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HOSPITAL GENERAL de MÉXICO
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EDITORIAL

Beyond pediatric nutritional diagnosis and care

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Nutritional overview in Mexico

In Mexico, the National Health and Nutrition Surveys (ENSANUT) have highlighted key trends in childhood malnutrition, dietary habits, the role of family members in nutrition, and the nutritional status of hospitalized children. According to the 2023 ENSANUT reported a prevalence of chronic malnutrition of 13.9% in children under five, while overweight affected 7.7% of this group. Among school-aged children and adolescents, the combined rates of overweight and obesity reached 37% and 40%, respectively. This epidemiological landscape presents a significant challenge for healthcare institutions, requiring structured nutritional monitoring and treatment in general and hospitalized pediatric populations. This process begins with a Nutritional Status Evaluation (NSE)[1,2].

NSE consists of identifying patients' nutritional status through assessment using anthropometric, biochemical, clinical, dietary, lifestyle, and pharmacological measures[3]. Poor nutritional status increases the risk of complications, chronic infections, and worse disease outcomes.

The American Society for Parenteral and Enteral Nutrition and the European Society for Clinical Nutrition and Metabolism recommend routine nutritional screening to identify patients at risk of malnutrition. This is a fundamental component of the Nutrition Care Process (NCP). This process is established as a universal, structured, and systematic cycle that should be conducted in any nutritional assessment. The first step in the NCP is nutritional screening, a tool that allows for the early identification of patients at nutritional risk, especially in hospital settings. This enables prioritization of care and timely interventions[3,4].

An NSE is performed, during which detailed objective and subjective information are collected from the patient. This comprehensive assessment establishes a nutritional diagnosis, documented using the PES acronym (problem, etiology, signs, and symptoms). Establishing a nutritional diagnosis will allow for the design of an appropriate intervention, with clear goals and specific actions to improve the patient's nutritional status.

Once the nutritional diagnosis has been identified, a nutritional intervention is conducted based on the energy and protein requirements, which vary significantly according to age. To establish these requirements in the pediatric population, it is recommended to follow the FAO/WHO guidelines, which are widely recognized for their applicability in different clinical and population contexts. Finally, patients are monitored and followed up, during which specific time points are established to evaluate the factors targeted for improvement through the intervention.

NCP is a dynamic process that allows for patient reassessment based on the goals established during the intervention. Its guidelines always seek to utilize evidence-based nutrition, clinical thinking, adherence to the code of ethics, and collaboration within public health, private practice, and social and economic systems (Fig. 1).

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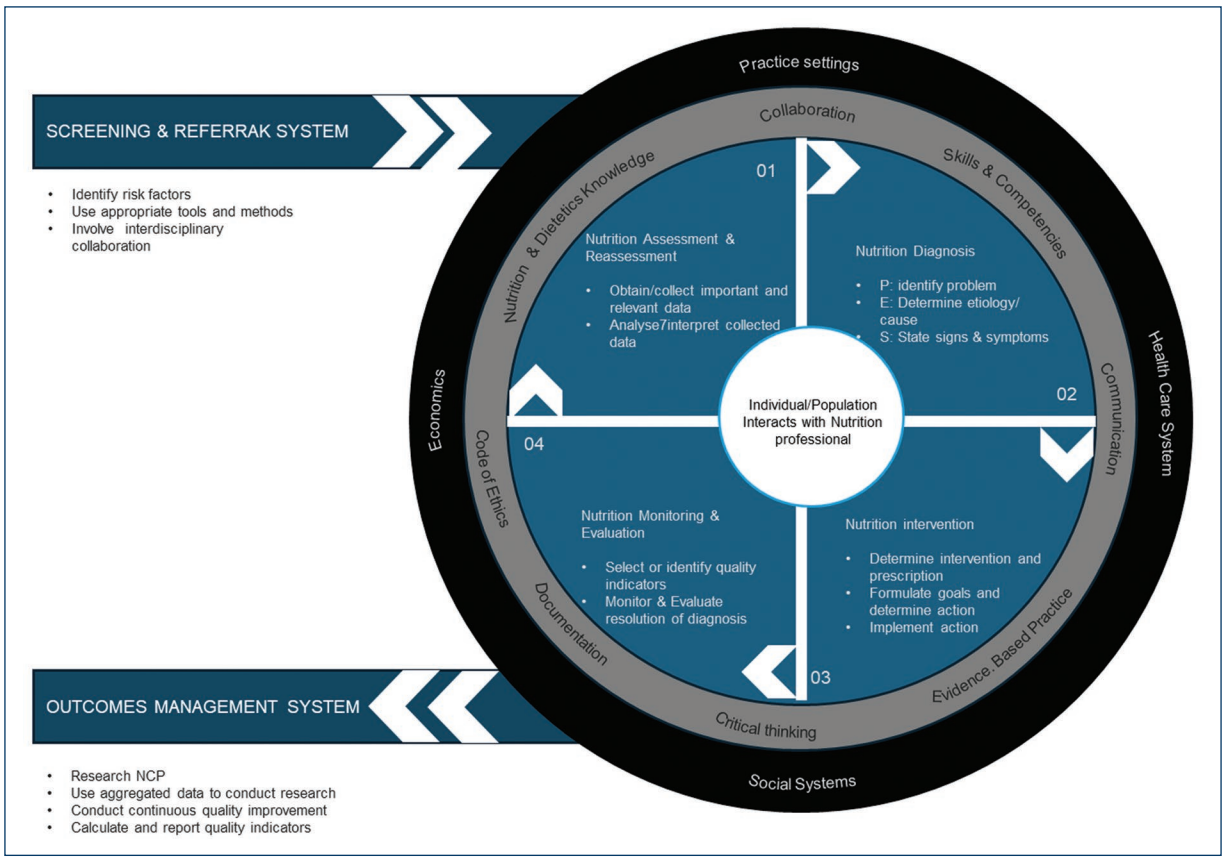

Figure 1. Diagram of the nutrition care process. *Last updated by Swan et al., 2017.*

Furthermore, childhood malnutrition can have long-term consequences such as growth retardation, wasting, underweight, micronutrient deficiency or insufficiency, overweight, or obesity. These conditions alter screening scores, and on admission, the patient presents a high nutritional risk, exacerbated by acute illnesses or physiological stress.

Proper nutritional screening can predict a child's nutritional and medical prognosis. Poor or negative nutritional status can affect morbidity and mortality, hospital stay, growth, costs, and readmission rates. However, this is not currently a mandatory or routine process in most health institutions in Mexico.

The screening tool for the assessment of malnutrition in pediatrics (STAMPs) as a nutritional screening tool for children in Mexico

The STAMP is designed to assess the general nutritional status of pediatric patients. It identifies nutritional risk on hospital admission using three key questions related to anthropometric measurements, dietary intake, and medical diagnosis. Most importantly, the score provides an action plan for the patient[5].

Various pediatric nutritional screening tools have been developed and validated internationally; however, the STAMP is one of the most reproducible. Studies in Mexico using this tool have reported that up to 48% of admitted patients present with some degree of malnutrition. It has shown a sensitivity of 97.88% (95% CI, 94.67-99.42) and a specificity of 45.05% (95% CI, 35.59-54.78) for detecting nutritional risk in Mexican population.

Nutritional support in the pediatric population

Nutritional support in pediatric patients is considered a fundamental therapeutic option when a child cannot meet their energy and nutritional requirements orally due to feeding difficulties, severe malnutrition, or neurological conditions that limit independent feeding. Multiple factors that influence energy requirements must be

Table 1. Comparison of enteral and artisanal formulas in composition and their main characteristics

Formula type	Protein	Carbohydrates	Lipids	Kcal/100 mL	Characteristics
Polymeric	Intact (non-hydrolyzed) protein	Easily digestible polysaccharides such as dextrins, sucrose	Vegetable oils and medium-chain triglycerides	1-1.2 kcal/mL	Suitable for patients with normal digestive function
Oligomeric	Short peptides and some free amino acids	Easily digestible polysaccharides such as dextrins	Medium-chain triglycerides	1-1.2 kcal/mL	For patients with malabsorption or digestion issues
Elemental	Free amino acids	May contain glucose	Medium-chain triglycerides	1-1.2 kcal/mL	For patients with severe malabsorption; easily absorbed
Homemade	Whole proteins	Poorly digestible polysaccharides (e.g., starch), disaccharides like lactose or sucrose	Vegetable oils	Approx. 0.7-1 kcal/mL	Requires hygienic preparation; proper knowledge and training needed for safe use.

The composition of enteral formulas allows their use in most pathologies, in contrast to homemade formulas, which require proper food safety and preparation training to ensure safe administration.

considered, such as nutritional status, fasting period, underlying pathologies, age, sex, degree of metabolic stress, and, unlike in adults, growth factor status. Growth factor status is essential to ensure adequate physical development, regardless of the child's clinical condition. To estimate energy requirements in this population, widely recognized formulas such as those proposed by the FAO/WHO or the Schofield formula are used.

The first step in providing nutritional support is to determine the integrity of the gastrointestinal tract. If it is in optimal condition, enteral nutrition is indicated, which offers metabolic advantages over parenteral nutrition. Depending on patient tolerance and treatment duration, enteral nutrition can be provided through a nasogastric tube or percutaneous endoscopic gastrostomy.

Step 2 in this approach involves choosing an appropriate formula based on its composition. Enteral formulas are classified according to the complexity of their nutrients, allowing for individualized use depending on the patient's clinical and digestive conditions (Table 1). Artisanal formulas, prepared with blended conventional foods, can be used in home settings with proper training and hygiene measures, but they present disadvantages in the hospital environment.

Several studies have compared artisanal diets with polymeric formulas, concurring that the former presents significant nutrient losses during preparation due to cooking, blending, and straining. This requires calculating higher requirements to meet nutritional goals, resulting in mixtures lacking the appropriate tube feeding consistency. For these reasons, polymeric formulas are favored in clinical settings, as they offer greater control, safety, and efficacy in meeting the nutritional requirements of pediatric patients.

Conclusions

The NCP is a universal and systematic process essential for the comprehensive management of pediatric patients. Nutritional intervention, along with medical treatment, is a fundamental pillar.

Due to its stressful nature and the presence of underlying pathologies, the hospital environment represents an additional risk factor for deteriorating nutritional status. The use of nutritional screening tools in the pediatric population allows for early detection of at-risk patients, facilitating timely interventions. In Mexico, nutritional screening should be mandatory; however, its use remains limited, leading to late nutritional assessments, hindering timely interventions, and compromising the clinical prognosis of the pediatric population.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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ORIGINAL ARTICLE

Adaptation in Spanish in Mexico of the neonatal nutritional risk screening tool

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Abstract

Introduction: *The neonatal stage is a vulnerable time, where the newborn is more likely to contract diseases. Screening identifies individuals with risk for some pathology according to each patient's characteristics and risk factors. Few tools detect nutritional risk in neonates, therefore, it is important to have more information, as well as studies in our population.* **Objective:** *The aim of the study was to perform translation and content validation with experts in neonatology of the neonatal nutritional risk screening tool (NNRST).* **Material and methods:** *The validation was realized in the Pediatrics area of Hospital General de Mexico Dr. Eduardo Liceaga, and the translation of the screening into Spanish by three people certified in English and pediatrics. Questions from a questionnaire about the tool were designed and applied to 25 experts in neonatology who met the selection criteria.* **Results:** *The average number of years worked for the study population was reported to be 14 ± 13 years, with a greater predominance of work in the public sector at 52% and the private sector was 48%. 80% of the participants were assigned to the neonatology service. Overall, the tool had an average total content validity index of 0.74 ± 0.17 scores. In each item, observations were made by the neonatologists, who considered whether to make modifications to the tool.* **Conclusions:** *The NNRST is content valid with expert judgment for neonatal nutritional risk screening.*

Keywords: *Screening. Nutritional risk. Newborn. Neonatal nutritional risk screening tool.*

Introduction

Food is one of the fundamental pillars in human life[1,2]. Inadequate nutrition in the short term generates greater morbidity and mortality, prolonged hospital stay, as well as higher medical costs; in the long term, it can cause delayed growth and development, with learning difficulties and increased risk of diseases[3,4].

The objective of a screening is to identify patients who require special intervention with a test or systematized examination[5]. Nutritional risk is defined under the concept of a group of hospitalized patients who, secondary to the severity of their disease, require nutritional support[6].

Although there are multiple screening tools for the detection of nutritional risks in the pediatric setting, there is still a lack of validated tools for newborns that are practical in their application[7-13]. Some tools that assess birth weight, birth height, head circumference, and arm circumference may be useful, however, arm circumference is not routinely measured in an intensive care unit, which is an impractical instrument and without published data on its validity, does not allow its applicability[3,14], or they are usually validated only in intensive care neonates[7].

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In China, a group of experts developed a neonatal nutritional risk screening (NNRST) tool (supplementary data), which assesses four items: birth status, weight change, form of nutrient intake, and diagnosis of diseases[3,15]. This tool has shown a sensitivity of 85.11%, specificity 91.07%, positive predictive value 60.61%, and negative predictive value of 97.43%[3,16]. However, it is not validated and culturally adapted for use in the Mexican population, which is of special interest to the Mexican population. Due to the above, the objective of this study was to translate and validate content with experts in Spanish, of the NNRST in the Pediatrics area of the Hospital General de México Dr. Eduardo Liceaga.

Material and methods

A study of content validity and cultural adaptation of the NNRST was carried out in Mexico, through a cross-sectional study with a group of experts from the Mexican Association of Pediatrics.

Ethical responsibilities

The study was carried out under the statutes of the general health law on research in Mexico and the Declaration of Helsinki. The protocol was approved by the hospital's research ethics committee, with registration number DI/23/505/03/026. All neonatologists participating in the study signed the informed consent letter and answered the questionnaire about the tool.

Validation

The translation into Spanish and cultural adaptation was carried out by three bilingual people certified in the native Spanish language, two neonatologist pediatricians, and a researcher in the sciences who are experts in nutrition and with experience in validation studies. The content validity of the questionnaire, based on the categories of clarity, coherence, relevance, and sufficiency, was carried out with a pilot test with 25 experts in neonatology.

Participants

Physicians with the specialty of Pediatrics and subspecialty of Neonatology, with experience of 3-10 years, both sexes, residents of the Mexican Republic, in coordination or collaboration in a Neonatology service, were included. Doctors with a conflict of interest or members of a pharmaceutical company were excluded. The method of selection of the evaluating physicians and their respective hospitals was according to the availability of time to participate in the study.

Sample size

In accordance with the methodology established by Galicia et al.[17], for the validity of the content of the screening tool, 5 medical experts were included for each item. In this case, the tool comprises 4 items, for which a minimum sample of 20 neonatologists was required[18], plus 5 physicians due to the losses that occurred during the evaluation. The sample size was 25 neonatologists of both sexes.

Statistical analysis

A database was made to perform the statistical analysis with the Statistical Package for the Social Sciences version 22.0 program. Items with low scores were reviewed. The comparisons of the variables were made with the content validity index (CVI) proposed by Lawshe, to make agreements between experts. A discussion was held on corrections, reworking of items, increasing or omitting items, according to the specific observations mentioned by the experts. Sample estimate with 95% confidence level, population of 25 experts[19].

Results

25 expert neonatologists from different hospitals in the Mexican Republic were included in the period from July 25 to August 11, 2023, who met the selection criteria. Of the total population, a slight majority of the female gender (52%) and 12 people of the male sex (48%) were found.

With regard to the distribution of the place of residence of neonatologists in the subspecialty of Pediatrics, the Instituto Nacional de Perinatología was the most frequent, with a total of 8 people representing 32%, followed by the Hospital Español with 7 people and 28%; third place was occupied by the Instituto Mexicano del Seguro Social with a total of 6 people representing 24%; the Hospital General de México was placed in fourth place with a total of 2 people and 8%. The Hospital Infantil de México and the Hospital Angeles Lomas were in fifth place, with the presence of one person, represented by 4%, in both hospitals (Fig. 1A).

The mean number of years worked of the study population was 13.92 years with a standard deviation of 12.

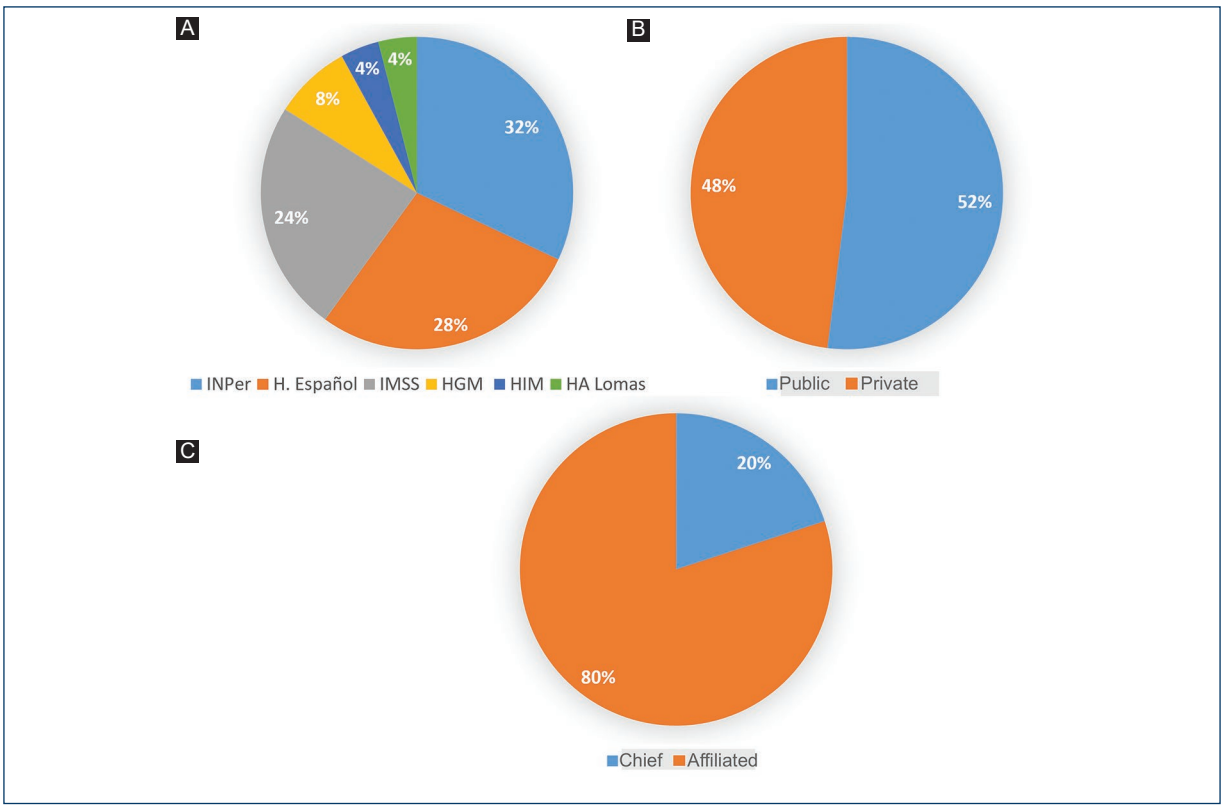

Figure 1. A: distribution of place of residence in neonatology. **B:** public and private sector. **C:** present job position.

Regarding the work hospital, we found a slight predominance of work in the public sector with a total of 13 participants, corresponding to 52%. On the other hand, there were a total of 12 participants, representing 48%, who work in the private sector (Fig. 1B).

Of the total population studied, a total of 20 participants were assigned to the neonatology service, which represented 80%, and 5 of the participants (20%) indicated that they were heads of the pediatrics and/or neonatology service (Fig. 1C).

With the 25 participating experts, according to Lawshe (1975)[20], a CVI of at least 0.54 is sufficient to indicate that each of the items has been assessed as essential. Thus, at the end of the analysis, of the 4 items that make up the initial version of the instrument, all were maintained because they resulted in an average CVI of 0.68 in item 1, 0.74 in item 2, 0.67 in item 3 and 0.87 in item 4.

Similarly, the categories of the items were reported with an adequate average CVI, with 0.63 in the clarity category, 0.77 in the coherence category, 0.94 in the relevance category, and 0.62 in the sufficiency category. Overall, the tool had a total inferior vena cava (IVC) average of 0.74 ± 0.17 (Table 1).

In each item, a fifth question was added to allow the experts to write comments or suggestions, which are summarized in table 2, and which were evaluated for the writing of the Spanish version of the tool.

Discussion

The European Society for Clinical Nutrition and Metabolism, the American Society for Parenteral and Enteral Nutrition, and the European Society of Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) recommend the application of screening tools to determine the level of nutritional risk in hospitalized pediatric patients[8].

Nutritional screening allows non-specialist staff to identify patients at nutritional risk who need further assessment and support from specialist staff. Due to the lack of validated screening tools for nutritional risk in neonates, the objective of the study was to translate and validate content with experts in Spanish, from the NNRST. In China, due to the large annual number of births and shortage of nutritional support equipment in newborns, as well as the lack of

Table 1. Categories

Items	Clarity		Coherence		Relevance		Adequacy		Average CVI
	Experts in favor	CVI	Experts in favor	CVI	Experts in favor	CVI	Experts in favor	CVI	
1 birth status	14	0.56	19	0.76	23	0.92	12	0.48	0.68
2 weight change	16	0.64	20	0.8	23	0.92	15	0.6	0.74
3 form of nutrient intake	12	0.48	17	0.68	24	0.96	14	0.56	0.67
4 diagnosis of diseases	21	0.84	21	0.84	24	0.96	21	0.84	0.87
Average CVI		0.63		0.77		0.94		0.62	0.74 ± 0.17

CVI: content validity index = # people in agreement/# total number of participants.
Reference: Tristán et al.[20].

Table 2. Synthesis of proposals for change

Items	Remarks
1	– It is suggested to modify the weeks of gestation and add the days to division – Specify what percentiles and grams refer to, as it creates confusion – Establish a parameter that determines the weeks of gestation (date of past menstruation, ultrasound, Capurro) – Clarify if it is only for pre-term and term babies – Consider adding in weight section: intrauterine growth restriction.
2	– Specify the timing of the assessment for weight loss – Indicate that the newborn must be weighed under the same conditions every day – It is suggested to change the term "decreased weight"
3	– It is recommended to add mixed feeding: tube and suction – Consider adding feeding without a tube – Specify the terms full and partial parenteral nutrition – Specify the type of milk: breast, fortified breast, or formula.
4	– It is suggested to define what is acute disease or injury – Consider the following options: surgery, drainage, probes, and ventilation – Instead of recurrent diarrhea, consider other diagnoses such as intolerance without enterocolitis or allergy – Diseases such as diarrhea are not common – Consider adding patent ductus arteriosus with or without hemodynamic repercussions, state of shock – Consider adding a V item with the use of probiotics, lactase, ACD vitamins, and AEC vitamins, as part of the management of pre-mature infants.

nutritional tools in this age group, a group of experts created the NNRST, demonstrating its reliability and detection accuracy[3].

Even if an instrument has been validated in one population, it is important to measure its psychometric properties when it is used in other areas or populations; for this, the process must first begin with the translation of the tool and then validate the instrument[21]. In this way, the translation of the screening into Spanish was carried out and to validate the instrument, it had to be compared with the gold standard; however, in the nutritional screening tools in neonates, there is no one.

