15 million premature births occur each year, a significant proportion of which involve infants born before 28 weeks of gestation, classified as extremely preterm [1,2]. Despite advances in neonatal intensive care over the past decades, the survival of these patients continues to be associated with high rates of long-term respiratory, neurological, and neurodevelopmental complications.

The main pathophysiological problem lies in the fact that many of these patients are born during critical stages of organ maturation, particularly during the canalicular and early saccular phases of lung development. During this period, the lung exhibits significant structural immaturity, characterized by poor alveolar development, incomplete vascularization, and insufficient surfactant production, severely limiting the ability to perform effective gas exchange outside the intrauterine environment [2,3]. As a result, survival often depends on mechanical ventilation, oxygen therapy, and multiple invasive procedures that, although essential, contribute to the development of lung injury and multisystem damage.

In addition to pulmonary immaturity, premature birth forces the fetal body to undergo an abrupt physiological transition to neonatal life when multiple systems are not yet prepared to function outside the intrauterine environment. The shift from placenta-dependent circulation to a physiology based on pulmonary ventilation and independent postnatal circulation can trigger hemodynamic instability, systemic inflammation, oxidative stress, and alterations in cerebral perfusion, contributing to complications such as bronchopulmonary dysplasia, intraventricular hemorrhage, white matter lesions, and encephalopathy of prematurity [1,4].

Although contemporary neonatal strategies have improved survival, functional outcomes remain limited in patients at the threshold of viability, particularly due to the persistence of long-term pulmonary and neurological sequelae [2].

In this context, interest has resurfaced in recent decades in developing technologies capable of partially preserving fetal physiology outside the maternal uterus. Contemporary extrauterine fetal support systems, including artificial placenta and artificial uterus platforms, aim to maintain fetal circulation, extracorporeal gas exchange, and fluid-filled lungs, thereby partially preventing premature neonatal transition [3,5]. These devices are not intended to achieve complete ectogenesis, but rather to prevent the severe lung and brain damage that occurs when immature lungs are exposed to air prematurely, thereby prolonging the physical environment of the uterus (Figure 1).

Unlike conventional neonatal care, whose primary goal is to rapidly adapt the preterm infant to extrauterine life, these technologies aim to temporarily prolong the fetal physiological state to allow for organ maturation that more closely resembles normal intrauterine conditions.

The development of modern platforms such as EXTEND and Biobag has experimentally demonstrated the possibility of maintaining prolonged physiological support in extremely preterm animal models, including preservation of fetal circulation, hemodynamic stability, and progressive lung development [5,6]. These advances have transformed extrauterine fetal support from a historically theoretical concept into a potentially viable experimental strategy for the future management of extreme prematurity.

However, the eventual clinical application of these technologies in humans continues to face significant physiological, technical, obstetric, and ethical challenges. Limitations persist regarding the miniaturization of extracorporeal circuits, anticoagulation, umbilical cannulation, infection control, and long-term neurological safety, in addition to bioethical questions concerning fetal viability, informed consent, and the limits of medical intervention [7,8].

The objective of this narrative review is to analyze and synthesize the physiological basis of extrauterine fetal support, the evolution of the main contemporary models, the available experimental results, and the technical, physiological, and ethical barriers that will influence its future clinical application in humans.

METHODS

This work presents a narrative literature review focused on the development and current status of extrauterine fetal support technologies, artificial placenta, and artificial uterus applied to the management of extreme prematurity. The manuscript was prepared through a non-systematic review of contemporary scientific literature related to fetal physiology, extracorporeal fetal support, perinatal bioengineering, and experimental models of artificial gestational support.

The literature search was conducted using international biomedical databases, including PubMed, Scopus, and Google Scholar, covering the last 10 years. Relevant historical studies prior to this period, which were fundamental to understanding the conceptual and experimental evolution of the field of partial ectogenesis techniques, were also included.

Search terms related to “artificial uterus”, “artificial placenta”, “extrauterine fetal support”, “EXTEND”, “Biobag”, “ectogenesis”, “prematurity”, “fetal physiology”, “extracorporeal life support”, and “fetal circulation” were used. In addition, the bibliographic references of articles considered relevant were reviewed to identify further publications of physiological, historical, and translational interest.