However, other methods can be used to carry out validity, and among the most used are: construct, criterion, and content validity[17]. Therefore, content validity was carried out through expert judgment, defined as an informed opinion of people with a background in the subject, who are recognized by others as qualified experts in it, and who can provide information, evidence, judgments, and evaluations[17].

In the analysis of the data, authors report using Lawshe's statistical test to determine the degree of agreement among the judges, observing a CVI with values between –1 and +1; when the value is positive it indicates that more than half of the judges agree and, when it is negative, it means that less than half of the experts agree[22].

In our study, 25 neonatologists were recruited, who were a balanced population when they completed the neonatology residency and were working in hospitals in both the public and private sectors; the majority of them were personnel assigned to the neonatology service, who are in constant and close contact with the neonates, thus providing information based on their experience.

As previously mentioned, the items were analyzed using the Lawshe CVI, with a total average of 0.74, which tells us that the tool in general is adequate to assess nutritional risk. Similarly, the average CVI of

each category on the items was adequate (clarity 0.63, coherence 0.77, relevance 0.94, and sufficiency 0.62), where together with the observations made by the experts, they were taken into account to make the modifications in the tool.

With respect to item 1, birth situation, an average CVI of 0.68 was reported, indicating that it is essential in the tool, however, with a CVI of 0.56 in clarity and 0.48 in sufficiency, the following modifications were made: the lack of division in the weeks of gestation was a constant observation among the experts, and even as mentioned by the ESPGHAN there is not total uniformity in the definition of the subgroups of pre-term birth; however, it was decided to use the terminology of common subgroups used to establish the weeks of gestation, adding a division between weeks 32 and 37, modifying to 32.1-33.7 with a score of 2, and 34.1-36.7 with a score of 1, as it is a very wide range[23].

In the same way, the days and value of a term newborn were added to avoid future confusion for the evaluators. In the same item, it was requested to specify what the percentiles and grams refer to, which is indicated in the tool, since each one represents a different risk score; and to have clarity with the score corresponding to neonates > 2500 g, a box was added for this value, equivalent to a score of zero.

To establish the parameter that determines the weeks of gestation, according to Ventura (2015), he mentions that the Capurro test tends to overestimate the gestational age compared to the ultrasound of the first trimester, therefore when the latter data are available, the gestational age should not be modified with the pediatric exam; therefore, it was annexed in the specifications of the tool, that the weeks of gestation will be obtained by ultrasound report, and if this value is not available, use the Capurro or Ballard method[24].

One of the indicators recommended by the experts to be included was intrauterine growth restriction, which represents a significant increase in the risk of perinatal morbidity and mortality by not reaching its growth potential. Because of the definition established for small for gestational age in the tool, it was important to make modification and clarification at this point to avoid confusion, where intrauterine growth restriction is defined as: growth of the fetus below the 10th percentile for gestational age with abnormality of the feto-placental circulation or a weight <3rd percentile for gestational age, and as for the definition of small for gestational age, they are those whose weight is between the 3rd and 10th percentiles, with an anatomical assessment within normal limits[25].

Regarding item 2, weight change, an average CVI of 0.74 was calculated, but as it presented a CVI of 0.64 in clarity and a CVI of 0.6 in sufficiency, specific modifications were made for a better understanding of the item. I am confused by the moment of evaluation for weight loss; Because most neonates have a period of weight loss immediately after birth, with weight regain around the 3rd day of life, and because the application of screening tools in hospitalized children is < 24 h, the evaluation points were added in the tool (24 h, 1st week, 2nd week and 3rd week), as well as the time of evaluation in weight loss > 15% and > 10%[4,26].

Similarly, a box was added referring to weight loss < 10% and weight gain > 10 g/kg/day with a score of zero, to avoid confusion in the evaluation staff. Another modification was the change from “decreased weight” to “previous weight reduction or intact weight”, since the term was not specified in the tool, being doubtful.

Similarly, the specifications of the tool were added the way to obtain the weight of the newborn to prevent excessive changes in weight, as well as the use of Fenton’s growth charts in children under 37 SDG and the World Health Organization (WHO) for those over 37 SDG, to determine small for gestational age and large for gestational age. As well as the growth evaluation that includes: Weight, length, and head circumference[27].

Regarding item 3, form of nutrient intake, it was shown to be essential in the tool by having an average IVC of 0.67; although having a CVI of 0.48 in clarity and a CVI of 0.56 in sufficiency, the tool was complemented with more options, since the experts referred to considering adding mixed feeding as part of the tool.

As mentioned by Pineda et al., the feeding technique associated with weight gain is the mixed technique with orogastric tube and feeder, demonstrating significant benefits, so that it was added to the tool with a score of 0, in conjunction with single sucking feeding; breastfeeding with breast and infant formula has the same effectiveness in covering the caloric requirements necessary for growth, therefore, the type of milk was not added in instrument[28].

In the same item, the observation was made to specify the terms complete and partial parenteral nutrition, so the definitions were added at the bottom of the tool, referring to complete parenteral nutrition, that which all nutrients are administered intravenously, and partial parenteral nutrition, when enteral nutrition is combined to complete contributions[29].

Finally, in item 4, diagnosis of diseases, an average CVI of 0.87 was reported, where not only was it

essential in the tool, but also adequate CVI scores were reported in clarity (0.84), coherence (0.84), relevance (0.96) and sufficiency (0.84), so minimal modifications were made. The classification of diseases is based on the degree of catabolism and its effects on the nitrogen balance, considering serious those with a negative nitrogen balance in the patient, with insufficient amino acid administration in the 1st days of life being an important factor[30].

Kondrup et al. (2003) mention that the disease process can increase nutritional needs due to stress metabolism associated with serious diseases such as major surgery, sepsis, and multiple trauma[16]. For this reason, assessing the observation of acute disease or injury, as well as evaluating other options (surgery, drainage, probes, ventilation), reference is made to situations that cause negative nitrogen balance such as shock or major surgery, without incorporating sepsis, as it is a disease already included in the variable of severe infection.

In the case of the term recurrent diarrhea in neonates, it has not been clearly established, and as our experts mention, diseases such as recurrent diarrhea is not frequent in the newborn, however in a study carried out by Dol et al., they have evidence that between days 8 and 28 of life, one of the causes of neonatal mortality is diarrhea, considering maintaining the disease, defined by the WHO, as three or more bowel movements per day, or with a greater frequency than normal, of loose or liquid stools[31,32].

With regard to patients with congenital heart disease, the main factors that influence nutritional requirements are: the nutritional status, type of heart disease and hemodynamic status of the patient, where in the latter the presence of symptoms of heart failure determines greater energy needs, therefore it was decided to add as an option: “congenital heart disease with hemodynamic repercussions” with a score of 2, and establishing “congenital heart disease without hemodynamic repercussions” with a score of 1[33,34].

Finally, it was recommended to add a fifth item with the use of probiotics, lactase, ACD vitamins, AEC vitamins, as part of the management of pre-mature infants, however, as it is a single recommendation, an expert judgment should be made focused on assessing adding this item and its score, to determine if it is appropriate or not. However, the plans to be followed were added according to the risk classification presented by the newborn, providing complete and timely care[10].

Conclusions

The content validation with expert judgment, from the NNRST (Supplementary data), had an adequate CVI where the four original items of the tool were maintained.

In each item, modifications were made according to the observations made by the neonatologists, as well as in the instructions for the correct filling of the tool, thus allowing a better understanding and easy use in clinical practice.

In the same way, the behaviors to be followed for cases of high, medium, and low nutritional risk were added, providing a complete tool from how to classify the patient to the action plan to be carried out.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The study was carried out under the statutes of the general health law on research in Mexico and the Declaration of Helsinki. The protocol was approved by the hospital’s research ethics committee, with registration number DI/23/505/03/026. All neonatologists participating in the study signed the informed consent letter and answered the questionnaire about the tool.

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely obtained and anonymized clinical data, so informed consent was not necessary. Relevant guidelines were followed.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

Supplementary data

Supplementary data are available at Revista Médica del Hospital General de México online (DOI: 10.24875/HGMX.24000066). These data are provided by the corresponding author and published online for the benefit

of the reader. The contents of supplementary data are the sole responsibility of the authors.

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ORIGINAL ARTICLE

National reference center for the diagnosis and management of placenta accreta spectrum (PAS). Five years of experience

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Abstract

Introduction: *Placenta accreta spectrum (PAS) is a serious obstetric complication where the placenta abnormally adheres to the uterus, posing risks of severe hemorrhage and maternal and neonatal mortality. Since 2018, has implemented multidisciplinary protocols to improve outcomes, promoting appropriate surgical management in a specialized center.* **Objective:** *To evaluate the effectiveness of the diagnostic and management algorithms for PAS implemented at the Hospital General de México Dr. Eduardo Liceaga over 5 years.* **Material and methods:** *This observational, cross-sectional, and descriptive study was conducted at the Hospital General de México Dr. Eduardo Liceaga and included 100 patients between. Various factors were evaluated, including age, parity, history of previous uterine surgeries, placenta previa, early ultrasonographic diagnosis, type of accreta, surgical management (cesarean, hysterectomy, and arterial embolization), maternal and neonatal complications, transfusions, and histopathological data.* **Results:** *In our studied population, with an average age of 32.38 ± 6.1 years and an 3 ± 1.0 pregnancies, a high association was found between placental accreta and factors such as previous cesareans (average 1.46), placenta previa (62%), and type of accreta (31% acreta, 33% increta, and 35% percreta). Total hysterectomy was the predominant treatment (89%) with few complications, highlighting vesical injuries in 10%. A low maternal mortality rate and a high preterm birth rate in neonates (average gestational age 35.3 weeks and average weight 2567.3 g) were reported.* **Conclusions:** *This study demonstrates that the implementation of a specialized diagnostic and multidisciplinary surgical management protocol at the Hospital General de México has significantly improved outcomes for patients with PAS. Early identification through ultrasonography and color Doppler, along with surgical techniques such as uterine artery embolization and the placement of double J catheters, contributed to low maternal mortality and effective management of complications.*

Keywords: *Placenta accreta spectrum. Embolization. Uterine arteries. Hysterectomy. Hemorrhage.*

Introduction

The placenta accreta spectrum (PAS) is defined as an abnormal adherence of the placenta to the uterine wall. It is traditionally classified as placenta accreta, increta, and percreta according to the depth of attachment of the placenta to the myometrium: superficial, deep, serous, and adjacent structures[1]. PAS occurs when there is damage at the boundary between the endometrium and myometrium, allowing the placental trophoblast to grow into or through the uterine wall[2].

It represents a devastating obstetric complication characterized by trans cesarean hemorrhage, in addition to disseminated intravascular coagulation (DIC), dysfunction, multiorgan failure, and death[3]. In Mexico, obstetric hemorrhage is the leading cause of maternal death; although studies have been conducted to predict

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the risk of obstetric hemorrhage through blood biometry or coagulogram analysis, this has not decreased its incidence[4].

The worldwide incidence of placental accreta is three cases per 1,000 pregnancies. In our country, there are publications that report an estimated incidence of 0.6% and one case per 642 births[5,6].

The most important risk factor for the development of PAS is the increased incidence of cesarean section, which may occur in association with other uterine surgeries such as myomectomy, curettage, endometrial ablation, or a history of Asherman's syndrome[7]. It is strongly associated with placenta previa, which affects approximately 0.5% of all full-term pregnancies. This figure rises to 5% or more depending on the number of cesarean sections previously performed. All patients with placenta previa should be evaluated for abnormal placentation[8,9]. The gold standard for the diagnosis of placenta accreta is a histopathologic examination of the uterus and placental attachment. The main diagnostic tool for early detection of PAS is high-definition ultrasonography plus color Doppler, in addition to three-dimensional reconstruction, performed by highly trained imaging physicians[10-16]. Ultrasonographic features suggestive of placenta accreta are: loss of echolucent area between placenta and uterus as well as between placenta and bladder wall, multiple placental lacunae, focal exophytic masses extending into the bladder. Color Doppler findings include vascular lakes with turbulent flow (< 15 cm/s.) hypervascularity of the serosa-bladder interface, abnormal vessels crossing the thickness of the placenta (bridging vessels), diffuse or focal lacunar flow, power Doppler, 3D with hypervascularity, abnormal vessels at the serosa-bladder interface, and abnormal cotyledonary and intervillous circulation with chaotic branching and aberrant vessels[10-16]. Ultrasonography performed as screening allows prenatal detection; however, up to 50% of cases remain undiagnosed, resulting in poor maternal prognosis.

Once the diagnosis of PAS is established, it is necessary to implement an organized and interdisciplinary medical-surgical management plan. The key points to be included are: the type of accretism, placental location, timing of delivery, surgical approach chosen (hysterectomy or conservative treatment), and the use of adjunctive treatment and techniques. An intervention plan is also recommended in case the patient requires an earlier delivery due to unexpected or persistent hemorrhage[15-17]. PAS is responsible for 38% of cesarean hysterectomies and is associated with significant Maternal and Neonatal Morbidity and Mortality[15]. The recommended options in the literature for the management of PAS are cesarean hysterectomy with placenta in utero, expectant management with intentional placental retention, and conservative management with uterine preservation surgery[18-24].

Both the American College of Obstetricians and Gynecologists and the Royal College of Obstetricians and Gynecologists recommend management by a multidisciplinary team with expertise in the diagnosis of abnormal placentation and the management of complex pelvic surgeries, preferably in a specialized SBP center with access to blood products, adult and neonatal intensive care units, and interventional radiology to assist with hemorrhage control during surgery1[8-24].

As of August 18, 2018, the Hospital General de México Dr. Eduardo Liceaga, is recognized by the National Center for Equity and Gender and Reproductive Health, as the "National Center for the Diagnosis and Care of PAS." Since then, several diagnostic and medical-surgical management algorithms have been implemented in the gynecology and obstetrics service (Figs. 1 and 2), with the aim of reducing the incidence of morbidity and mortality at the maternal-fetal level.

Objective

To evaluate the effectiveness of the diagnostic and medical-surgical management algorithms implemented at the Hospital General de México Dr. Eduardo Liceaga, during a 5-year period for the management of PAS, analyzing their impact on the reduction of maternal and neonatal morbidity and mortality, through the evaluation of demographic characteristics, high definition ultrasound diagnosis, types of surgical treatment, complementary procedures, blood transfusions, and maternal and neonatal outcomes, and comparing these results with the current literature on the condition.

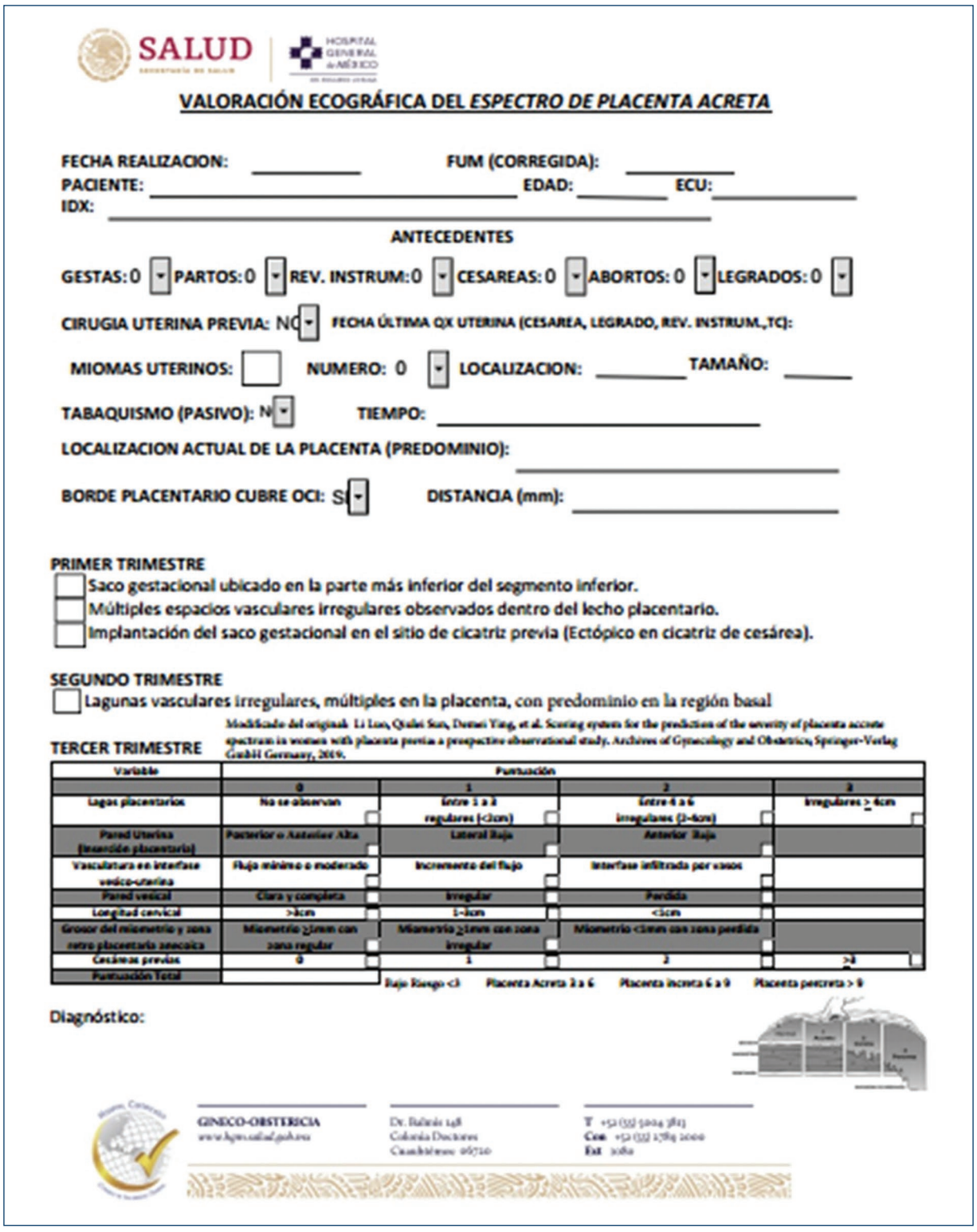
Material and methods

The observational, cross-sectional, descriptive study was conducted at the Hospital General de México Dr. Eduardo Liceaga.

This study included 100 patients in a period from January 2019 to April 2024 to our diagnostic and treatment algorithm.

We present our format for calculating the PAS scale as shown in Fig. 1. In addition, the following flowcharts of the diagnostic and therapeutic protocol were performed in our reference center (Fig. 2).

The incidence of the condition in the patients was reported in relation to: age, parity, hospital or site of



SALUD

HOSPITAL GENERAL de MÉXICO

VALORACIÓN ECOGRÁFICA DEL *ESPECTRO DE PLACENTA ACRETA*

FECHA REALIZACION: _____ FUM (CORREGIDA): _____

PACIENTE: _____ EDAD: _____ ECU: _____

IDX: _____

ANTECEDENTES

GESTAS: 0 PARTOS: 0 REV. INSTRUM: 0 CESAREAS: 0 ABORTOS: 0 LEGRADOS: 0

CIRUGIA UTERINA PREVIA: NO FECHA ÚLTIMA QX UTERINA (CESAREA, LEGRADO, REV. INSTRUM.,TC):

MIOMAS UTERINOS: ☐ NUMERO: 0 LOCALIZACION: _____ TAMAÑO: _____

TABAQUISMO (PASIVO): N TIEMPO: _____

LOCALIZACION ACTUAL DE LA PLACENTA (PREDOMINIO): _____

BORDE PLACENTARIO CUBRE OCI: S DISTANCIA (mm): _____

PRIMER TRIMESTRE

☐ Saco gestacional ubicado en la parte más inferior del segmento inferior.
☐ Múltiples espacios vasculares irregulares observados dentro del lecho placentario.
☐ Implantación del saco gestacional en el sitio de cicatriz previa (Ectópico en cicatriz de cesárea).

SEGUNDO TRIMESTRE

☐ Lagunas vasculares irregulares, múltiples en la placenta, con predominio en la región basal

TERCER TRIMESTRE

Modificado del original: Li Luo, Qubi Sun, Demei Ying, et al. Scoring system for the prediction of the severity of placenta accreta spectrum in women with placenta previa a prospective observational study. Archives of Gynecology and Obstetrics, Springer-Verlag GmbH Germany, 2019.

Variable	Puntuación			
	0	1	2	3
Lagos placentarios	No se observan ☐	Entre 1 a 3 regulares (<2cm) ☐	Entre 4 a 6 irregulares (2-4cm) ☐	Irregulares > 4cm ☐
Pared Uterina (Inserción placentaria)	Posterior o Anterior Alta ☐	Lateral Baja ☐	Anterior Baja ☐	
Vasculatura en interfase vesico-uterina	Flujo mínimo o moderado ☐	Incremento del flujo ☐	Interfase infiltrada por vasos ☐	
Pared vesical	Clara y completa ☐	Irregular ☐	Perdida ☐	
Longitud cervical	>4cm ☐	1-4cm ☐	<1cm ☐	
Grosor del miometrio y zona retro placentaria anecoica	Miometrio ≥1mm con zona regular ☐	Miometrio ≥1mm con zona irregular ☐	Miometrio <1mm con zona perdida ☐	
Cesáreas previas	0 ☐	1 ☐	2 ☐	≥3 ☐
Puntuación Total		Bajo Riesgo <3	Placenta Acreta 3 a 6	Placenta Increta 6 a 9 Placenta percreta > 9

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Figure 1: Placental accreta scale format.

delivery, previous uterine surgeries, placenta previa and/or low insertion, ultrasonographic detection by early screening, gestational age, PAS scale, type of accreta (accreta, increta, and percreta), performance of cystoscopies, ureteral catheter placement, fetal pulmonary maturity scheme used, type of cesarean section and hysterorrhaphy, trans cesarean hemorrhage, newborn data (gender, average weight, APGAR, CAPURRO,

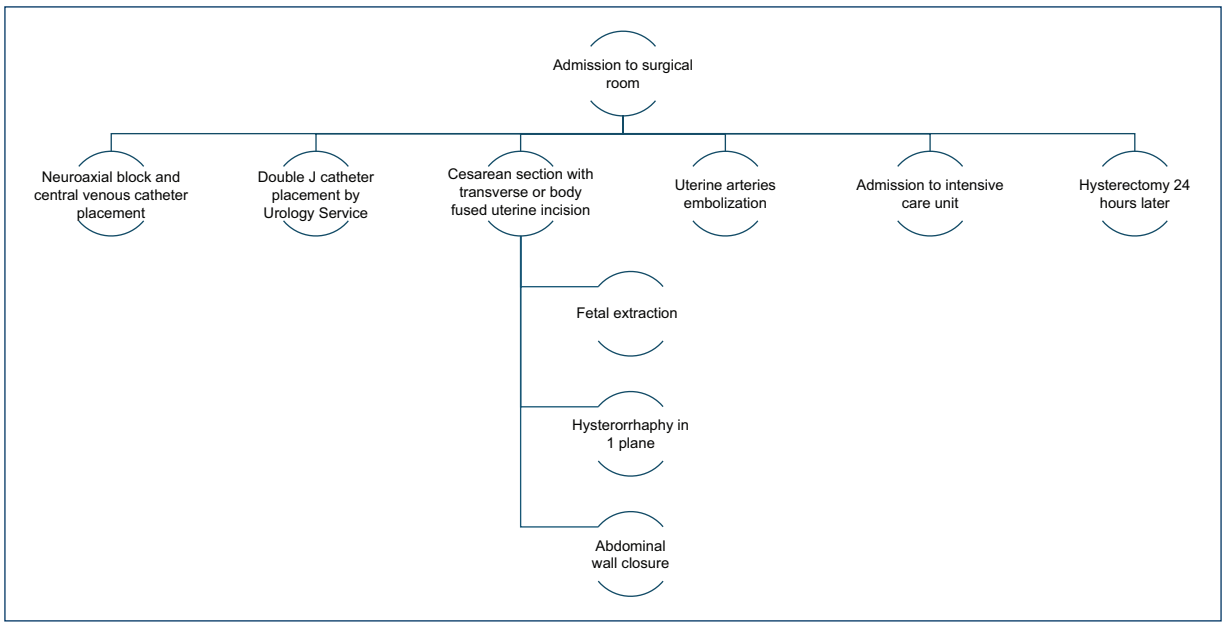

Figure 2: Surgical algorithm.

and early neonatal complications), type of uterine and collateral artery embolization, material used, average procedure time and complications, type of hysterectomy, trans-hysterectomy hemorrhage, neighboring organ injury, number of cases referred to Intensive Medical Care, need for blood transfusion and hemo-components, rate of puerperal infections, recommended antibiotic regimen, days of stay until discharge, maternal deaths and ultrasonographic correlation with the histopathological analysis of the surgical specimen.

Results

According to our study population, our patient profile has a mean age of 32.38 years (standard deviation [SD] 6.15) with a range of 20-45 years, which shows a population of active reproductive age. Regarding parity, we found an average of three pregnancies (SD 1.04), suggesting a higher exposure to risk factors such as uterine scars (Table 1).

Regarding obstetric history, we found an average of 1.46 (SD 0.91) in previous cesarean sections, which reinforces its association with placental accretism. Abortions and ectopic pregnancies have a low incidence in our population (0.44% and 0.03%, respectively).

Regarding placental characteristics, placenta previa, and low insertion placenta represent the majority of cases (62 and 34%), confirming their strong link with the disorder (Table 2). The cases are distributed among the types of accreta as follows: accreta (31%), increta (33%), and percreta (35%).

In consideration of surgical procedures and complications, total hysterectomy is the predominant management (89%). The lesions associated with the procedure are unusual, but bladder lesions stand out at 10%. Maternal mortality is low, with only one case reported.

Regarding maternal and neonatal outcomes, we found that the average bleeding increased according to the severity of the accreta: 800 cc in placenta accreta, 1,200 cc in increta, and 1,400 cc in percreta. Blood product transfusions were necessary in 56% of the cases with an average of 3.5 units of erythrocyte concentrates. The newborns had a mean gestational age of 35.3 weeks (SD 4.58) and a mean weight of 2567.3 g (SD 659.6), indicating a high rate of prematurity.

Regarding protocols and management, uterine embolization was used in 100% of the cases as part of the management protocol designed by our institution. In 67% of the cases double J catheter placement was performed as suggested in our therapeutic algorithm. The average length of stay after hysterectomy was 4.78 days (SD 10.9), whereas the total length of stay from diagnosis to discharge was 10.24 days (SD 4.8).

Discussion

In our country, obstetric hemorrhage is the first cause of maternal death. Therefore, measures should be taken regarding timely diagnosis and treatment. Early detection by means of high-definition ultrasonography with Doppler allows planning adequate management strategies.

Table 1. Clinical parameters of the population studied

Parameter	Media (range)	SD
Age (years)	32.38 (20-45)	6.15
Parity	3 (1-5)	1.04
Delivery	0.32 (0-2)	0.74
Caesarean section	1.46 (0-4)	0.91
Abortions	0.44 (0-2)	0.65
Ectopics	0.03 (0-1)	0.17
Average embolization time	2.5 hours	
Placental accretism	800 mL	
Placental Incretism	1200 mL	
Placental percretism	1400 mL	
Days of stay Post-hysterectomy	4.78 (2-29)	10.9
Days of stay diagnosis-management	10.24 days (4-57)	4.8
Newborn data Gestational age (weeks) Weight (gr) CAPURRO APGAR	 35.3 (14-40) 2567.3 (1090-3350) 33.5 weeks 7/8	 4.58 659.6

The diagnosis of PAS by ultrasonography remains a mainstay in the early identification of this high-risk obstetric condition. In our population, we found that placenta previa and low insertion were the most frequent sonographic findings, accounting for 62 and 34% of cases, respectively, reflecting a strong association with PAS. The high frequency of placenta previa in our population underscores the importance of carefully monitoring patients with an obstetric history that includes cesarean section, as this condition is associated with a significant increase in trophoblastic invasion.

In relation to ultrasound findings, it is important to note that although ultrasound is highly effective in identifying abnormal placental features such as placenta previa or low insertion, accurate identification of the type of PAS (accreta, increta, or percreta) through ultrasound alone may be limited. As noted by Lizárraga-Verdugo *et al*. (2024), ultrasound is a key initial tool, but in cases of deep myometrial invasion, magnetic resonance imaging (MRI) has been shown to be an essential adjunct to confirm the extent of placental invasion. In our series, the distribution of PAS types (31% accreta, 33% increta, and 35% percreta) is consistent with the literature, which describes variability in the severity of the disorder. However, isolated ultrasound evaluation may not be sufficient to distinguish between these types of PAS definitively, especially in cases of percreta, which present deeper invasion.

The use of MRI has been suggested in studies such as those by Markfeld-Erol *et al*. (2024) and Tadayon *et al*. (2022) as an effective means to more accurately determine the extent of myometrial invasion, especially when ultrasound does not provide a clear assessment. Although MRI was not routinely used in our study, we recognize that its implementation could have complemented the diagnosis in more complex cases, providing crucial details for planning surgical management.

In addition, the studies reviewed (Lizárraga-Verdugo *et al*., 2024; Markfeld-Erol *et al*., 2024) highlight that, although ultrasonography can identify suspicious placental characteristics, the definitive diagnosis of SBP is sometimes only confirmed by post-operative procedures, such as histopathology. This aspect highlights the importance of maintaining a high clinical suspicion in women with risk factors and relevant obstetric history, and of not relying exclusively on ultrasound to determine the severity of the condition.

In the population included in our study, the findings are consistent with global trends reported in the literature on the PAS, particularly in terms of risk factors, placental characteristics, associated complications, and

Table 2. Characteristics of the population studied

Parameter	Percentage
Previous uterine surgeries	16
Placental insertion site Placenta Prior Low Insertion Placenta loud	 62 34 4
PAS Scale Result Accreta Incretism Percretism	 31 33 35
Correlation of SBP scale and histopathological result Accreta Incretism Percretism	 31 29 40
Type of caesarean section (fundic) Transverse Vertical	 25 75
Type of hysterectomy Total Subtotal	 89 11
Injuries associated with surgical procedure Bladder injury Ureteral injury Uterine artery injury	 10 1 1
Embolization-associated injuries Perforation of the right uterine artery Postpartum infections	 1 1
Maternal deaths	1
Newborn data	
Application of lung maturity scheme Betametasona 70% Dexametasona 30%	 72
Sending Hospital Hospital General de México Hospital de la Mujer ISSEMYM Instituto Nacional de Perinatología Others	 52 20 10 4 14

maternal and neonatal outcomes. The mean age of 32.38 years in our sample is within the range described in several studies, such as that of Tadayon *et al*. (2022), which reports that women with PAS are usually in their reproductive age range, with an increased prevalence in women older than 30 years. This could reflect increased exposure to risk factors, such as previous cesarean sections and other uterine procedures[25].

Regarding parity, our population with an average of three gestations is in line with the findings of previous studies, where it has been identified that PAS is more frequent in women with a higher number of gestations, which increases the probability of uterine scarring and, therefore, placental alterations. In fact, as highlighted by Markfeld-Erol *et al*. (2024), the presence of previous cesarean sections and parity are key risk factors for the development of PAS, which explains the high prevalence of cesarean sections in our population (1.46 previous cesarean sections on average) [26].

A relevant finding is the strong association between PAS and placenta previa, which accounts for 62% of cases in our population. This data reinforces what was

reported by Lizárraga-Verdugo *et al*. (2024) and Markfeld-Erol *et al*. (2024), who emphasize that placenta previa, especially in women with previous cesarean sections, significantly increases the risk of developing PAS. Furthermore, the distribution of the types of accreta in our population (31% accreta, 33% increta, and 35% percreta) reflects the variability in the severity of the disorder, a finding that is consistent with studies suggesting that the severity of SBP correlates with the type of placental insertion and myometrial invasion[26,27].

Regarding surgical management, the fact that total hysterectomy is the predominant treatment in our series (89%) is consistent with the recommendations of several studies, such as those of Markfeld-Erol *et al*. (2024), which emphasize the need for radical surgical procedures in severe cases to prevent complications such as massive hemorrhage and preserve maternal life. The low maternal mortality observed in our series, with only one case, reflects the efficacy of well-established surgical protocols, such as uterine embolization and the use of double J catheters to minimize renal complications, as suggested by Arakaza *et al*. (2023) [28].

It is interesting to note that the average bleeding increases according to the severity of SBP (800 cc in placenta accreta, 1200 cc in increta, and 1400 cc in percreta), which is an expected finding and aligned with the literature, which documents that more severe cases (percreta) tend to have more significant bleeding (Tadayon *et al*., 2022). Blood product transfusions, which were necessary in 56% of cases, also reflect the demands in terms of resources and intensive care to manage these complications. This is an aspect pointed out by Lizárraga-Verdugo *et al*. (2024), who discuss how the management of SBP requires a multidisciplinary approach to mitigate these risks.

The low birth weight and prematurity in the newborns (mean weight of 2567 g and gestational age of 35.3 weeks) are also consistent with previous studies, such as that of Markfeld-Erol *et al*. (2024), which report a high rate of preterm delivery and low birth weight newborns in women with PAS. This high rate of prematurity is probably related to the obstetric interventions needed to manage complications, such as bleeding, which often require induction of preterm labor.

Finally, the multidisciplinary approach and the implementation of standardized protocols, such as uterine embolization and the use of double J catheters, are crucial to managing PAS cases safely, as noted in the literature (Markfeld *et al*., 2024; Arakaza *et al*., 2023). These protocols allow safer and more effective management, reducing mortality and associated complications and favoring a faster recovery for patients, as reflected by the average hospital stay of 10.24 days in our series.

Conclusion

PAS is a high-risk obstetric disorder with significant implications for maternal and neonatal health. Early identification and appropriate management are crucial to reduce the morbidity and mortality associated with this condition. In this study, we demonstrate that the implementation of a multidisciplinary diagnostic and surgical management protocol in our national referral center has substantially improved clinical outcomes for both mother and neonate.

Early diagnosis through high-definition ultrasonography and color Doppler, as was performed in our population, is essential for the detection of abnormal placental features, such as placenta previa and low insertion, which are key risk factors for the development of PAS. These initial ultrasound findings allow early identification of the disorder and facilitate surgical planning, minimizing the risks associated with massive hemorrhage and other complications.

Surgical management in our series, which consisted mostly of total hysterectomies (89%), is consistent with current guidelines that recommend radical treatment in severe cases to prevent complications, such as massive hemorrhage. The use of complementary techniques, such as uterine artery embolization and double J catheter placement, also played a crucial role in reducing complications and improving maternal outcomes, as indicated by previous studies. These interventions were essential for the control of intraoperative hemorrhage, as well as for the prevention of renal injuries, which, although rare, were detected in 10% of the cases.

The low maternal mortality observed in our study (with only one case reported) highlights the effectiveness of well-established surgical protocols and specialized care at referral centers. This result is especially noteworthy given that PAS is known for its high rate of serious complications, such as hemorrhagic shock, DIC, and multiorgan failure. Effective management of these cases is essential to save lives and reduce long-term sequelae.

On the other hand, findings related to neonatal health show that PAS has a significant impact on perinatal outcomes. The high rate of prematurity (with an average gestational age of 35.3 weeks) and low birth weight (average 2567 g) are consistent with what is reported in other studies, which associate the need for obstetric interventions such as early cesarean section and trans cesarean hemorrhage with an increase in

preterm deliveries. These factors reflect the need for intensive neonatal care and close follow-up of the newborns, highlighting the importance of preparedness for associated neonatal complications.

While ultrasound is the key initial tool for the diagnosis of PAS, our experience reinforces what other studies have reported: definitive confirmation of the diagnosis and classification of the severity of the disorder may require the combination of several diagnostic methods. MRI, although not routinely used in our study, has been shown to be a useful adjunct, especially in the more complex cases where placental invasion is deep and difficult to evaluate with ultrasound alone.

An important aspect that is also reflected in our results is the need for a multidisciplinary approach to the management of PAS. Specialized teams, including obstetrician-gynecologists, surgeons, radiologists, anesthesiologists, and neonatologists, are essential to ensure comprehensive care and minimize risks during pregnancy, delivery, and postpartum. The use of advanced surgical techniques, together with access to adult and neonatal intensive care units, is crucial for the management of complications that may arise during treatment.

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ORIGINAL ARTICLE

Association of the presence of adenomyosis and clinical characteristics in post-hysterectomy patients

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Abstract

Introduction: *It has been estimated that the prevalence of adenomyosis is 5-70% in Mexico. For the correct study of adenomyosis, the histopathological study of the hysterectomy specimen remains the only confirmatory diagnosis. For this reason, there are not many current studies that tell us the prevalence of this pathology, which is why it is important to carry out intentional searches.* **Objective:** *To estimate the prevalence of adenomyosis in patients undergoing total and subtotal hysterectomy, abdominal, laparoscopic, and vaginal hysterectomy in the period from 2019 to 2021 in Ciudad Juárez and to determine whether there are clinical factors associated with the presence of adenomyosis.* **Material and methods:** *Cross-sectional, retrospective, descriptive study. This study was conducted in patients who underwent total and subtotal abdominal, laparoscopic, and vaginal hysterectomy, whose histopathological reports were collected from January 2019 to December 2021. Patients with a subtotal hysterectomy were excluded.* **Results:** *A total of 332 patients were studied, in which a prevalence of 29.5% was observed, like that established in the general bibliography.* **Conclusions:** *Adenomyosis is the second gynecological pathology in order of frequency, only below leiomyomatosis, by histopathological diagnosis. According to the study, the clinical profile of patients to be ruled out for adenomyosis would be a history of previous uterine surgery, multiparity, in the fifth decade of life (specifically between 40 and 50 years of age), overweight, or obese.*

Keywords: *Adenomyosis. Hysterectomy. Uterine hemorrhage. Uterine diseases. Mexico.*

Introduction

Dysfunctional uterine bleeding is the main cause of bleeding in adult women; its diagnosis is the exclusion of anatomical alterations, so the clinician must initially rule out any organic or endocrinological pathology. It is estimated that around 10 million women in Mexico suffer from uterine bleeding, and annually, only 6 million of them seek medical attention[1].

The exact pathogenesis of adenomyosis has not been established, but some theories have been widely accepted and adopted by physicians[2]. The most common theory suggests that adenomatosis results from the invagination of endometrial glands and stroma in the thickness of the myometrium, together with hyperplasia and hypertrophy of smooth muscle fibers of the latter[3]. Another possible theory is that the adenomyotic lesions are due to the metaplasia of displaced Müllerian remains or to the differentiation of adult stem cells[4].

The prevalence of adenomyosis as an anatomopathological finding is highly variable, ranging from 5% to 70%, depending on the depth limit considered in the microscopic finding of foci in myometrial thickness[1]. Arellano Pichardo et al. in a study carried out in the Mexican population, they showed that the prevalence of

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adenomyosis in hysterectomy specimens was 33.33% (86 out of 258 patients)[3], as well as a study carried out in the United States in which a total of 135,162 women between 16 and 60 years of age were analyzed in 2015, in which 1,068 women had a previous diagnosis of adenomyosis. Thus, the prevalence of adenomyosis in 2015 was observed to be 0.8-1.5%; being higher among women aged 41-45 years[5].

The confirmatory diagnosis requires hysterectomy, in order to study the entire piece. The minimum distance required to make the diagnosis has remained under debate, but ranges from half to two low-power fields from the endomyometrial junction or a minimum depth of invasion ranging from 1 to 4 mm. The involvement of at least 25% to one-third of myometrial thickness is another diagnostic criterion that has been used in magnetic resonance imaging (MRI)[6,7].

Hysterectomy is the only definitive treatment for adenomyosis, which allows us to perform the histopathological study of the specimen and thus obtain the microscopic result and obtain the definitive diagnosis[8].

The objective of this study is to determine if there is an association between clinical variables and the presence of adenomyosis in patients undergoing total abdominal and subtotal hysterectomy at the Ciudad Juárez Women's Hospital, with the following specific objectives: (1) to know the age groups with the highest frequency of adenomyosis at the Ciudad Juárez Women's Hospital, (2) to identify the comorbidities present in patients diagnosed with adenomyosis at the Women's Hospital of Ciudad Juárez, (3) to perform inference between patients with adenomyosis and without adenomyosis, and (4) to perform a multivariate model to identify variables associated with the presence of adenomyosis.

Material and methods

An observational, retrospective, cross-sectional, descriptive, and analytical study was conducted in 332 women after total and subtotal non-obstetric hysterectomy at the Hospital de la Mujer of Ciudad Juarez, from January 01, 2019, to December 31, 2021. Clinical records were reviewed, and a database was built in Microsoft Excel 2019. As selection criteria, patients undergoing hysterectomy, both of obstetric and gynecological origin, with total or subtotal technique, from January 01, 2019 to December 31, 2021, had a histopathological report, as well as patients who had in their clinical history the variables studied (age, multigestation, and body mass index [BMI], history of previous gynecology and obstetrics, adenomyosis, diabetes mellitus, and systemic arterial hypertension), as non-inclusion criteria we take patients who are not in the virtual or physical clinical record, patients whose clinical history lacks the previously mentioned variables and finally because they do not have a pathology report.

Statistical analysis

To perform the analysis and graphs of this work, the statistical program IBM Statistical Packages for the Social Sciences V.23 for Windows 10 was used. Kolmogorov-Smirnov normality tests were applied to assess the distribution of variables. The inference analysis for the quantitative variables was performed using Student's t-test or Mann-Whitney's U-test, as appropriate, while Pearson's Chi-square test was used for the qualitative variables. Logistic regression was performed considering statistically significant variables as independent variables for adenomyosis status. The best model was constructed using the backward step technique considering Wald's statistic. A value of $p < 0.05$ was considered to be statistically significant for all statistical tests used.

Results

In a sample of 332 women post-operated obstetric hysterectomy at the Hospital de la Mujer of Ciudad Juarez, from January 01, 2019 to December 31, 2021. A total of 98 (29.5%) patients with histopathological diagnosis of adenomyosis were detected; in this way, it was determined that the prevalence of adenomyosis in the studied population was 29.5% (98 of 332 patients). The sample found a median age of 45 years with an interquartile range of 39-50 years. In our sample, a total of 234 women (70.4%) had a BMI > 25 kg/m^2. A total of 212 women (63.9%) had a history of cesarean section, and 242 (72.9%) were categorized as multigestation. 19% (63) of the women in this study had a diagnosis of diabetes and 28.6% (95) had hypertension. Among the causes of hysterectomy, it was found that 63.6% (211) were due to uterine myomatosis, 11.7% (39) were due to pelvic organ prolapse, 9.9% (33) due to obstetric hemorrhage, and 6.6% (22) due to placental alteration, the rest of the causes are described in table 1.

A total of 98 women (29.5%) had a diagnosis of adenomyosis according to the pathological study (Table 1). Patients were grouped according to the histopathological diagnosis of adenomyosis, finding that the median age in women without adenomyosis was 44 (36-49)

Table 1. General characteristics of the population

Variable	Total (%)	Adenomyosis (%)		p
		No (234)	Yes (98)	
Age (years)	45 (39-50)	44 (36-49)	47 (42-50)	**0.010*u**
BMI > 25 kg/m^2 Yes No	 235 (70.8) 97 (29.2)	 161 (68.8) 73 (31.2)	 74 (75.5) 24 (24.5)	 0.220Xi
Previous gynecological and obstetrical surgeries Yes No	 212 (63.9) 120 (36.1)	 156 (66.7) 78 (33.3)	 56 (57.1) 42 (42.9)	 0.099Xi
Multigesta Yes No	 242 (72.9) 90 (27.1)	 173 (73.9) 61 (26.1)	 69 (70.4) 29 (29.6)	 0.510Xi
Causes of hysterectomy Placental alteration Obstetric bleeding Myomatosis NIC 1 NIC 2 NIC 3 Oncologic process Pelvic organ prolapse Others	 22 (6.6) 33 (9.9) 211 (63.6) 3 (0.9) 4 (1.2) 5 (1.5) 8 (2.4) 39 (11.7) 7 (2.1)	 19 (8.1) 27 (11.5) 145 (62) 2 (0.9) 4 (1.7) 5 (2.1) 5 (2.1) 22 (9.4)	 3 (3.1) 6 (6.1) 66 (67.3) 1 (1) 0 (0) 0 (0) 3 (3.1) 17 (17.3)	 **0.035*Xi**
Diabetes Yes No	 63 (19) 269 (81)	 43 (18.4) 191 (81.6)	 20 (20.4) 78 (79.6)	 0.781Xi
Hypertension Yes No	 95 (28.6) 268 (81)	 67 (28.6) 167 (71.4)	 28 (28.6) 70 (71.4)	 > 0.999pXi

This table shows median and IQR 25-75% and frequency in number and percentage
*: statistical significance (p < 0.05).
u: Mann Whitney´s U test.
Xi: Pearson´s Chi squared.
BMI: body mass index; NIC: neoplasia intraepitelial cervical.

while in women with adenomyosis it was 47 (42-50), p = 0.010 (Fig. 1). In the group of women without adenomyosis, 68.8% had a BMI > 25 kg/m^2 and in the group of women with adenomyosis, 75.5% had a BMI > 25 kg/m^2 (p = 0.220). Regarding the history of previous obstetric surgeries, the history was present in 57.1% of the women in the group with a diagnosis of adenomyosis, whereas the history was present in 66.7% of the women without adenomyosis (p = 0.099) (Table 1). Regarding the categorization of multigest, 73.9% and 70.4% of the group without adenomyosis and with a diagnosis of adenomyosis were found to be multigest, respectively (p = 0.510). 18.4% of women without adenomyosis had diabetes, and the same diagnosis occurred in 20.4% of women with adenomyosis (p = 0.667). 28.6% of women with and without adenomyosis had hypertension (p = 0.991). 2 logistic models were performed, in the first (Table 2), all binary variables were entered, taking the presence of adenomyosis as a dependent variable, finding statistical significance with age (B = 0.026 [odds ratio (OR) = 1.026 95% confidence interval (CI) = 1.002-1.051], p = 0.035). Due to the result obtained, the elimination of covariates was carried out using Wald's statistical criterion (Table 3), finding statistical significance for age (B = 0.026 [OR = 1.026 95% CI = 1.003-1.049], p = 0.026].