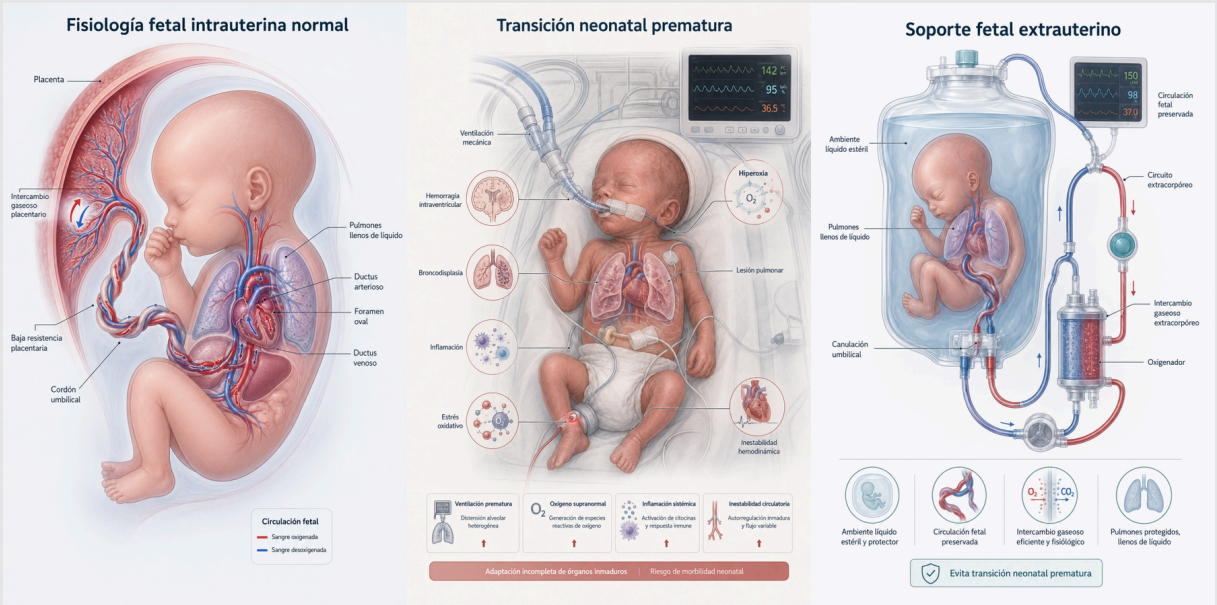


Figure 1. Pathophysiological basis of extrauterine fetal support. Comparative diagram illustrating normal intrauterine fetal physiology (left panel; labeled in the original image as “Fisiología fetal intrauterina normal”), premature neonatal transition (center panel; labeled as “Transición neonatal prematura”) in extremely preterm infants, and the physiological principle of extrauterine fetal support (right panel; labeled as “Soporte fetal extrauterino”), based on the preservation of fetal circulation and extracorporeal gas exchange. *Image created by the authors with the assistance of artificial intelligence tools. The original labels within the figure are presented in Spanish.*

Original articles, narrative reviews, experimental studies, and publications focused on fetal cardiovascular physiology, lung development, neurodevelopment, and contemporary artificial fetal support platforms were included. Priority was given to recent work and studies considered fundamental within the historical development of the field, particularly those related to modern extrauterine fetal support systems and their potential future clinical applications.

The information gathered was organized according to the main thematic areas of the review, including: physiological foundations of extrauterine fetal support, fetal-neonatal transition, historical evolution of the artificial placenta and artificial uterus, main contemporary experimental models, reported physiological outcomes, and translational challenges for their future clinical application in humans. The manuscript was prepared following the SANRA (Scale for the Assessment of Narrative Review Articles) guidelines, with an emphasis on thematic clarity, methodological transparency, and critical reasoning.

The selection and interpretation of the literature were based on the physiological, experimental, and translational relevance of each publication, as well as its contribution to the conceptual development of the field. Due to the narrative nature of this work, a formal systematic protocol, quantitative evaluation, and statistical analysis were not applied; therefore, the findings should be interpreted as a critical narrative synthesis and not as a quantitative estimate of the effect of these technologies.

PHYSIOLOGICAL BASIS OF EXTRAUTERINE FETAL SUPPORT

The development of extrauterine fetal support systems is based on the need to artificially preserve fetal physiology during critical stages of organ maturation. Unlike conventional neonatal intensive care, whose main objective is to rapidly adapt the premature newborn to extrauterine life, artificial placenta and artificial uterus technologies seek to temporarily maintain a fetal physiological state, preventing or delaying the premature transition to neonatal physiology [3,7].

During intrauterine life, the placenta is the primary organ for gas exchange, metabolic regulation, and fetal hemodynamic support. Fetal circulation is characterized by a specialized parallel system in which structures such as the ductus arteriosus, foramen ovale, and ductus venosus redistribute oxygenated blood to priority organs while the lungs remain functionally inactive and filled with fluid [3,5]. Under normal physiological conditions, the placenta also represents the vascular territory of least resistance within the fetal circulation, allowing for adequate cardiac preload and stable cardiac output with minimal ventricular afterload [9].

Unlike neonatal physiology, fetal gas exchange occurs exclusively at the placental level. As a consequence, the fetal lungs do not actively participate in blood oxygenation and remain filled with fluid throughout gestation. This fluid environment is essential for normal alveolar and pulmonary vascular development, while elevated pulmonary vascular resistance limits pulmonary blood flow and promotes the maintenance of physiological fetal shunts [7].