Discussion

Total hysterectomy is the most common gynecological surgery in the world. In our study, hysterectomies performed in 1 year (n = 332) were considered, using laparotomy, laparoscopy, and vaginality. The type of surgery to be performed is decided according to the characteristics of the uterus and the concomitant pathologies[3,9].

Table 2. Multiple logistic regression for the presence of adenomyosis in women after hysterectomy obstetric

Variable	B	Wald	p	OR (95% CI)
BMI > 25 kg/m^2	0.307	1.189	0.275	1.359 (0.783-2.359)
Previous gyneco-obstetrical surgeries	0.306	1.436	0.231	1.358 (0.823-2.240)
Multigesta	–0.259	0.871	0.521	0.772 (0.448-1.329)
Diabetes	0.111	0.124	0.725	1.117 (0.603-2.068)
Hypertension	–0.188	0.430	0.512	0.829 (0.473-1.452)
Age	0.026	4.442	0.035*	1.026 (1.002-1.051)

B: logistic regression coefficient; Wald: Wald statistic; p: value of p; OR: *odds ratio*; 95% CI: Confidence interval at 95%. ; BMI: body mass index.
*: statistical significance ($p < 0.05$).

Table 3. Multiple logistic regression for the presence of adenomyosis in women after obstetric hysterectomy

Variable	B	Wald	p	OR (95% CI)
Age	0.026	4.935	0.026*	1.026 (1.003-1.049)

B: logistic regression coefficient; Wald: Wald statistic; p: value of p; OR: *odds ratio*; 95% CI: confidence interval at 95%.
*: statistical significance ($p < 0.05$).

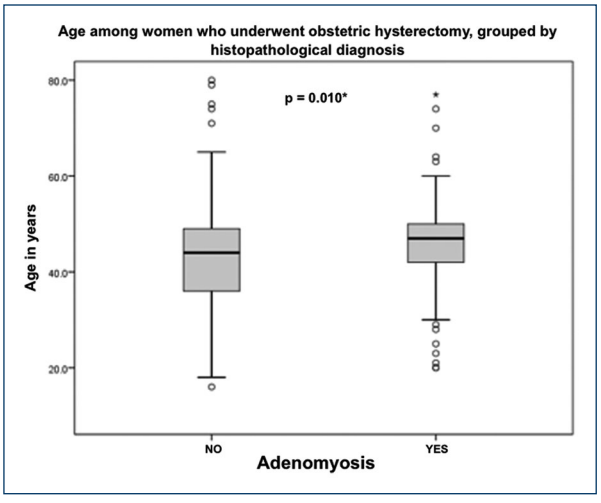

Figure 1. Age of the patients included in the study according to diagnosis of adenomyosis. The p value corresponds to the Mann's U-test.

In the literature, abnormal uterine bleeding with or without leiomyomatosis is reported as the main cause of hysterectomy. Leiomyomatosis is the cause of up to 55%[10]. In our study, uterine leiomyomatosis was the most frequent definitive diagnosis, with 211 cases, representing 63.5% of the sample, a percentage higher than what was reported worldwide. Either alone or in combination with other conditions, was the second most frequent diagnosis, with a prevalence of 29.5%. This finding is consistent with global reports, where prevalence ranges from 2.6% to 70% in pathology specimens. However, in none of the procedures was adenomyosis the primary indication for hysterectomy, as it was diagnosed histopathologically and justified by other clinical causes[11,12].

Endovaginal ultrasound is the most important imaging technique in gynecological patients. The radiologist requires experience to identify adenomyosis. This is explained by the great difficulty in making the prior diagnosis. There are studies that mention that ultrasound and MRI can establish the diagnosis with a sensitivity of 89%[13-15]. However, to suspect adenomyosis, a detailed description of the myometrium described in the morphological uterus sonographic assessment criteria is required, which is not done routinely and only has the experience of some physicians assigned to gynecology; for this reason, it is emphasized that each of these criteria is made known to all personnel and thus be able to carry out an adequate approach to this pathology[16].

Adenomyosis is a condition with variable frequency depending on the population studied. It is most commonly diagnosed between 40 and 50 years of age, accounting for up to 80% of cases. For the purposes of this study, and to better localize the pathology, patients were grouped by decades. The highest frequency of diagnosis was found in the 40-50-year age group, with a rate of 63.2%, which is consistent with findings reported in the global literature[9]. Regarding obstetric history, 70.4% of patients with adenomyosis were multigested. Patients with 2 or fewer gestates accounted for 29.6% of reported cases of adenomyosis. According to several authors, most cases of adenomyosis occur in multigestation patients (90%), consolidating itself as one of the main risk factors[4,7,17].

Regarding the history of previous uterine surgery and the presence of adenomyosis, it occurred in 57.1% of the patients, specifically the history of cesarean section and instrumented uterine curettage. Uterine trauma during a cesarean section, curettage, or myomectomy are the classic risk factors[17]. BMI also plays an important role[18]. Overweight patients or with some degree of obesity make up 70.7% of the total number of patients

studied in our sample, of which 75.5% were diagnosed with adenomyosis. In adenomyosis, the role of hyperestrogenism plays an important role, as it is a risk factor and is frequently found in overweight or obese women[11].

The presence of diabetes mellitus or systemic arterial hypertension are variables that in our study, we did not find with statistical significance, a total of 63 patients presented a diagnosis of diabetes mellitus (18.9%), of which twenty presented a diagnosis of adenomyosis (20.4%), similar figures with systemic arterial hypertension, in which we have 95 reported cases (28.6%) of which 28 patients presented a diagnosis of adenomyosis (28.6%). However, we found that age is associated with the presence of adenomyosis (OR = 1.026, [95% CI = 1.003-1.049], p = 0.026).

Clinical diagnosis is difficult, due to nonspecific signs and symptoms, which often coexist with other pelvic diseases[1]. In the present study, most of the patients had abnormal uterine bleeding as their main antecedent; in 73.4% of them, so in all patients with a study protocol for abnormal uterine bleeding, adenomyosis should be considered as a diagnostic probability, and the appropriate protocol for its diagnosis should be performed.

Currently, there is a limited series of studies, but important to perform for presurgical diagnosis, which are, in addition to clinical suspicion, ultrasound and, in some cases, MRI, this in an attempt by gynecologists to define the various characteristics resulted in the criteria for morphological sonographic evaluation of the uterus[19]. In these cases, adenomyosis is considered when the uterus has a globular configuration and multiple areas of shadow, sometimes described as fan-shaped, are visible, with difficulty in differentiating the myometrium from the junction zone and cystic changes in the junction zone and myometrium[20]. Additional features that can be observed include an irregular or interrupted area of conjunction with islands[18,20]. Unfortunately, there are no classic findings on physical examination or laboratory studies that identify it as a probable diagnosis[20].

Future applications of artificial intelligence (AI) in medicine, specifically related to our topic of adenomyosis classification[16,18], and need to be discussed. Systems based on conjunction zone anomalies have shown promising results in terms of observer agreement and correlation with clinical symptoms. Recently, there has been growing interest in the potential of AI to improve the accuracy and consistency of the diagnosis and classification of adenomyosis. It has been suggested that AI-based ultrasound or MRI image analysis could accurately identify and classify different types of adenomyosis based on the abnormalities of the conjunction zone[16]. This approach has the potential to improve the standardization and reproducibility of presurgical diagnosis of adenomyosis, as AI algorithms can analyze large datasets and identify patterns that may not be immediately apparent to human physicians[15,16,21]. However, as in many areas of medicine, more research is needed to evaluate these approaches and explore whether they provide answers to clinically relevant questions.

Conclusions

The prevalence of adenomyosis at the Ciudad Juárez Women's Hospital is 29.4%. Adenomyosis is the second gynecological pathology in order of frequency, only below leiomyomatosis, by histopathological diagnosis. According to the study, the clinical profile of patients to be ruled out for adenomyosis would be a history of previous uterine surgery, multiparity, in the fifth decade of life (specifically between 40 and 50 years of age), overweight, or obese. Previous uterine surgery is an important factor, found in 57.2% of patients. The most common surgery is cesarean section. It is essential to include in the study protocol of patients with suspected adenomyosis, an ultrasound that includes a complete description of the myometrium, subendometrial space, and endometrium. The outpatient service does not have sonography equipment, so the diagnosis of adenomyosis is impossible. In none of the patients who underwent hysterectomy was the presence of adenomyosis diagnosed before the surgical event. Training is required for the resident and affiliated physicians of our institute due to the evident lack of knowledge and expertise for the preoperative diagnosis of adenomyosis. None of the patients was the suspicion of adenomyosis contemplated in the clinical file. Age may be a factor associated with the presence of adenomyosis; however, more observational studies are required to corroborate these findings.

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Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely obtained and anonymized clinical data, so informed consent was not necessary. Relevant guidelines were followed.

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REVIEW ARTICLE

Pharmacological treatment of acute severe hypertensives in Obstetrics: literature review

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Abstract

In obstetrics, hypertensive emergency is a critical state that merits the intervention of a multidisciplinary team that resolves the crisis, evaluates the well-being of the fetus, and performs adequate monitoring of the mother's organic function. This serious condition puts the binomial at vital risk, mortality and morbidity of both can be reduced if the appropriate use of antihypertensive drugs is used. This document reviews the pharmacological management of severe arterial hypertension at initial clinical presentation, generally in the emergency department and in intensive care.

Keywords: *Hypertensive emergency obstetrics. Severe hypertension. Anti-hypertensive treatment.*

Introduction

Hypertensive disorders of pregnancy (HDP) remain one of the major causes of pregnancy-related maternal and fetal morbidity and mortality worldwide. Affected women are also at increased risk for cardiovascular disease later in life, independently of traditional cardiovascular disease risks[1]. Affected women and newborns also have an increased risk of cardiovascular disease later in life, independent of traditional cardiovascular disease risks. Despite these risks, recommendations for optimal diagnosis and treatment have changed little in recent decades, probably due to fear of the fetal repercussions of decreased blood pressure (BP) and possible drug toxicity[2]. Gestational hypertension and pre-eclampsia without severe features can be managed with BP monitoring, laboratory testing for disease progression, antenatal testing for fetal well-being, and delivery at 37 weeks' gestation. The use of antihypertensive drugs to control non-severe hypertension in the setting of gestational hypertension and pre-eclampsia does not improve outcomes and is not recommended[3].

HDP can be classified into four groups depending on the onset of hypertension and the presence of target organ involvement: chronic hypertension, pre-eclampsia, gestational hypertension, and superimposed pre-eclampsia on chronic hypertension. Early diagnosis and proper treatment for pregnant women with hypertension remain a priority since this leads to improved maternal and fetal outcomes. Labetalol, nifedipine, methyldopa, and hydralazine are the preferred medications to treat hypertension during pregnancy[4].

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Despite major advances in the pharmacologic treatment of hypertension in the non-pregnant population, treatments for hypertension in pregnancy have remained largely unchanged over the years. There is recent evidence that a more adequate control of maternal BP is achieved when the first given antihypertensive drug is able to correct the underlying hemodynamic disorder of the mother besides normalizing the BP values[5]. In obstetrics, hypertensive emergency is defined as SBP BP ≥ 160 mm Hg or diastolic BP ≥ 110 mm Hg, confirmed 15 min apart[6].

Pregnant and postpartum women rarely need the involvement of intensivists in their care. When they do, it is crucial for their critical care physicians to be prepared to provide the best, most well-informed care by an interdisciplinary team including the obstetrician, maternal-fetal medicine specialist, anesthesiologist, and other relevant specialties. A fundamental knowledge of obstetric critical illness and specific aspects of maternal care and physiology is essential. This document reviews the pharmacological management of severe arterial hypertension at initial clinical presentation, generally in the emergency department and the intensive care unit.

Methods

The researchers met to organize the content of the manuscript to be discussed. The academic article was carried out including the keywords (Hyper tensive Emergency Obstetrics, Severe Hypertension, Anti-hypertensive treatment) were used with a time limit of 2014-2024. The PUBMED database returned 411 results, and the 34 most relevant that had a focus on were chosen, We eliminated results that contained topics unrelated to keywords and manuscript structure (treatment of hypertensive crisis according to the hemodynamic phenotype of pre-eclampsia or treatment goals according to the type of hypertensive emergency) The objective of the manuscript is not to carry out a systematic review, but to consult recent literature on the treatment of hypertensive emergency during pregnancy and the puerperium, giving the reader an overview of the ways to treat this very frequent clinical problem.

Definition

In pregnancy and the postpartum period, the diagnosis of hypertension is defined as SBP BP ≥ 140 mm Hg and/or a diastolic pressure ≥ 90 mm Hg in at least two readings more than 4 h apart. For non-obstetric providers in the urgent care and emergency setting, it is crucial for enhanced awareness of hypertension in pregnancy and the potential for late presentation in the postpartum setting[7].

Hypertensive emergency is a life-threatening pathology, characterized by a rapid increase in BP, exceeding the systolic value of 180 mmHg and/or diastolic value of 120 mmHg, associated with acute damage to one or more target organs[8]. Other situations with BP in severe ranges without damage to the target organ will be called episodes of severe acute uncontrolled hypertension[9]. Therefore, the elevation of BP alone (without the presence of damage to the target organ), does not define a hypertensive emergency; no matter how high the value of it may be[10]. There is consensus that a SBP BP ≥ 160 mmHg or a diastolic BP (DBP) ≥ 110 mmHg in an obstetric patient should be considered a hypertensive emergency and hospitalization is indicated[11], therefore the distinction between these two clinical entities is essential, due to the different approach and management. Hypertensive emergency will require immediate management and admission to the intensive care unit, while severe acute uncontrolled hypertension will generally not require admission and can be managed by initiating or intensifying previously prescribed antihypertensive treatment[12].

Initial approach

When we assist a hypertensive pregnant patient in the emergency department, it is important that the provider identify the disease process, presence of severe features, and initiate treatment to minimize symptoms and help prevent progression to eclampsia. It has been shown that prompt treatment within 30-60 min or as soon as reasonably possible can prevent serious fetal and maternal complications. Some organizations have recommended using SBP 140 mm Hg or DBP 90 mmHg as the threshold for initiation of antihypertensive medication. The degree to which the BP should be lowered is similarly debated, as there are mixed data regarding the BP level below which there may be a risk for placental hypoperfusion and growth restriction. First-line antihypertensive agents for the treatment of HDP are labetalol, nifedipine, hydralazine, and methyldopa[13].

The immediate therapeutic strategy for hypertensive emergency includes a brief history and physical examination, accompanied by paraclinical and cabinet studies, with early initiation of intravenous antihypertensive drugs being essential, respecting the goals of BP reduction and

the different specific treatment protocols for each etiology, to preserve organic perfusion; therefore, a personalized approach is justified to limit morbidity and mortality[14].

There are multiple routes for the administration of antihypertensive drugs; however, intravenous drugs are preferred due to their rapid onset of action and titration capacity (short half-life). A general objective could be the gradual and controlled reduction of BP by no more than 25% within the first 24 h, to avoid organic hypoperfusion, reaching normal BP levels between 24 and 48 h[15]. There are exceptions according to the type of injury to the target organ, sometimes requiring more or less aggressive approaches and management, such as hypertensive encephalopathy and pre-eclampsia; in which randomized trials have been carried out to arrive at a target BP, as well as for the choice of first-line drug, however, there are multiple factors that affect the combination of these results, such as the exclusion to a large extent of obstetric patients with extremely high BPs (systolic BP > 220 mmHg and/or diastolic BP > 110 mmHg), a situation of importance since taking the patient to the target BP goals established by most international obstetric protocols (systolic BP < 160 mmHg and/or diastolic BP < 110 mmHg), would be detrimental according to the theory of brain autoregulation. Therefore, a lot of emphasis should be placed on individualizing management according to the affected organic condition[16].

Antihypertensive treatment according to hemodynamic characteristics

The opinion on the mechanisms underlying the pathogenesis of pre-eclampsia still divides scientists and clinicians. This common complication of pregnancy has long been viewed as a disorder linked primarily to placental dysfunction, which is caused by abnormal trophoblast invasion, however, evidence from the previous two decades has triggered and supported a major shift in viewing pre-eclampsia as a condition that is caused by inherent maternal cardiovascular dysfunction, perhaps entirely independent of the placenta. In fact, abnormalities in the arterial and cardiac functions are evident from the early subclinical stages of pre-eclampsia and even before conception. Moving away from simply observing the peripheral BP changes, studies on the central hemodynamics reveal two different mechanisms of cardiovascular dysfunction thought to be reflective of the early-onset and late-onset phenotypes of pre-eclampsia. More recent evidence identified that the underlying cardiovascular dysfunction in these phenotypes can be categorized according to the presence of coexisting fetal growth restriction instead of according to the gestational period at onset, the former being far more common at early gestational ages[17]. Gestational hypertension and pre-eclampsia are the two main types of hypertensive disorders in pregnancy. Non-invasive maternal cardiovascular function assessment, which helps obtain information from all the components of circulation, has shown that venous hemodynamic dysfunction is a feature of pre-eclampsia but not of gestational hypertension. Venous congestion is a known cause of organ dysfunction, but its potential role in the pathophysiology of pre-eclampsia is currently poorly investigated. Body water volume expansion occurs in both gestational hypertension and pre-eclampsia, and this is associated with the common feature of new-onset hypertension after 20 weeks of gestation. BP, by definition, is the product of intravascular volume load and vascular resistance (Ohm's law). Fundamentally, hypertension may present as a spectrum of cardiovascular states varying between two extremes: one with a predominance of raised cardiac output and the other with a predominance of increased total peripheral resistance. In clinical practice, however, this bipolar nature of hypertension is rarely considered, despite the important implications for screening, prevention, management, and monitoring of disease[18].

However, there are identified various hemodynamic patterns dependent on gestational age at the time of diagnosis of pre-eclampsia, attributing a hemodynamic pattern with low cardiac output, increased peripheral vascular resistance, and a decrease in intravascular volume when the hypertensive state was diagnosed before 34 weeks of gestation (early-onset pre-eclampsia), and a hemodynamic pattern with increased cardiac output, decreased peripheral vascular resistance, and increased intravascular volume when the hypertensive state was diagnosed after 34 weeks of gestation (late-onset pre-eclampsia)[19].

However, in 2018 Tay et al. conducted a study including pregnant women diagnosed with pre-eclampsia between 24 and 40 weeks of gestation, adapting the hemodynamic patterns measured according to the gestational age of diagnosis of the hypertensive state, demonstrating that although early-onset and late-onset pre-eclampsia are considered different diseases, the hemodynamic characteristics of both were not related to gestational age, but these hemodynamic characteristics were strongly associated with the presence or

absence of fetal growth restriction (FHR), demonstrating a hemodynamic pattern with low cardiac output, increased peripheral vascular resistance and decreased intravascular volume in cases of pre-eclampsia associated with FHR and a hemodynamic pattern with increased cardiac output, decreased peripheral vascular resistance and increased intravascular volume in cases of pre-eclampsia without CRF, regardless of gestational age at diagnosis[20].

For this reason, it is essential to know not only the BP of the obstetric patient but also the cardiac output and systemic vascular resistance, parameters that can be obtained in real-time using a variety of non-invasive technological tools, such as Doppler ultrasound or impedance devices commonly used in operating rooms, emergency units, and critical care. Hemodynamic changes in women who eventually develop hypertensive complications are substantially different. Serial monitoring and plotting against developed normograms can identify women at risk and may allow timely intervention[21].

According Wang et al., Diltiazem is the most effective in reducing BP in pre-eclampsia patients; labetalol and nicardipine also had good effects. Diltiazem is preferred for the treatment of patients with severe hypertension[22].

According Bhat et al., oral calcium-channel blockers ranked highest for treatment success. Ketanserin achieved target BP fastest, warranting additional research[23].

Wu et al. demonstrated the superiority of oral nifedipine 50,60,90 mg, especially oral nifedipine 50 mg tablets, in the treatment of severe hypertension during pregnancy than IV labetalol 300 mg, while oral nifedipine 60,90 mg also showed superiority in the successful treatment rate of severe hypertension during pregnancy than IV hydralazine 15,25 mg[24]. Maternity care providers should feel comfortable initiating the management of severe hypertension in pregnancy using oral nifedipine, labetalol, and methyldopa[25,26].

Finally, the main goal of treatment in patients with hypertensive emergency in Obstetrics is to achieve hemodynamic stabilization of the patient, through BP reduction goals, but maintaining adequate organic perfusion, including placental perfusion, as well as preparing her for an eventual termination of pregnancy if she is still pregnant. Critically, ill patients during the postpartum period do not benefit from specific antihypertensive regimens. However, since the pregnant or postpartum patient can be critically complicated with organ dysfunctions at different levels, therapeutic options should also be taken into account according to the affected organ. Table 1 summarizes the treatments of choice for each situation.

Severe hypertensive crisis during pregnancy according to most international guidelines limits its treatment options to labetalol, nifedipine, hydralazine, and methyldopa, probably in that order of priority[27]. Once in the puerperal stage, the treatment options are wider, since there is no concern about placental perfusion that affects fetal hemodynamics. Acute increases of BP values are common causes of patients' presentation to emergency departments, and their management represents a clinical challenge. They are usually described as "hypertensive crises," "hypertensive urgencies," terms that should be abandoned because they are misleading and inappropriate according to a recent task force of the European Society of Cardiology, which recommended to focus only on "hypertensive emergencies." The latter can be easily identified using the brain, arteries, retina, kidney, and/or heart strategy as herein described[28]. Hypertensive emergencies and hypertensive urgencies are a frequent cause of access to emergency departments, with hypertensive urgencies being significantly more common. BP levels alone do not reliably predict the presence acute hypertension-mediated organ damage, which should be suspected according to the presenting signs and symptoms[29]. Despite the general consensus on outpatient BP management, guidance on inpatient management of elevated BP without symptoms is lacking, which may contribute to variable practice patterns[30]. Table 2 summarizes each possible option according hemodynamics patterns in pregnancy patients.

In the expert consensus of the Pan American Health Organization, it is concluded that regarding the choice of an antihypertensive drug for severe hypertension during pregnancy and its route of administration, the evidence is limited. Hydralazine, methyldopa, β-blockers (including labetalol), and nifedipine appear to be reasonable options until more evidence is available. The use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and sodium nitroprusside should be avoided for their safety in women who are still pregnant[31].