Normal birth triggers a complex physiological transition characterized by pulmonary aeration, elimination of fetal alveolar fluid, decreased pulmonary vascular resistance, and a progressive increase in pulmonary blood flow. Simultaneously, clamping of the umbilical cord eliminates placental circulation and forces a complete cardiovascular reorganization, with progressive closure of fetal shunts and establishment of independent neonatal circulation [3]. However, in extreme prematurity, this transition occurs when multiple organs remain structurally and functionally immature. In particular, the lung remains in early canalicular or saccular stages, characterized by incomplete alveolar development, immature vascularization, and insufficient surfactant production [2].

Early exposure of the immature lung to oxygen and positive pressures represents one of the main mechanisms of prematurity-induced lung injury. Several studies have shown that even brief periods of ventilation can trigger alveolar inflammation, oxidative stress, vascular alterations, and arrest of physiological lung development, significantly contributing to the development of bronchopulmonary dysplasia and chronic respiratory disease [1,3]. In this context, the pathophysiological problem lies not only in lung immaturity but also in the need to prematurely force the transition to a neonatal physiology for which the fetal organism is not yet prepared.

In addition to lung injury, premature neonatal transition significantly alters fetal cardiovascular physiology. Abrupt changes in intrathoracic pressure, vascular resistance, and blood flow can modify cerebral perfusion and promote serious neurological complications, such as intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL). The germinal matrix of the extremely premature infant has a particularly fragile vascularization and is susceptible to hemodynamic fluctuations, increasing the risk of intraventricular hemorrhage and cerebral white matter injury [4].

Extreme prematurity is also associated with relative hyperoxia, systemic inflammation, metabolic disturbances, and early exposure to environmental stimuli that exceed the neonate's physiological maturity. These conditions contribute to the development of necrotizing enterocolitis, sepsis, encephalopathy of prematurity, and long-term neurodevelopmental disorders [1]. Recent transcriptomic studies have further demonstrated activation of multiple inflammatory pathways and molecular alterations related to energy metabolism, mitochondrial function, and neuronal development in extremely premature infants [4].

In this pathophysiological scenario, the modern concept of extrauterine fetal support emerges. Unlike conventional neonatal therapy, which aims to rapidly adapt the premature infant to extrauterine life, artificial placenta and artificial uterus systems seek to prevent or delay this premature physiological

transition. The central principle consists of preserving functional fetal circulation, maintaining fluid-filled lungs, and providing extracorporeal gas exchange through low-resistance circuits that partially replicate the functions of the physiological placenta [3,5].

The most advanced contemporary models, such as EXTEND and Biobag, typically use pumpless arteriovenous circuits powered by the fetal heart itself, associated with closed, sterile liquid environments designed to recreate normal intrauterine conditions [6]. This strategy attempts to minimize hemodynamic disturbances, avoid premature air ventilation, and allow organ maturation to continue under physiological conditions closer to the fetal environment.

Overall, extrauterine fetal support proposes a paradigm shift: not to adapt an immature organism early to neonatal physiology, but to temporarily prolong fetal physiology while organic maturation continues.

HISTORICAL EVOLUTION AND CONTEMPORARY MODELS

The development of extrauterine fetal support technologies began shortly after the emergence of the first extracorporeal circulation systems in the mid-20th century. From the outset, the primary objective was to attempt to keep extremely immature fetuses alive by artificially replacing placental functions, particularly gas exchange and fetal hemodynamic support [2,5].

One of the most important precedents is the experiment conducted by Westin in 1958, who successfully cannulated previable human fetuses using rudimentary extracorporeal oxygenation systems, with limited survival times of a few hours [2]. Subsequently, during the 1960s and 1970s, several groups developed experimental models, primarily in ovine fetuses, using umbilical cannulation and arteriovenous circuits designed to partially reproduce fetal placental circulation.

However, most of these systems presented significant limitations related to thrombosis, hemolysis, fetal edema, umbilical vasospasm, and progressive hemodynamic instability. Many models used mechanical pumps that significantly increased extracorporeal vascular resistance, generating fetal cardiac overload and decreased umbilical flow. These findings led to the understanding that the fetal heart has a limited capacity to tolerate increases in afterload and that any successful system must reproduce the low-resistance characteristics of physiological placental circulation [6].

Subsequently, the development of prenatal corticosteroids, exogenous surfactant, and advanced neonatal ventilation partially shifted the focus away from conventional neonatal intensive care. However, as it became recognized that many of these interventions continued to be associated with significant pulmonary and neurological injury, interest in strategies to avoid premature neonatal transition resurfaced [1,3].