One of the largest systematic reviews in existence published by Abalos et al., out of 63 trials, which evaluated the effects of antihypertensive therapy versus placebo in patients with mild to moderate hypertension during pregnancy, noted that treating pregnant women with mild to moderate hypertension did not reduce the incidence of complications such as the development

Table 1. Hypertensive emergencies blood pressure goals and treatment options

Category	BP goal (mm Hg)	Treatment option	Usual dose
Acute ischemic stroke: Lytic or endovascular candidate	< 185/110 before treatment < 180/105 post-treatment	Nicardipine Labetalol Clevidipine	Start with 5 mg/h, can be increased every 15 min to 2.5 mg/h, maximum up to 15 mg/h in continuous infusion. Start with 10-20 mg bolus, the dose can be doubled every 30 min up to a maximum of 80 mg per bolus, it can also be used in infusion 0.5-2 mg/min. Starting with an infusion of 1-2 mg/h, the dose can be adjusted every 5-10 min, up to a maximum of 20 mg/h.
Acute ischemic stroke: non-candidate	< 220/110	Nicardipine Labetalol Clevidipine	Same dose
Intracerebral hemorrhage	SBP < 160	Nicardipine Labetalol Clevidipine	Same dose
Hypertensive encephalopathy	Rapid MAP reduction of 25% (1st h), then gradual over 24 h	Nicardipine Labetalol Clevidipine Nitroprusside	Nitroprusside: should be started very slowly with doses of 0.1 mcg/kg/min and increased every 3-5 min by 0.1 mcg/kg/min, up to a maximum of 10 mcg/kg/min. Monitor for cyanide toxicity as a metabolite of nitroprusside
Aortic dissection	SBP < 120 and heart rate ≤ 60 bpm	Esmolol Labetalol Nicardipine Clevidipine Nitroprusside	Esmolol hydrochloride, 250 mcg per kg is administered as a bolus, later infusion at a dose of 50-300 mcg kg min, the bolus can be repeated 5 to 10 minutes after the first dose. Rest of drugs at previously mentioned doses.
Acute pulmonary edema	Rapid MAP reduction of 25% (1st h), then gradual over 24 h	Nitrates and loop diuretics, nicardipine, urapidil, or even nitroprusside	Furosemide bolus of 20-40 mg in patients who have not previously used diuretics, in users of this drug it can be administered at 0.5-2 mg per kg. Urapidil 50 mg administered intravenously in 20 minutes, the dose can be repeated after 5 minutes if necessary, infusion: 5-50 mg/hour. Rest of drugs at previously mentioned doses.
Acute coronary ischemia	MAP reduction of 15-20% (1st h), then gradual over 24 h	Nitroglycerin, labetalol or esmolol, morphine as adjuvant.	Same dose
Pheochromocytoma	MAP reduction of 25%, then gradual over 24 h	Phentolamine clevidipine nicardipine	Phentolamine: intravenous 1-15 mg is usually given every 5-15 min. Maximum 15 mg. Rest of drugs at previously mentioned doses.
Eclampsia, HELLP syndrome	Generally BP < 160/110 within 60-180 min	Labetalol, nifedipine, hydralazine, metildopa nicardipine, clevidipine	Labetalol same dose IV, nifedipine 10 mg oral every 20-30 min, max 40 mg, Hydralazine 5-10 mg every 10-20 min, max 20 mg, Metildopa 1 g oral dose.

SBP: systolic blood pressure; MAP: mean arterial pressure.

of PE, pre-term birth or maternal and fetal mortality, however, a decrease in the occurrence of severe hypertension was observed in the treated patients[32].

Finally, most guidelines and consensus recommend the use of β blockers and calcium channel blockers as first-line agents for the treatment of hypertension.

Labetalol, thanks to its mixed α and β-adrenergic blocking effect, is the most commonly used and has been shown to be safe. Pindolol and metoprolol are less studied but their use is considered acceptable as an alternative. Atenolol should be avoided during pregnancy as it is associated with fetal growth restriction and low birth weight.

Nifedipine extended-release has the advantage of acting faster and being easier to administer than labetalol.

Table 2. Summarizes the hemodynamic patterns that have been identified and the most beneficial treatment for these circulatory characteristics

Cardiovascular parameter	Low cardiac output and high vascular resistance phenotype	High cardiac output and low vascular resistance phenotype
Maternal heart rate	< 70 bpm Calcium channel blockers (e.g., nifedipine) Nitric Oxide (NO) donors and fluids.	90 bpm α- and β-blockers (e.g., α methyldopa, labetalol) preferred
Cardiac output	< 5 L/min Calcium channel blockers (e.g., nifedipine), NO donors, and fluids. (early-onset pre-eclampsia).	> 8 L/min α- and β-blockers (e.g., α methyldopa, labetalol) (late-onset pre-eclampsia)
Systemic vascular resistance	> 1400 dynes.s.cm 5 Calcium channel blockers (e.g., nifedipine), NO donors, and fluids (early-onset pre-eclampsia)	< 900 dynes.s.cm 5 α- and β-blockers (e.g., α methyldopa, labetalol) (late-onset pre-eclampsia)

Alpha-methyldopa has been widely used in pregnant women and with a safety record in follow-up for decades.

The second line of treatment includes thiazide diuretics and hydralazine. The use of thiazide diuretics may be associated with a significant decrease in volume, so close monitoring is recommended as it could affect amniotic fluid volume and fetal growth.

Hydralazine may cause associated side effects, including hypotension, headache, tremors, and edema. In addition, it can cause episodes of extreme hypotension, which could lead to adverse effects, both maternal and fetal[33].

Other agents, such as clonidine, are considered third-line. The use of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, direct renin inhibitors, and mineralocorticoid receptor antagonists are contraindicated in pregnancy due to teratogenic effects, fetal renal abnormalities and failure, fetal growth restriction, malformations, and death, but can be used relatively safely during the postpartum period. In women with chronic salt-sensitive hypertension or chronic kidney disease and reduced glomerular filtration rate, diuretics can be used safely, although perhaps in lower doses, recent studies show that they can be very useful and effective in postpartum hypertension[34].

Conclusion

Hypertensive emergency should be evaluated conscientiously, taking into consideration the hemodynamic phenotype, as well as the type of organic emergency. Several trials and systematic reviews have shown that treating mild to moderate hypertension does not benefit the mother or the gestational product in morbidity or mortality; however, it reduces the occurrence of severe hypertension, which is ultimately beneficial. In pregnant patients, treatment options are generally limited to labetalol, nifedipine, hydralazine, and methyldopa, with the first two options being the first-line options, however, once pregnancy is over, it can be treated with the same options as non-obstetric patients. Reliably assessing the hemodynamic phenotype of a patient with hypertensive emergency will be limited to access to certain material and personnel resources in health care units.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of human and animal. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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REVIEW ARTICLE

Efficacy of glucocorticoids versus placebo on mortality in patients with community-acquired pneumonia: systematic review

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Abstract

The use of glucocorticoids (GCS) in acute respiratory distress syndrome is well documented; however, their use in community-acquired pneumonia (CAP) is controversial, and their impact on mortality is not well defined. The objective is evaluating the efficacy of GCS use compared to placebo in patients with CAP through a systematic review. A systematic review of the literature was conducted in databases such as PubMed, Scopus, and Web of Science for randomized clinical trials published between 2019 and 2024. Articles were classified according to the level of evidence by the Oxford Center for Evidence-Based Medicine. In the results, seven original articles were included, all of which were randomized clinical trials. The studies included a total of 2847 participants, evaluating outcomes such as mortality, days of mechanical ventilation use, length of hospital stay, need for vasopressor use, development of shock, and ARDS. The use of hydrocortisone showed a significant benefit in reducing mortality at 28 days and the need for mechanical ventilation and vasopressors. In contrast, the use of dexamethasone and methylprednisolone did not show significant differences compared to placebo.

Keywords: *Corticosteroids. Pneumonia. Mortality. Placebo. Systematic review.*

Introduction

Community-acquired pneumonia (CAP) is defined as acute lung infection involving the alveoli that occurs in a patient with no recent exposure to healthcare[1]. In Latin America (Argentina, Brazil, Chile, Colombia, Mexico, and Venezuela), an incidence ranging from 32.6 to 80.4/10,000 person-years is reported in a population over 50 years of age[2].

CAP-related mortality remains a major concern, especially for the elderly and in patients admitted to the intensive care unit (ICU)[3]. Since the first identification in Wuhan, China, in December 2019, more than 20 million COVID-19 cases and 750,000 deaths had been reported worldwide as of August 2020. One class of agents that has received considerable attention is corticosteroids or also called glucocorticoids (GCS)[4].

Randomized clinical trials over several decades have compared the safety and efficacy of different corticosteroids (hydrocortisone, methylprednisolone, and dexamethasone) in the treatment of patients with CAP and have shown a trend of better results with corticosteroid administration. Despite the encouraging results, the use of these drugs remains controversial as current guidelines present different recommendations[5].

Overall, discrepancies regarding the benefit of corticosteroids on mortality in patients with CAP are perhaps

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due to the heterogeneity found within the populations studied. Corticosteroids may only work in select groups of patients, such as those with a high systemic inflammatory response[6].

Therefore, it is important to continue investigating its effects through the analysis of randomized clinical trials, outside the spectrum of acute respiratory distress syndrome type 2 and septic shock, to evaluate its possible implications for outcomes such as mortality, days of hospital stay, need for use of mechanical ventilation, admission to the ICU, and prevention of the development of septic shock and ARDS.

Objective

The objective of this study was to assess the efficacy of GCS use compared to placebo in patients with CAP through a systematic review of clinical trials.

Methods

This systematic review was integrated by searching PubMed, Scopus and Web of Science for randomized trial published between 2019 and 2024, up to October 6, 2024, with the adapatation of the descriptors (DeCS/MeSH) (Corticosteroids OR steroids OR GCS OR Prednisone OR methylprednisolone) AND (Pneumonia OR respiratory infection OR CAP OR lung infection) AND (Mortality OR survival OR clinical outcomes) AND (Placebo OR control) AND (severe OR critical) AND (adults OR ≥18 years) AND (randomized controlled trials OR RCT). Mediante el seguimiento de las directrices del modelo PRISMA 2020[7].

Inclusion criteria

Clinical trials were selected that met the following characteristics: (1) patients over 18 years of age diagnosed with moderate-to-severe CAP, (2) presence of use of 1 or more GCS (including hydrocortisone, prednisone, dexamethasone, and methylprednisolone) compared to placebo or another steroid, (3) studies published in English, and (4) studies reporting clinical outcomes (mortality, days of mechanical ventilation use, days of hospital stay, need for vasopressor use, development of shock, and ARDS).

Exclusion criteria

Articles were excluded where it will be observed: (1) duplicate populations, (2) studies that do not report numbers or that do not allow data extraction, (3) patients with mild pneumonia, (4) patients with underlying lung disease (COPD, asthma, cystic fibrosis, tuberculosis, etc.), (5) hospitalizations before 90 days, (6) patients with septic shock, (7) known malignancy, and (8) presence of respiratory distress syndrome.

Research question

The PICO system used was patients with moderate-to-severe CAP, with the intervention of GCS use compared to placebo and its results in mortality. The research question was; What is the effect of GCS use compared to placebo on mortality and complications?

Data extraction

A standardized form was designed for the extraction of relevant data from the selected studies. Data extracted included participant characteristics, interventions, clinical outcomes, and mortality outcomes. Data extraction was performed by two independent review authors, and any discrepancies were resolved by consensus.

Risks of bias

We assessed the quality of the included studies using the Cochrane tool for assessing risk of bias in randomized clinical trials. Aspects such as randomization, concealment of assignment, blinding, data integrity, and declaration of conflicts of interest were considered.

Results

From the search in PubMed, Scopus, and Web of science, with the search matrix presented in the methodology, 573 articles were collected, of which 242 articles were preliminarily subtracted by automation methods by date and type of article, which later through the reading of the title and abstract ten randomized clinical trials were selected for 100% reading. Of these, once read, seven articles were selected from the initial 10, 3 being excluded due to the presence of duplicates and the initial presence of the population with ARDS (Fig. 1).

This review included seven randomized clinical trials totaling 2847 patients with CAP, in which the presence of clinical outcomes such as mortality, days of hospital

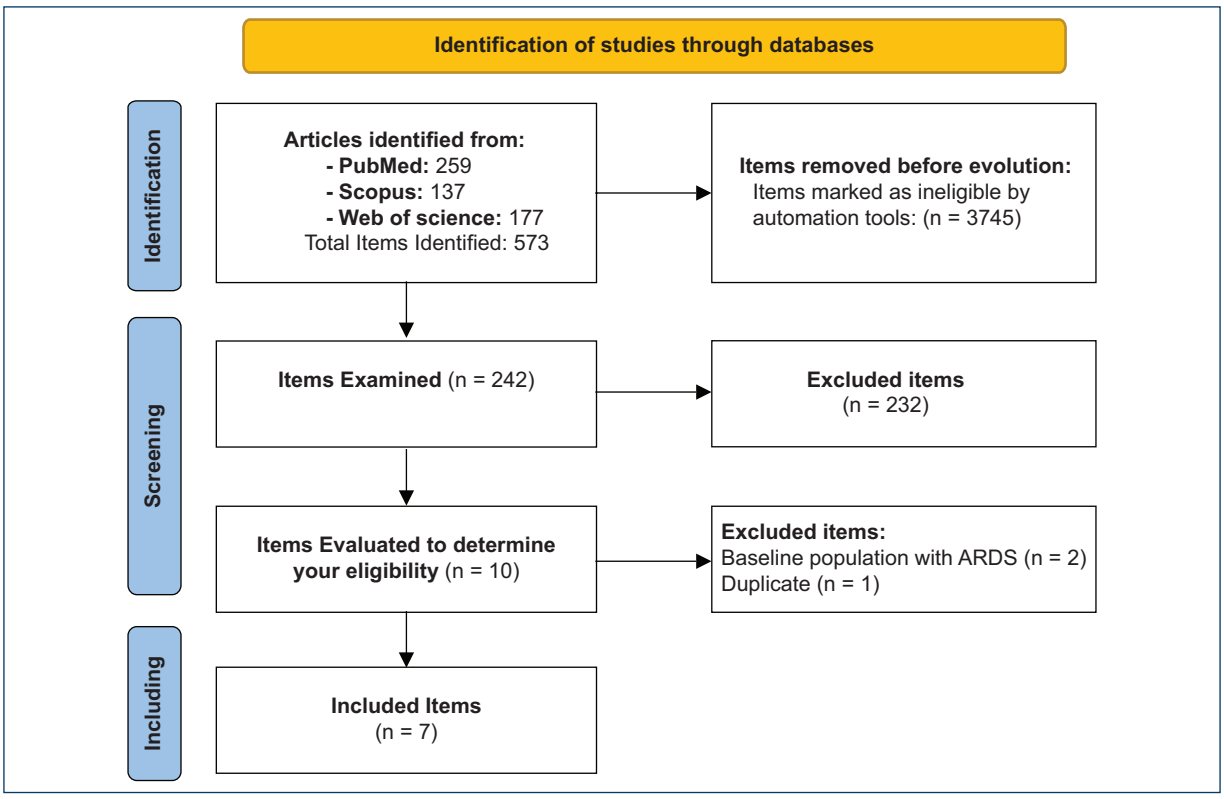

Figure 1. PRISMA diagram. In which the initial identification is shown by the search matrix, then the elimination by automation methods, year, and type of article. In the screening, articles were selected and eliminated by reading titles and abstracts of these selected 3 were excluded for not meeting the research criteria, where finally seven articles were selected to be included in this review.

stays, admission to the ICU, need for invasive or non-invasive mechanical ventilation, use of vasopressors, as well as development of ARDS and septic shock (Table 1).

Analysis of the data revealed that the use of hydrocortisone showed a significant benefit in reducing mortality at 28 days compared to placebo. In one specific study, mortality was observed to be 6.2% in the hydrocortisone-treated group (200 mg IV every 24 h for 7 days) versus 11.9% in the placebo group, with an absolute difference of −5.6% (95% CI −9.6-−1.7; p = 0.006). In turn, of the 442 patients who did not require mechanical ventilation at the beginning, 18% of the hydrocortisone group were intubated, while 29.5% of the control group were intubated with an OR of 0.59; 95% CI (0.40-0.86) and of the 703 patients who did not receive vasopressors, the cumulative incidence of initial vasopressor was 15.3% in the hydrocortisone group while 25% in the placebo group with OR 0.59 with 95% CI (0.43-0.82)[8].

In terms of days of hospital stay, the results were mixed. Some studies suggested a trend towards a reduction in length of stay in the GCS group. In the Wittermans et al., the dexamethasone group had a mean hospital stay of (4.5 days, 95% CI 4.0-5.0 days) while in the placebo group, it was (5.0 [95% CI 4.6-5.[4] days). The OR at discharge was (1.14 [95% CI: 0.93-1.39]) for all patients, in turn the study Tang et al. The use of methylprednisolone in-hospital stay was 17 days in participants in the methylprednisolone group and 13 days in the control group OR 1.3 95% CI (0.844-2.022) p = 0.235. No significant differences were found in both study groups[9,10].

The incidence of ARDS and the need for vasopressors due to septic shock was also evaluated. Methylprednisolone in the Meduri et al. did not show a significant reduction in the incidence of these adverse events in the GCS group compared to placebo, the need for vasopressor uses, and development of shock in the methylprednisolone group was present in 5% (n = 13) while in the placebo group, 4% (n = 3) with

Table 1. Studies included in the review

Title, author, and level of evidence	Population	Intervention	Results
Title: Adjunctive treatment with oral dexamethasone in non-uci patient hospitalised with community acquired pneumonia: randomised clinical trial Author: Wiittermans Esther Level of evidence: 2b	Total population 401 patients were randomized; dexamethasone group (n = 203) and placebo (n = 198)	Receive 6 mg of dexamethasone or placebo once daily for 4 days	Primary outcome: hospital stay was shorter in the dexamethasone group (4.5 days, 95% CI 4.0-5.0 days) than in the placebo group (5.0 (95% CI 4.6-5.4 days). The OR at discharge was (1.14 [95% CI 0.93-1.39]) for all patients, while 1.19 (95% CI 0.92-1.54) was 1.19 (95% CI 0.92-1.54) in the mild pneumonia group and 1.06 (95% CI 0.76-1.48) in the severe pneumonia group Secondary result: ICU admission had a lower ratio in the dexamethasone group (n = 5) compared to placebo (n = 14), with an OR 0.64 95% CI (0.22-1.87) p = 0.41. Respiratory failure is the most common cause of admission to the ICU There were no differences in mortality at 30 days between the two groups (dexamethasone group [n = 3], while in the placebo group [n = 5] with an OR of 0.62, 95% CI (0.15-2.29), p = 0.49
Title: Early use of corticosteroid may prolong SARS-CoV-2 shedding in non-intensive care unit patients with COVID-19 pneumonia: a multicenter, single-blind, randomized control trial Author: Xiao Tang Level of evidence: 2b	Total population of 86 patients were randomized; methylprednisolone group (n = 43) and placebo (n = 43)	The methylprednisolone group received 1 mg/kg body weight per day diluted in 100 mL of 0.9% saline administered once daily for 7 days, while in the control group only 100 mL of 0.9% saline solution was administered	Primary outcome: clinical deterioration within 14 days after randomization was 4 participants in the methylprednisolone group, while 2 in the control group with OR 1 95% CI (0.134-7.442), p = 1 Secondary outcomes: admission to the ICU was 2 participants in the methylprednisolone group and 2 in the control group with OR 1 95% CI (0.134-7.442) p = 1 Mortality was 0 participants in the methylprednisolone group and 1 in the control group OR 0.977 95% CI (0.93-1.02) p = 0.314 In-hospital length of stay was 17 participants in the methylprednisolone group and 13 in the control group OR 1.3 IC 95% (0.844-2.022) p = 0.235
Title: Effect of EARLY administration of dexamethasone in patients with COVID-19 pneumonia without acute hypoxemic respiratory failure and risk of development of acute respiratory distress syndrome: (EARLY-DEX COVID-19 trial) Author: Franco-Moreno Anabel Level of evidence: 2b	Total population of 126 patients; dexamethasone group (n = 58) and control group (n = 68)	Receive dexamethasone 6 mg intravenously 1 time daily for 7 days, while the group controlled only the standard management established by COVID-19 management guidelines	Primary outcome: patients in the control group developed ARDS in 14.7% while 17.2% in the dexamethasone group developed SRDA, with no significant differences, p = 0.8 Secondary outcomes: use of non-invasive or invasive mechanical ventilation occurred in 2.9% (n = 2) of the control group, while in 9.6% (n = 4) of the intervention group, with no significant differences, p = 0.71 Admission to the ICU occurred in 0% of patients in the control group and in 1.6% (n = 1) of patients in the experimental group, with no significant differences, p = 0.45 Days of hospital stay were 6.6 days in the control group, while in the experimental group 6.4 days with no significant differences, p = 0.89

(Continues)

Table 1. Studies included in the review *(continued)*

Title, author, and level of evidence	Population	Intervention	Results
Title: Adjunct prednisone in community-acquired pneumonia: 180-day outcome of multicenter, double-blind, randomized. Placebo-controlled trial (STEP trial) Author: Blum Claudine A. Level of evidence: 2b	Total population of 727 patients; prednisone group (n = 361) and Control group (n = 366)	To receive 50 mg of prednisone every 24 h for 7 days versus placebo to assess mortality at 180 days	Primary outcome: no significant differences were found in all-cause mortality at 180 days with OR 1.15 (95 CI [0.68-1.95]) p = 0.601 Secondary outcomes: the presence of pneumonia recurrence in the prednisone group with significant differences OR 2.57 (95% CI [1.29-5.12]) p = 0.007
Title: Effect of intravenous pulses of methylprednisolone 250 mg versus dexamethason 6 mg in hospital adults with severe COVID-19 pneumonia: an open-label randomized trial Author: Corral-Gudino Luis Level of evidence: 2b	Total population of 128 patients; dexamethasone group (n = 64) and methylprednisolone group (n = 64)	Receive dexamethasone 6 mg intravenously 1 time a day for 10 days or methylprednisolone 250 mg 1 time a day for 3 days	Primary outcome: mortality at 28 days occurred in 5% (n = 3) of the methylprednisolone group, as well as in the dexamethasone group with an OR of 1 95% CI (0.2-5.1) p = 0.984 Secondary outcomes: admission to the ICU occurred in 16% (n = 10) of the methylprednisolone group, while the dexamethasone group occurred in 15% (n = 9) with an OR of 1.1 95% CI (0.4-3.0) p = 0.833 Use of non-invasive mechanical ventilation was present in 5% (n = 3), while in the dexamethasone group it was present in 3% (n = 2) with an OR of 1.5 95% (0.2-9.3) p = 0.661 The need for orotracheal intubation occurred in 13% (n = 8) of the methylprednisolone group, while in 12% (n = 7) of the dexamethasone group with an OR of 1.1 95% CI (0.4-3.0) p = 0.809
Title: Hydrocortisone in severe community-acquired pneumonia Author: Dequin PF Level of evidence: 2b	Total population of 795 patients, the hydrocortisone group was made up of 400 patients while the control group was made up of 395	Receive hydrocortisone 200 mg 1 time daily for 4-7 days, followed by tapering for a total of 8-14 days or receive placebo	Primary outcome: mortality at 28 days occurred in 25 of 400 patients (6.2% with 95% CI 3.9-8.6) in the hydrocortisone group and in 47 of 395 patients (11.9%; 95% CI 8.7-15.1) in the placebo group with an absolute difference of–5.6%, CI–9.6-–1.7; p = 0.006 Secondary result: mortality at 90 days occurred in 9.3% of patients in the hydrocortisone group, while in the control group it occurred in 14.7% with an absolute percentage difference of–5.4 with 95% CI–9.9-–0.8 Of the 442 patients who did not require mechanical ventilation at the beginning, 18% of the hydrocortisone group were intubated, while 29.5% of the control group had an OR of 0.59; 95% CI (0.40-0.86) Of the 703 patients who did not receive vasopressors, the cumulative incidence of initial vasopressor was 15.3% in the hydrocortisone group while 25% in the placebo group with OR 0.59 with 95% CI (0.43-0.82)

(Continues)

Table 1. Studies included in the review *(continued)*

Title, author, and level of evidence	Population	Intervention	Results
Title: Low-dose methylprednisolone treatment in critically ill patients with severe community-acquired pneumonia Author: Meduri G. Umberto Level of evidence: 2b	Total population of 584 patients, the methylprednisolone group was made up of 297 patients while the control group was made up of 287	Receive an intravenous loading bolus of 40 mg methylprednisolone followed by 40 mg every 24 h for 7 days and a progressive reduction over the 20-day course of treatment	Primary outcome: mortality at 60 days from any cause occurred in 16% (n = 47) of the methylprednisolone group, while in 18% (n = 50) of the placebo group, with no significant differences with OR 0.89 95% CI (0.58-1.38) p = 0.61 Secondary result: the need for vasopressor and the development of shock in the methylprednisolone group was present in 5% (n = 13), while in the placebo group 4% (n = 3) with no significant differences, with OR 1.08, 95% CI (0.48-2.4), p = 1.00 Development of SRDA in the methylprednisolone group occurred in 4% (n = 10), while in the placebo group 3% (n = 8) with no significant differences, with OR 1.14, 95% CI (0.44-2.94), p = 1.00

no significant differences with OR 1.08 95% CI (0.48-2.4) p = 1.00. While the development of SRDA in the methylprednisolone group was present in 4% (n = 10), while in the placebo group, 3% (n = 8) with no significant differences, with OR 1.14, 95% CI (0.44-2.94), p = 1.00[11]. Dexamethasone, on the other hand, in the Moreno et al. study, the control group developed ARDS in 14.7%, while 17.2% of the dexamethasone group developed SRDA, with no significant differences, p = 0.8[12].