The major turning point occurred with the development of the EXTEND (EXTrauterine Environment for Neonatal Development) system by the group at the Children's Hospital of Philadelphia, described by Partridge *et al.* in 2017 [5,6]. This system introduced the modern concept of the "Biobag", a closed, sterile liquid environment designed to replicate intrauterine physiological conditions.

EXTEND uses a pumpless arteriovenous circuit powered directly by the fetal heart, connected to a low-resistance oxygenator and physiological umbilical cannulation. Unlike previous models, this strategy avoided the use of mechanical pumps and minimized hemodynamic alterations related to increased afterload and fetal cardiovascular dysfunction.

In the original study published in Nature Communications, Partridge and colleagues successfully maintained extremely premature lambs for up to four weeks with hemodynamic stability, progressive somatic growth, and continued lung maturation [6]. Furthermore, some animals subsequently achieved successful transition to conventional ventilation and prolonged survival after removal of the system.

From these advances, other relevant contemporary platforms began to emerge, whose main technical and physiological characteristics are summarized in Table 1. The EVE (Ex Vivo Uterine Environment) system, developed in Australia and Japan, shares multiple physiological principles with EXTEND, including pumpless arteriovenous circuits and closed liquid environments. The main difference between the models lies in the type of circuit and its limitations.

However, although it allowed successful support in smaller ovine fetuses, closer in weight to extremely premature human infants, the results showed greater difficulties related to somatic growth, fetal hydrops, and prolonged system stability [2,3]. These differences suggest that simply reproducing fetal gas exchange is not enough; sustained hemodynamic and metabolic stability remains one of the main determinants of the physiological success of extrauterine support.

Other models, such as those developed in Toronto and Michigan, explored alternative configurations using porcine fetuses and mechanically pumped systems. While these platforms provided important information on miniaturization, vascular accessibility, and prolonged extracorporeal support, they also highlighted one of the field's main limitations: the more complex and artificial the circulatory support becomes, the more difficult it is to preserve normal fetal physiology. Pump-assisted systems can stabilize extracorporeal flow, but they increase vascular resistance and hemodynamic alterations that deviate from physiological placental circulation, promoting thrombosis, umbilical vasospasm, and progressive cardiovascular instability [2,3].

Currently, EXTEND continues to be the experimental model with the most consistent physiological results, although its human application remains in the preclinical phase (Figure 2).

Table 1. Comparison of the main contemporary models of extrauterine fetal support.

Model	Type of extracorporeal circuit	Use of a mechanical pump	Experimental species	Main results	Main limitations	Development stage
Historical systems (1960–1990)	Extracorporeal arteriovenous (ECV)	Yes, in many models	Primarily sheep	Demonstrated initial viability of extrauterine fetal support.	Thrombosis, hemolysis, fetal edema, umbilical vasospasm, and hemodynamic instability.	Historical experimental
EXTEND (Biobag)	Low-resistance pumpless arteriovenous (PRAV)	No	Sheep	Support up to 4 weeks, hemodynamic stability, somatic growth, lung maturation, and subsequent transition to conventional ventilation.	Human application is still preclinical; challenges of miniaturization, anticoagulation, and umbilical catheterization.	Advanced preclinical
EVE (Ex Vivo Uterine Environment)	Pumpless arteriovenous (PRAV)	No	Sheep	Partial reproduction of intrauterine conditions in ovine models more closely resembling extreme human prematurity.	Fetal hydrops, reduced somatic growth, and limited prolonged stability.	Preclinical
Toronto Model	Assisted extracorporeal circuit.	Yes	Swine	Relevant information on miniaturization and prolonged support.	Increased vascular resistance and difficulty in preserving normal fetal physiology.	Experimental
Michigan Model	Assisted extracorporeal circuit.	Yes	Swine	Advances in vascular accessibility and extracorporeal fetal support.	Pump dependence, thrombosis, and cardiovascular instability.	Experimental

Comparison of the physiological and technical characteristics of modern artificial placenta and artificial uterus platforms, including type of extracorporeal circuit, use of mechanical pump, experimental species, main results and reported limitations.