A heterogeneity analysis was performed between the included studies. The I² statistic was used to assess the variability between the results of the different trials. Heterogeneity was moderate, suggesting that although the studies presented consistent results overall, there were differences in the population studied and in treatment protocols that could influence the results.

Despite the positive findings associated with the use of hydrocortisone, several limitations should be considered. The methodological quality of the included studies was generally high, but variability in study designs and patient characteristics may have influenced the results. In addition, the lack of data on long-term effects and variability in GCS dosing between studies limit the generalizability of the findings.

Discussion

The findings suggest a possible benefit of hydrocortisone use in patients with severe CAP. Importantly, the heterogeneity of the inflammatory response in different subgroups of patients with CAP may influence the response to GCS treatment, underscoring the need to identify biomarkers that can predict individual response.

Nie et al.[13] conducted a meta-analysis that included RCTs that used corticosteroids as adjuvant treatment in populations with CAP from 1956 to 2011. Demonstrating that the use of corticosteroids was associated with better survival in patients with severe CAP, supported by Confalonieri et al.[14] who conducted a meta-analysis which included trials with severe and non-severe CAP, observing a decrease in mortality in favor of steroids in patients with severe CAP.

Emerging evidence of GCS use in COVID-19 patients, such as the RECOVERY trial, has demonstrated efficacy in reducing mortality and the need for mechanical ventilation. These results are consistent with our finding that hydrocortisone can significantly improve clinical outcomes in patients with CAP. The mechanisms underlying these beneficial effects could be related to the inhibition of the production of proinflammatory cytokines and the stabilization of lysosomal membranes[15].

Several randomized controlled clinical trials have investigated the benefits of adjuvant corticosteroids on mortality in patients with severe CAP, but the results have been inconclusive. For example, trials, such as Extended Stereoid in Use in CAP and Santeon-CAP (Dexamethasone in CAP), describe that the use of methylprednisolone and dexamethasone did not improve mortality in severe CAP. However, the CAPE COD (CAP: Evaluation of corticosteroid) trial showed

that hydrocortisone reduces mortality in patients with CAP admitted to the ICU[16].

In patients with ARDS, a survival benefit may be associated with early corticosteroid use. Nevertheless, these patients constitute a heterogeneous group of underlying diagnoses with significant disease severity, and no direct extrapolation can be made to patients with CAP[17].

Pitre et al. conducted a systematic review and meta-analysis of the use of corticosteroids in bacterial CAP, with an identification of 18 RCTs evidencing a decrease in mortality in patients with severe CAP (RR 0.62 [95% CI: 0.45-0.85]), while these may have no effect on less severe CAP (RR 1.08 [95% CI: 0.83-1.42])[18]. It is necessary to evaluate whether corticosteroids have a lasting effect beyond 30 days as did the STEP trial study where 727 patients with CAP were evaluated, where randomizing patients to receive 50 mg of prednisone every 24 h for 7 days against placebo to assess mortality at 180 days, no significant differences were found with OR 1.15 (95 CI [0.68-1.95]) p = 0.601. When evaluating the secondary outcomes, the presence of pneumonia recurrence in the prednisone group was highlighted, with significant differences OR 2.57 (95% CI [1.29-5.12])[19].

Emphasis should be placed on the limitations found in the different studies included in this systematic review, such as the fact that the studies included populations with very diverse clinical characteristics, such as disease severity, comorbidities, and age. Some studies had relatively small sample sizes, which may limit statistical power and increase the risk of type II errors. As well as the inclusion of different methodological designs, which can influence, the results obtained.

Different types of GCS (dexamethasone, prednisone, and methylprednisolone) and doses were used, making it difficult to identify an optimal regimen. The variety of GCS used, the severity of the patients, and the outcomes evaluated make direct comparison between studies difficult. This heterogeneity limits the ability to generalize findings and makes it difficult to identify an optimal treatment protocol for all patients with CAP.

Despite these limitations, studies suggest potential benefits of GCS use in certain subgroups of patients with CAP. These findings suggest that the benefits of GCS may be more pronounced in patients with more severe disease.

The comparison with studies on COVID-19 is interesting, but the differences between the two diseases must be taken into account. While GCS have been shown to be beneficial in some patients with COVID-19, the mechanisms of action and response to treatment may differ in CAP. Importantly, NAC is caused by a wide variety of pathogens, while COVID-19 is caused by a specific virus.

The methodological quality of the studies included in our review is variable, which limits the generalizability of the results. Clinical heterogeneity of patients, in terms of disease severity, comorbidities, and causal pathogens, may also influence the interpretation of results. Despite these limitations, the findings of our review suggest that GCS may have a role in the management of severe CAP, especially in those patients with an exacerbated inflammatory response.

Conclusion

The use of hydrocortisone in patients with severe CAP showed a significant benefit in reducing mortality at 28 days and in the need for more invasive interventions such as mechanical ventilation and vasopressor use, which could indicate its usefulness in this specific group. In contrast, the other studies on the use of dexamethasone and methylprednisolone showed no significant differences in terms of mortality or clinical course, especially in the context of COVID-19 pneumonia, suggesting that their effectiveness could depend on patient-specific factors and the type of pneumonia.

The current evidence on the use of GCS in CAP is heterogeneous and does not allow definitive recommendations to be made for all patients. While some studies suggest benefits in patients with severe CAP, further studies are needed to identify the specific groups of patients in which they benefit from GCS use and to explore the possibility of a “therapeutic window” in which early initiation of treatment can maximize benefits and minimize risks to confirm these findings and determine the exact role of GCS in treatment of this disease. Clinicians should individualize the treatment of each patient, considering the severity of the disease, comorbidities, and potential adverse effects of GCS.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the Institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that artificial intelligence was used in this manuscript, specify Chat GPT y mybib.com for the writing of the Abstract and bibliographies.

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CLINICAL CASES

Sarcoidosis: unusual presentations in a rare entity

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Abstract

Sarcoidosis is a granulomatous inflammatory disease of unknown etiology that usually affects certain structures such as lungs, skin, eyes, liver, and lymph nodes. Three unusual clinical cases are illustrated and discussed in this paper: Hereford syndrome characterized by fever, anterior uveitis, and salivary gland hypertrophy in its incomplete form; the association of sarcoidosis with thymoma and myasthenia gravis as an expression of an autoimmune complex; and finally, pulmonary hypertension as an epiphenomenon to sarcoidosis, which showed a partial response to immunosuppressants. The reporting of the rare manifestations of this disease is meant to serve as a reminder that symptoms from various systems can come together to form a single diagnostic algorithm, and it also demonstrates the wide range of presentations that can be observed in clinical practice.

Keywords: *Sarcoidosis. Heerfordt's syndrome. Thymoma. Pulmonary hypertension.*

Introduction

Sarcoidosis is a systemic inflammatory disease whose pathological substrate is the formation of granulomas in several organs. It generally affects adults between 25 and 40 years of age and shows a higher incidence among Scandinavians and African-Americans. Their natural history is variable, and they may represent asymptomatic or self-limiting entities or manifest as chronic or rapidly progressive diseases[1].

Epidemiology, pathophysiology, diagnosis, and treatment

The annual incidence of sarcoidosis varies according to the region studied, with the highest rates in northern European countries (11-15/100,000) and the lowest in East Asian countries (0.5-1/100,000). The true epidemiological burden of the disease is unknown as even within countries they can vary. Thus, in the United States, it can be noted that the incidence among African-Americans is much higher than among Caucasians. The etiology of the disease is unknown and it is postulated that the interaction of a certain genetic terrain with environmental factors (antigens such as vimentin, bacterial or fungal particles, and even fragments of mycobacteria) could be the causal factors in the context of certain risk factors such as family history, smoking, occupational exposure, and obesity[2].

Although it can involve any organ, the lungs and lymph nodes are preferential sites (> 90%), followed by the skin (14-32%), eyes (8-20%), liver (11-18%), spleen (7-20%), joints (8-9%), heart (2-11%), and nervous system (2-7%). Regardless of the presence or absence of respiratory symptoms, nearly half of patients with sarcoidosis have extrapulmonary findings and diagnosis is usually made by biopsy of accessible affected tissues where sarcoid granulomas are described. A fundamental clinical gesture is the exclusion of other

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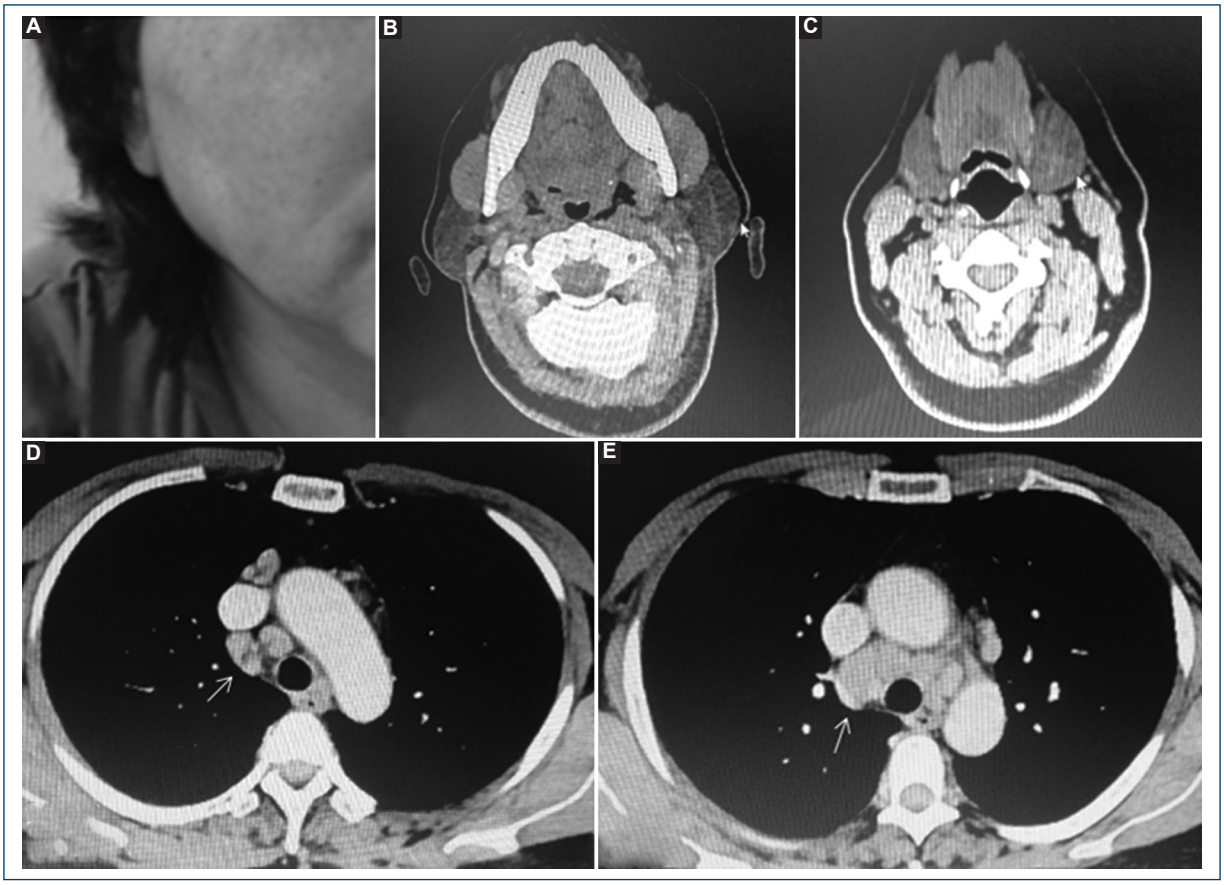

Figure 1. A: swelling of the right parotid region. **B:** computed tomography (CT) scan of the neck showing hypertrophy of both parotid glands. **C:** CT of the neck indicating hypertrophy of the submaxillary glands. **D:** CT of the chest (mediastinal window) in which right paratracheal nodes are indicated. **E:** CT of the chest showing retrocavoaortic and subaortic peritracheal mediastinal nodes.

granulomatous diseases, which is a high priority in regions where tuberculosis and some mycoses are endemic. The first line of treatment is usually corticosteroids, although in cases of therapeutic failure or involvement of certain organs, they are associated with immunosuppressants and/or biological agents[3].

Considering the less frequent manifestations of sarcoidosis is relevant, as they have a significant burden of relative morbidity and mortality. In this report, we present three clinical cases of sarcoidosis of unusual presentation seen in a referral hospital in our country and that have little reference in the Hispanic medical literature.

Presentation of cases

Case 1

A 53-year-old female healthcare provider, non-smoker with no comorbidities, presented with a 3-week history of conjunctival irritation with a feeling of dry eyes and dark spots in bilateral vision accompanied by bilateral and progressive swelling of the parotid and submaxillary regions. A week earlier, she reported intermittent palpitations and shortness of breath accompanied by feverish sensations. Vital signs: heart rate 88 × min, respiratory rate 20 × min, axillary temperature 37.5°C, oxygen saturation 94% at room air. Physical examination revealed moderate swelling of parotid and submaxillary regions (Fig. 1A-C), with no palpable peripheral lymphadenopathy and no signs of paresis or facial paralysis. Normal blood count, erythrocyte sedimentation 1 h: 24 mm, C-reactive protein 10 mg%, anti-nuclear antibody + (1/80), negative rheumatoid factor, human immunodeficiency virus (–), immunoglobulin M antibodies to Epstein–Barr virus, toxoplasmosis, rubella and cytomegalovirus (–), β-2 microglobulin 2.14 mg% (normal < 3 mg/dL), PPD 0 mm. In view of the findings of chest computed tomography (CT) scan

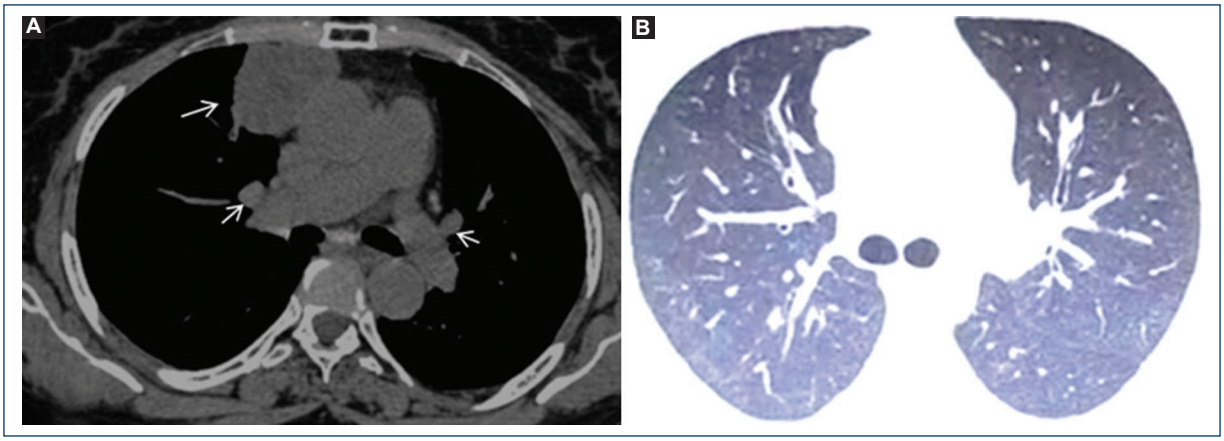

Figure 2. A: CT scan (mediastinal window) denoting mass in the anterior mediastinum (long arrow) and some adenomegaly (short arrows). **B:** high-resolution CT scan of the chest (pulmonary window) showing confluent subpleural nodular opacities in the right posterior region and slightly more scattered in the left lung.

(Fig. 1D and E), mediastinoscopy and lymph node biopsy are suggested. The pathological report mentions a chronic granulomatous inflammatory process with negative stains for acid–fast bacillus and fungal elements, compatible with sarcoidosis. The diagnosis is incomplete Heerfordt syndrome, with a good evolution after oral treatment and decreasing with prednisone (50 mg) for 12 months. After 4 years of follow-up, no recurrence was reported.

Case 2

A 34-year-old male was a non-smoker with a history of hospitalization in the intensive care unit due to severe COVID-19 6 months before the consultation and whose routine check-ups detected an anterior mediastinal mass and mediastinal and supraclavicular polyadenopathy (Fig. 2). Weeks after the second dose of ChAdOx1, he presented regurgitation of fluids through the nose, with fatigue of the oral and facial muscles plus swallowing disorders without weakness of limbs. Electroneuromyography confirms a pattern of post-synaptic neuromuscular plaque and mild positive repetitive stimulation (discrete polyneuropathy to axonal motor predominance). Elevated levels (5.85 nmoL/L) of anti-acetylcholine receptor antibody by radioimmunoassay (normal value < 0.05 nmoL/L) were noted. Biopsy of two right supraclavicular nodes showed extensive granulomatous lymphadenitis with no evidence of microorganisms or proliferative process, suggestive of sarcoidosis. Subsequent excision of the mediastinal mass allows its pathological classification as thymoma, subtype 2. Neurological symptoms improve and lymph nodes decrease considerably in size after multidisciplinary management (cisplatin-based chemotherapy, radiotherapy, and prednisone 50 mg). The proposed single diagnosis was thymoma, sarcoidosis, and myasthenia gravis. At 3-year follow-up, he showed a good clinical evolution.

Case 3

A 59-year-old woman was a long-term hypertensive, non-smoker, who consulted for slowly progressive dyspnea of 10 years of evolution that is made with slight exertion in the past 3 months, drumstick fingers, basal bilateral crackles. Known diagnosis of sarcoidosis by transbronchial biopsy, 2 years before consultation and history of treatment with prednisone for a short time. Heart rate 98 × min, respiratory rate 28 × min, blood pressure 100/70 mmHg, O_2 saturation: 92% (FiO_2: 21%). Chest X-ray: basal bilateral reticulonodular opacities. Chest CT: bilateral panalization (Fig. 3), spirometry shows forced vital capacity of 70% of the predicted (Hankinson), paO_2: 62.5 mmHg, echocardiography that reports significant elevation of estimated pulmonary artery systolic pressure (PSAP) (61 mmHg and 81 mmHg), mild left ventricular hypertrophy and left ventricular ejection fraction: 74%, ergometry: negative for ischemia, Doppler ultrasound of the lower limbs without signs of deep vein thrombosis, D-dimer within normal values. The proposed diagnosis was stage IV sarcoidosis (Scadding) and pulmonary hypertension (PH). Azathioprine (50 mg/d) and prednisone (20 mg/d)

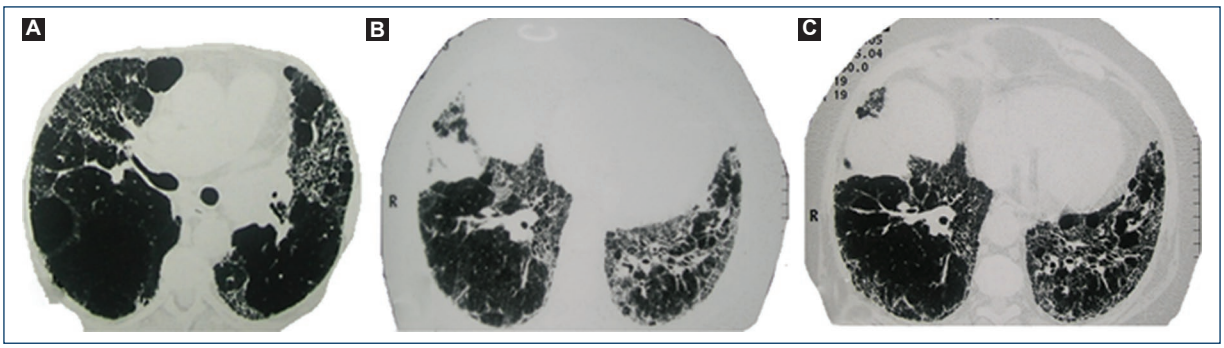

Figure 3. A: CT scan of the thorax where the considerable caliber of the right branch of the pulmonary artery in relation to the aorta can be observed. **B:** CT scan of fine sections of the chest that in lower regions shows areas of parenchymal distortion, areas of normal structure, and patched areas of ground glass. There are traction bronchiectasis and areas of peripheral panalization, insinuating, however, a peribronchial predominance of opacities. **C:** chest CT performed 9 months after immunosuppressive treatment, in which an apparent improvement of the ground glass pattern is observed, but an aspect that should be interpreted with caution since the techniques used for CT are clearly different.

were initiated at the request of the patient and as compassionate therapy. Six months later, he reported a marked improvement in dyspnea without objective changes in the control tomography. Follow-up echocardiography reports PSAP: 25 mmHg, EF: 70%. The patient remains stable for three more months and then decides to abandon treatment, seeing in weeks a new progressive worsening until dyspnea at rest.

Discussion

The wide range of clinical-pathological presentations of sarcoidosis has justified the nickname of "great imitator." Less frequent forms (1-5%) include involvement of the salivary glands, bones, bone marrow, gastrointestinal tract, and upper airways[4]. In relation to the cases presented here, there are only 111 reports of sarcoidosis associated with PH, 74 cases of Heerdfort syndrome, and only 1 case report of thymoma and myasthenia gravis associated with sarcoidosis in two reference databases (PUBMED and Lilacs).