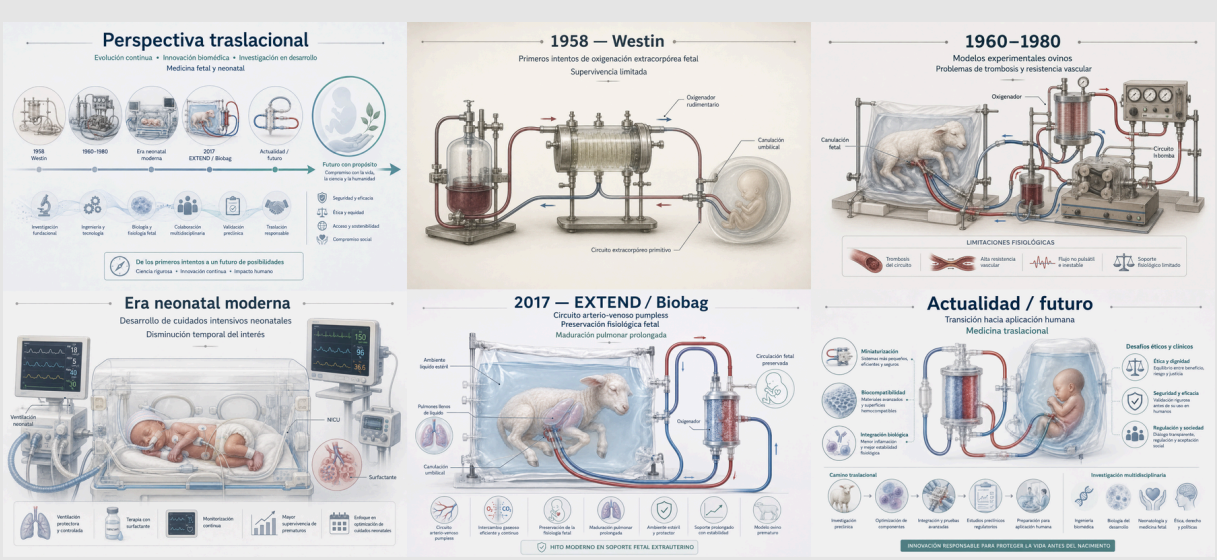


Figure 2. Historical evolution of extrauterine fetal support and artificial uterus technologies. Timeline illustrating the major milestones in the development of artificial placenta and artificial uterus technologies, including the first extracorporeal fetal oxygenation experiments by Westin (1958), experimental ovine models developed between 1960 and 1980, the emergence of modern neonatal intensive care, the development of the EXTEND/Biobag platform in 2017, and current translational perspectives toward clinical application. The figure also summarizes the main physiological advances, technological innovations, and ethical considerations associated with each stage. *Image created by the authors with the assistance of artificial intelligence tools. The original labels within the figure are presented in Spanish.*

PHYSIOLOGICAL COMPONENTS AND OUTCOMES

Contemporary extrauterine fetal support systems aim to temporarily preserve fetal physiology through extracorporeal support, an artificial fluid environment, and the maintenance of conditions similar to the intrauterine environment [3,7].

The central component of these platforms is the extracorporeal circuit, which replaces the placental functions of oxygenation and carbon dioxide elimination. The most physiological models, particularly EXTEND and EVE, utilize pumpless arteriovenous configurations powered directly by the fetal heart, avoiding mechanical pumps that have historically been associated with increased vascular resistance, hemolysis, and fetal hemodynamic instability [2,6].

The low resistance of the circuit is a critical aspect because the physiological placenta normally represents the vascular territory of lowest resistance within the fetal circulation. The fetal heart, especially the right ventricle, has a limited capacity to tolerate significant increases in afterload. Consequently, small variations in extracorporeal resistance can significantly alter cardiac output and compromise cerebral and systemic perfusion [9].

Studies using the EXTEND system demonstrated that progressive increases in resistance decrease combined cardiac output and alter fetal Doppler parameters; however, they also showed preservation of hemodynamic redistribution mechanisms aimed at maintaining cerebral and coronary perfusion, findings consistent with physiological fetal cardiovascular autoregulation [9]. These results suggest that extrauterine fetal support can preserve authentic fetal hemodynamic responses and not merely function as a passive platform for extracorporeal oxygenation.

Umbilical cannulation allows for partial replication of placental circulation through arterial drainage to the oxygenator and fetal venous reinfusion [5]. However, it remains a major technical limitation due to the risk of vasospasm, thrombosis, and progressive reduction of extracorporeal flow, especially in extremely small human fetuses. To reduce these complications, atraumatic microsurgical strategies, strict thermal control, preservation of cord-free segments, and the use of topical vasodilators have been proposed [3].

Another characteristic component of the modern artificial uterus is the artificial liquid environment. The “Biobag” system, developed by the Philadelphia group, introduced the concept of a closed, sterile liquid chamber where the fetus remains completely submerged during extracorporeal support [6]. The integration of these components can be schematically represented as a system composed of a liquid environment, umbilical cannulation, extracorporeal circuit, oxygenator, filtration, and continuous fetal monitoring (Figure 3).

Maintaining a fluid-filled environment has several important physiological implications. In addition to reducing ventilator-associated lung injury, it promotes thermal stability, musculoskeletal development, and a decrease in excessive environmental stimuli. It also helps preserve hemodynamic conditions closer to those found in utero [1].

Modern systems also incorporate filtration and infection control mechanisms designed to maintain prolonged sterility. Some models use continuous exchange of artificial amniotic fluid, microbiological filters, and ultraviolet radiation systems to reduce the risk of bacterial contamination and fetal sepsis [10]. This is especially relevant considering that many causes of extreme prematurity are associated with intrauterine infection.

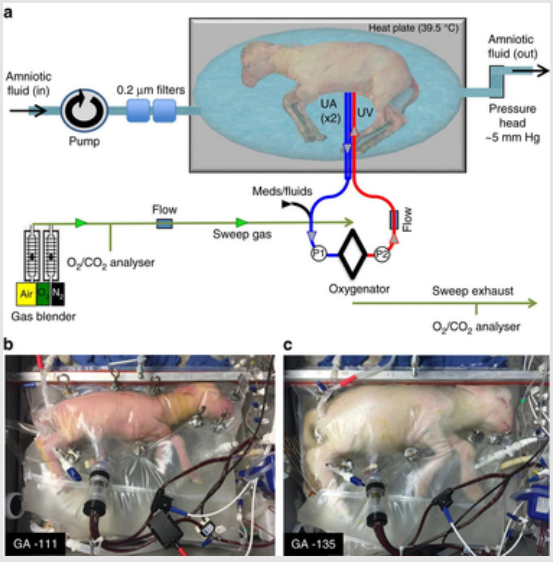


Figure 3. Main components of a modern artificial uterus system. (a) The system consists of a pump-free arteriovenous extracorporeal circuit, a low-resistance oxygenator, a closed liquid chamber with continuous exchange of artificial amniotic fluid, and an umbilical vascular interface. The diagram shows the artificial amniotic fluid inlet and outlet, filters, thermal control system, gas mixer, O2/CO2 analyzers, oxygenator, and umbilical vascular connections. (b) The lower images show a cannulated fetal lamb at 107 days of gestation on day 4 of support, and (c) the same animal on day 28, demonstrating somatic growth and progressive maturation during extrauterine support. *Adapted from Partridge et al. (2017) [11].*

One of the main physiological goals of extrauterine fetal support is to preserve lung development by preventing premature neonatal transition. At gestational ages of less than 24 weeks, the lung remains in early canalicular and saccular stages, characterized by incomplete alveolar development, immature vascularization, and insufficient surfactant production [2]. Early exposure to air ventilation can induce alveolar inflammation, barotrauma, and arrest of physiological lung development.

Several experimental studies have demonstrated favorable pulmonary outcomes using artificial uterus systems. In the EXTEND model, the lungs showed normal histological progression to more advanced saccular stages, with alveolar architecture comparable to intrauterine controls of equivalent gestational age [5,6]. Furthermore, some animals subsequently achieved successful transition to conventional ventilation, suggesting sufficient lung development for later neonatal adaptation.

Other studies have shown less pulmonary inflammation and reduced tissue injury compared to premature infants who underwent early conventional mechanical ventilation [1]. These findings support the hypothesis that a significant portion of the lung damage associated with extreme prematurity stems from early exposure to air ventilation rather than solely from structural lung immaturity.

Neurodevelopment is another of the most relevant aspects evaluated in contemporary models. Extreme prematurity is frequently associated with intraventricular hemorrhage, white matter injury, and neurocognitive impairments secondary to systemic inflammation, hyperoxia, and hemodynamic instability [4]. Therefore, one of the potential benefits of the artificial uterus is providing a hemodynamic and metabolic environment closer to that of intrauterine life.

Initial histological studies using EXTEND showed macroscopically normal brains, with no significant evidence of hemorrhage or cerebral infarctions [6]. Subsequently, Cohen *et al.* performed comparative transcriptomic analyses between brains of control preterm infants, normal intrauterine fetuses, and animals maintained in EXTEND. The authors found that the brain molecular profiles of the animals subjected to extrauterine fetal support were considerably more similar to physiological fetal controls than to conventional preterm infants [4].

Specifically, they observed reduced activation of inflammatory pathways mediated by TNF, IL-1, and TGF-β, as well as better preservation of mechanisms related to energy metabolism and neuronal mitochondrial function. These findings suggest that extrauterine fetal support could reduce some molecular mechanisms involved in encephalopathy of prematurity.

Taken together, the experimental evidence suggests that these systems can partially preserve hemodynamic stability, umbilical circulation, lung development, and some neuroprotective mechanisms.

The main physiological outcomes reported in contemporary models are summarized in Table 2. However, miniaturization, anticoagulation, and biocompatibility continue to limit their clinical translation.

Table 2. Main physiological results reported in experimental models of extrauterine fetal support.