The analysis of five cases of uveoparotid fever (Heerfordt, 1909) associated with neurological symptoms resulted in the proposal of a different manifestation of sarcoidosis by Jan Waldestrom in his original article of 1937[5]. Heerfordt–Waldestrom syndrome is considered complete when it shows all four main symptoms (fever, anterior uveitis, parotid and/or salivary gland hypertrophy, and facial paralysis) or incomplete when it shows two of the following: anterior uveitis, parotid hypertrophy, and facial paralysis[6,7]. The first case, illustrated in this essay, presented the incomplete form of this entity, but as a manifestation of a systemic involvement, proven by the results of mediastinoscopy. The presence of facial paralysis in this syndrome has an incidence of approximately 25-50% and the complete form constitutes only 0.3% of all cases of sarcoidosis[8,9]. Ocular manifestations represent the most common symptom of the syndrome. In a capital series of 83 patients, Darlington et al. found that 84.5% of ocular sarcoidosis cases develop lymphadenopathic hypertrophy and pulmonary infiltrates at a 2-year follow-up. A useful clinical fact is that in 40% extrapulmonary manifestations (skin lesions, cranial nerve palsy, or hypercalcemia) can be seen. It is interesting to note that although pulmonary involvement is not described as part of the syndrome, it can occur in up to 81% of cases. The diagnosis is clinical and is supported by histopathological findings (biopsy of lymph nodes, salivary glands, skin, or lungs)[10]. Heerfordt syndrome responds quite well to corticosteroid therapy and, as seen in the evolution of the case reported here, which was very favorable at 4 years of follow-up.

The second clinical case of this work illustrates the finding of a mediastinal mass in the context of a polyadenopathic syndrome that develops myasthenia gravis with bulbar involvement. Thymoma accounts for 90% of thymic neoplasms and is one of the most common tumors in the anterior mediastinum; however, metastases in regional nodes are not common. A systematic review has described lymphatic involvement in 3.3%, compared with 18.6% in thymic carcinoma and 28% in neuroendocrine thymic tumors[11]. The histopathological report of sarcoidosis in lymph node biopsy as a

comorbidity is an exceptional finding and, surprisingly, a case of regression of skin and lung lesions associated with sarcoidosis after thymectomy is reported[12,13]. It is appropriate, however, to point out many conditions that can be mimicked as sarcoidosis-like granulomatous reactions (infections, neoplasms, vasculitis, and inflammatory responses to environmental and occupational exposure). Some idiopathic inflammatory responses such as (granulomatous lesions of unknown significance syndrome), granulomatous interstitial lung disease related to common variable immunodeficiency, and necrotizing sarcoid granulomatosis are also cited as differentials. Taking into account this battery of differentials, it is understandable what Judson writes as the introduction to his publication: "*the diagnosis of sarcoidosis is arbitrary, not standardized and is never completely certain*"[14].

The neuromuscular involvement of the patient presented here stands out. Myasthenia gravis is the most prevalent paraneoplastic syndrome in the context of autoimmune dysregulation that induces thymoma as certified in a systematic review by Blum et al., who found a relative frequency of 63% in 507 patients operated on for the tumor. Dozens of other autoimmune entities with varied organ and system involvement are also cited[15]. Although it may be a simple coincidence or a real association, the medical literature suggests a bidirectional relationship between sarcoidosis and myasthenia gravis[16,17]. Sawada et al. describe a case of rheumatoid arthritis and sarcoidosis that develops neuromuscular symptoms, reflecting in the discussion 19 cases of sequential sarcoidosis to myasthenia gravis, 6 of them associated with thymic hyperplasia (4 cases) or thymoma (2 cases)[18]. The effects of rain depend on its intensity and also on the soil it wets. Why think of a sequential appearance of isolated diseases and not interpret them as an expression of the same substrate? Like Spinoza's God. In the case described here, the hypothesis of the cluster of entities resulting from an autoimmune flow is very seductive in noting that the neurological symptoms continue shortly after immunization without necessarily having a causal relationship, a phenomenon that meets the criteria of autoimmune syndrome after COVID-19 vaccine or generically: autoimmune/inflammatory syndrome by adjuvant[19]. Total resolution of symptoms after thymectomy and multimodal treatment also supports the theory. An updated review of the immunological mechanisms underlying sarcoidosis was recently published[20].

The third case described in this study deals with the association of sarcoidosis and PH. The overall prevalence of sarcoidosis in patients with sarcoidosis is 2.9-20% and entails significant morbidity and mortality, and it should be considered that multiple factors can contribute to its development: pulmonary parenchymal involvement, left ventricular dysfunction, veno-occlusive disease, thromboembolic phenomena, extrinsic vascular compression, granulomatous vascular inflammation, and sleep apnea, among others[21]. The gold standard for diagnosis is right cardiac catheterization which establishes PH when the PSAP > 20 mmHg[22], but screening should be initiated with transthoracic echocardiography when one of the following variables is found: persistent dyspnea despite treatment, when there are clinical signs of right ventricular failure, significant functional compromise (< 300 m walked or drop in saturation > 5% in the 6-min walk test), high levels of BNP, if > 20% pulmonary fibrosis is found on CT scan, increased ratio between pulmonary artery diameter and aorta or other signs of PH, decrease of > 15% in DLCO[23]. Hemodynamic study rooms are scarce in public health services in Paraguay, so sometimes a complete approach is not given, as in the case presented here.

The clinical response of the patient during the course of treatment with immunosuppressants was striking. There is currently no specific treatment for PH in sarcoidosis, although it is suggested that a multidisciplinary team evaluates on a case-by-case basis. Cases of hemodynamic response to treatment with corticosteroids or immunosuppressants are reported, although lines of research are preferentially aimed at vasodilators, which positively changed the history and prognosis of other forms of PH[24,25]. When the disease is very advanced, the option would be lung transplantation. This procedure has never been performed in Paraguay and there are currently no immediate plans.

Conclusion

This paper describes three clinical cases of infrequent forms of presentation of sarcoidosis (Heerdfordt syndrome, association with PH, and association with thymoma), seen in a public health hospital in Paraguay, together with a brief analysis of the relevant literature.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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CLINICAL CASE

Fungal multivalvular endocarditis: literature review and case report

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Abstract

The incidence of fungal endocarditis (FEs) has decreased in most developed countries with access to harm-reduction policies and with improved infection control procedures during cardiac surgery. Use of specific blood culture bottles for diagnosis of FEs has decreased due to the optimization of media and automated culture systems. New antifungal agents available since the early 2000s may represent a dramatic improvement for FEs. The optimum antifungal therapy still remains debatable. Treating Candida endocarditis can be difficult because the Candida species can form biofilms on native and prosthetic heart valves. Combined treatment appears superior to monotherapy. Combination of antifungal therapy and surgical debridement might bring about better prognosis. In this clinical case report, we aim to make a literature review and present a challenging and rare clinical case.

Keywords: *Endocarditis. Multivalvular endocarditis. Fungal cardiac infections.*

Introduction

Fungal endocarditis (FEs) accounts for 1-3% of all infective endocarditis (IEs) cases, is associated with high morbidity and mortality (>70%), and presents numerous challenges during clinical care. *Candida* spp are the most common causes of FEs, implicated in over 50% of cases, followed by *Aspergillus* and *Histoplasma* spp. Important risk factors for FEs include prosthetic valves, prior heart surgery, and injection drug use[1,2].

This complication is an extremely debilitating disease associated with high morbidity and mortality. It is most prevalent in patients who are immunosuppressed and intravenous drug users. Most patients present with constitutional symptoms, which are indistinguishable from bacterial endocarditis, hence a high index of suspicion is required for pursuing diagnosis[2].

FEs, a relatively rare disease, has a high rate of mortality and is associated with multiple morbidities. Late or mistaken diagnosis contributes to delayed and incorrect management of patients[3].

Despite the advancement in medicine, there is still a lack of understanding of the sex disparities in disease onset, progression, treatment, and outcome. In some life-threatening acute conditions, despite most patients with these illnesses being males, females have a significantly higher chance of mortality[4].

The diagnosis of IEs is based on microbiological analyses and diagnostic imaging of cardiac manifestations. Echocardiography (ECHO) is preferred for

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visualization of IE-induced cardiac manifestations. There is an association between bacterial infections and specific IE manifestations diagnosed by ECHO to be considered[5].

There are case reports of patients with COVID-19 pneumonia and its complications in which cases are very often receiving steroids such as methylprednisolone, subsequently developing disseminated *Aspergillus* endocarditis[6].

The present manuscript presents a literature review from the most actual articles about this topic, additionally, we report a rare case of multivalve FEs and highlight the challenges encountered in diagnosis, complications, and predictors of poor prognosis.

Etiology

Candida spp., in particular, *Candida albicans*, are the most common organisms of FEs. Non-albicans species associated include *Candida parapsilosis, Candida tropicalis*, and *Candida glabrata. Aspergillus* sp. including *Aspergillus flavus, Aspergillus fumigatus, and Aspergillus niger. Aspergillus* species are more prevalent in prosthetic valves endocarditis[7]. Other organisms associated with FEs are *Histoplasma* species, *Cryptococcus neoformans, Trichophyton* species, *Microsporum* species, *Fusarium* species, *Paecilomyces* species, and *Pseudallescheria boydii*[8]. Similar organisms are associated with FEs in children. *Candida* infection rates decrease, and *Aspergillus* infection rates increase with older age in children through the age of 19[7,8]. Risk factors for FEs include:

- History of open-heart surgery, prosthetic grafts
- Presence of central line
- Long-term antibiotic therapy IN drug use
- Pre-existing congenital heart disorder
- Immunosuppressed state, prolonged use of corticosteroids

In most cases, FEs affects prosthetic valves[9].

Epidemiology

FEs is associated with immunocompromised states, intravenous drug use, prolonged antibiotic use, and long-term parenteral nutrition, individuals with prosthetic heart valves or a history of reconstructive cardiac surgery, native valve FEs can occur in organ transplants recipients on immunosuppressive agents, patients with myelodysplastic syndrome, and on long-term glucocorticoids and cytotoxic drugs users[10].

Candida species are commensal organisms in the gastrointestinal tract, lower genital tract, and oral cavity. The risk of candidiasis increases dramatically if the host of immunocompromised due to various reasons[11].

Aspergillus spp. are ubiquitous organisms in the environment. Renovation of old buildings, including hospitals and contaminated air conditioning systems, may be the source of infection as airborne transmission is common for *Aspergillus* spp[2].

Pathophysiology

Source of fibrin/platelet bed, infection risk, impaired host defense mechanisms, and fungal adherence/virulence factors are necessary elements leading to FEs. The pathophysiology occurs in classic steps:

- First step of FEs is the inoculation and colonization of the bloodstream by the yeast or molds
- The second step is associated with the conversion of blastospores into a filamentous form, also known as phenotypic switching, which allows for the adherence to the endocardium and invasion. Different factors such as cell surface proteins in the fungal wall, the int1p protein in Candida species, and leucocyte-induced adhesion molecule allow for adherence to the heart valves
- The third steps occur when fungal adhesion is followed by proliferation and tissue destruction[9].

Clinical approach

It is very difficult to differentiate FEs from bacterial etiology. FE usually presents as subacute endocarditis. The most common presentation in all patients with FE is fever, which is usually prolonged (more than 2 weeks) and is often associated with chills, sweating, and fatigue. A new, previously unrecognized, or change in the quality of previously recognized murmur is a common finding. Other clinical signs of FE include peripheral embolization in the extremities, brain, lung, kidneys, and gastrointestinal tract. Septic pulmonary embolism usually presents with fever, dyspnea, pleuritic chest pain, cough, and hemoptysis. Embolism to the gastrointestinal tract can cause acute abdomen secondary to mesenteric ischemia. With valvular destruction, may develop heart failure, and can also present with clinical signs ranging from weight loss, clubbing, petechial rash, splenomegaly, hypotension, septic shock, and death. It is rare to see peripheral findings unique to particular fungal infections, such as cutaneous macronodules in candidiasis[12].

Diagnostic evaluation

The diagnosis of FEs is difficult due to the poor yield from blood cultures, which are positive in < 50% of the time. Laboratory techniques such as lysis centrifugation can improve the yield from blood cultures. The blood culture yield of yeast is better than the mold. The processing of blood cultures can be tedious and time-consuming. Mannan antigen is a cell wall constituent of *Candida* spp. For candidemia, mannan antigen and antibody have a sensitivity and specificity of 83% and 86%, respectively, a cell wall polysaccharide of a fungal wall, 1,3 β-d-glucan (BDG) has a sensitivity and specificity of 69.9% and 87.1%, respectively, the detection of galactomannan, along with 1,3 BDG, can help to diagnose infection by *Aspergillus* spp[12].

The histopathological examination must be done in culture-negative cases to determine the diagnosis from the examination of the explanted valve. The molecular methods, such as polymerase chain reaction (PCR) to detect fungal nuclear material like DNA in explanted valves, can expedite the diagnosis[13].

ECHO is an important tool in diagnostic evaluation. Characteristically, the lesions are large, left-sided (bilateral lesions are common in immunocompromised patients), and occasionally non-valvular. ECHO can also detect abscesses of the valve ring. Trans-esophageal ECHO is more sensitive and specific for the diagnosis of endocarditis than transthoracic ECHO. ECHO is preferred for visualization of cardiac manifestations. There is an association between bacterial infections and specific IE manifestations diagnosed by ECHO to be considered[5].

Blood work may reveal elevated white blood cells and C reactive protein. Thrombocytopenia is commonly seen in neonates and immunocompromised patients[9].

Treatment

An interprofessional approach is required for the management of FEs. Early valve replacement surgery of the infected valve (natural or prosthetic) should be recommended (class I indication) in almost all patients with FEs, and a long course of anti-fungal medication should be initiated. The initial antifungal treatment for *Candida* spp. Endocarditis should be lipid formulation of amphotericin B with or without flucytosine or a high-dose echinocandin (caspofungin or micafungin or anidulafungin). Once the patient has stabilized, and follow-up blood cultures are negative, step-down therapy with oral fluconazole (if susceptible) is recommended. If candida isolate is not susceptible to fluconazole, oral voriconazole or posaconazole can be considered. Infected pacemakers and cardiac defibrillators should be removed, and anti-fungal therapy should be initiated. For ventricular assist devices that cannot be removed, the antifungal regimen should be started, and chronic suppressive therapy with fluconazole (if susceptible) should be continued as long as the device is in place. The endocarditis caused by Histoplasma capsulatum is managed with the lipid formulation of amphotericin B, followed by oral itraconazole for at least 12 months. For *Aspergillus endocarditis*, voriconazole is used for both induction and long-term suppression. It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. American Society of Infectious Diseases (IDSA) considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances[14].

The principles of treatment consist of isolating the fungus and assessing sensitivity to the different antifungal therapies available; in current medical management, the therapy is often empirical, based on echinocandins or amphotericin. In the presence of severe valve resistance and compromise, surgery is essential; vegetectomy or valve replacement may be performed[2,14].

In general, a longer period of induction treatment with antifungals is 6-8 weeks for native valve and up to 1 year for prosthetic valve infection, followed by long-term suppressive treatment of 1-2 years of therapy, especially when surgery is not performed[1,14,15].

The duration of treatment should be guided by clinical responses and other factors such as unresected lesions, intra- or extra-cardiac retention, prosthetic material, and immunosuppression[1,2,16]. When the involvement is multivalve, it is rarer, with high mortality and frequent complications, and most of the published data come from case reports and surgical treatment techniques of deceased patients[17].

Clinical case

The case corresponds to a 44-year-old female patient with a history of chronic arterial hypertension, chronic non-alcoholic liver disease, and chronic kidney disease on hemodialysis.

A patient presented with a 2-month history of unquantified fever with no time relationship, preceded by

chills, which improved with the use of antipyretics, which during the last 2 weeks before admission occurred during hemodialysis sessions.

The fever was associated with a respiratory condition of 1 week of evolution, characterized by dry cough and dyspnea of small exertion, for which he was admitted to a hospital with the diagnosis of bacteremia during intermittent dialysis plus pneumonia, as a result of an infection associated with health care.

Blood cultures were performed with growth of *Enterococcus faecalis*, in addition to transthoracic echocardiogram showing large vegetation (area of 3.2 cm) with pedicle adhered to the non-coronary leaflet (Fig. 1), producing severe aortic regurgitation, moderate mitral regurgitation, severe tricuspid regurgitation (Fig. 2), so management with meropenem, vancomycin and gentamicin was indicated for 14 days. A transesophageal echocardiogram was performed, and a) vegetation in the anterior mitral leaflet of 14 mm in size with perforation of the leaflet with aortomitral continuity (Figs. 2A and B).

However, without achieving an adequate therapeutic response, the patient was referred to a tertiary unit, where it was approached in a multidisciplinary manner with cardiothoracic surgery, cardiology, nephrology, intensive care, and infectious diseases; surgical management with aortic and mitral valve replacement was decided in view of persistent evidence of heart failure, uncontrolled sepsis, and high risk of cardioembolic complications.

He was taken to the operating room, where the trans surgical examination revealed large vegetation in the non-coronary leaflet of the aortic valve, with perforation of the non-coronary leaflet and mitral-aortic continuity with significant destruction of the anterior leaflet of the mitral valve (Fig. 3). Samples were taken for culture and histopathological studies (Fig. 4).

Aortic valve replacement was performed with a 21 mm Medtronic Open Pivot mechanical prosthesis plus mitral valve replacement with a 29 mm Bicarbon Fitline mechanical prosthesis plus Vega's tricuspid plasty plus coronary revascularization of the left saphenous vein-right coronary artery.

Negative control blood culture report, with elevation of inflammatory markers, which is why fungal infection is considered at that time, when calculating systemic fungemia score with high risk for it, therefore; to confirm diagnostic suspicion, PAS and Grocott stains are sent from the vegetations located in the mitral and aortic leaflets; With a positive result, the diagnosis of FEs is confirmed. It was then decided to start management with antifungal, Anidulafungin (echinocandin) 200 mg intravenously loaded followed by 100 mg daily in addition to continuing the antimicrobial regimen with Meropenem and Linezolid presenting clinical improvement, achieving withdrawal of vasopressor support, progression in ventilatory support until extubating was achieved and significant decrease in inflammatory and infectious markers, complying with management for 21 days at the hospital he was discharged in good clinical condition.

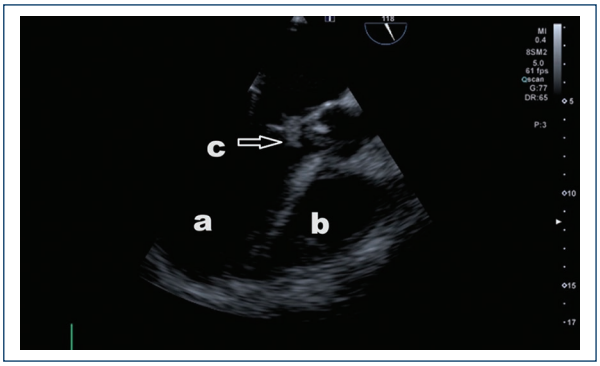

Figure 1. Transthoracic echocardiogram image (parasternal long-axis view). a: left ventricle, b: left atrium, c: vegetation in a large aortic valve of 3.2 cm (arrow).

Discussion

Invasive fungal diseases continue to increase with increasing immunodeficiency, increased numbers of patients with underlying malignant and rheumatological diseases; as well as the SARS-CoV-2 virus pandemic, which have resulted in a net increase in patients at risk for IFS. A rare but serious complication of yeast infection is endocarditis, which presents unique challenges in diagnosis and treatment[5,9,12,13].

While there are individual differences in epidemiology, diagnosis, and management for each pathogen, there are some general common characteristics. FEs account for 1-3% of all cases of IEs in prosthetic valves and affects nearly 0.1% of all native heart valves, is disproportionately associated with high morbidity and fatality rates (70%), especially for mold pathogens compared to bacterial endocarditis, and presents significant and often unique difficulties during clinical care[1,10,11].

The clinical presentation of endocarditis is highly variable and non-specific: a wide spectrum of symptoms such as fever, dyspnea, chest pressure, asthenia, altered mental status, new heart murmur, or signs of acute or chronic heart failure may be present[5,9,12,13]. Our patient presented very non-specific clinical symptoms,

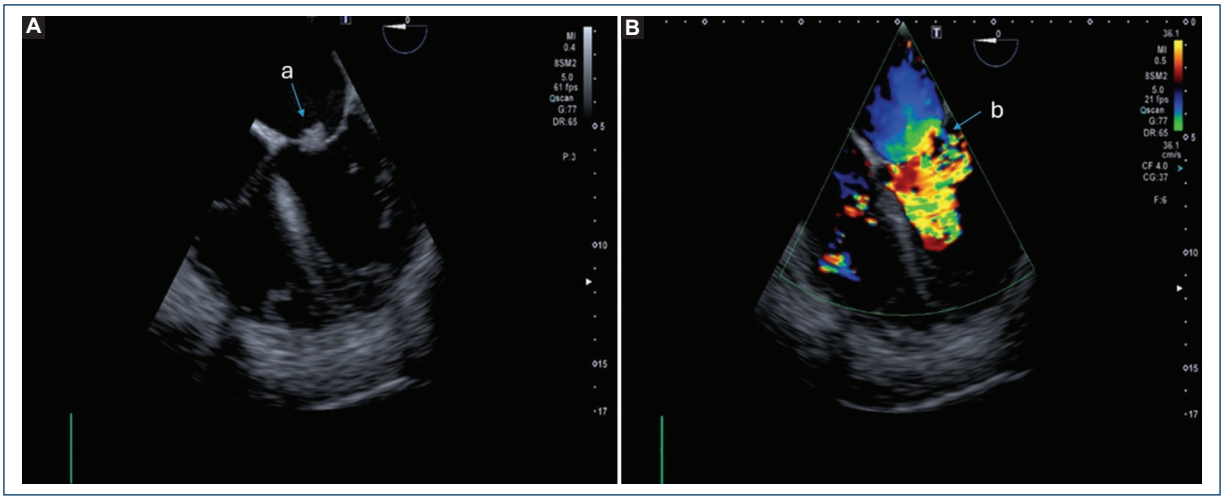

Figure 2. A: vegetation on the anterior mitral leaflet, 14 mm in size. **B**: perforation of the leaflet with aortomitral continuity.