Physiological area	Observations	Translational limitations
Cardiovascular	Preservation of fetal and umbilical circulation, with hemodynamic stability and partial autoregulation.	Sensitivity to circuit resistance, with risk of cardiac overload, thrombosis, and umbilical vasospasm.
Pulmonary	Lungs filled with fluid, progressive lung maturation, and less injury associated with mechanical ventilation.	Lack of human clinical evidence and uncertainty regarding its reproducibility in extremely premature human infants.
Neurological	Reduced exposure to hemodynamic fluctuations, systemic inflammation, and hyperoxia. Partial preservation of neuroprotective mechanisms.	Insufficient evidence on long-term neurodevelopment and differences between the ovine and human brain.

Continuation

Metabolic and inflammatory	Reduced activation of inflammatory pathways and better preservation of cellular energy metabolism.	Findings limited to preclinical models and experimental molecular analyses.
Global development	Progressive somatic growth and maintenance of physiological conditions similar to the intrauterine environment.	Challenges remain regarding miniaturization, anticoagulation, optimal duration of support, and human clinical application.

Summary of cardiovascular, pulmonary, and neurological findings observed in animal models subjected to extrauterine fetal support, as well as their main translational limitations.

TRANSLATIONAL CHALLENGES AND ETHICS

Despite the experimental advances achieved in recent years, the clinical application of the artificial uterus in humans continues to face significant technical, physiological, and bioethical limitations. Although platforms such as EXTEND have demonstrated partial preservation of fetal physiology and progressive organ development in animal models, there is still insufficient evidence to establish safety and efficacy in extremely premature human infants [2,3].

One of the main translational challenges is anticoagulation. Due to prolonged blood contact with extracorporeal surfaces, most current systems require systemic heparinization to prevent circuit thrombosis. However, extremely premature infants are highly susceptible to intraventricular hemorrhage and other hemorrhagic complications, making anticoagulation one of the main barriers to future clinical application in humans [3]. Consequently, several groups are currently working on biocompatible surfaces and less thrombogenic circuits that would reduce or even eliminate the need for prolonged systemic anticoagulation.

Miniaturizing the extracorporeal circuit presents another significant challenge. Many successful experimental models were developed using ovine fetuses, which are considerably larger than the most extremely premature human infants. Reducing the size of cannulas, oxygenators, and circuits involves complex difficulties related to vascular resistance, hemodynamic stability, and maintaining adequate flow driven solely by the fetal heart [2].

Furthermore, the obstetric transfer to the extrauterine fetal support system is one of the most physiologically critical phases of the process. The goal is to prevent the fetus from prematurely initiating the neonatal transition before establishing functional extracorporeal circulation. To this end, the most successful experimental models have used controlled cesarean sections and modified EXIT procedures, temporarily preserving placental circulation during umbilical cannulation [7]. However, standardized human obstetric protocols for this procedure are still lacking.

From a bioethical perspective, the artificial uterus raises complex questions related to fetal viability, informed consent, and the limits of medical intervention. These technologies partially modify the traditional boundaries between fetal and neonatal physiology, sparking debates about the definition of birth, reproductive autonomy, and candidate selection [8]. Most authors agree that initial clinical applications should focus on improving the functional prognosis of premature infants within the current limits of neonatal viability, rather than indefinitely expanding human viability.

DISCUSSION

The development of the artificial uterus represents a significant conceptual shift in the management of extreme prematurity, as it moves the therapeutic focus from supporting immature organs to temporarily preserving fetal physiology. Unlike conventional neonatal intensive care, which aims to sustain life after an established neonatal transition, extrauterine fetal support attempts to prevent this transition from occurring prematurely. This difference is not merely technical but also pathophysiological: the primary problem in extremely preterm infants lies not only in organ failure secondary to immaturity but also in the need to prematurely force the adaptation of a fetal organism to neonatal conditions for which it is not yet biologically prepared. From this perspective, the artificial uterus does not simply seek to replace pulmonary or cardiovascular functions but to modify the physiological timing of the transition to neonatal life.

Available experimental evidence suggests that preserving fetal physiology can reduce some of the central injury mechanisms associated with extreme prematurity. Maintaining fluid-filled lungs, preserving umbilical circulation, and avoiding early air ventilation reduce the exposure of the immature lung to positive pressures, relative hyperoxia, and mechanical inflammation. This explains why the most promising results have been observed in lung development, hemodynamic stability, and partial preservation of neurodevelopment [4,5].

However, this enthusiasm should be interpreted with caution. Most of the evidence comes from animal models, primarily sheep, whose physiology does not fully replicate the human condition. This limitation is particularly relevant in the central nervous system, as the human premature brain has specific vulnerabilities, such as germinal matrix fragility and an increased risk of intraventricular hemorrhage. Therefore, although the transcriptomic and structural findings are promising, they do not yet allow us to conclude that the artificial uterus will be neuroprotective in humans.