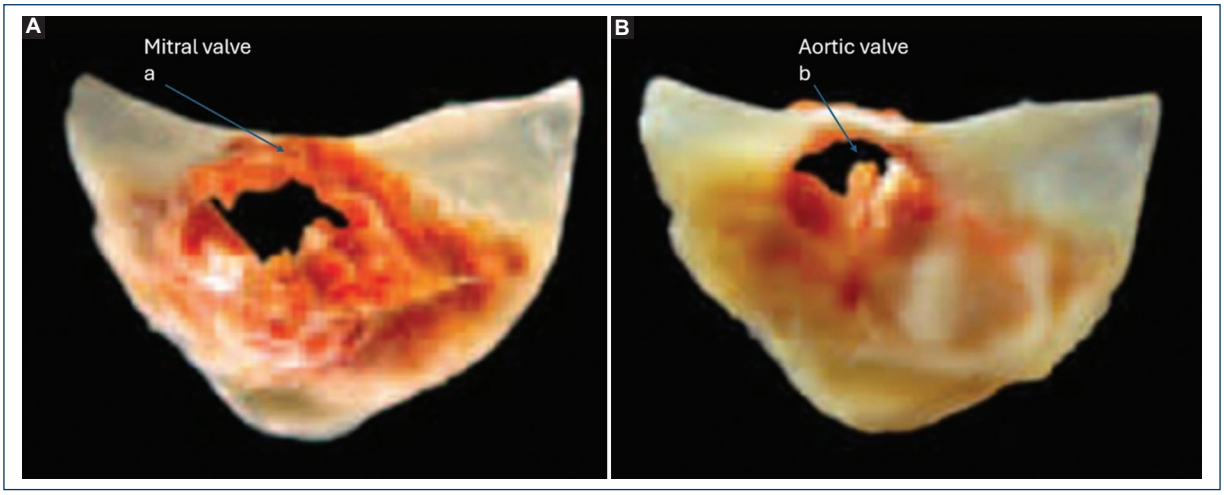

Figure 3. A: dried mitral valve with warty vegetation 1.8 cm long, and, **B:** aortic valve with 5 mm warty lesions.

which were associated with a respiratory condition for which he was initially managed as a pulmonary condensation syndrome, however, the association of risk factors (chronic comorbidities) allowed the complete diagnostic approach to be carried out, confirming the diagnosis of definitive endocarditis according to the modified Duke criteria, finding positive blood cultures for Enterococci faecalis in addition to echocardiographic finding of valvular vegetations, which conditioned severe valvular insufficiencies causing greater clinical deterioration with very poor response to medical management.

In addition, the diagnosis of FEs is even more challenging in view of its low overall incidence and, therefore, low pre-test probability in the absence of other suggestive information, non-specific clinical findings, and limitations in diagnosis because fungi are demanding microorganisms that take at least 5 days to appear in blood cultures. In addition, the sensitivity of blood cultures is far from admissible, accounting for about 50%[1,5,9,12,13].

Therefore, an accurate diagnosis requires an understanding of the factors that expose patients to an increased risk, which by means of internationally certified scales such as the *Candida* score and the Ostrosky criteria for assessing the risk of developing invasive candidiasis in critically ill patients allowed the patient to be at greater risk, whose did not present the expected

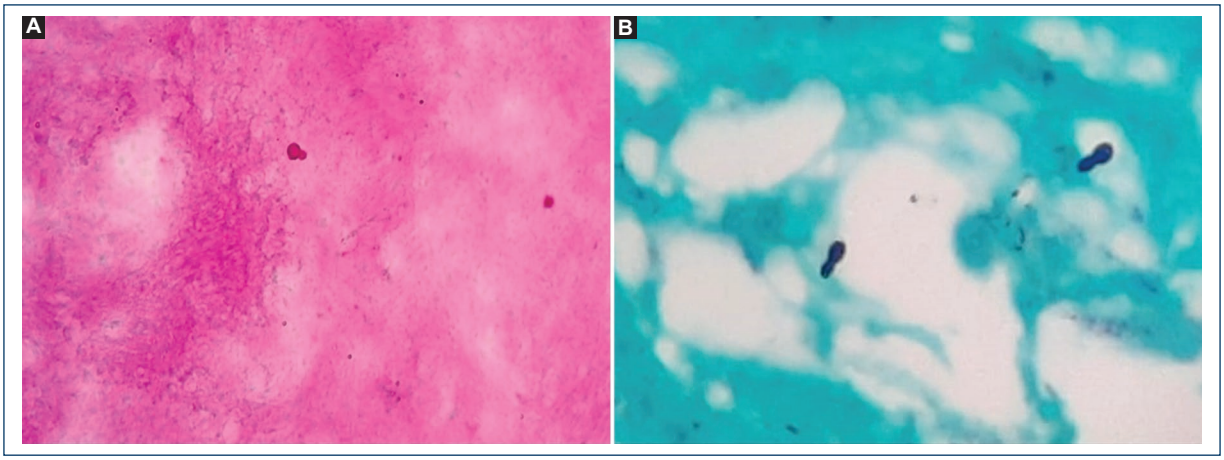

Figure 4. A: positive Schiff's periodic acid (SBP). **B:** grocott stain, mitral valve with thrombotic material with the presence of conidia.

therapeutic response, with negative blood cultures, to initiate antifungal management with echinocandin, in the context of chronic renal patients on renal replacement therapy with Anidulafungin at high doses, achieving clinical improvement and confirming the diagnosis by means of histopathological tests and biomarkers (mannan antigen detection). Biomarkers and molecular-based techniques can provide complementary diagnosis and prognostic information during the care of patients with Candida infections[1,12,13].

Antigen and antibody tests (detection of mannan antigen and antimannan antibody or BDG) and PCR-based tests are generally accessible in most second or tertiary hospital services, although their role in the diagnosis and treatment of endocarditis is limited, but they can guide the etiology of this cardiac complication. In cases of invasive candidiasis, candida man and galatoman antigens have a sensitivity between 87 and 97.5% sensitivity and 87.7% specificity, BDG have a sensitivity ranging from 76.7 to 100% and a specificity from 40.0 to 91.8%, with a high negative predictive value[1,5,9].

In a recent systematic review, BDG was positive in 24 of 27 cases of FEs (88.9%)[15]. However, detection of BDG should be interpreted with caution because positive results may also occur in patients with conditions associated with fungal translocation, including recent abdominal surgery, hemodialysis, or sepsis[1].

ECHO is the fundamental imaging technique when diagnosing suspected IEs. Although transthoracic ECHO (TTE) is widely available and relatively rapid, its sensitivity to adequately evaluate all valves is often limited, especially in the presence of prosthetic valves or intracardiac devices and in obese patients. In these cases, transesophageal ECHO (TEE) is the first-line imaging technique[1,5].

The reported sensitivity of TTE for IEs in native valves is 70% and 50% for prosthetic valve endocarditis, while the sensitivity of TEE is 96% for native valves and 92% for prosthetic valves. Although ECHO does not distinguish Candida endocarditis from endocarditis due to other pathogens, certain features may lead to suspicion of large and solitary lesions. The case of the patient described in the clinical case was that he had large vegetations in both the aortic and mitral valves, which conferred a high diagnostic suspicion[1,5,9].

European guidelines recommend routine screening of endocarditis by ECHO and frequent physical examinations in patients with candidemia, however, it is not recommended in current IDSA guidelines due to the relatively low prevalence (1.9-5.9%) of endocarditis in patients with candidemia[1,2,9,13].

The principles of treatment consist of isolating the fungus and assessing sensitivity to the different antifungal therapies available; In current medical management, the therapy is often empirical, based on echinocandins or amphotericin. In the presence of severe valve resistance and compromise, surgery is essential; vegetectomy or valve replacement may be performed[1,2,14-17].

In general, a longer period of induction treatment with antifungals is 6-8 weeks for native valve and up to 1 year for prosthetic valve infection, followed by long-term suppressive treatment of 1-2 years of therapy, especially when surgery is not performed[1,14,15].

The duration of treatment should be guided by clinical responses and other factors such as unresected lesions, intra- or extra-cardiac retention, prosthetic material, and immunosuppression[1,2,16].

Conclusion

Fungal endocarditis is a severe infection with high morbidity and mortality. This complication is best treated with a multidisciplinary team (should include a cardiology, infectious disease, critical care, cardiac surgery, and rehabilitation). The care of patients suffering from this condition should be done in the Intensive Care Unit specially during the critical period. The key to reducing mortality is prevention, early detection and treatment. Immunocompromised patients have the worst clinical outcomes. In most cases, recurrence is common, and the risk of embolization is very frequent. In the clinical case of the patient we present, there was a good evolution thanks to the multidisciplinary team that was in charge of the diagnosis, treatment and rehabilitation.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that artificial intelligence was not used in the writing of this manuscript.

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CLINICAL CASE

Reconstruction of anatomofunctional in a patient with short urethra, genital dysgenesis, and total incontinence with Turner syndrome in mosaic

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Abstract

The case of a 34-year-old female patient with Turner syndrome (TS) mosaicism (45X, 46XX) and severe urogenital malformations is presented. These malformations include clitoral agenesis, hypoplasia of the labia minora, and a short, patulous urethra that resulted in total urinary incontinence. After a multidisciplinary evaluation and a series of advanced surgical interventions, a significant improvement in urinary function and the patient's quality of life was achieved. This case highlights the clinical and surgical complexity associated with TS mosaicism, a condition that can present atypical and severe manifestations in the urogenital tract. Congenital short patulous urethra in women is a rare condition that delays diagnosis and treatment. Clinical identification, such as total incontinence, is a key sign for precise diagnosis and detailed surgical planning, essential for the effective management of patients with congenital anomalies. Advanced surgical techniques, such as subtrigonal sling placement and mobilization of vaginal wall flaps, have proven to be effective in the treatment of stress urinary incontinence, significantly improving quality of life.

Keywords: *Turner syndrome mosaicism. Urogenital malformations. Urinary incontinence. Genitourinary reconstruction. Subtrigonal sling. Congenital anomalies of the urinary tract.*

Introduction

Turner syndrome (TS) is a disease that affects women. The genetic background of the phenotype is highly variable, and karyotype analysis can improve disease understanding[1]. Previous reports indicate that the most common clinical manifestations are short stature, gonadal dysfunction, renal malformations, and certain phenotypic traits in external sexual organs[2]. When the syndrome presents as a mosaic karyotype, clinical presentations are usually uncommon[3]. Here, we describe the case of a female patient with TS mosaicism (45X, 46XX) with a patulous urethra leading to total urinary incontinence.

Congenital short patulous urethra in women is a rare condition and has been previously reported in association with epispadias. Congenital anomalies affecting the distal segment of the urogenital sinus (which gives rise to the female urethra and vagina) can result in abnormal urethral development ranging from an absent urethra to a markedly deficient urethra, leading to total urinary incontinence[4].

Clinical case

A 34-year-old female patient presented to the clinic with continuous urinary leakage that worsened with effort. As relevant history, she requires diaper

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changes 5 times a day, accompanied by a lack of urinary urge. The patient has two full-term parturient, which is not common in TS in the literature; however, due to mosaicism, it is highly probable that her uterus is healthy and she was able to conceive two children. Throughout her illness, she denied episodes of hematuria or dysuria. The patient was initially evaluated through history taking and physical examination, revealing that the condition began in childhood. Physical examination showed urogenital malformations, such as clitoral agenesis, hypoplasia of the labia minora, and abnormalities in the size of the urethra (Fig. 1).

A urinary tract evaluation was performed through urethrocystography, revealing separation of both pubic branches, a bladder volume of approximately 270 mL prevoiding with onset of incontinence, and spontaneous urine leakage. The micturition phase could not be evaluated due to involuntary urine leakage at 270 mL, and complete emptying was seen in the post-micturition phase (Fig. 2).

In the protocol in patient's TS is necessary a second study to rule out kidney malformations, a computed tomography scan with contrast of the chest and pelvis was performed, showing a decrease in the size of the urethra, fluid exiting through the vagina with no evidence of bladder wall defect, and a normal path of the ureters to the bladder and subsequently to the vagina (Fig. 3).

In collaboration with the genetics department, and due to the abnormal findings, a karyotype analysis was performed, revealing mosaic TS (45X, 46XX) (Fig. 4).

The patient underwent surgery by the urology service. The urethra was reconstructed and the urethral sphincter was increased using autologous fascia lata as a subtrigonal sling. During this process, dense fibrous scar tissue between the urethra and vagina was dissected. After mobilizing the remaining urethra, a flap of the vaginal wall was used to lengthen the urethra and reconstruct the external urethral meatus. Finally, a subtrigonal sling was placed. Synthetic slings are the most common primary surgical treatment for incontinence. Placing a subtrigonal sling is an effective surgical intervention for treating stress urinary incontinence in women. This procedure is performed through two incisions, one vaginal and one abdominal. In the vagina, an opening is created and the tissue is dissected to access the trigonal space formed by the urethra and both ureters, through which a sling is passed that adheres to the adjacent tissue. Following this, reconstruction of the clitoris, labia, and mons pubis was performed. The technique used for the mons pubis was plication with 1 Prolene of the aponeurosis of the rectus abdomen, increasing the subcutaneous cellular tissue in the mons pubis. For clitoris reconstruction, the internal face of the right and left half clitoris was sectioned, fusing with monocryl. Finally, for labial reconstruction, a minor labiaplasty was performed. Subsequently, the patient showed a drastic improvement and was completely dry at the 3-month follow-up (Fig. 5).

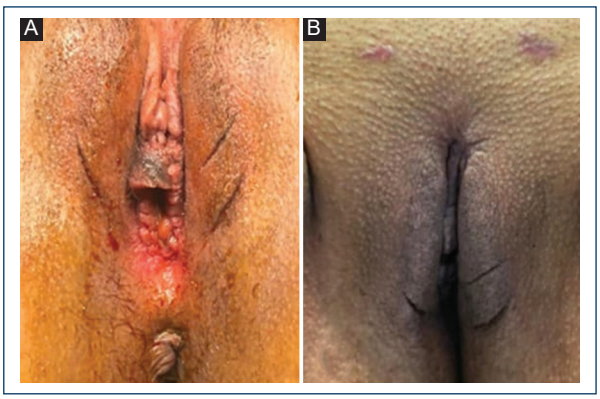

Figure 1. A: pre-operative findings show malformation of the labia majora, unfused clitoris, and hypoplasia of the labia minora. **B:** post-operative findings at 3-month follow-up show fused labia, intact clitoris, with proper healing of the fascia lata sling forming the mons pubis.

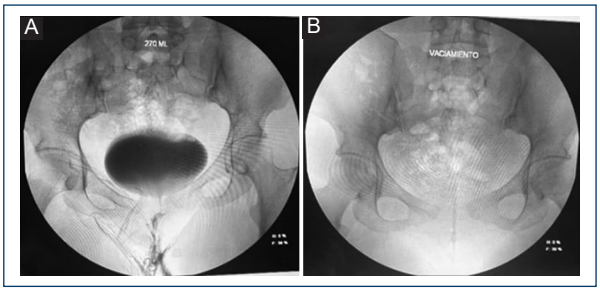

Figure 2. Urethrocystography. **A:** bladder with an approximate volume of 270 mL pre-micturition, well-defined edges, and spontaneous urine output was confirmed. **B:** the voiding phase was not assessable due to the involuntary leakage of urine, although complete emptying was evident in the post-micturition phase.

Discussion

TS can be classified according to the form of X chromosome deletion as follows: 50% of X chromosome deletions are in the classical form of TS (45,X), the mosaic form (45,X/46,XX) represents 15-25%, and the remaining cases of TS have structural abnormalities in the X chromosome[5]. The mosaic form of TS may

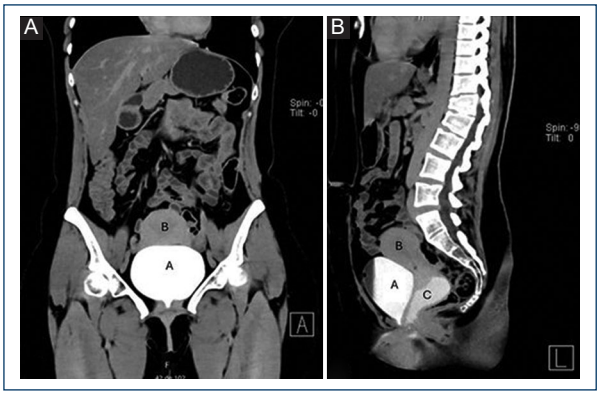

Figure 3. CT urography in coronal A the entire bladder **A:** is observed in the elimination phase with the proximal urethra above the uterus **B:** urography in sagital we observe the bladder (A) above this the uterus (B) in the usual way, on the left side of the image we observe the vagina (C) in which there is passage of contrast medium from the urethra in dorsal decubitus position showing the deficiency of the urethra to retain urine.

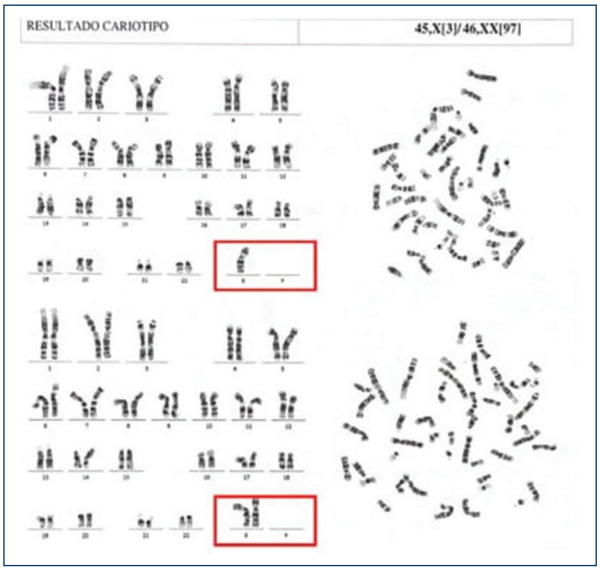

Figure 4. Karyotype results: mosaic with 3 cell lines of monosomy of the affected chromosome (45X), and a chromosome according to normalcy (46XX) in peripheral blood samples.

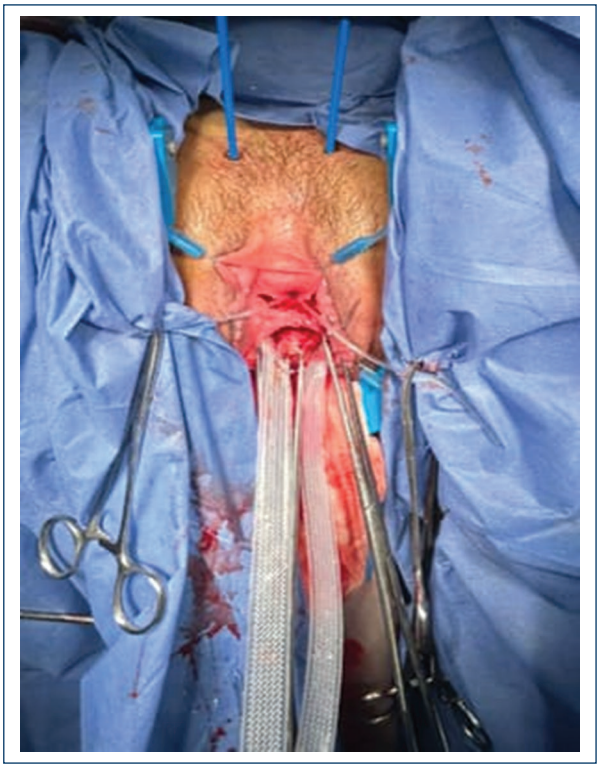

Figure 5. Urethra reconstruction with increased urethral sphincter using autologous polypropylene sling. Dense fibrous scar tissue used as a flap of the vaginal wall to lengthen the urethra and reconstruct the external urethral meatus.

overlook many of the known features of TS, leading to a delayed diagnosis similar to our patient's.

The most common urological clinical manifestations associated with TS include horseshoe kidney, with a frequency of 7-14%. It is also known that in TS, there can be a duplicated collecting system and unilateral renal agenesis. These anomalies are collectively referred to as congenital anomalies of the kidney and urinary tract (CAKUT), which are one of the leading causes of pediatric chronic kidney disease[6]. Although renal function in TS is considered normal, it has not been thoroughly studied. Studies reported in the literature indicate that the frequency of CAKUT in mosaic karyotype is 25.0%[6].

Considering what is reported in the literature and as per protocol, a contrast-enhanced computed tomography was performed to rule out possible malformations associated with TS, the findings were observed the entire bladder is observed in the elimination phase with the proximal urethra above the uterus. The bladder above this the uterus in the usual way, we observe the vagina in which there is passage of contrast medium from the urethra in dorsal decubitus position showing the deficiency of the urethra to retain urine.

The spatiotemporal nature of molecular alterations defines the renal and urinary tract defects of individuals. Early embryonic development can lead to renal parenchymal malformations, while later interferences underlie ureteral anomalies[7].

The female urethral development occurs from the pelvic and phallic part of the urogenital sinus. The abnormal

division of the urogenital sinus with possible malrotation that occurs during development is the probable hypothesis in reported cases of short and wide urethras. The exact embryological defects are unknown[8].

The reported case shares similarities with the phenotype of Turner congenital malformations, such as clitoral agenesis and hypoplasia of the labia minora. However, there is no necessary information to directly link a patulous urethra to the syndrome. Congenital short patulous urethra in women is a rare condition and has been previously reported in association with epispadias, hypospadias, and urogenital sinus anomalies. Congenital anomalies affecting the distal segment of the urogenital sinus (which give rise to the female urethra and vagina) can lead to abnormal urethral development ranging from an absent urethra to a markedly deficient urethra[4].

Youthful women with epispadias will have a bifid clitoris, a patulous urethral meatus, a vaginal opening located anteriorly, and a malformed or absent mons pubis, poorly developed lips, and occasional symphyseal separation[8].

Epispadias is a rare and sporadic congenital defect with a worldwide estimated incidence of 2.4/100,000 live births[9]. The condition is more common in men than in women, with an estimated ratio of 1.4:1, but the incidence in girls is likely to be greatly underestimated due to the difficulty of diagnosis[10].

The retrosymphyseal form can present with complete incontinence and an extremely small bladder capacity. The most severe forms may demonstrate a urethral cleft affecting the bladder neck with prolapse of the bladder mucosa. Genetic, developmental, and environmental factors are believed to play a role in the etiology of epispadias, although the underlying cause is unknown[11]. In women, urinary incontinence is a typical finding in the clinical picture[12].

Urinary incontinence can be simply defined as loss of bladder control or involuntary urination.

Urinary stress incontinence (USI) is the involuntary loss of urine associated with physical effort that increases pressure in the abdomen, such as sneezing, coughing, laughing, or simply walking. It occurs when the intravesical pressure exceeds the urethral opening pressure, as a result of a failure in the mechanisms of urethral resistance, due to two non-exclusive causes: urethral hypermobility, secondary to the weakness of the structures that make up the pelvic floor and support the urethra, and intrinsic sphincter deficiency, caused by a defect in the urethral sphincter closure system, resulting in inadequate coaptation of its walls. Synthetic slings are the most common primary surgical treatment for USI. A recent systematic review reported cure rates of 65-98%[13].

The results demonstrate that the subtrigonal sling technique with abdominal fascia is useful for resolving complex USI, and its effectiveness is comparable to that obtained with the use of suburethral tapes, but with a lower rate of obstructive complications, including urinary retention[14]. This technique was chosen based on the patient's condition, as she had a short urethra that did not have the necessary diameter for a sling. In addition, urethral elongation was performed, so if a synthetic material were to be placed in the reconstructed area, there could be a risk of fistula formation; hence, an independent working area from the urethra was selected.

Female intimate surgery has developed significantly in recent years.

The main objective of genital esthetic surgery in women, as well as in men, is to improve the subjective appearance of the external genital organs and potentially provide psychological or functional improvement in sexual satisfaction[15].

Conclusion

This case highlights the complexity and challenges in genitourinary reconstruction of a patient with TS mosaicism (45X, 46XX) and congenital anomalies in short urethra and urinary incontinence. The treatment of short urethra and severe urinary incontinence due to a deteriorated embryological defect, as part of a developmental anomaly, justifies multiple surgical reconstructions. In this case, socially acceptable continent periods were achieved through advanced surgical interventions and a multidisciplinary approach. However, more information and research are needed to reach more accurate conclusions about the optimal management and long-term implications of these conditions.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

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