Another critical point is that the system's success hinges on a delicate physiological balance: the circuit must perform sufficient gas exchange without increasing resistance to the point of overloading the fetal heart. This tension explains why miniaturization, vascular resistance, and umbilical cannulation remain

key barriers. Furthermore, even if physiological stability is safely achieved, uncertainties persist regarding the optimal duration of support, candidate selection, and the actual impact on long-term neurodevelopment.

Comparisons between systems show that an ideal model has yet to emerge. EXTEND has demonstrated the most consistent results with its physiological approach using a pumpless arteriovenous circuit and a closed fluid environment, but other models, such as EVE, Michigan, and Toronto, show that some technical solutions can improve certain aspects while sacrificing others. Pumped systems can stabilize flow but deviate further from fetal physiology; pumpless systems are more physiological but depend critically on fetal cardiac function and minimal extracorporeal resistance.

The difference between conventional mechanical ventilation and the liquid support of the "Biobag" system lies not only in the use of more advanced technology, but also in a profound transformation of the physiological approach to extremely premature infants. While mechanical ventilation attempts to artificially replace respiratory function by introducing air into structurally and functionally immature lungs, exposing them to pressure, oxygen, and the risk of lung injury, the Biobag system avoids forcing a premature respiratory transition and maintains the fetus in a liquid environment similar to the intrauterine environment. In this model, gas exchange does not depend on the lungs, but on extracorporeal circulation connected to the umbilical cord, which allows for the preservation of fetal physiology and promotes the progressive maturation of organs. Therefore, the artificial uterus should not be understood merely as a technical improvement over mechanical ventilation, but as a paradigm shift: instead of adapting the immature fetus to the conditions of the extrauterine world, it seeks to temporarily preserve the biological conditions of the uterus to allow for a more natural and physiological development.

From a translational perspective, the main challenge will be defining whether this technology should aim to increase overall survival or improve survival without severe disability. This distinction is clinically relevant. If the artificial uterus merely shifts the viability threshold without improving functional outcomes, it could reproduce some of the dilemmas already present in critical neonatology. Conversely, if it succeeds in reducing pulmonary and neurological injury, its clinical value would be far greater: it would not only allow for longer life but also for living with fewer long-term consequences.

Clinical application will also necessitate a redesign of the relationship between obstetrics and neonatology. Fetal transfer to the artificial uterus will likely be one of the most complex moments, since any early exposure to air, loss of umbilical blood flow, or thermal instability could trigger the neonatal transition that is precisely what the technology seeks to prevent [7]. Therefore, future implementation will require highly specialized teams, neonatal rescue protocols, and rigorous candidate selection criteria.

Finally, the artificial uterus raises questions that extend beyond the technical aspects. Clinical extrapolation from ovine models remains uncertain due to significant differences in brain, cardiovascular, and placental development, as well as small sample sizes, limited follow-up, and methodological heterogeneity. There are also no defined criteria for candidate selection, optimal duration of support, neonatal rescue strategies, or long-term neurological safety parameters. Therefore, this technology should be understood as a promising experimental platform, but one still far from routine clinical practice. Its true impact will depend on whether it improves functional survival, not just artificially prolonging viability.

CONCLUSIONS

Extrauterine fetal support and artificial uterus technologies represent one of the most innovative areas of contemporary fetal and neonatal medicine. Their development has allowed progress from rudimentary models of extracorporeal oxygenation to physiological platforms capable of partially preserving fetal circulation, maintaining fluid-filled lungs, and promoting organ maturation outside the uterus.

Experimental evidence demonstrates that systems such as EXTEND can maintain hemodynamic stability, continuous lung maturation, and neurodevelopmental profiles relatively close to normal fetal physiology in extremely premature animal models. These findings suggest that a significant portion of the injury associated with extreme prematurity may be related not only to organ immaturity but also to premature neonatal transition and early exposure to air ventilation.

However, human clinical application remains limited by challenges related to anticoagulation, miniaturization, umbilical cannulation, infection control, neurological safety, and ethical regulation. Overall, the artificial uterus continues to be a promising preclinical technology. Its future value will depend on whether it succeeds in improving functional survival and reducing long-term consequences in extremely premature infants.

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Conflicts of interest

The authors declare no financial, academic, institutional, or personal conflicts of interest that could influence the preparation, interpretation, or presentation of this manuscript.

Ethical considerations

This work is a narrative literature review and therefore did not involve the direct participation of human subjects, the collection of identifiable clinical data, intervention on patients, or the performance of experimental procedures on animals. For this reason, it did not require approval from a research ethics committee or informed consent. The information analyzed comes exclusively from previously published scientific articles, reviews, and experimental studies. However, because the topic of the artificial uterus involves relevant bioethical debates regarding fetal viability, informed consent, limits of medical intervention, candidate selection, and future clinical application in humans, these aspects were critically addressed within the manuscript.

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